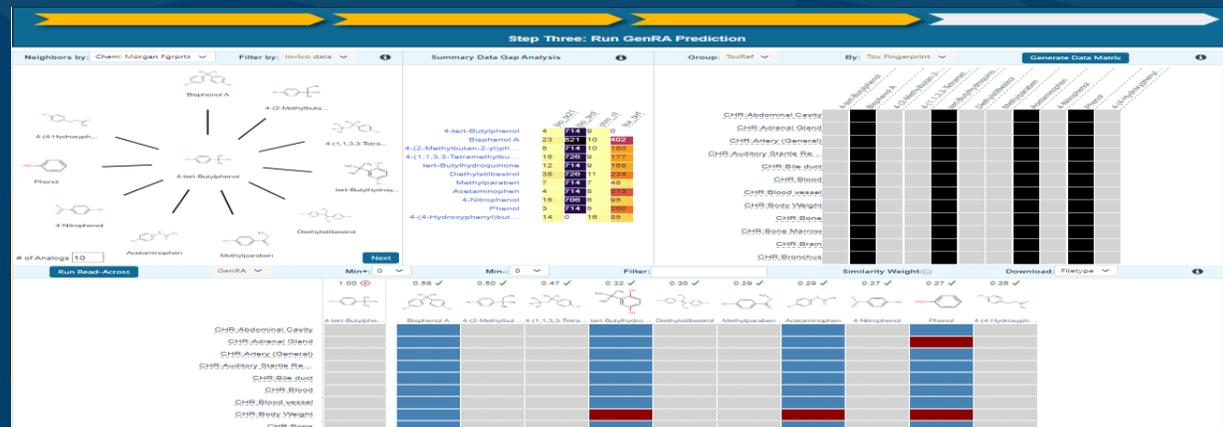


# PFAS Prioritisation for Targeted Testing



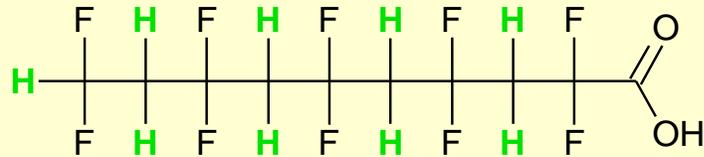
Grace Patlewicz  
 National Center for Computational Toxicology (NCCT), US EPA

- What are PFAS?
- What is the Landscape of PFAS?
- What are PFAS of potential interest to the Agency?
- How many substances might be procurable?
- What constitutes a representative set of PFAS to propose for targeted testing?
- Structural categories - current and future
- Some next steps

# Per- and Polyfluoroalkyl Substances (PFAS)

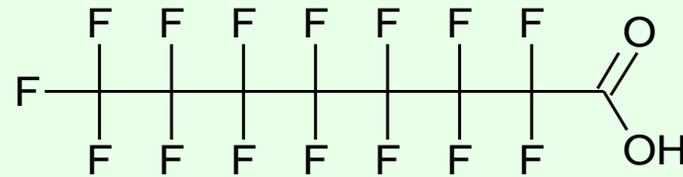
Thousands of PFAS are associated with the production of industrial and consumer products.

Poly fluorinated = many fluorines

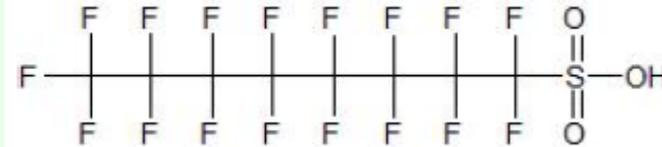


Polyfluorinated carboxylic acid from the production of polyvinylidene fluoride (PVDF) plastic

Per fluorinated = fully fluorinated



Perfluorooctanoic acid (PFOA ,C-8)



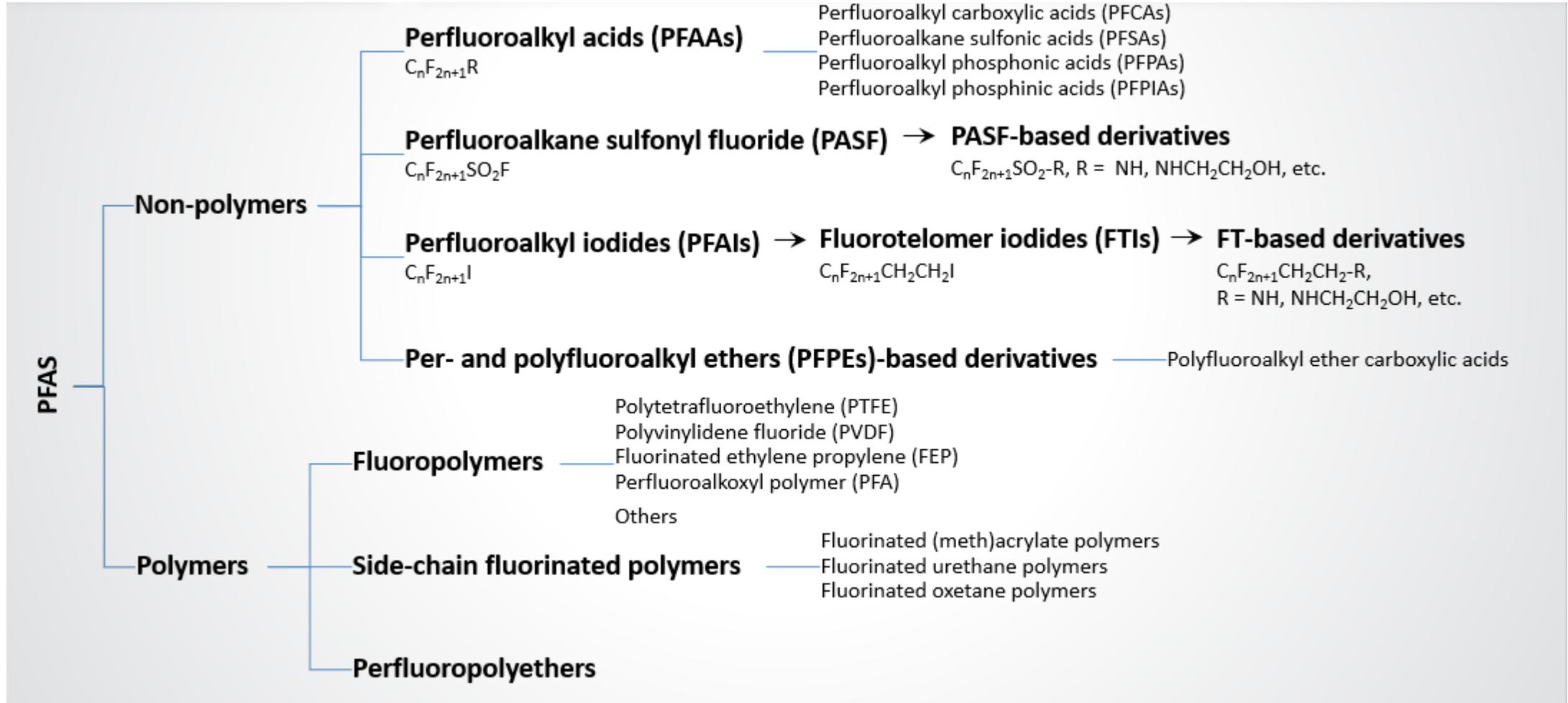
Perfluorooctanesulfonate (PFOS)

# Per- and Polyfluoroalkyl Substances (PFAS)

- A class of man-made chemicals that are ubiquitous due to:
  - Wide variety of industrial and consumer uses
  - Persistence
  - High mobility
- They are a concern due to:
  - Known or suspected toxicity, especially for PFOS and PFOA
  - Bioaccumulation
  - Long half lives (e.g., several years), especially in humans
  - Mobility - shorter chain PFAS tend to be highly mobile, longer chain PFAS less mobile
- Information on PFAS is rapidly evolving

