

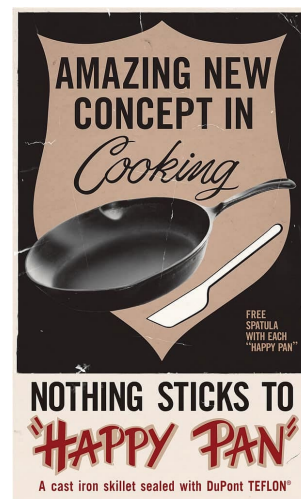
The evolving PFAS landscape: challenges and considerations for pharmaceuticals

Emily Pennoyer, PhD, MPH
April 17, 2025
ISPE Boston Chapter

Overview

- What are “PFAS”? – history and current uses
- Health effects
- How are PFAS regulated in the US?
- Defining PFAS as a class
- Implications for organofluorine pharmaceuticals

Introduction to PFAS: History and uses



perfluorooctanoic acid (PFOA)



perfluorooctanesulfonic acid (PFOS)

WWII

1930s

1940s

1950s

1960s

PFAS in daily life: a source of global contamination

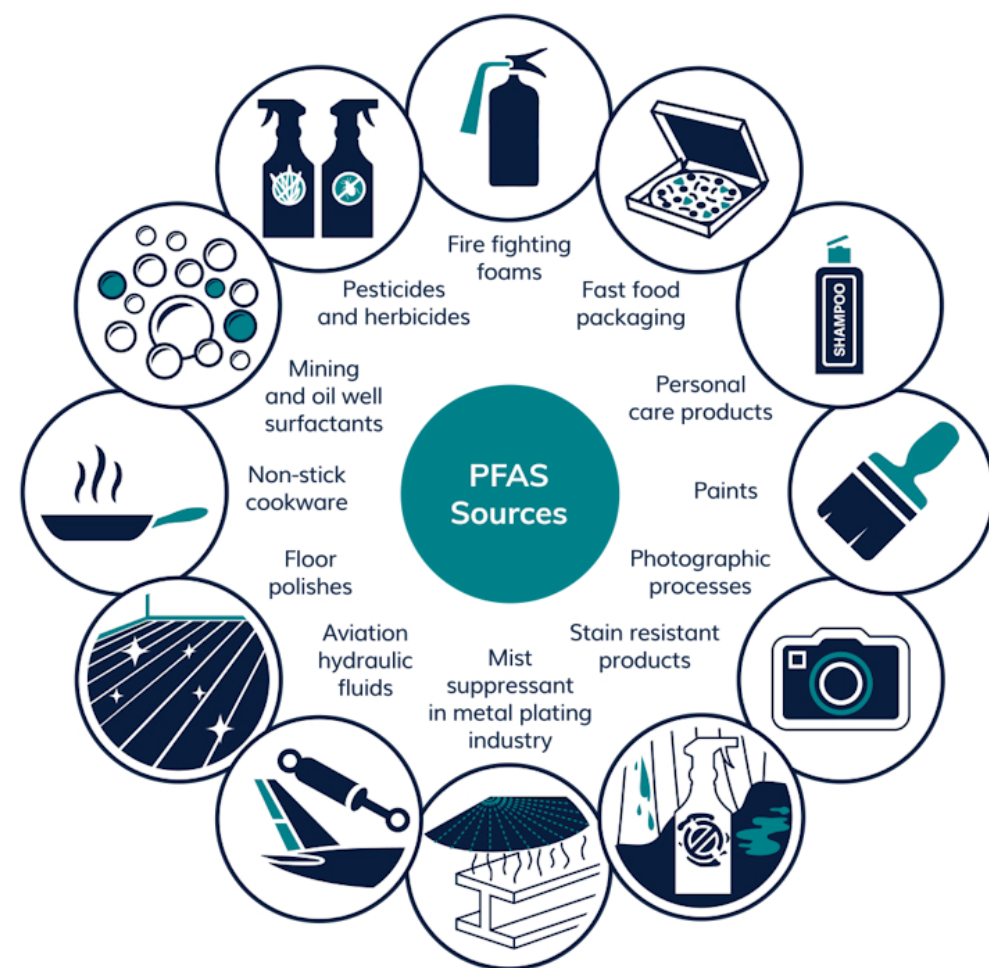


Image adapted from Australia Department of Defence



Carpets, rugs, textiles

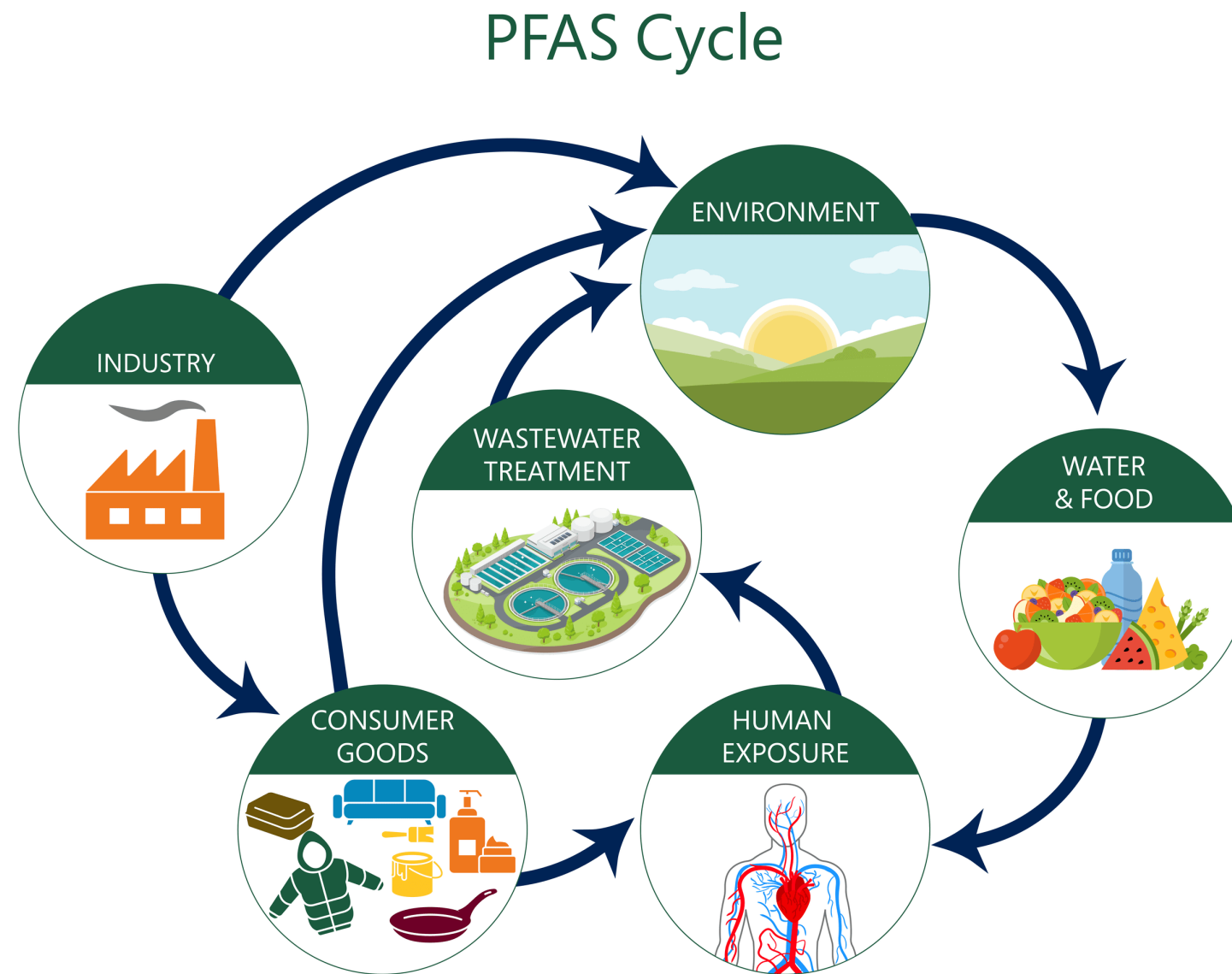


Food packaging



Class B Firefighting foam

PFAS are found in air, soil, water, biota globally



<https://www.wellingtonfl.gov/2157/PFAS>

Biden-Harris Administration Finalizes First-Ever National Drinking Water Standard to Protect 100M People from PFAS Pollution

