

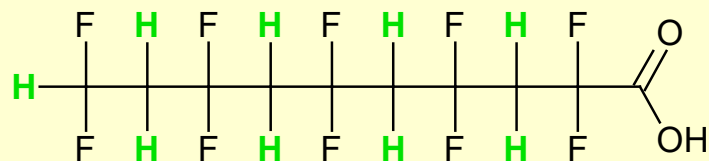


- What are PFAS?
- What is the Landscape of PFAS?
- What are PFAS of potential interest to the Agency?
- How many substances might be procurable?
- What constitutes a representative set of PFAS to propose for targeted testing?
- Structural categories - current and future
- Some next steps

Per- and Polyfluoroalkyl Substances (PFAS)

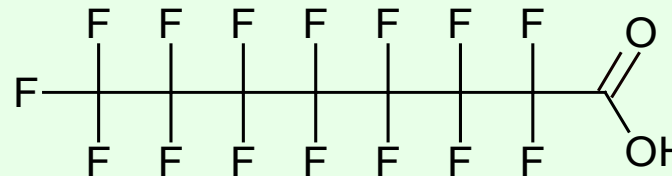
Thousands of PFAS are associated with the production of industrial and consumer products.

Poly fluorinated = many fluorines

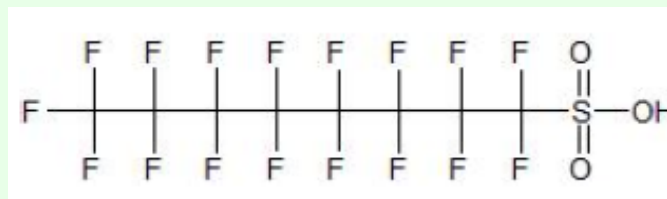


Polyfluorinated carboxylic acid from the production of polyvinylidene fluoride (PVDF) plastic

Per fluorinated = fully fluorinated



Perfluorooctanoic acid (PFOA ,C-8)



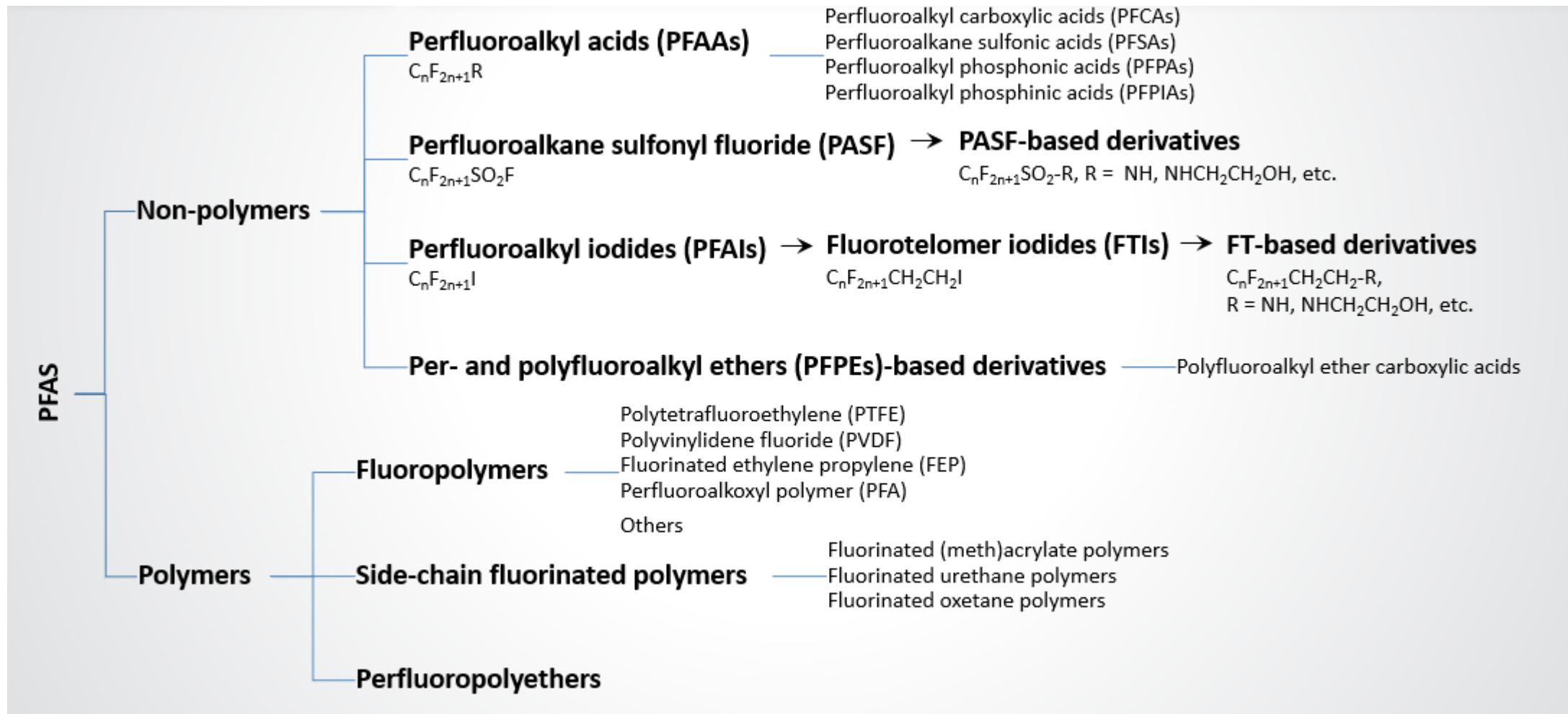
Perfluorooctanesulfonate (PFOS)