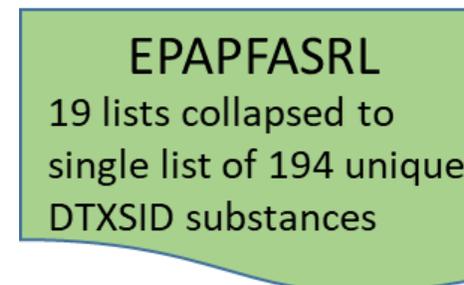
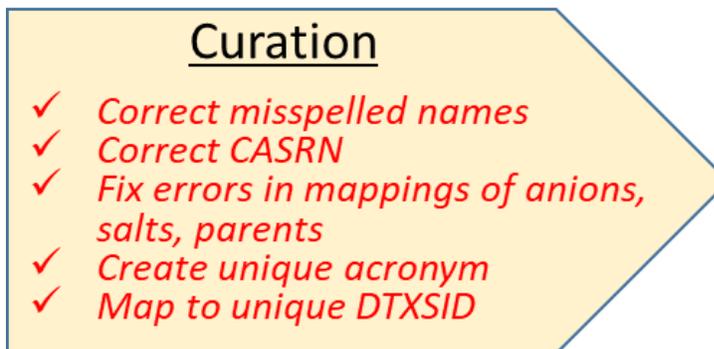
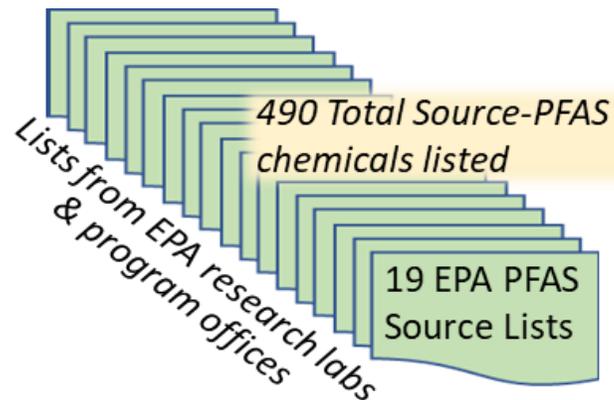


# Thousands of Chemicals: More Than Just PFOA and PFOS



# PFAS: EPA Cross-Agency Research List (Late 2017)

[https://comptox.epa.gov/dashboard/chemical\\_lists/epapfasrl](https://comptox.epa.gov/dashboard/chemical_lists/epapfasrl)

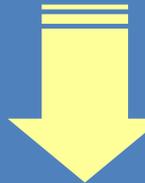


DTXSID	Substance_Name	Substance_CASRN	Source_Name (incorrect or ambiguous)	Source_CASRN (incorrect or invalid)	Source_Acronym (incorrect or ambiguous)	Unique_Acronym
DTXSID20874028	2H,2H,3H,3H-Perfluorooctanoic acid	914637-49-3	5:3 Polyfluorinated acid	914637-49-3	5:3 acid	5:3 PFOA
DTXSID7027831	N-Methyl-N-(2-hydroxyethyl)perfluorooctanesulfonamide	24448-09-7	N-Methyl perfluorooctanesulfonamide ethanol		NMeFOSE, MeFOSE	NMeFOSE
DTXSID10892352	Perfluoro-2-([perfluoro-3-(perfluoroethoxy)-2-propanyl]oxy)ethanesulfonic acid	749836-20-2	Ethanesulfonic acid, 2-[1-[difluoro(1,2,2,2-tetrafluoroethoxy)methyl]-1,2,2,2-tetrafluoroethoxy]-1,1,2,2-tetrafluoro	749836-20-2	PFESA Byproduct 2	PFESA Byproduct 2
DTXSID70892479	Perfluoropentanesulfonate	175905-36-9	Perfluoropentanesulfonate	2706-91-4	PFPeS	PFPeS_ion
DTXSID8071354	Ammonium perfluoropentanesulfonate	68259-09-6	Ammonium perfluoropentanesulfonate	68259-09-6		APFPeS
DTXSID40881350	4,8-Dioxa-3H-perfluorononanoic acid	919005-14-4	2,2,3-Trifluoro-3-(1,1,2,2,3,3-hexafluoro-3-(trifluoromethoxy)propoxy)propanoic acid	919005-14-4	ADONA	ADONA parent acid
DTXSID00874026	Ammonium 4,8-dioxa-3H-perfluorononanoate	958445-44-8	Ammonium 4,8-dioxa-3H-perfluorononanoate	958445-44-8	ADONA	ADONA
DTXSID3037707	Potassium perfluorobutanesulfonate	29420-49-3	Potassium perfluoro-1-butanesulfonate		PFBS	PFBS-K
DTXSID5030030	Perfluorobutanesulfonic acid	375-73-5	Perfluorobutanesulfonic acid	375-73-5	PFBS	PFBS

# PFAS Library and Chemical Selection

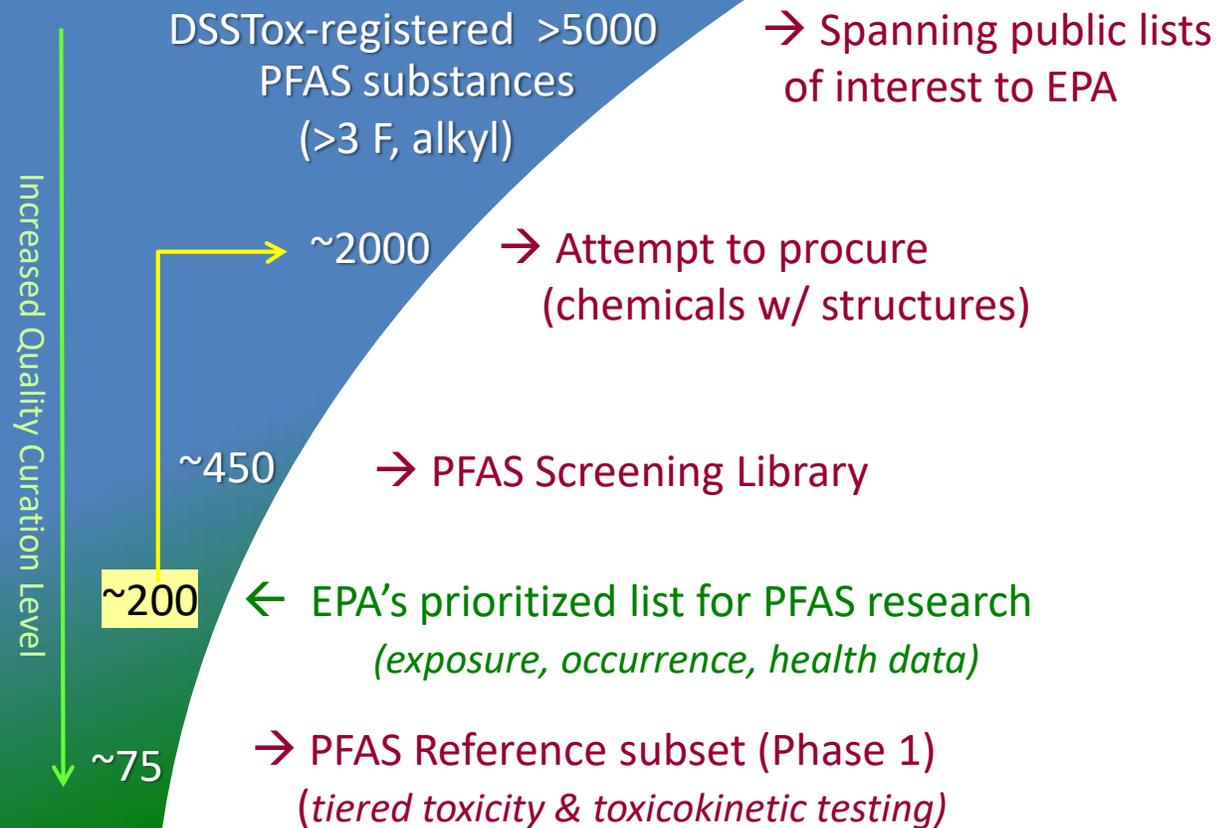
<https://comptox.epa.gov/dashboard>

EPA DSSTox Database: > 758K chemicals



- Chemical structures, downloadable files
- Predicted phys-chem properties
- External links & list overlaps

## PFAS Chemical Landscape:



## Per(poly)-fluorinated substances (PFAS)

- PFAS chemical names, acronyms, synonyms
- PFAS chemical structure categories

PFOS  
1763-23-1 | DTXSID3031864

Searched by Approved Name: Found 1 result for PFOS.