As part of the Administration's commitment to combating PFAS pollution, EPA announces \$1B investment through President Biden's Investing in America agenda to address PFAS in drinking water

April 10, 2024

NATIONAL NEWS RELEASE

Millions in the U.S. may rely on groundwater contaminated with PFAS for drinking water supplies

Estimates according to a new USGS predictive model. Exposure to some PFAS may lead to adverse health risks.

In a First, the E.P.A. Warns of 'Forever Chemicals' in Sludge Fertilizer

Levels of PFAS in sewage sludge used as fertilizer can pose risks that sometimes exceed safety thresholds "by several orders of magnitude," the agency said.

U.S. NEWS

Court approves 3M settlement over 'forever chemicals' in public drinking water systems

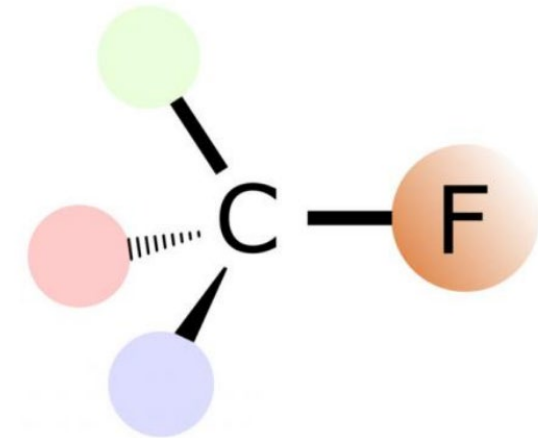
POLITICS | EUROPE

EU wheels in 'forever chemicals' ban for children's toys

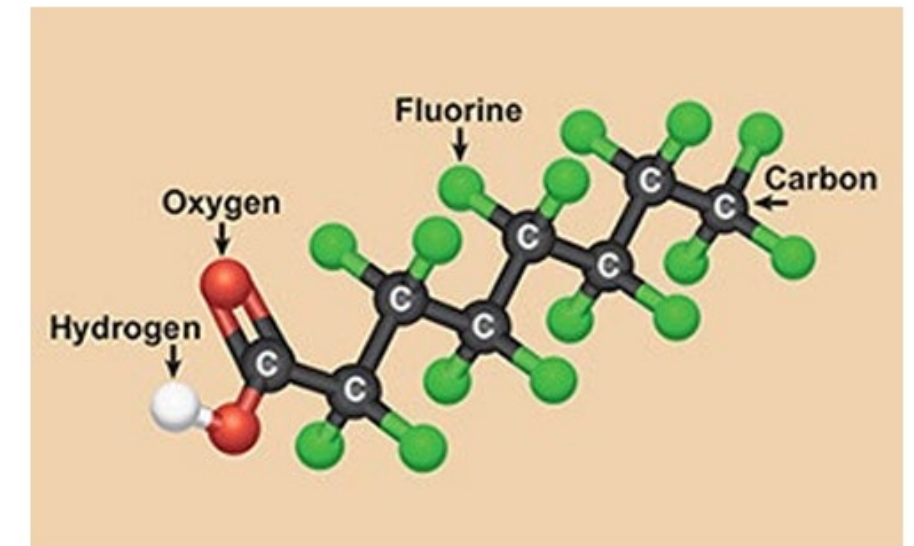
Richard Connor with dpa, AFP
04/11/2025

PFAS are a large class of compounds (1000s)

