State of the Science on the Health Effects Associated with PFAS Exposure

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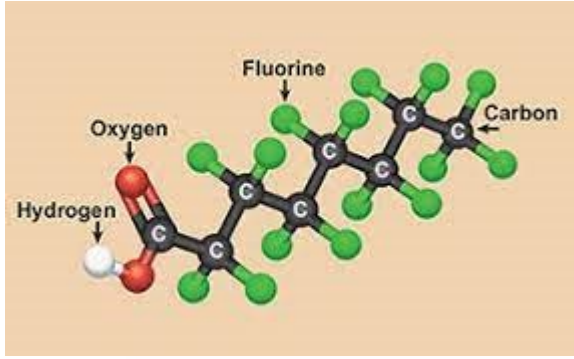
The views and opinions expressed in this presentation are those of the author and do not necessarily represent the views or opinions of the U.S. Environmental Protection Agency

Outline

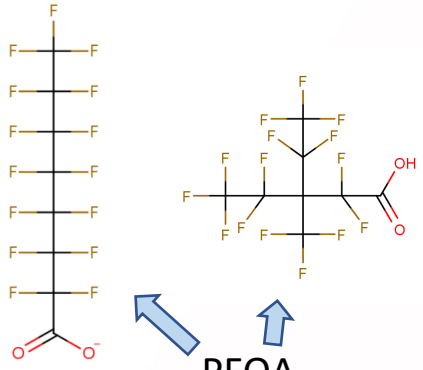
- PFAS – What are they? Where are they found?
- Human exposure
- PFAS Toxicokinetics
- State of PFAS Toxicity

PFAS – what are they?



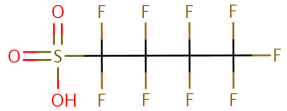
- Per- and Polyfluoroalkyl substances (PFAS)
  - Man-made chemicals generally characterized by carbon chain(s) substituted with fluorine instead of hydrogen atoms
  - Large landscape of diverse structures; number in the 1000's in commerce
- Several authoritative sources provide different definitions of what constitutes a PFAS (EPA, OECD, CDC/ATSDR)
  - In general, a PFAS is identified as any substance with at least one perfluorinated carbon (i.e., -CF_2-) (OECD, 2021)
  - More refined definitions have also been proposed: EPA/OPPT suggested PFAS be defined as any chemical substance or mixture that structurally contains the unit R-(CF2)-C(F)(R')R'' where both the CF2 and CF moieties are saturated carbons and none of the R groups can be hydrogen (TSCA, 2021)
  - Using the basic (OECD) definition as a search filter in the EPA's CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard/), of 906K+ total chemicals listed, 38,382 are identified as a PFAS; using the TSCA (2021) definition results in 9,389 PFAS

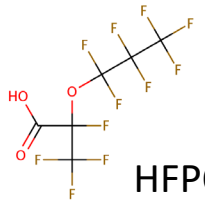
PFAS – what are they?

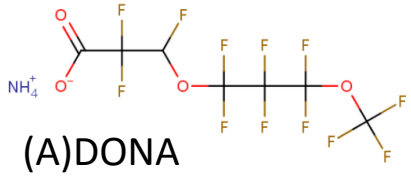


- Perfluorocarboxylic acids (PFCAs) and perfluorosulfonic acids (PFSAs)
  - Most well known/studied (e.g., PFOA, PFOS)
  - C8 Science Panel conclusions resulted in discontinuation of manufacturing C8

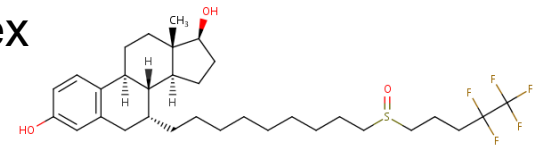
- Chemistry of PFAS evolved
  - Typically involved the addition or reduction of carbons in a structure
  - Shorter-chain (e.g., PFBS, GenX, ADONA)
  - Still confer desired product characteristics (compared to C8s)
  - Manufacturers also recognized the need to decrease transit/storage time in biota/human serum/tissues

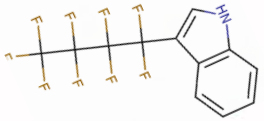

PFBS


HFPO-DA
(a.k.a. GenX)