Wikipedia  
Perfluorooctanesulfonic acid (conjugate base perfluorooctanesulfonate) (PFOS)  
Read more

Intrinsic Properties

Structural Identifiers

Related Compounds

Presence in Lists

Record Information

Potassium perfluorobutanesulfonate 29420-49-3

Ammonium perfluorooctanoate 3825-26-1

Potassium perfluorohexanesulfonate 3871-99-6

10:2 Fluorotelomer acrylate 17741-60-5

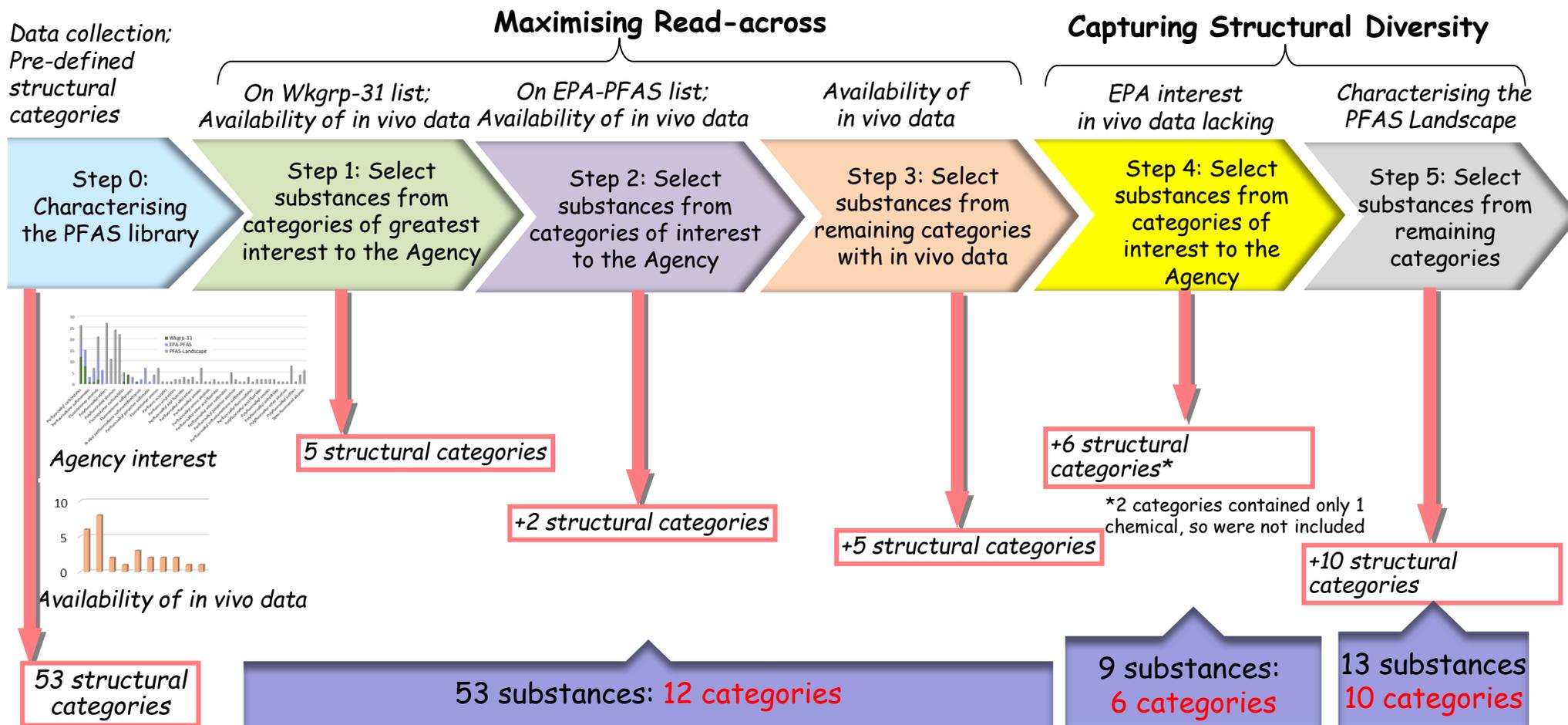
6:2 Fluorotelomer acrylate 17527-29-6

Perfluorooctanesulfonamide 754-91-6

Perfluorodecanesulfonic acid 335-77-3

Pentafluoroiodoethane 354-64-3

# Workflow to prioritise structural categories to inform the PFAS for targeted testing

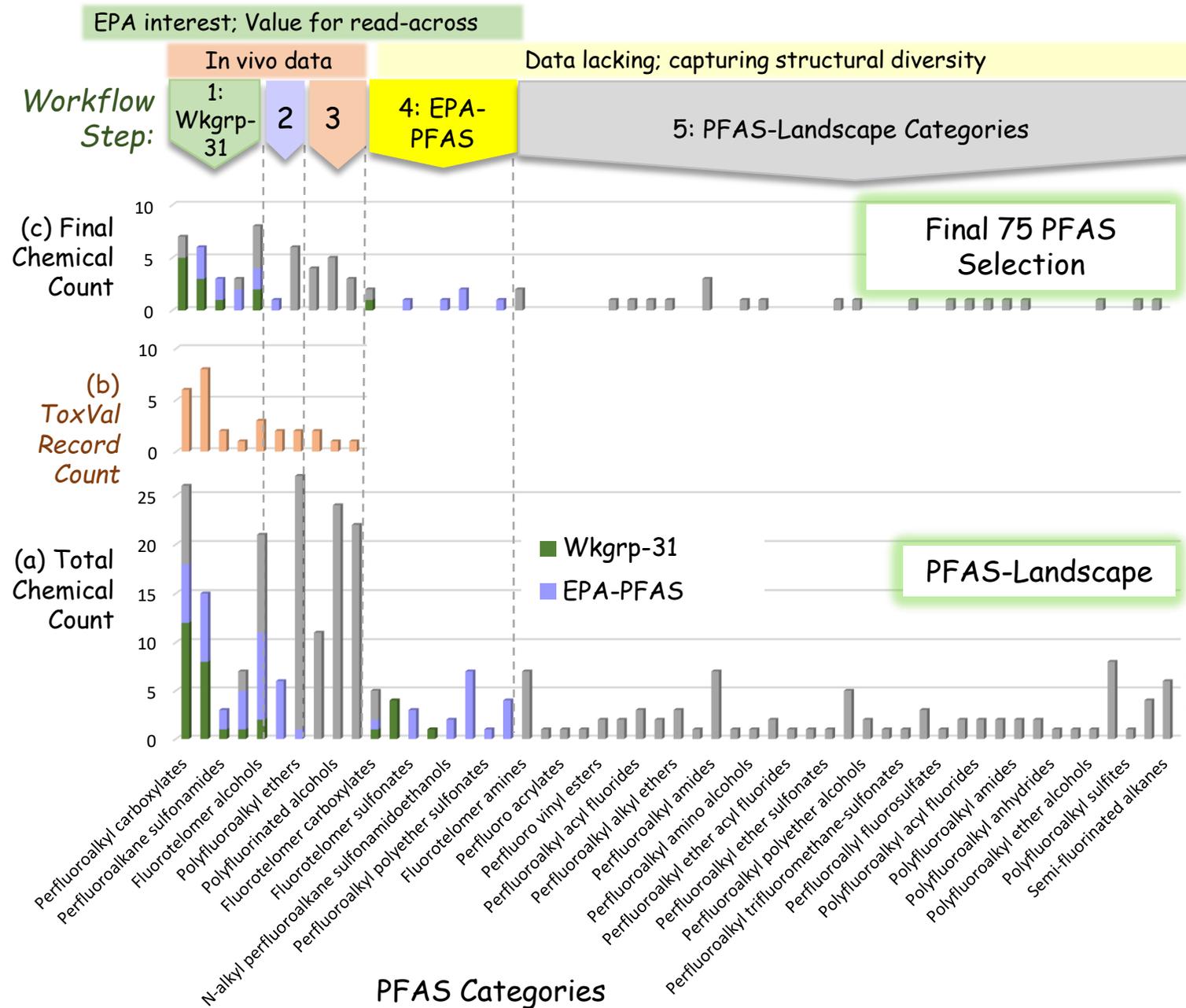


# Step 0: Characterising the PFAS library

## Structural Categories

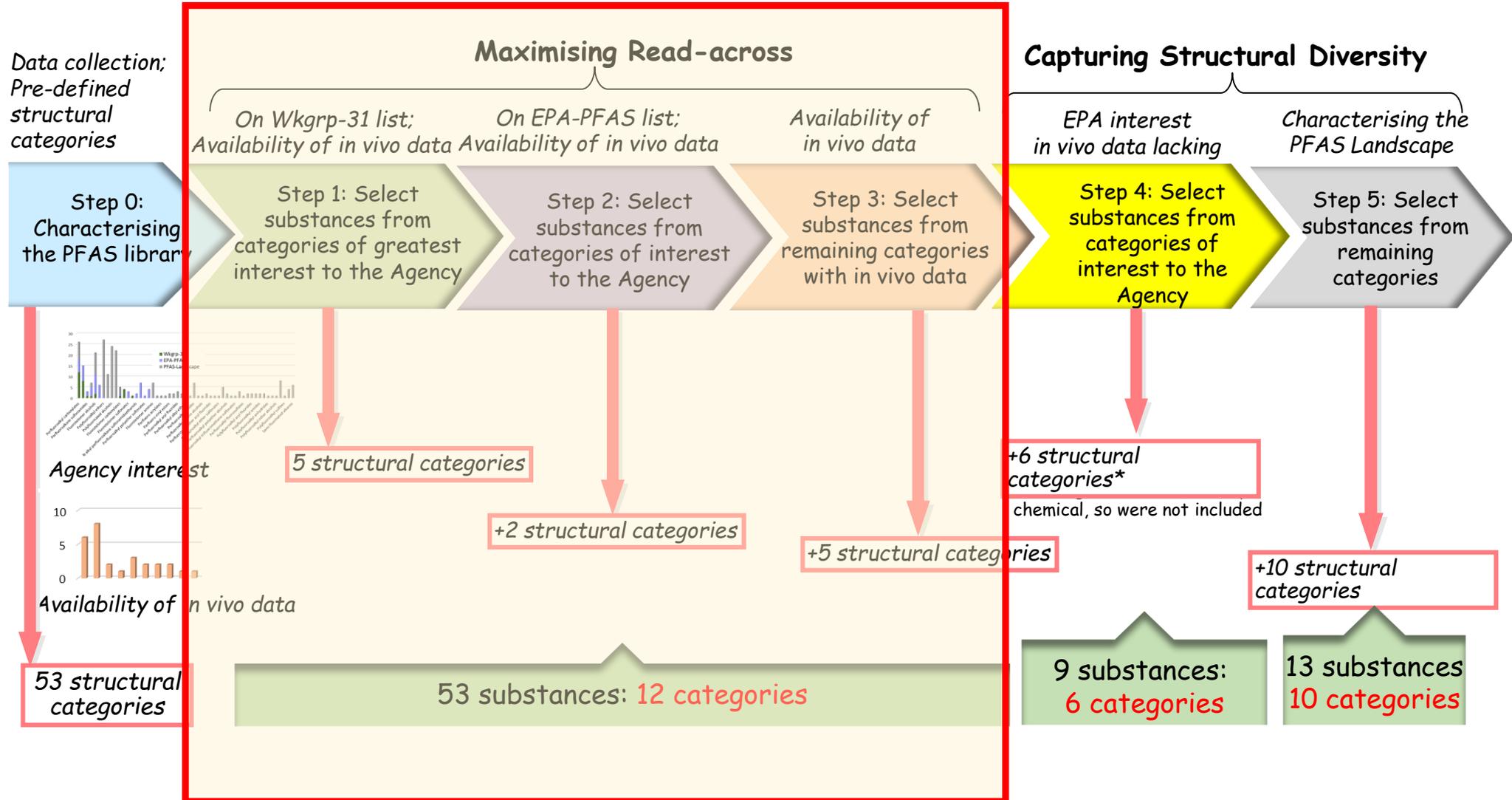
- Manually annotated the 'procurable' substances into structural categories
- Categories built upon those defined by Buck et al (2011)
- Characterised on the standard nomenclature - fluorotelomers, perfluorinated substances etc.