- PFAS structures are typified by carbon-fluorine bond
- “Forever Chemicals” are persistent in the environment
- “Legacy” PFAS are mobile in the environment and can bioaccumulate in organisms

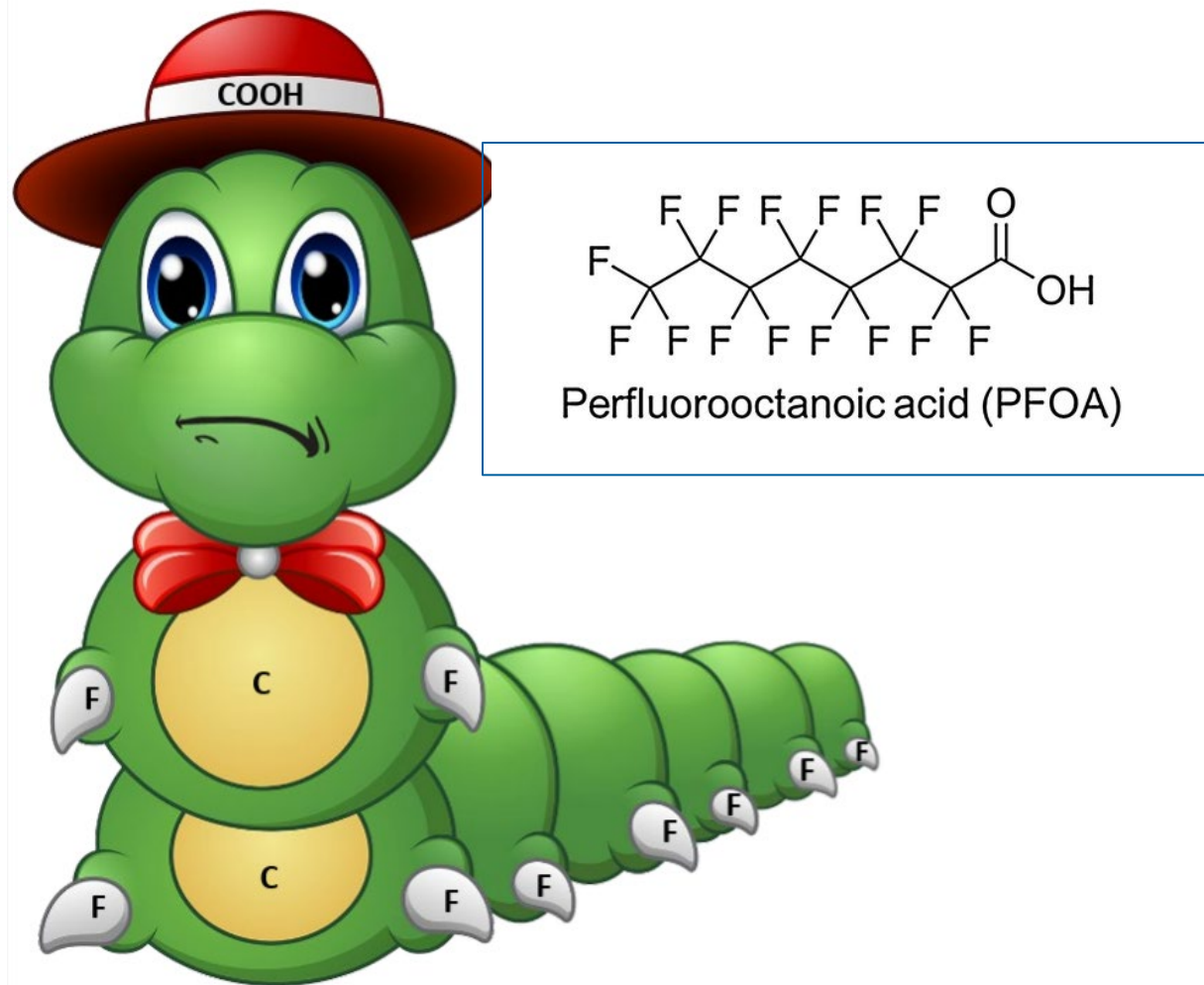


Example: PFOA
Perfluorooctanoic acid

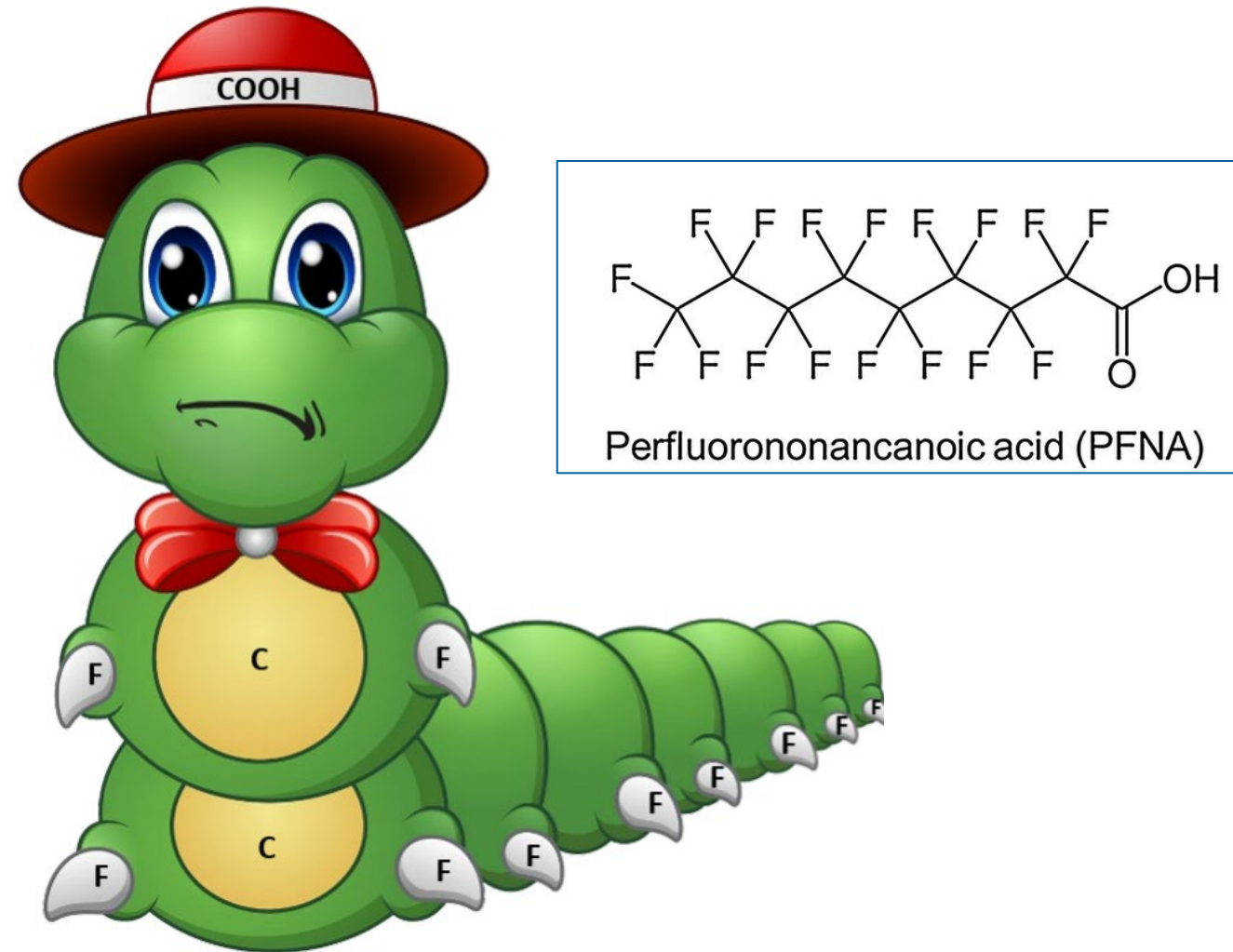


“Legacy” PFAS:

Perfluoro**OCT**anoic acid



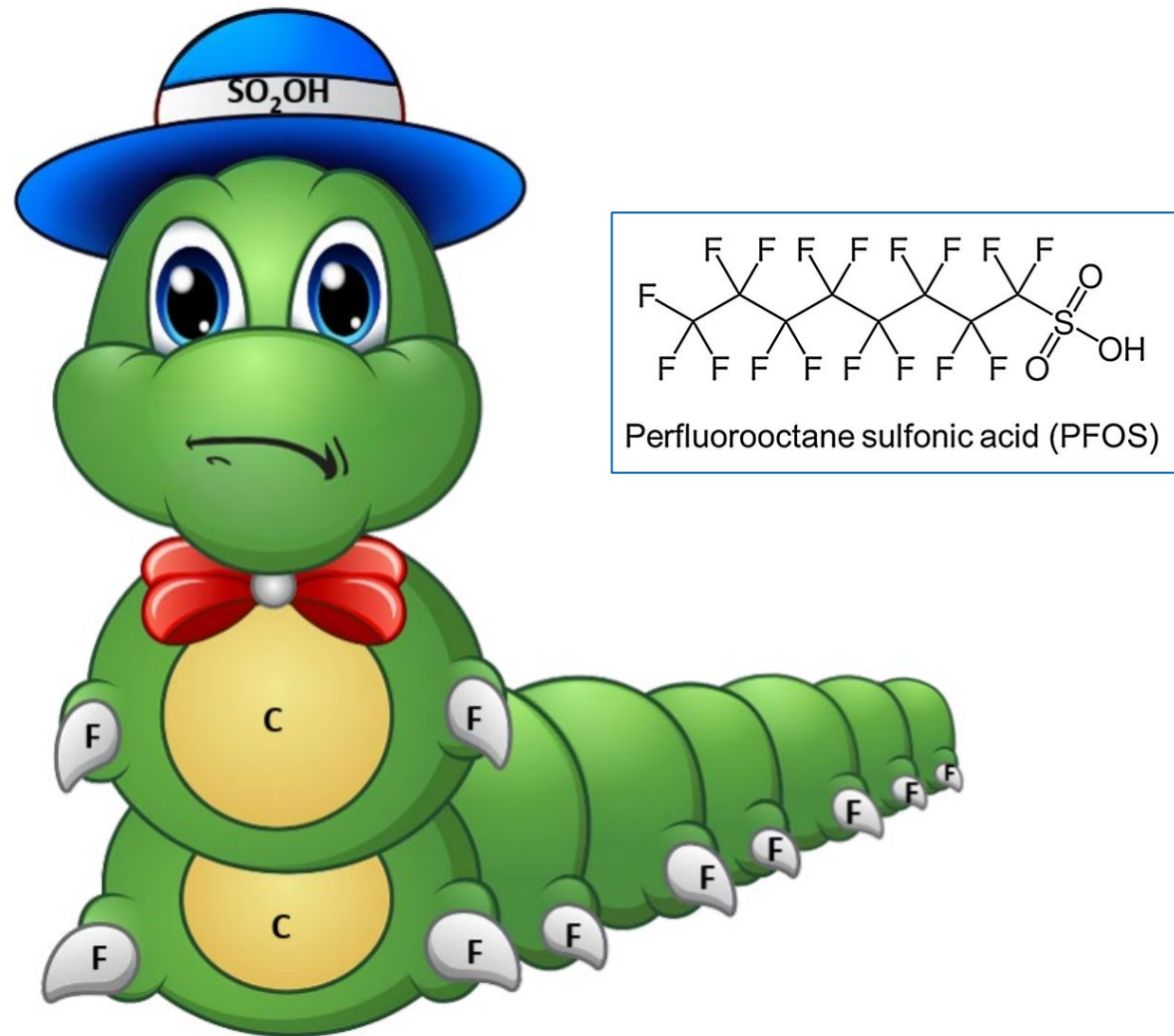
Perfluoro**NONA**anoic acid



Adapted from slides by Dr. Kathleen Attfield

“Legacy” PFAS:

Perfluorooctane**SULFONIC** acid



- Phased out of production in the U.S.
- Still produced in other parts of the world
- Newer replacement PFAS continue to be produced

Adapted from slides by Dr. Kathleen Attfield

Health effects

- Science to understand the health effects of legacy PFAS is ongoing
- Legacy PFAS affect multiple organ systems in the body
- IARC monograph designates PFOA as carcinogenic (Group 1) and PFOS as possibly carcinogenic (Group 2B)



Increases in cholesterol levels (PFOA, PFOS, PFNA, PFDA)



Changes in liver enzymes (PFOA, PFOS, PFHxS)



Lower antibody response to some vaccines (PFOA, PFOS, PFHxS, PFDA)