(A)DONA

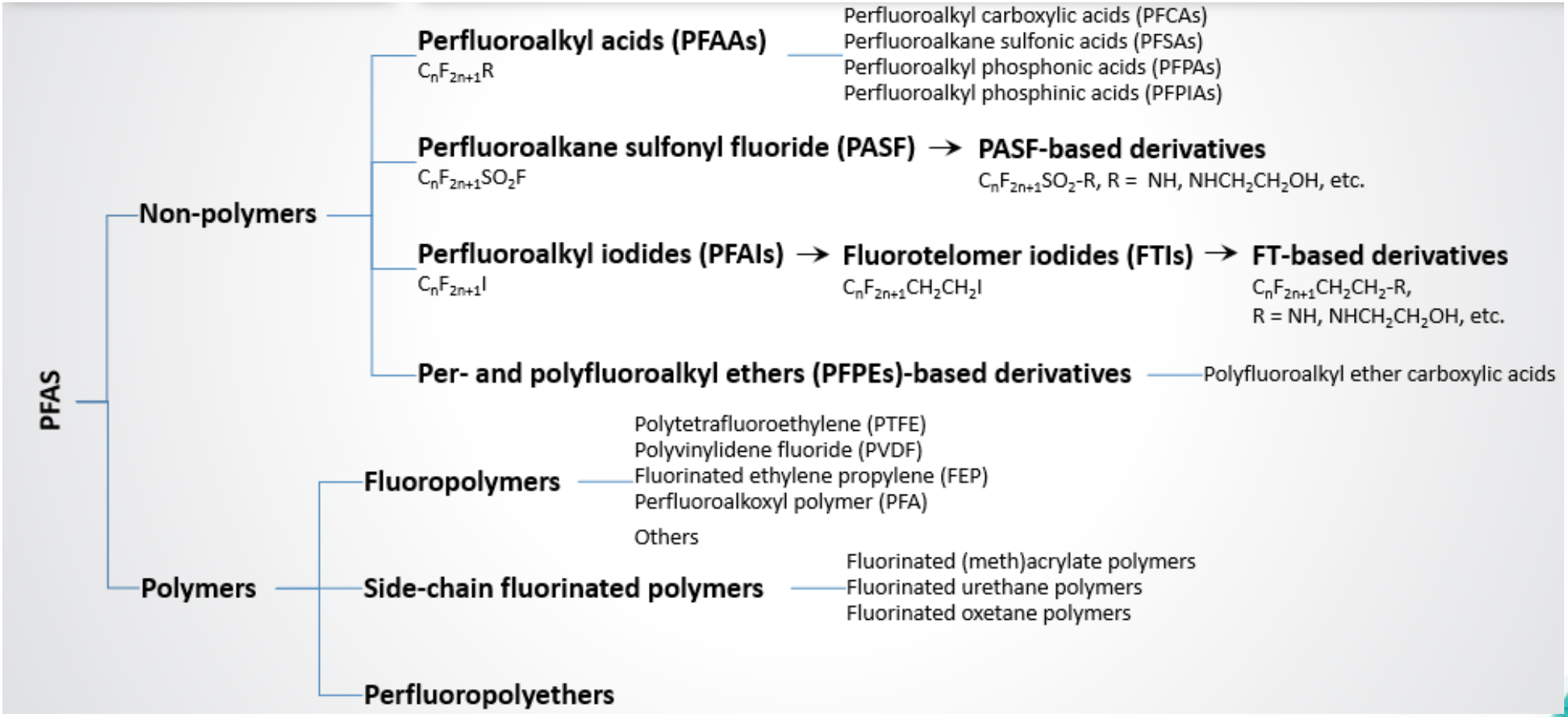
- Chemistries have also gotten more complex
  - Longer chains (e.g., PFNA, PFDA, etc.)
  - Cyclics, aromatics, complex multi-moiety





PFAS – what are they?

- Parent chemicals; by-products; environmental degradants



PFAS – where are they found?

- Widespread commercial application
  - Stain-resistant fabrics, nonstick cookware, food packaging, plastic, firefighting foam, polishes, waxes, paints, surfactants, lubricants
- Environmental Fate and Transport
  - Some PFAS are persistent and do not rapidly break down due to strength of C-F bonds
- Environmental Occurrence
  - PFAS structures vary in water/lipid solubility, vapor pressure
  - Found in several environmental matrices (e.g., water, soil, and air)