- Identified 53 unique structural categories
- These represent a generalised description of a category
- In some cases these can be subcategorised into greater detail
  - e.g. n:2 fluorotelomer alcohol vs fluorotelomer alcohols

# Step 0: Characterising the PFAS library



- Availability of *in vivo* toxicity information in the context of the pre-defined structural categories
- Representation of PFAS of interest to the Agency in the context of the pre-defined structural categories

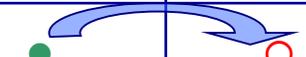
# Workflow to prioritise structural categories to inform the PFAS for targeted testing



# Steps 1-3: Maximising read-across

Known information on the property of a substance (**source chemical**) is used to make a prediction of the same property for another substance (**target chemical**) that is considered "similar" i.e. Endpoint & often study specific

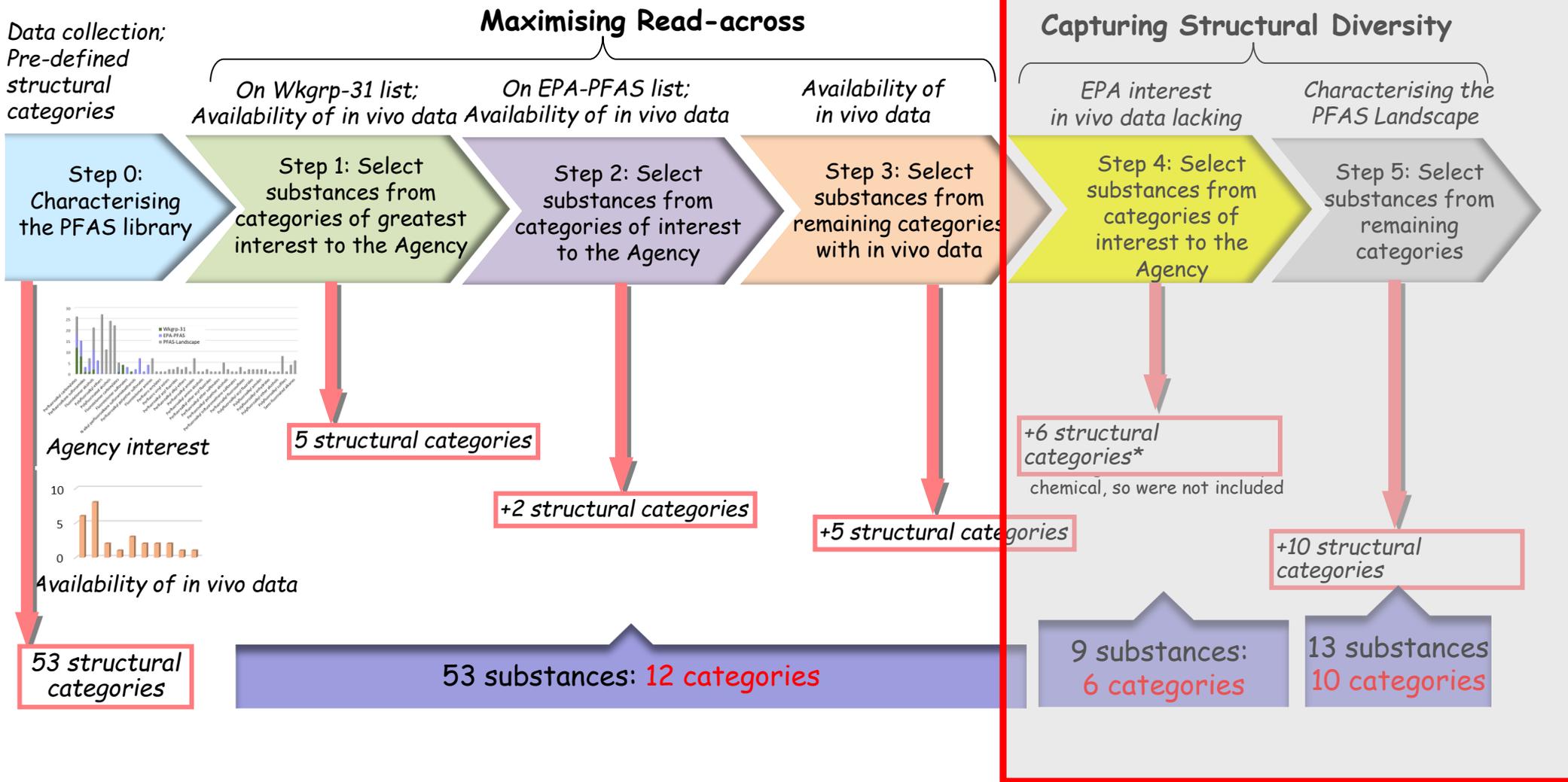
	Source chemical	Target chemical
Property	●	○