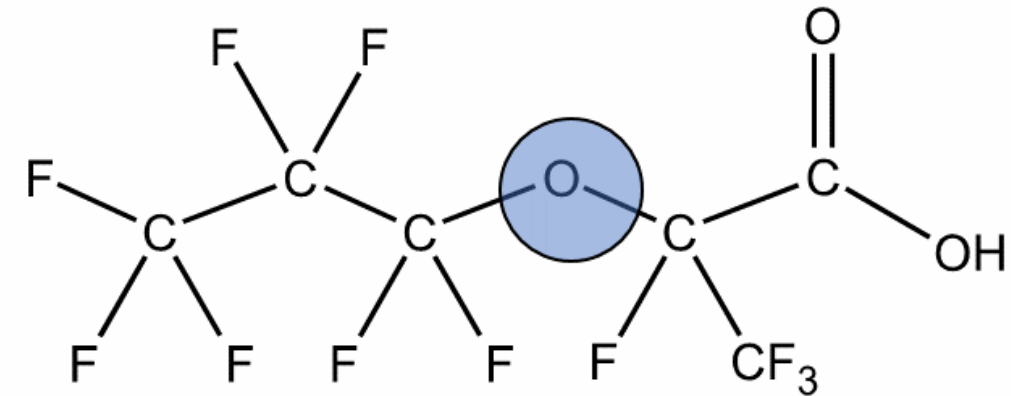
Kidney and testicular cancer (PFOA, PFOS)

Image adapted from ATSDR

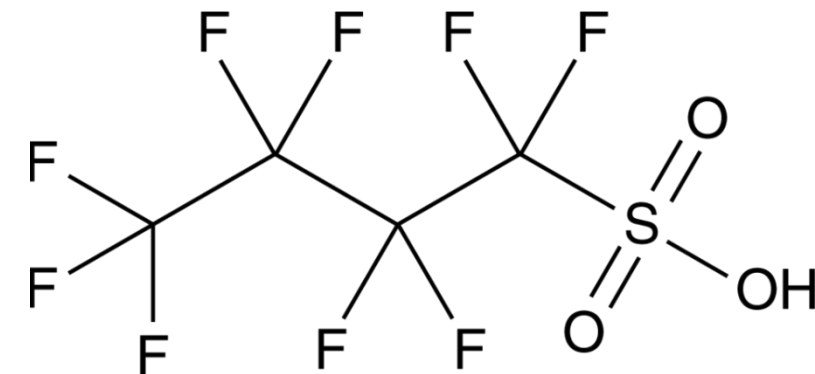
Replacement PFAS: new challenges

- Replacement PFAS – “regrettable substitutes” (1000s)
- Less research into health effects
- Shorter chain compounds are highly mobile.

hexafluoropropylene oxide dimer acid
(HFPO-DA) aka “GenX”



Perfluorobutanesulfonic acid “PFBS”



Regulatory framework for PFAS

Biden-Harris Administration Finalizes First-Ever National Drinking Water Standard to Protect 100M People from PFAS Pollution



Federal Regulations:

- EPA Maximum Contaminant Levels in drinking water (6 PFAS)
- Toxic Substances Control Act (TSCA) Reporting Rule
- Toxics Release Inventory (TRI)

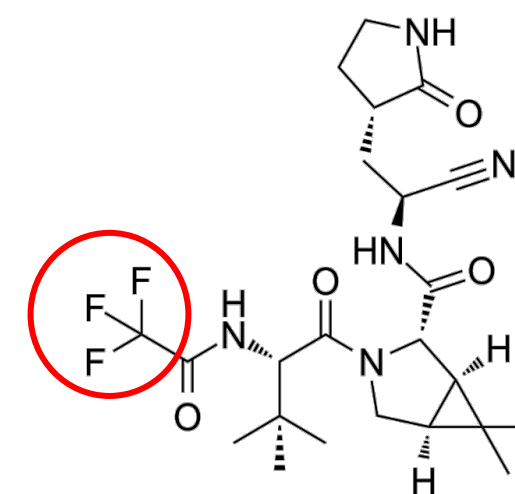
State-level Regulations:

- Maine
- California
- Vermont
- Washington
- Minnesota
- Colorado
- New Hampshire
- Rhode Island

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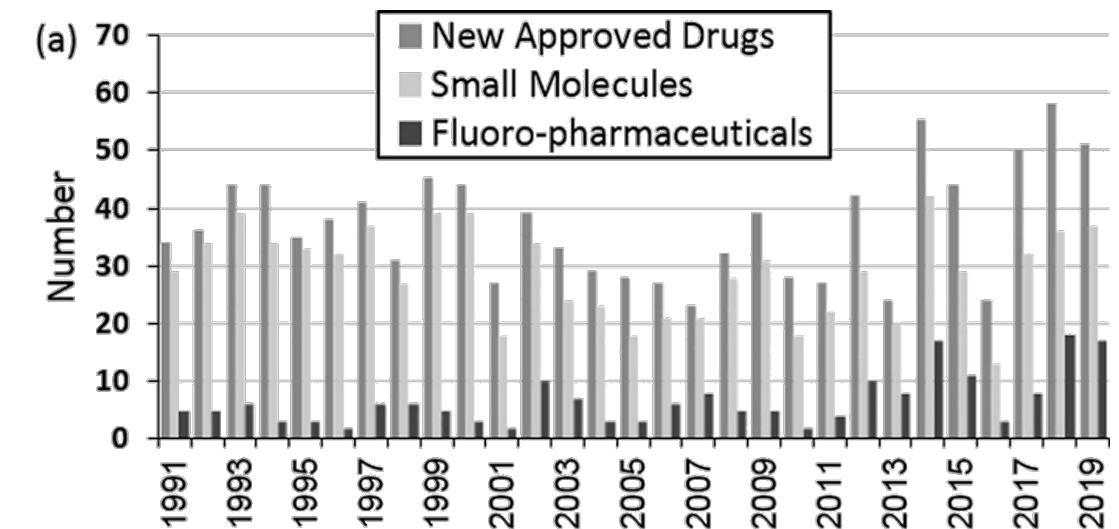
Defining PFAS as a class

- Challenges in addressing PFAS one at a time
 - Class-based approaches proposed
- Multiple structural definitions of PFAS exist (broad vs. narrow)
- Organofluorine is used in pharmaceutical industry



Nirmatrelvir (Paxlovid)

Organofluorine Pharmaceuticals



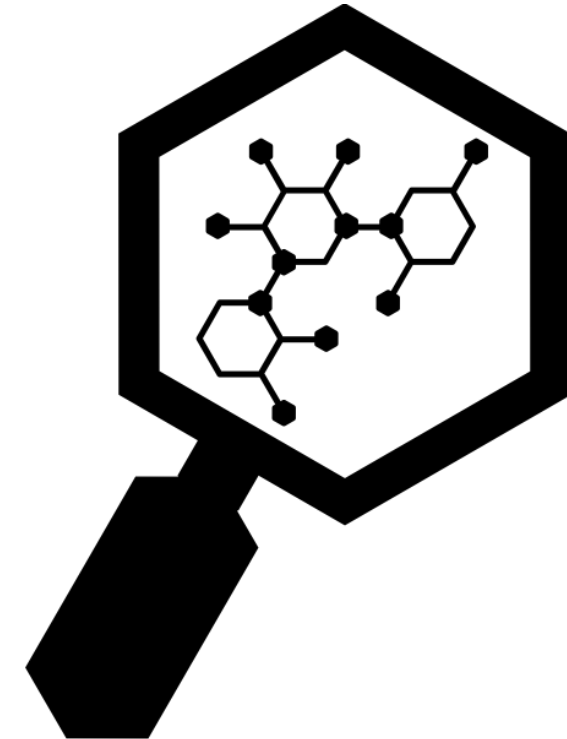
Inoue et al., 2020, PMID: 32455181

How are PFAS definitions used?

Organizations define PFAS based on *structure*

Definitions used for a range of purposes:

- Regulation of PFAS in commercial products and the environment
- Human biomonitoring
- Non-regulatory definitions

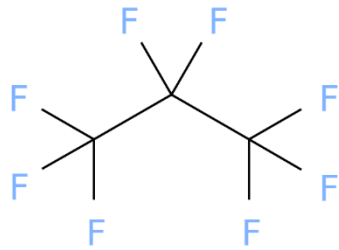


Definition	Regulatory?
Buck et al. (2011)	No
OECD (2018, 2021)	No
Glüge et al. (2020)	No
US EPA Office of Pollution Prevention and Toxics (OPPT) (2021)	Yes
TURA Program of MA (2021a, 2021b)	Yes
≥1 Fully Fluorinated Carbon	Yes
All Organofluorine	No

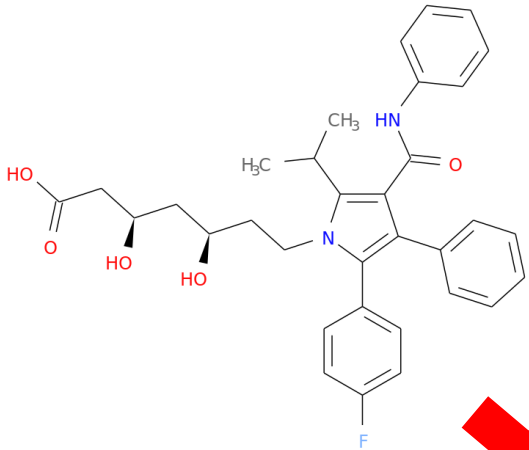
iScience
CellPress
OPEN ACCESS

Article
Implications of PFAS definitions using fluorinated pharmaceuticals
Emily Hammel,^{1,3,*} Thomas F. Webster,¹ Rich Gurney,² and Wendy Heiger-Bernays¹