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

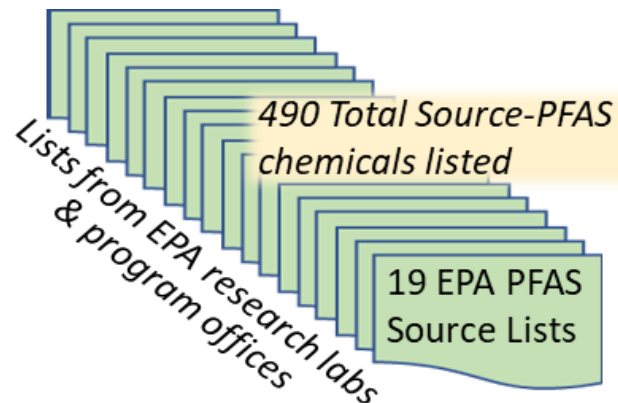


Thousands of Chemicals: More Than Just PFOA and PFOS



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

https://comptox.epa.gov/dashboard/chemical_lists/epapfasrl



Curation

- ✓ Correct misspelled names
- ✓ Correct CASRN
- ✓ Fix errors in mappings of anions, salts, parents
- ✓ Create unique acronym
- ✓ Map to unique DTXSID

EPAPFASRL

19 lists collapsed to single list of 194 unique DTXSID substances

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	Perfluoropentansulfonate	2706-91-4	PFPeS	PFPeS_ion
DTXSID8071354	Ammonium perfluoropentanesulfonate	68259-09-6	Ammonium perfluoropentansulfonate	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