- Reliable data
- Missing data

- Use of information for "PFAS source substances" is used to infer (read-across) missing information for a related similar PFAS target
- Similarity context as a pragmatic starting point is "structural similarity" using the structural categories that have been defined
- Requirement is *in vivo* toxicity information
- Depending on the structural diversity within the structural category - opportunities may exist to explore trends in activity - impact of chain length C4 vs C6 vs C8; impact of n:H in fluorotelomer alcohols n:3 vs n:1; impact of position of ether linkage etc.

# Workflow to prioritise structural categories to inform the PFAS for targeted testing



## Steps 4-5: Capturing Structural Diversity

- Characterising the biological activity of the PFAS landscape that comprises substances of current interest to the Agency
- Characterising the biological activity of the PFAS landscape beyond substances of current interest to the Agency
- Testing broad PFAS landscape may enable detection of hotspots in activity that could help in prioritising future PFAS research and anticipating future problem areas

# Considerations for PFAS selection

Aspect Name	Scoring
1) Structural diversity within a category	Approximated by category size, with score ranging from 1 (20 or more members) to 0 (1 member)
2) Data availability	Availability of in vitro ToxCast data (score=0.5) or ToxVal in vivo data (score=0.75) or both (score=1)
3) Data quantity	Number of ToxVal records for a substance indicating a stronger source-analogue for read-across, with scores ranging from 0.15 (for 1 record) to 1 (for 20 or more records)
4) Read-across category-level weight	Value of substance for anchoring read-across trends within a category (e.g., chain length etc.), serving as a source analog (score=0.5) or target analog (score=0.25), or as a target analog for capturing structural diversity (score=0.15)
5) Numerical indicator of EPA interest	Wkgrp-31 (score=1), other EPA-PFAS (score=0.75), only in PFAS-Landscape (score=0.5)
6) Phys-chem indicators of testability	Both LogKow and Vapor Pressure favorable (score=0.75), one favorable (score=0.5), both unfavorable (score=0). E.g. LogKow < 4.5, Vapor Pressure < 10 <sup>3</sup> mmHg considered favorable.
7) Figure. 1 Workflow Step	Step 1 (score=1), Step 2 (score=0.75), Step 3 (score=0.5), Step 4 (score =0.25), Step 5 (score=0)
Total Score	Summation of scores from the preceding considerations used to rank each PFAS substance

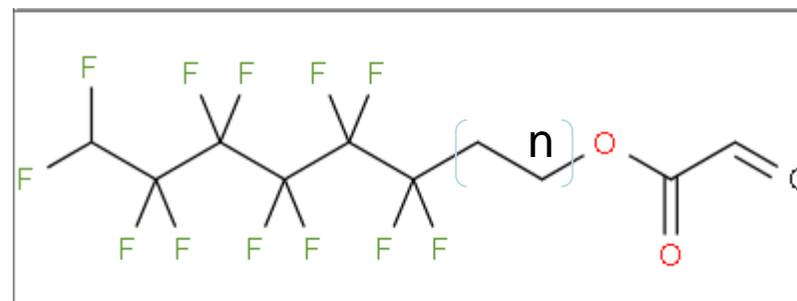
# Lists of PFAS on the Dashboard

[https://comptox.epa.gov/dashboard/chemical\\_lists/?search=PFAS](https://comptox.epa.gov/dashboard/chemical_lists/?search=PFAS)

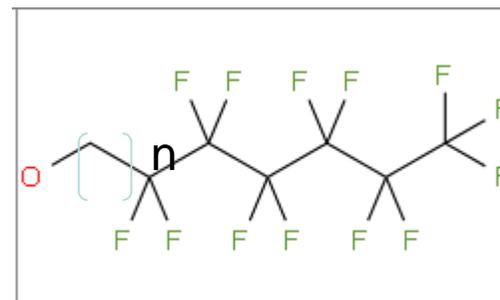
List Acronym	List Name	Last Updated	Number of Chemicals	List Description
EPAPFAS75S1	PFAS EPA: List of 75 Test Samples (Set 1)	2018-06-29	74	PFAS list corresponds to 75 samples (Set 1) submitted for initial testing screens conducted by EPA researchers in collaboration with researchers at the National Toxicology Program.
EPAPFAS75S2	PFAS EPA: List of 75 Test Samples (Set 2)	2019-02-21	75	PFAS list corresponds to a second set of 75 samples (Set 2) submitted for testing screens conducted by EPA researchers in collaboration with researchers at the National Toxicology Program.
EPAPFASCAT	PFAS EPA Structure-based Categories	2018-06-29	64	List of registered DSSTox "category substances" representing PFAS categories created using ChemAxon's Markush structure-based query representations.
EPAPFASDW	PFAS EPA: New EPA Method Drinking Water	2019-04-17	26	EPA is developing and validating a new method for detecting these PFAS in drinking water sources.
EPAPFASDW537	PFAS EPA: Existing EPA DW Method 537.1	2019-04-17	19	EPA has recently revised method 537.1 for the PFAS on this list to detect them in drinking water.
EPAPFASDWTREAT	PFAS EPA: Drinking Water Treatment Technology	2019-04-17	9	EPA is gathering and evaluating treatment effectiveness and cost data for removing these PFAS from drinking water systems.
EPAPFASINSOL	PFAS EPA: Chemical Inventory Insoluble in DMSO	2018-06-29	43	PFAS chemicals included in EPA's expanded ToxCast chemical inventory found to be insoluble in DMSO above 5mM.
EPAPFASINV	PFAS EPA: ToxCast Chemical Inventory	2018-06-29	430	PFAS chemicals included in EPA's expanded ToxCast chemical inventory and available for testing.
EPAPFASINVIVO	PFAS EPA: In Vivo Studies Available	2019-04-17	23	These PFAS have published animal toxicity studies available in the online HERO database.
EPAPFASLITSEARCH	PFAS EPA: Literature Search Completed:	2019-04-17	23	A literature review of published toxicity studies for these PFAS

# Manual Structural categories: examples used

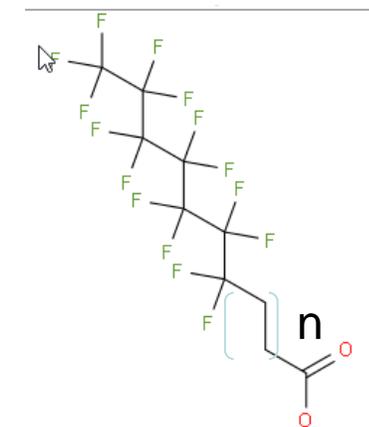
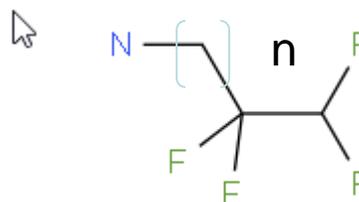
- Fluorotelomer acrylates 6 members
- Methacrylate & acrylates
- $n = 2$ ,  $nCF_2 = 6-10$



- Fluorotelomer alcohols 21 members
- $n = 1-4$ ,  $nCF_2 = 2-11$



- Fluorotelomer amines 7 members
- $n = 1$ ,  $nCF_2 = 2-6$
- Fluorotelomer carboxylates 5 members
- $n = 2$ ,  $nCF_2 = 3-5$



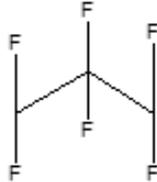
# Structural Categories

- Pragmatic approach for the initial PFAS library but...
- Subjective, manual..
- How to efficiently chart the PFAS landscape that is being tested against other PFAS inventories/libraries of interest e.g. OECD ?