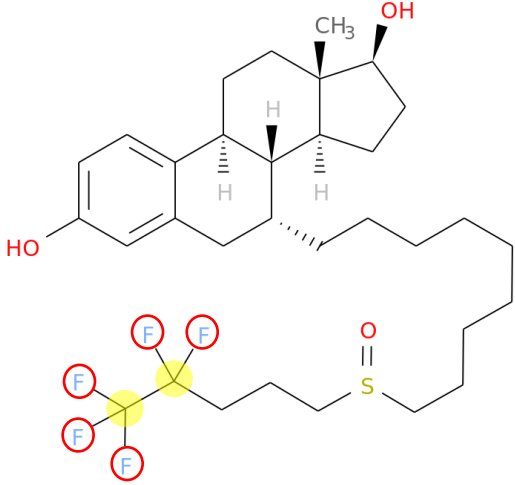
“R-CF₂-CF(R')(R''), where R, R', and R'' do not equal "H" and the carbon-carbon bond is saturated”



Optison (Perflutren)
Contrast agent;
echocardiography



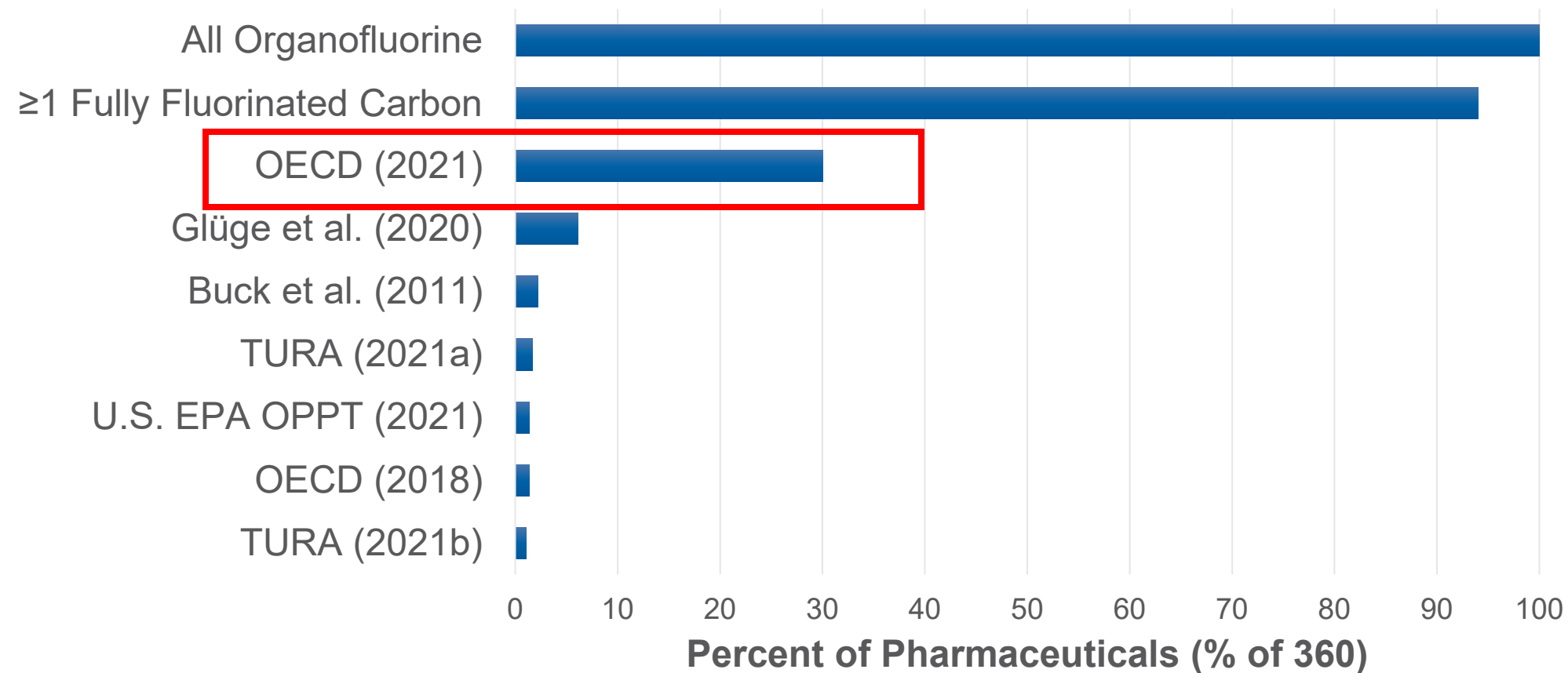
Atorvastatin (Lipitor)
Cholesterol lowering
medication



Fulvestrant (Faslodex)
Anti-estrogen, breast
cancer

Definitions can be broad or narrow

Organofluorine Pharmaceuticals Included in PFAS Definitions



Hammel et al., 2020, *iScience*

Implications for pharmaceuticals depend on context

Example: Regulation

Legislation defines PFAS as any “**substance containing at least one fully fluorinated carbon atom**” (WA, ME, CA, VT)

Maine LD 15013, 130th Legislature, An Act to Stop PFAS Pollution

- Regulatory exemptions for **currently unavoidable uses**
- Products already under federal regulations (e.g., FDA)