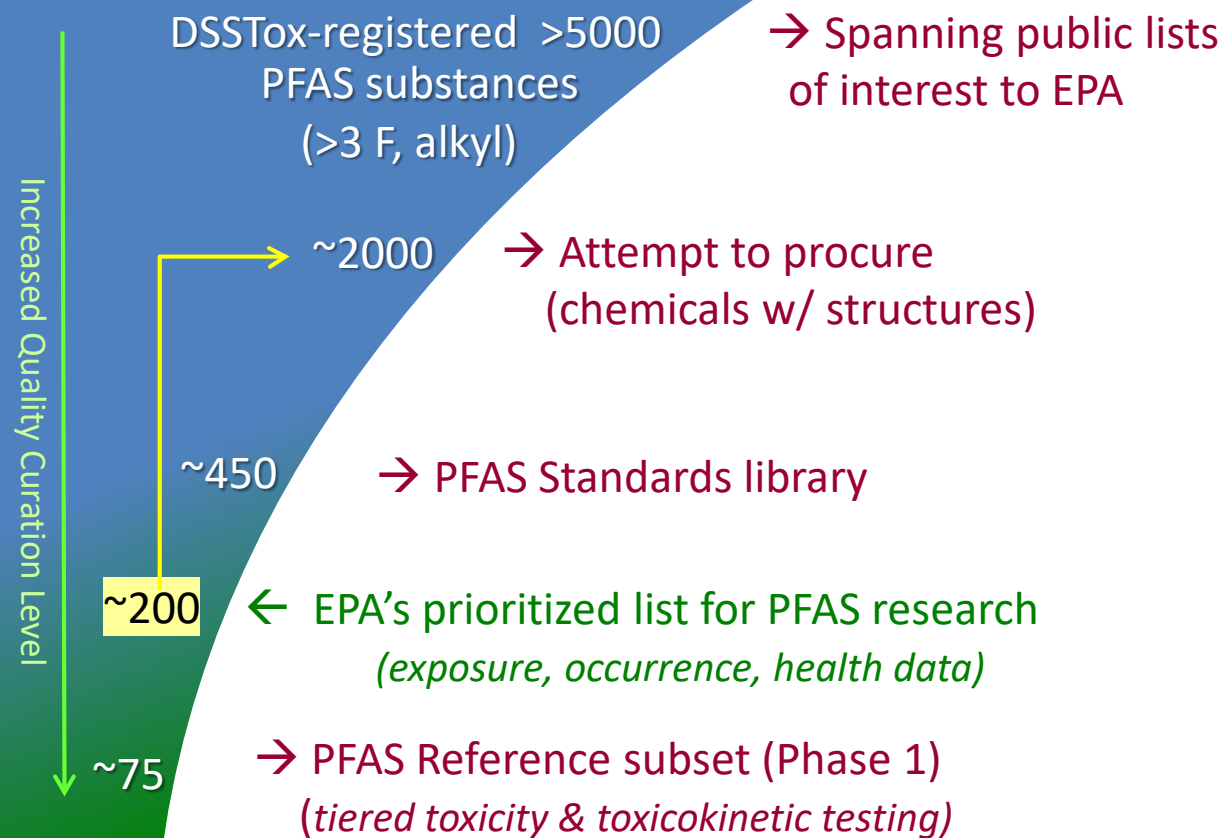
<https://comptox.epa.gov/dashboard>

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

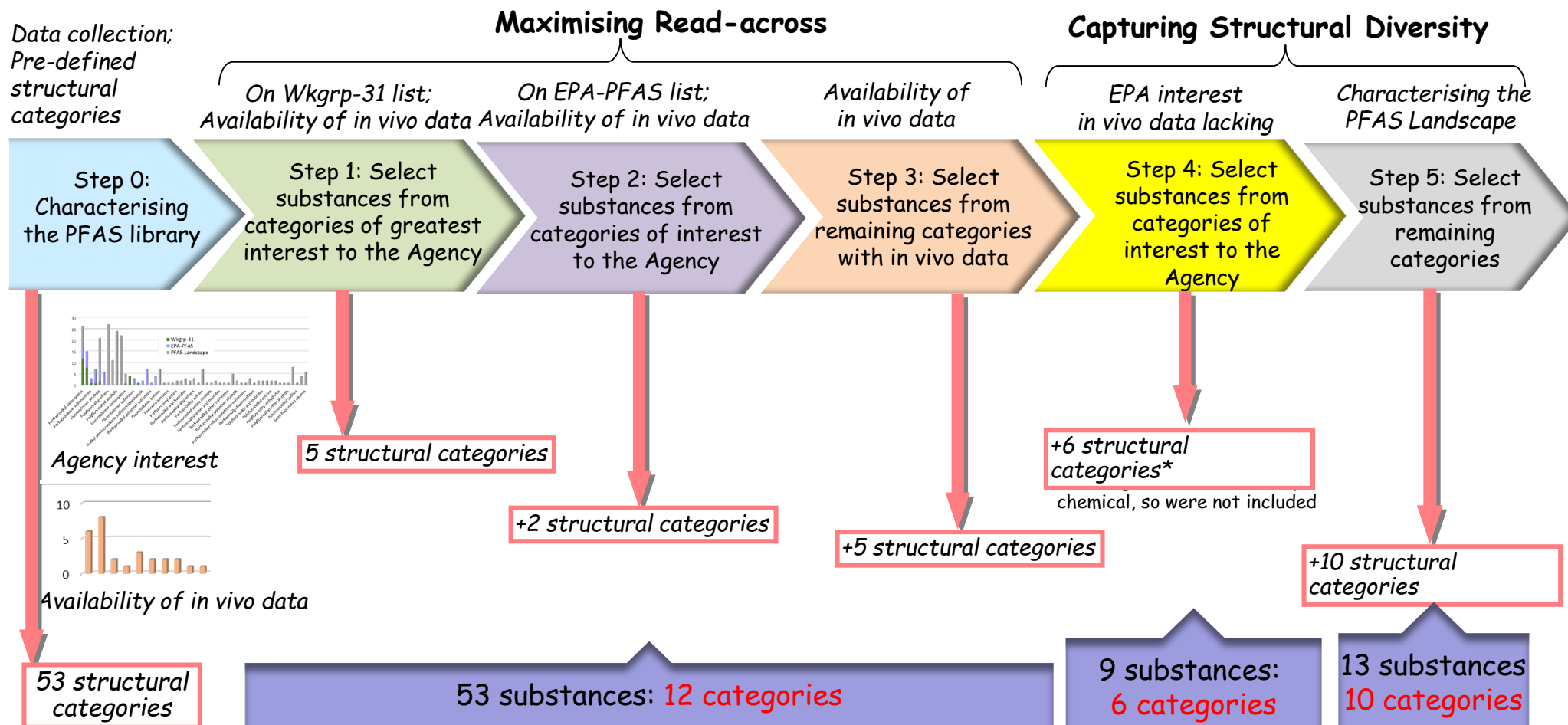
Presence in Lists

Record Information

Chemical structures and names for various PFAS compounds:

- 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

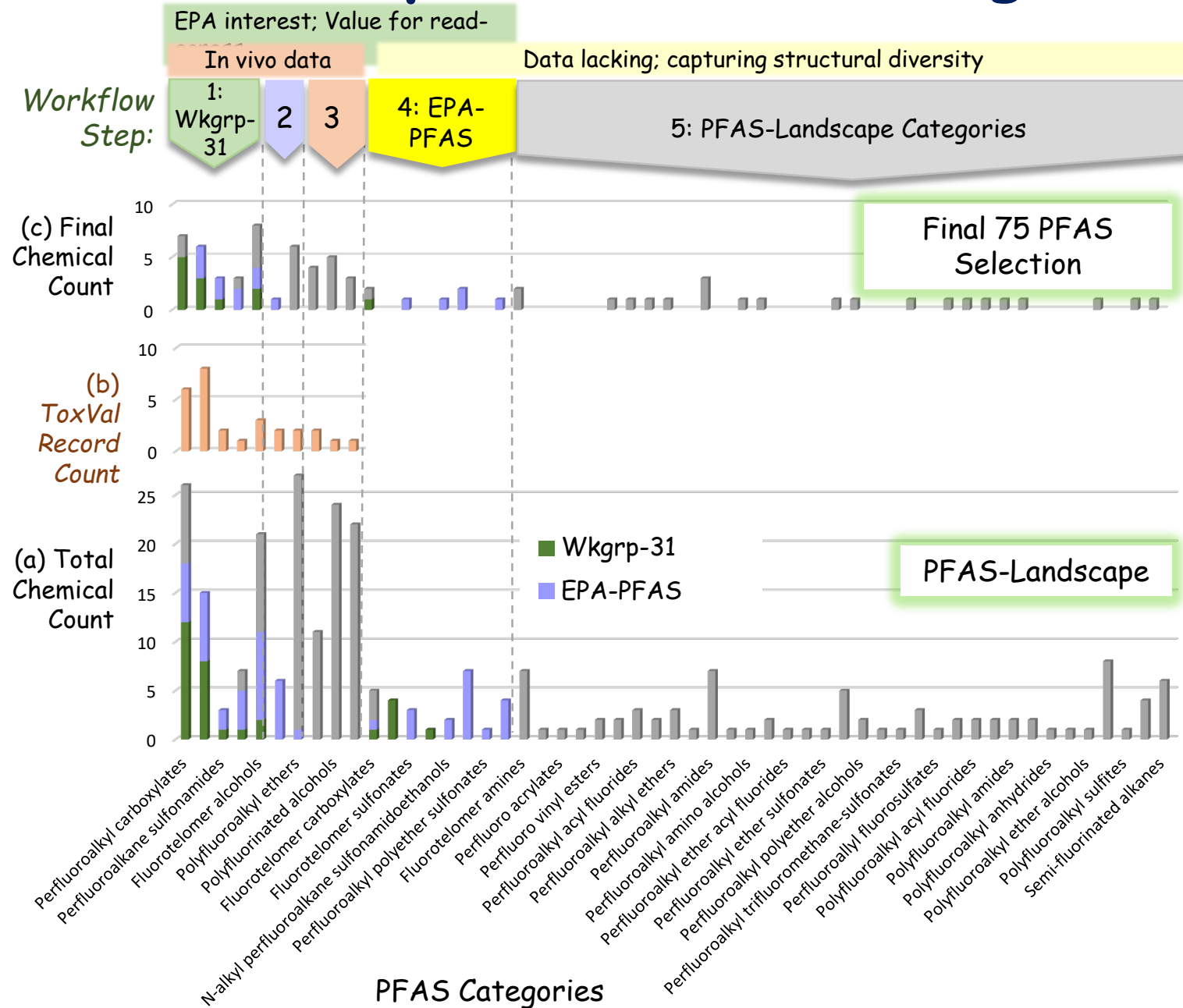


Step 0: Characterising the PFAS library

Structural Categories

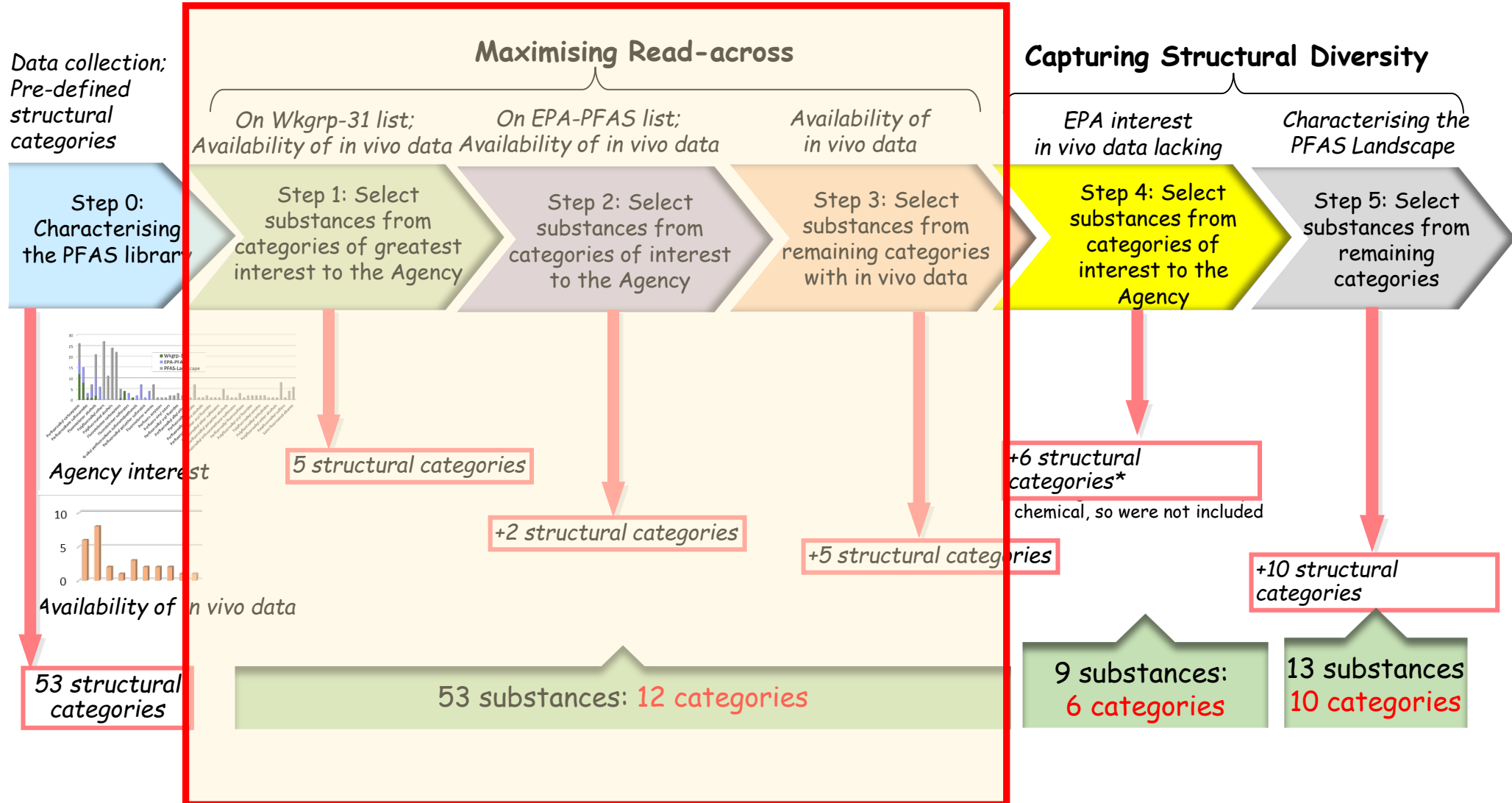
- Manually annotated the 'procurable' substances into structural categories
- Categories built upon those defined by Buck et al (2011)
- Characterised on the standard nomenclature - fluorotelomers, perfluorinated substances etc.
- Identified 53 unique structural categories
- These represent a generalised 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