# PFAS "Categories": Per & Poly-fluorinated alkyl substances

- "Expert"-assigned PFAS categories - manual, subjective
  - Buck et al. (DuPont), based on chemical & series informed by synthetic pathways (e.g., fluorotelomers)
  - data-gathering, occurrence reports, ecotox
  - OECD PFAS listing (>4500 chemicals) - manually assigned groupings

## Poly- and Perfluorochemicals



### Acyclic - Pure

Atoms: N, P, O, S, Si, Cl, Br, I = **NOT**

**AND** # of Cycles = 0

### Cyclic - Pure

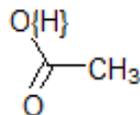
Atoms: N, P, O, S, Si, Cl, Br, I = **NOT**

**AND** # of Cycles ≥ 1

### Carboxylic Acids

Atoms: N, P, S, Si, Cl, Br, I = **NOT**

**AND**



## Expert category

Fluorotelomer acrylates  
 Fluorotelomer alcohols  
 Polyfluorinated alcohols  
 Fluorotelomer sulfonates  
 N-alkyl perfluoroalkyl sulfonamidoacetic acids  
 N-alkyl perfluoroalkyl sulfonamidoethanols  
 Perfluoroalkyl aldehydes  
 Perfluoroalkyl amides  
 Perfluoroalkyl carboxylates  
 Perfluoroalkyl acyl fluorides  
 Perfluoro vinyl esters  
 Perfluoroalkyl ketones  
 Semi-fluorinated alkenes  
 Perfluoroalkyl vinyl ethers  
 Perfluoroalkyl alkyl ethers  
 Fluorotelomer amines  
 Perfluoroalkyl sulfonamides

Class	Category_Name1	Category_Name2
Alcohol	Fluorotelomer alcohols	Fluorotelomer (linear) n:2 alcohols
Sulfonic Acid	Perfluoroalkyl sulfonic acids	Perfluoroalkyl (linear C4-C10) sulfonic acids

Polyfluoroalkyl carboxylates  
 Perfluoroalkyl ethers  
 Fluorotelomer phosphates

# OECD Database of PFAS



Follow us



Custom Search



- Released May 2018
- Substance Count 4729
- Category Count: 173

Portal on Per and Poly Fluorinated Chemicals

HOME ABOUT PFASS RISK REDUCTION ALTERNATIVES

Contribute to the development of risk reduction

### Why this Portal?

This Portal serves to facilitate the exchange of information on per and poly-fluorinated chemicals, for specifically on per- and polyfluoroalkyl substances (PFASs). In order to support a global transition to alternatives, the Portal provides information on the following areas:

› What are PFASs? › Alternatives › Information from

Toward a new comprehensive Global Database of Per- And Polyfluoroalkyl Substances (PFASs) —



Read the New Comprehensive Global Database of PFASs and the methodology report.

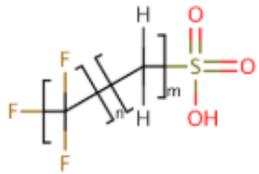
<http://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/>

# "Expert-assigned" OECD PFAS Categories, e.g.

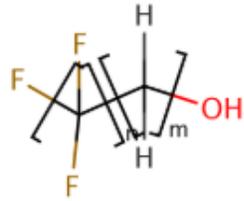
- 4730 PFAS in list
- 173 expert-assigned categories under 8 general headings (bold)
- Broad "catch-all" terms (in red)
- Structural elements, but NOT structure-based
- Requires expert to assign new chemicals to categories

<b>perfluoroalkyl carbonyl compounds</b>	<b>C<sub>n</sub>F<sub>2n+1</sub>_C(O)_R</b>
perfluoroalkyl carbonyl halides	R = F/Cl/Br/I
perfluoroalkyl carboxylic acids (PFCAs), <b>their salts and esters</b>	R = OH, ONa, OCH <sub>3</sub> , etc.
<b>other</b> perfluoroalkyl carbonyl-based nonpolymers	to be refined
perfluoroalkyl carbonyl amides / amido ethanols <b>and other alcohols</b>	R = NH <sub>2</sub> , NH(OH), etc.
perfluoroalkyl carbonyl (meth)acrylate	R = R'_OC(O)CH=CH <sub>2</sub>
perfluoroalkyl carbonyl (meth)acrylate <b>polymers</b>	
1-H perfluoroalkyl carboxylic acids	H(CF <sub>2</sub> ) <sub>n</sub> COOH
<b>perfluoroalkane sulfonyl compounds</b>	<b>C<sub>n</sub>F<sub>2n+1</sub>_S(O)(O)_R</b>
perfluoroalkane sulfonyl halides	R = F/Cl/Br/I
perfluoroalkane sulfonic acids (PFASs), their salts and esters	R = OH, ONa, OCH <sub>3</sub> , etc.
perfluoroalkane <b>sulfonyl-based</b> nonpolymers	
<b>per- and polyfluoroalkyl ether-based compounds</b>	<b>C<sub>n</sub>F<sub>2n+1</sub>_O_CmF<sub>2m+1</sub>_R</b>
per- <b>and polyfluoro</b> alkyl ether sulfonic acids (PFESAs), <b>their salts and esters, as well as derivatives</b>	C <sub>n</sub> F <sub>2n+1</sub> _O_CmF <sub>2m+1</sub> _SO <sub>3</sub> H
<b>fluorotelomer-related compounds</b>	
perfluoroalkyl iodides (PFAIs)	C <sub>n</sub> F <sub>2n+1</sub> _I
n:2 <b>fluorotelomer-based</b> non-polymers	C <sub>n</sub> F <sub>2n+1</sub> _C <sub>2</sub> H <sub>4</sub> _R, to be refined

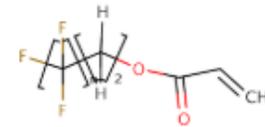
# Markush Record Creation



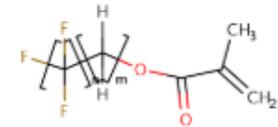
Fluorotelomer (linear) sulfonic acids  
DTXSID: DTXSID50892558  
CASRN: NOCAS\_892558  
TOXCAST: -



Fluorotelomer (linear) alcohols  
DTXSID: DTXSID10893581  
CASRN: NOCAS\_893581  
TOXCAST: -



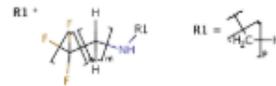
Fluorotelomer (linear) n:2 acrylates  
DTXSID: DTXSID70893582  
CASRN: NOCAS\_893582  
TOXCAST: -



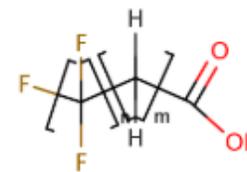
Fluorotelomer (linear) n:2 methacrylates  
DTXSID: DTXSID30893583  
CASRN: NOCAS\_893583  
TOXCAST: -



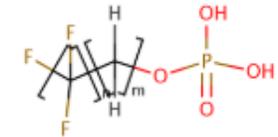
Fluorotelomer symmetric diols  
DTXSID: DTXSID90893584  
CASRN: NOCAS\_893584  
TOXCAST: -



Fluorotelomer (linear) amines (secondary)  
DTXSID: DTXSID50893585  
CASRN: NOCAS\_893585  
TOXCAST: -



Fluorotelomer (linear) carboxylic acids  
DTXSID: DTXSID10893586  
CASRN: NOCAS\_893586  
TOXCAST: -