EU proposal for universal PFAS restriction

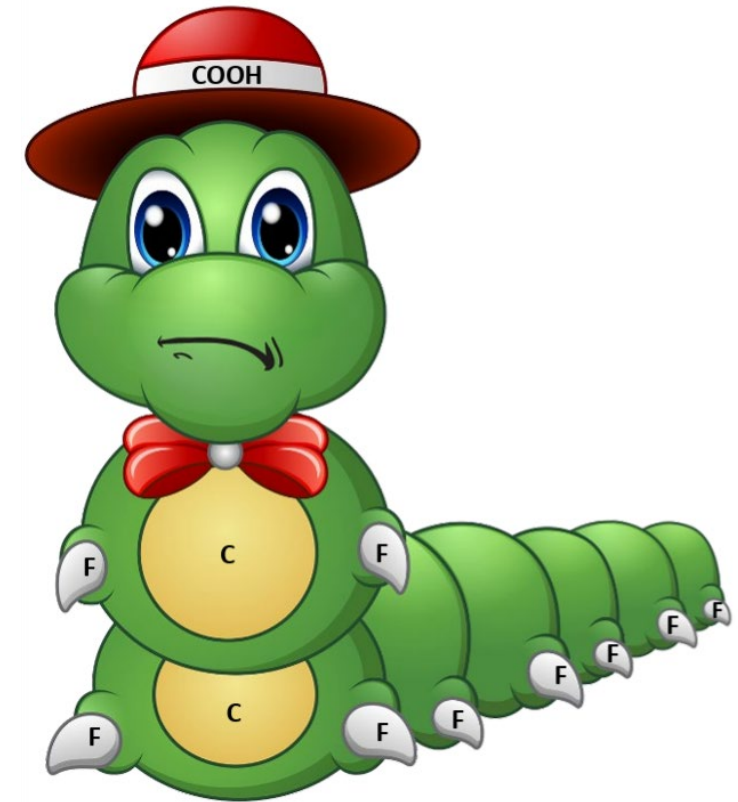
Joint proposal submitted to the European Chemical Agency (ECHA) to restrict the use of PFAS under REACH



- Exemptions for essential uses (e.g., medical applications)
- Assessing groups of PFAS e.g., substances of very high concern (SVHC)
- Exploring a holistic group approach to regulatory assessment to avoid regrettable substitutions

Conclusion

- PFAS are widely used and persistent in the environment and in people
- PFAS definitions range in their inclusion of organofluorines
- **Implications for organofluorines depend on how the definition is applied**



Thank you

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Extra slides

Properties of fluorine that impart advantageous effects

- (1) fluorine is, after hydrogen, the second smallest atom;
- (2) fluorine exhibits the highest electronegativity in the periodic table of elements;
- (3) fluorine forms the strongest single bonds with carbon.

Definition	Regulatory?	Definition (abbreviated)
Buck et al. (2011)	No	Aliphatic substances with the moiety (C _n F _{2n+1} –) attached to it. All H substituents in the nonfluorinated analogues from which they are notionally derived have been replaced by F atoms.
OECD (Europe) 2018, 2020	No	<p>“PFASs, including perfluorocarbons, that contain a perfluoroalkyl moiety with three or more carbons (i.e. –C_nF_{2n}–, n ≥ 3) or a perfluoroalkylether moiety with two or more carbons (i.e. –C_nF_{2n}OC_mF_{2m}–, n and m ≥ 1).”</p> <p>Revised:</p> <p>One fully fluorinated methyl or methylene carbon atom without H/Cl/Br/I atom attached to it (–CF₃), (–CF₂–).</p>
Glüge et al. (2020)	No	Substances containing C _n F _{2n+1} , where n≥1, including aromatic compounds, ethers and polymers with –CF ₂ – and non-polymers with –CF ₂ -CF ₂ - moiety.
US EPA Office of Pollution Prevention and Toxics (OPPT) (2021)	Yes	R-CF ₂ -CF(R')(R''), where R, R', and R'' do not equal "H" and the carbon-carbon bond is saturated.
TURA Program of MA 2021a	Yes	Chemicals containing a perfluoroalkyl moiety with three or more carbons (e.g., –C _n F _{2n} –, n ≥ 3; or C _{F3} –C _n F _{2n} –, n≥2) or a perfluoroalkylether moiety with two or more carbons (e.g., –C _n F _{2n} OC _m F _{2m} – or –C _n F _{2n} OC _m F _m –, n and m ≥ 1).
TURA Program of MA 2021b		<p>Revised:</p> <p>“Certain PFAS not otherwise listed includes those PFAS that contain a perfluoroalkyl moiety with three or more carbons (e.g., –C_nF_{2n}–, n ≥ 3; or C_{F3}–C_nF_{2n}–, n≥2) or a perfluoroalkylether moiety with two or more carbons (e.g., –C_nF_{2n}OC_mF_{2m}– or –C_nF_{2n}OC_mF_m, n and m ≥ 1), wherein for the example structures shown the dash (–) is not a bond to a hydrogen and may represent a straight or branched structure, that are not otherwise listed.”</p>
≥1 Fully Fluorinated Carbon	Yes	The US National Defense Authorization Act and the states of WA, ME, VT and CA have adopted legislation defining PFAS as any compound containing at least 1 Fully Fluorinated Carbon.
All Organofluorine	No	NGOs (Sierra Club of MA, Conservation Law Foundation) who advocate for broader definitions of PFAS to include all organofluorines.

Public Health Relevance

- Clinical guidelines to reduce exposure above 2 ng/mL
- Strategies for source reduction are needed

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