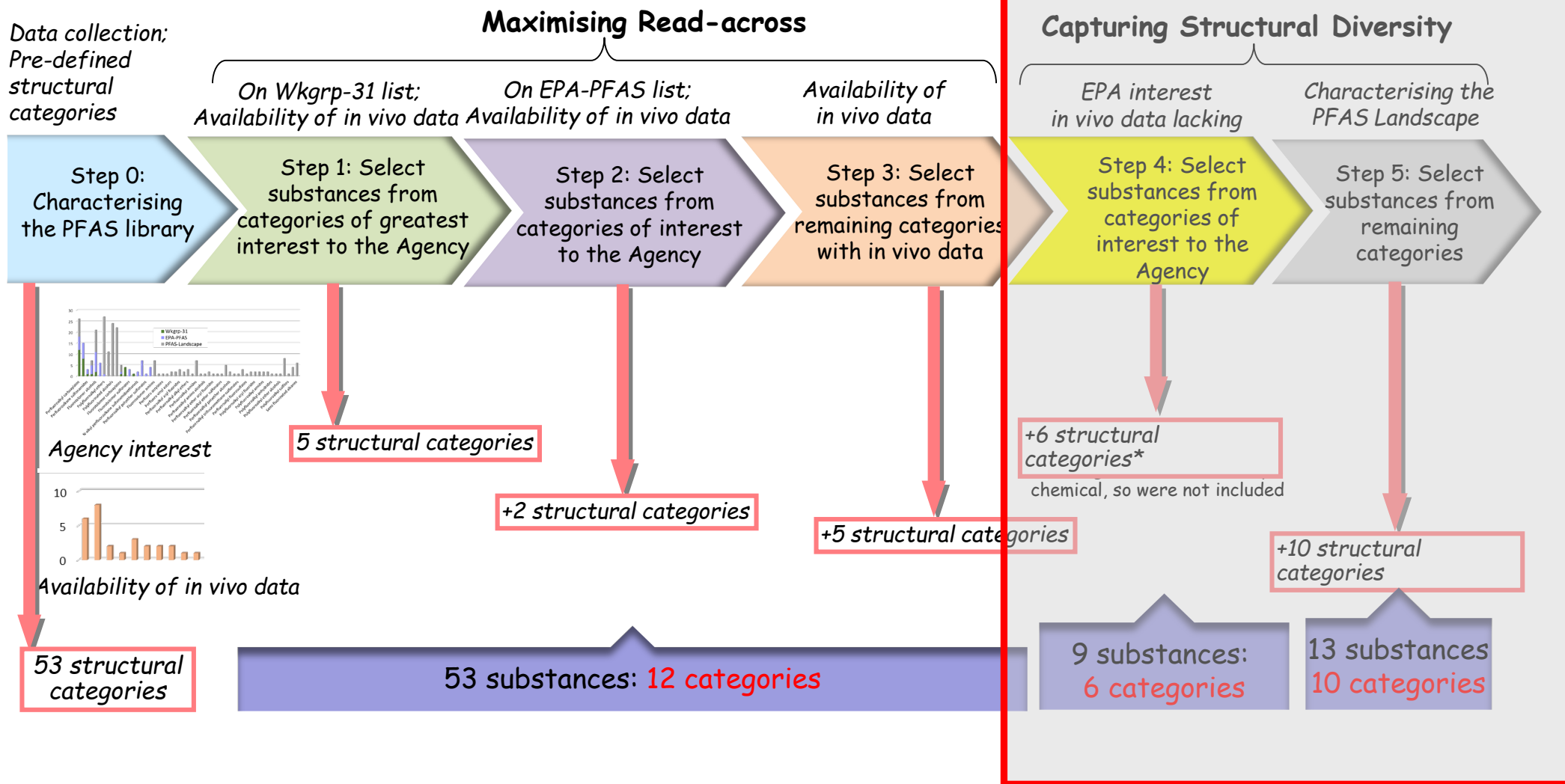
Known information on the property of a substance (**source chemical**) is used to make a prediction of the same property for another substance (**target chemical**) that is considered “similar” i.e. Endpoint & often study specific