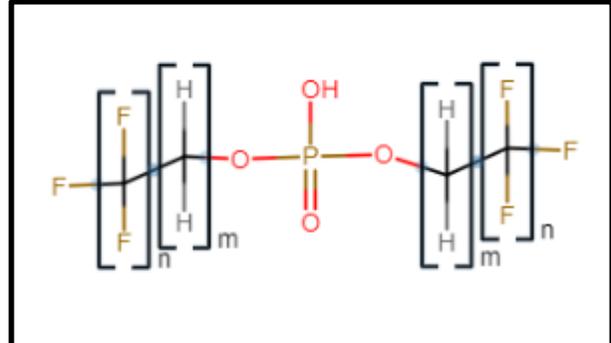
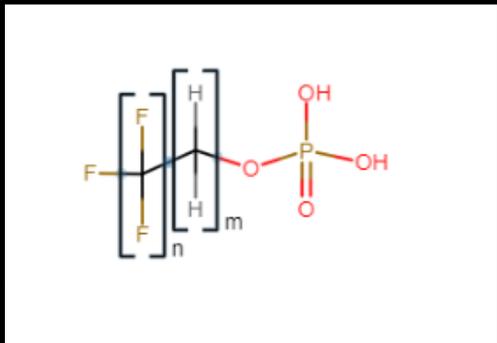
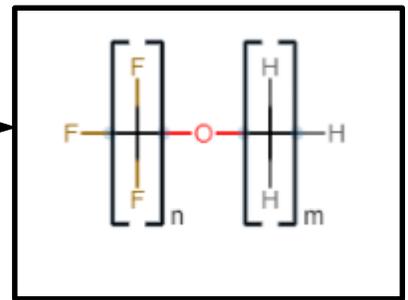
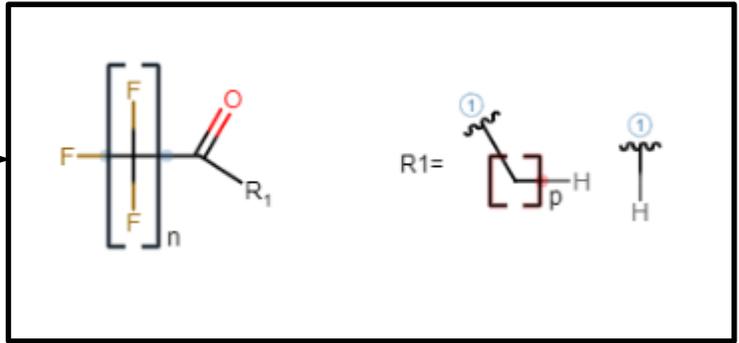
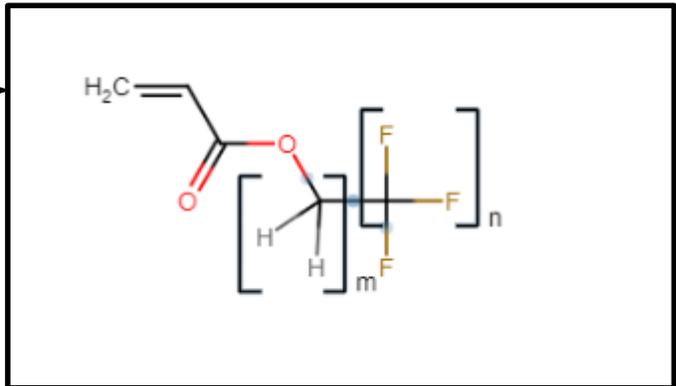
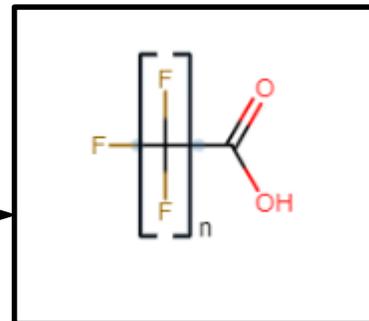
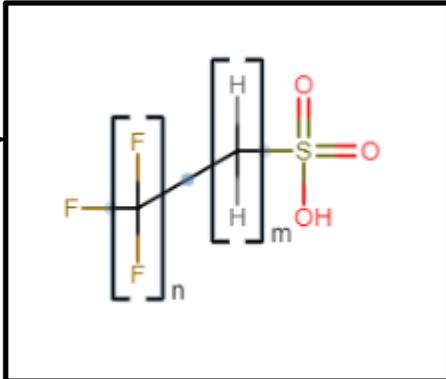
Fluorotelomer (linear) phosphate esters ...  
DTXSID: DTXSID30893588  
CASRN: NOCAS\_893588  
TOXCAST: -

Organic Form:

# Translating Expert Categories to Markush

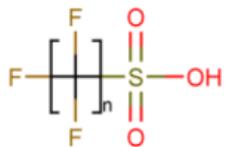
Expert category

- Fluorotelomer acrylates
- Fluorotelomer alcohols
- Polyfluorinated alcohols
- Fluorotelomer sulfonates
- N-alkyl perfluoroalkyl sulfonamidoacetic acids
- N-alkyl perfluoroalkyl sulfonamidoethanols
- Perfluoroalkyl aldehydes
- Perfluoroalkyl amides
- Perfluoroalkyl carboxylates
- Perfluoroalkyl acyl fluorides
- Perfluoro vinyl esters
- Perfluoroalkyl ketones
- Semi-fluorinated alkenes
- Perfluoroalkyl vinyl ethers
- Perfluoroalkyl alkyl ethers
- Fluorotelomer amines
- Perfluoroalkyl sulfonamides
- Semi-fluorinated alkanes
- Perfluoroalkyl sulfonates
- Perfluoroalkyl sulfonamido amines
- Polyfluoroalkyl carboxylates
- Perfluoroalkyl ethers
- Fluorotelomer phosphates