PFAS – Human Exposure

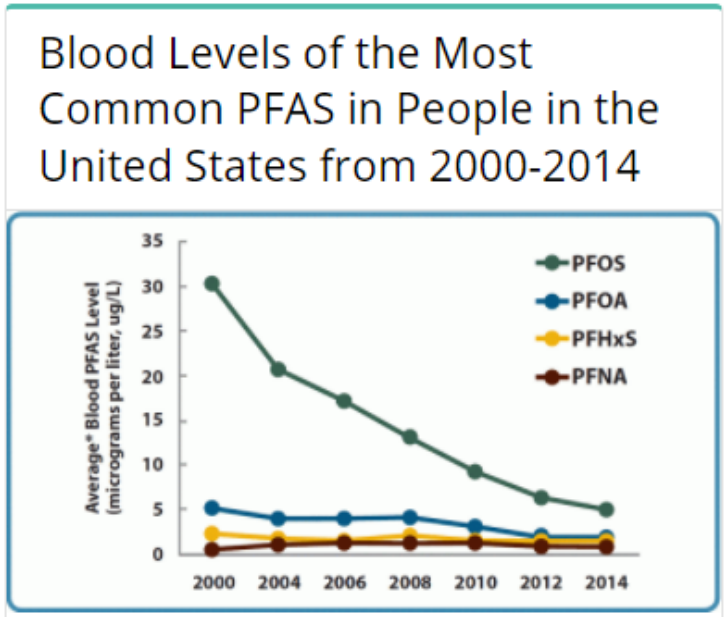
- Due to their widespread use and environmental persistence, virtually everyone in the U.S. has been exposed to one or more PFAS
- Human exposures are primarily via the oral route through drinking water ingestion and food consumption
- Dermal and inhalation exposures also occur particularly in occupational settings

Serum Perfluorooctanoic acid (PFOA) (2011 – 2018)

Sum of linear and branched PFOA isomers

Demographic Categories	Survey (years)	Geometric mean (95% CI)	50th Percentile (95% CI)	75th Percentile (95% CI)	90th Percentile (95% CI)	95th Percentile (95% CI)	Sample size
Total population	11-12	2.08 (1.95-2.22)	2.08 (1.96-2.26)	3.03 (2.76-3.27)	4.35 (3.82-4.85)	5.68 (5.02-6.49)	1904
Total population	13-14	1.94 (1.76-2.14)	2.07 (1.87-2.20)	3.07 (2.67-3.37)	4.27 (3.57-5.17)	5.57 (4.60-6.27)	2165
Total population	15-16	1.56 (1.47-1.66)	1.57 (1.47-1.77)	2.47 (2.27-2.57)	3.37 (3.07-3.57)	4.17 (3.87-4.67)	1993
Total population	17-18	1.42 (1.33-1.52)	1.47 (1.37-1.57)	2.07 (1.97-2.30)	2.97 (2.77-3.37)	3.77 (3.17-5.07)	1929

ATSDR (2020)



PFAS – Toxicokinetics

- Once ingested, inhaled, or dermally absorbed, some PFAS remain relatively unchanged in the body for long durations (e.g., long-chain PFCAs or PFSAs)
  - Days to years in humans and primates
  - Hours to months in experimental rodents

	PFBA (C4)		PFHxA (C6)		PFHxS (C6)		PFNA (C9)		PFDA (C10)	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Rat	1.0-1.8 hours	6-9 hours	0.4-0.6 hours	1.0-1.6 hours	1.8 days	6.8 days	1.4 days	30.6 days	58.6 days	39.9 days
Mouse	3 hours	12 hours	~1.2 hours	~1.6 hours	24-27 days	28-30 days	26-68 days	34-69 days	ND	
Monkey	1.7 days		2.4 hours	5.3 hours	87 days	141 days	ND		ND	
Human	3 days		32 days		8.5 years		4.3 years		12 years	

Data are summarized in Lau, C. (2015) Perfluorinated compounds: An overview. *Toxicological Effects of Perfluoroalkyl and Polyfluoroalkyl Substances*, ed. J. DeWitt, Humana Press, pp. 1-21. Darker shading indicates longer half-life.

State of PFAS Toxicity

Human Epi: https://public.tableau.com/app/profile/pfoapfos2021/viz/EpidemiologyStudiesonPFOAandPFOS/EpiLitInventory

Experimental animal: https://public.tableau.com/app/profile/pfoapfos2021/viz/ToxicologyStudiesonPFOAandPFOS/ToxLitInventory