# Example of Markush representation

Searched Chemical



Perfluoroalkyl sulfonates

DTXSID: DTXSID70892979

CASRN: NOCAS\_892979

markush



Perfluorobutanesulfonic acid

DTXSID: DTXSID5030030

CASRN: 375-73-5

markush



Perfluorooctanesulfonic acid

DTXSID: DTXSID3031864

CASRN: 1763-23-1

markush



Perfluorodecane sulfonic acid

DTXSID: DTXSID3040148

CASRN: 335-77-3

markush



Perfluorohexane sulfonic acid

DTXSID: DTXSID7040150

CASRN: 355-46-4

markush



Perfluoroheptane sulfonic acid

DTXSID: DTXSID8059920

CASRN: 375-92-8

markush



Perfluoropentane sulfonic acid

DTXSID: DTXSID8062600

CASRN: 2706-91-4

markush



Perfluorononane sulfonic acid

DTXSID: DTXSID8071356

CASRN: 68259-12-1

markush

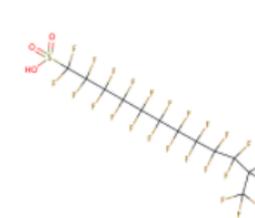


Perfluoropropane sulfonic acid

DTXSID: DTXSID30870531

CASRN: 423-41-6

markush



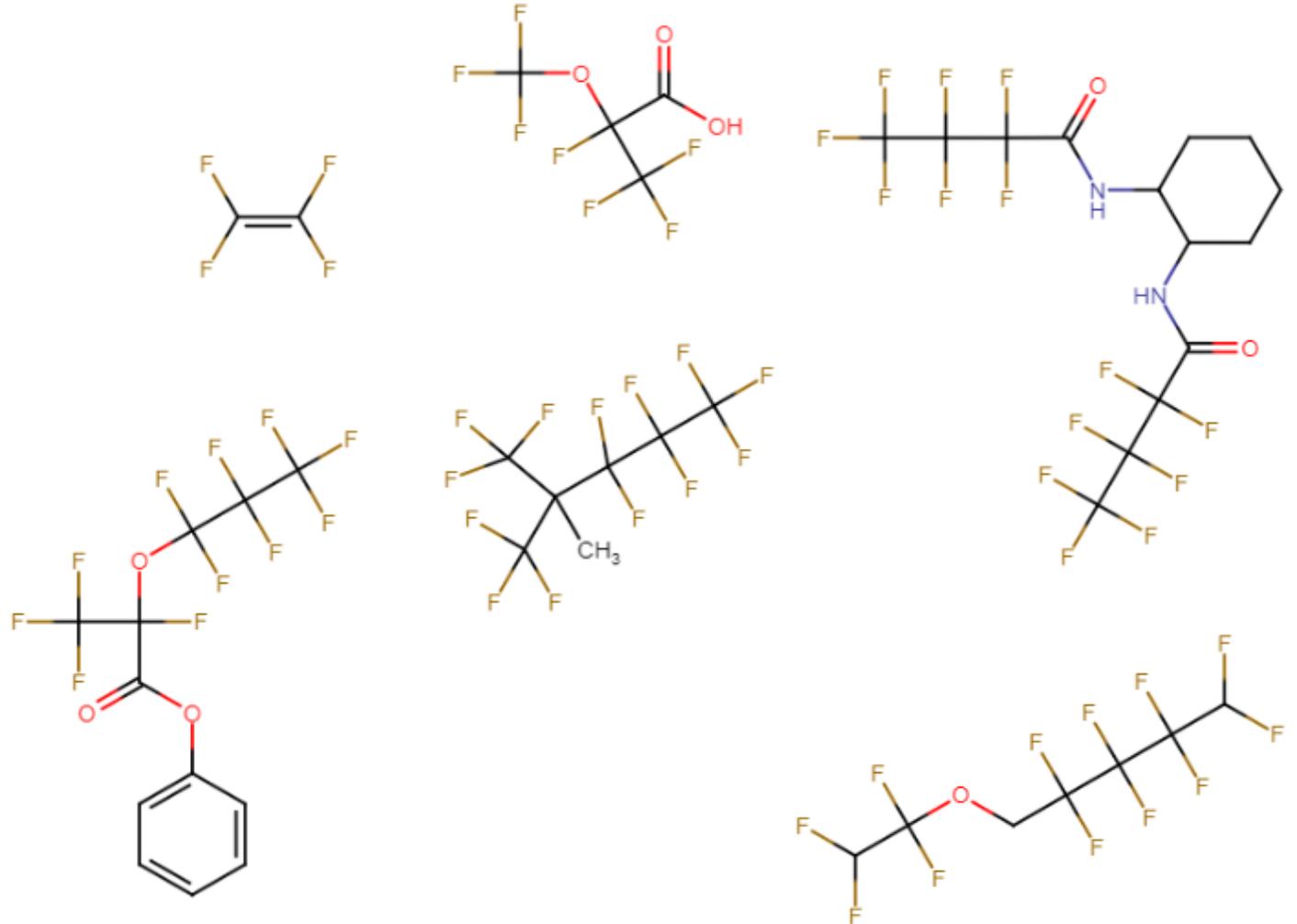
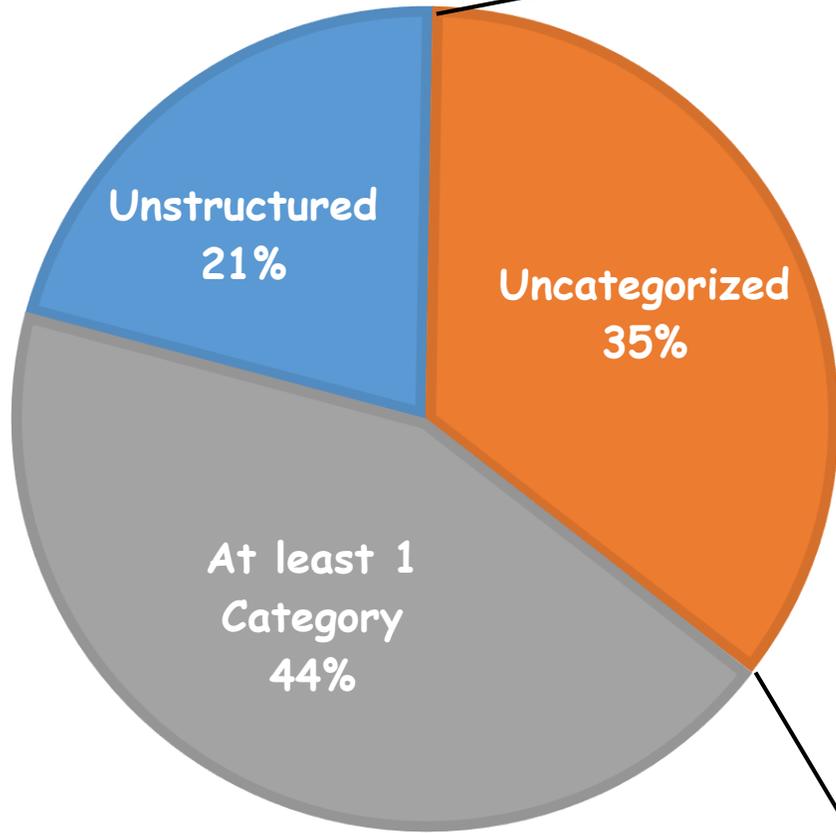
Perfluorododecane sulfonic acid (PFDOS)

DTXSID: DTXSID20873011

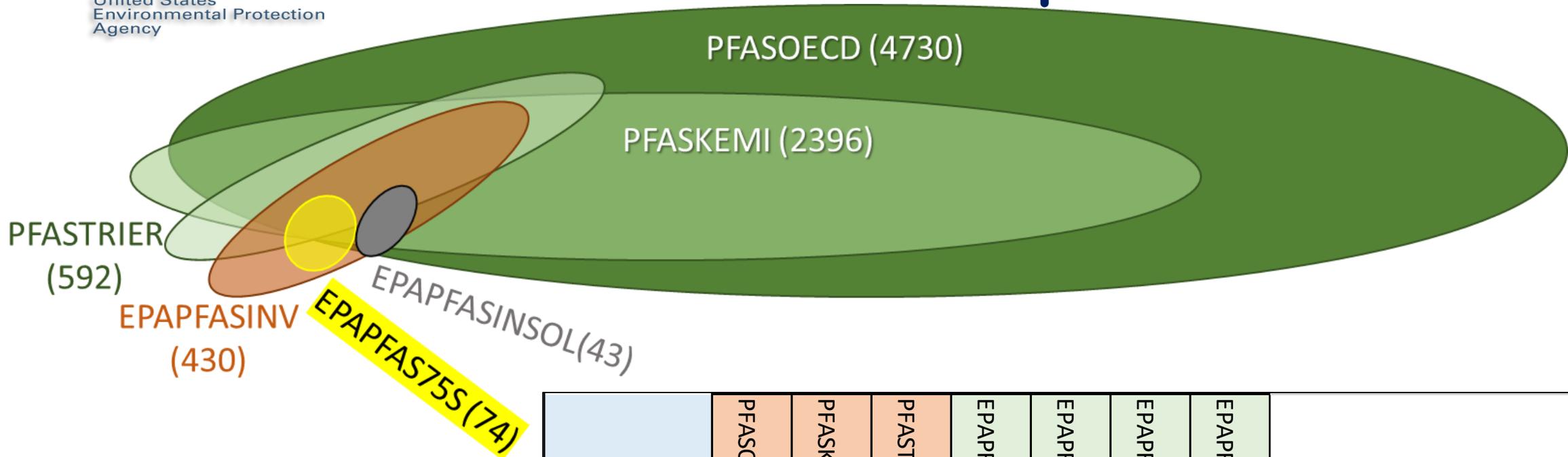
CASRN: 79780-39-5

# PFASMASTER Markush Category Coverage

[https://comptox.epa.gov/dashboard/chemical\\_lists/PFASMASTER](https://comptox.epa.gov/dashboard/chemical_lists/PFASMASTER)



# PFAS List Overlap



PFASMASTER LISTS	PFASOECD	PFASKEMI	PFASTRIER	EPAPFASRL	EPAPFASINV	EPAPFASINSOL	EPAPFAS75S1	
PFASOECD	4730							OECD PFAS List
PFASKEMI	2206	2396						KEMI (Swedish Chem Agency) PFAS List
PFASTRIER	493	578	592					Community PFAS List (2015)
EPAPFASRL	132	116	71	199				EPA PFAS Research List
EPAPFASINV	309	324	226	61	430			EPA PFAS Inventory (DMSO Soluble)
EPAPFASINSOL	43	42	24	12	0	43		EPA PFAS Inventory (DMSO Insoluble)
EPAPFAS75S1	51	47	38	25	74	0	74	EPA PFAS 75 Test Sample (Set 1)

# Next steps

- **Complete targeted testing**
- **Data analysis per NAM technology and integrated across technologies to inform both read-across efforts and structural categories**
- **Work to extend objective structural categories to facilitate harmonisation across different inventories**

# Acknowledgements



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