Overall Characteristics of Epidemiology Studies on PFOA and PFOS

Overview of Epidemiology Evidence Base

Health System	Study Design				Grand Total	Reproductive		Grand Total
	Case-control	Cohort	Cross-sectional	Other		Rat	Mouse	Rat	
Cancer	3	3	2	5	13	0	0	0	3
Cardiovascular	3	13	40	6	62	0	0	1	12
Dermal	0	1	0	0	1	4	0	3	25
Developmental	5	43	16	3	67	3	0	2	15
Endocrine	2	8	19	8	37	0	0	0	3
Gastrointestinal	1	6	0	0	7	0	0	0	5
Hematologic	0	0	8	1	9	1	0	2	35
Hepatic	1	5	14	4	24	0	0	1	16
Immune	5	25	12	3	45	0	0	1	9
Metabolic	7	34	27	5	73	0	0	0	1
Musculoskeletal	0	1	6	2	9	2	0	2	17
Nervous	3	27	5	3	38	0	0	1	11
Ocular	0	0	1	0	1	3	1	3	36
Renal	1	5	17	2	25	0	0	0	3
Reproductive, Male	0	7	14	2	23	1	0	3	34
Reproductive, Female	10	22	22	2	56	5	1	3	66
Respiratory	1	4	1	0	6				
Other	0	3	3	0	6				
Grand Total	35	154	140	27	356				

State of PFAS Toxicity

Pg. 2-21 of the "Systematic Review Protocol for the PFBA, PFHxA, PFHxS, PFNA, and PFDA IRIS Assessments'; EPA/635/R-20/131
https://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=542033

LEGEND: +++ (~10+ studies) | ++ (~5 studies) | + (~1-2 studies) | - (Not Studied)

	PFDA and salts					PFNA and salts					PFHxA					PFHxS and salts					PFBA and salts				
	Oral: Long[1]	Oral: Short[1]	Inhal.	Dermal	Human	Oral: Long[1]	Oral: Short[1]	Inhal.	Dermal	Human	Oral: Long[1]	Oral: Short[1]	Inhal.	Dermal	Human	Oral: Long[1]	Oral: Short[1]	Inhal.	Dermal	Human	Oral: Long[1]	Oral: Short[1]	Inhal.	Dermal	Human
Cardiovascular	-	+	-	-	++	-	+	-	-	+++	-	+	-	-	+	+	+	-	-	+++	-	+	-	-	+
Developmental	-	+	-	-	+++	-	++	-	-	+++	-	-	-	-	-	-	+	-	-	+++	-	+	-	-	+
Endocrine (Thyroid)	-	+	-	-	+++	-	+	-	-	+++	-	+	-	-	++	+	+	-	-	+++	-	+	-	-	+
Gastro-intestinal	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-	-	+	-	-	-	-	-	-	-	-
Hematologic	-	+	-	-	+	-	+	-	-	+	+	++	-	-	+	+	+	-	-	+	-	+	-	-	-
Hepatic	-	+++	-	-	+++	-	+++	+	-	+++	+	+	-	-	++	+	++	-	-	+++	+	++	-	-	+
Immune	-	++	-	-	+++	-	++	-	-	+++	-	+	-	-	+	+	+	-	-	+++	-	-	-	-	-
Musculo-skeletal	-	+	-	-	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	+	-	-	-	-	-
Nervous	-	+	-	-	++	-	-	-	-	+++	+	+	-	-	-	+	+	-	-	+++	-	+	-	-	-
Ocular	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Reproductive	-	+	-	-	+++	-	++	-	-	+++	-	+	-	-	+	+	+	-	-	+++	-	+	-	-	+
Respiratory	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-	-	+	-	-	-	-	-	-	-	-
Urinary	-	+	-	-	+	-	+	-	-	+++	+	+	-	-	+	+	+	-	-	+++	-	-	-	-	-
General Toxicity/ Other	-	+++	-	-	+	-	+++	+	-	+	+	++	-	-	+	+	++	-	-	+	+	++	-	-	-
Cancer	-	-	-	-	+	-	-	-	-	++	+	-	-	-	-	-	-	-	-	++	-	-	-	-	-

State of PFAS Toxicity

- Reproductive effects such as decreased fertility or increased blood pressure in pregnant women.
- Developmental effects or delays in offspring, including low birth weight, accelerated puberty, neurological delays, or behavioral changes.
- Increased risk of some cancers, including prostate, kidney, and testicular cancers.
- Reduced ability of the immune system to fight infections, including reduced vaccine response.
- Interference with synthesis and/or signaling of the body's natural hormones (e.g., thyroid hormones; T4/T3).
- Increased cholesterol levels, risk of obesity/metabolic syndrome
- Liver effects (e.g., increased organ weight; altered tissue architecture)
- Kidney effects

State of PFAS Toxicity

- Several tox information domains appear to be poorly studied or characterized for PFAS to date
  - Dermal exposure
  - Inhalation exposure
  - Chronic duration exposure
  - Carcinogenicity
  - Gastrointestinal, Musculoskeletal, Ocular, and Respiratory effects

- Systematic literature searching and evidence evaluation across a broader landscape of PFAS (i.e., PFAS 150) has revealed opportunities to inform a larger universe of potential human health outcomes

State of PFAS Toxicity (PFAS 150)

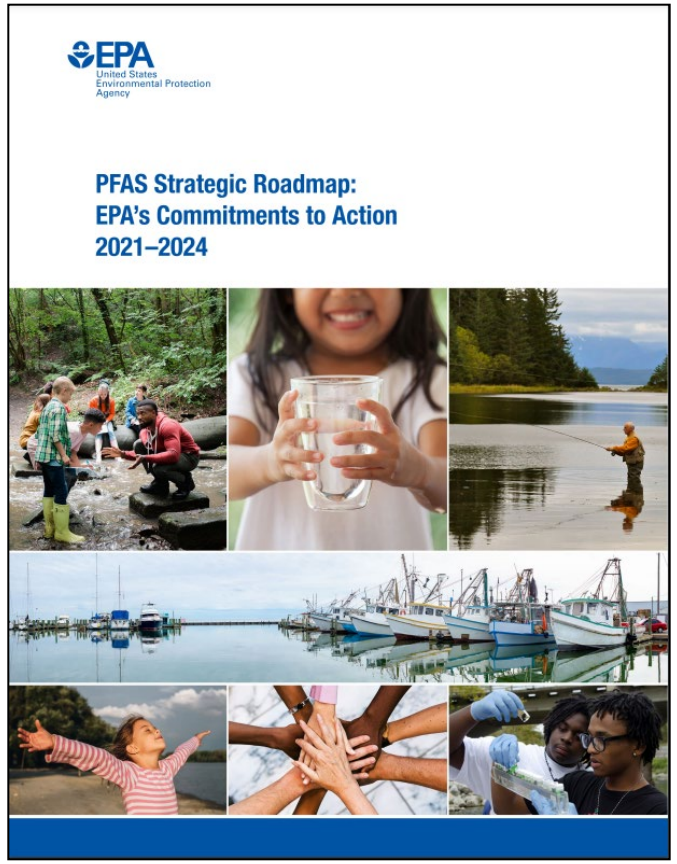
https://public.tableau.com/app/profile/literature.inventory/viz/ComprehensivePFASEvidenceMapVisualizations/AnimalStudies

Toxicological Studies Examining Exposure to PFAS by Study Design and Health System

Heat Map Hover over column headers and click the small [+] to expand species headers.

	acute	short-term	less than 4 weeks	subchronic	chronic	developmental, F1	developmental, F2	reproductive	not reported	Grand Total
Cancer					3					3
Cardiovascular	18	29	11	14	5	11		2		88
Dermal	8	7	2	5		2				24
Developmental						52	1	4		53
Endocrine	2	25	9	15	3	16		5		70
Exocrine	1		1							2
Gastrointestinal	14	16	5	13	2	5		2		56
Hematologic		28	6	20	3	9		2		66
Hepatic	14	52	22	21	4	23	2	10		134
Immune	11	33	12	18	3	9	2	4		88
Lymphatic		8		1		1				10
Metabolic		8	4	6	3	3				22
Musculoskeletal/Conne..		15	3	8		4		1		30
Nervous	28	26	4	18	3	14	2	4		91
not reported									2	2
Not reported (but NOAE..	21	20		2		7				48
Ocular	10	11	3	15	3	3		1		46
Other						1				1
Renal	13	35	7	19	5	19	2	4		97
Reproductive	9	31	7	17	4	41		16		114
Respiratory	33	22	4	13	3	10	1	3		88
Sensory	2		1	1						4
Systemic/Whole Body	116	63	25	22	5	23	1	7		247
Urinary			2					2		4
Grand Total	130	76	30	25	8	53	2	16	2	304

EPA PFAS Resources and Plans



https://www.epa.gov/pfas

Toxicity/Human Health Assessment Activities

- Updated HHRA of PFOA and PFOS
- Completion of PFBS (Apr 2021) and GenX (Oct 2021) assessments
- Additional HHRAs under development (PFBA, PFHxA, PFHxS, PFNA, PFDA)
- National PFAS Testing Strategy under TSCA (Oct 2021)
- TRI data on PFAS released (July 2021)
- Tiered tox testing approach (on-going; e.g., PFAS 150)