	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: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 ³ 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

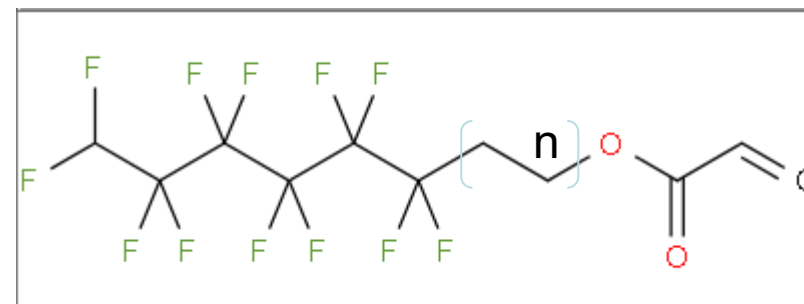
Lists of PFAS on the Dashboard

https://comptox.epa.gov/dashboard/chemical_lists/?search=PFAS

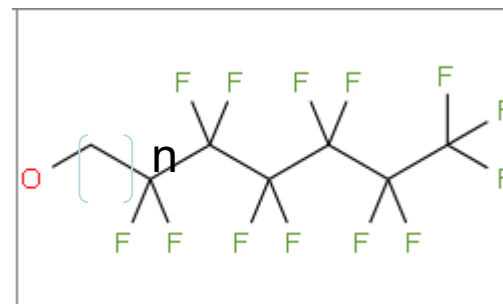
List Acronym	List Name	Last Updated	Number of Chemicals	List Description
EPAPFAS75S1	PFAS EPA: List of 75 Test Samples (Set 1)	2018-06-29	74	PFAS list corresponds to 75 samples (Set 1) submitted for initial testing screens conducted by EPA researchers in collaboration with researchers at the National 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

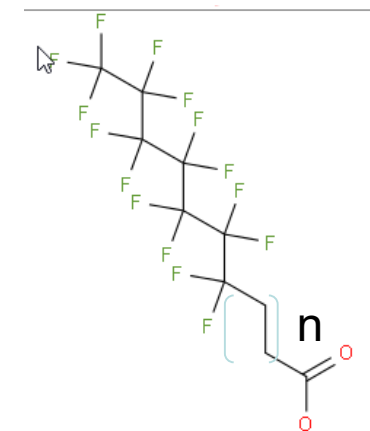
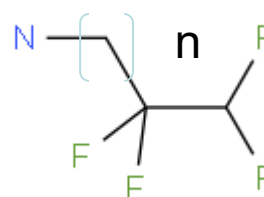
- Fluorotelomer acrylates 6 members
- Methacrylate & acrylates
- $n = 2$, $nCF_2 = 6-10$



- 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
- $n = 2$, $nCF_2 = 3-5$



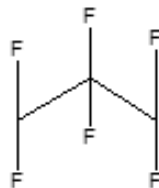
Structural Categories

- 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

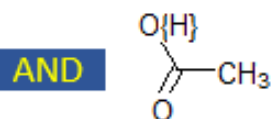
Cyclic - Pure

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**



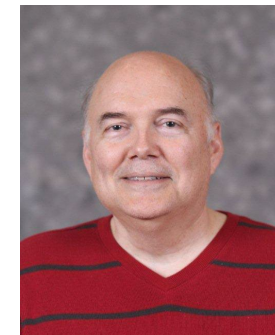
Expert category

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 PFAS 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](#).

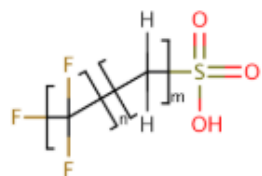
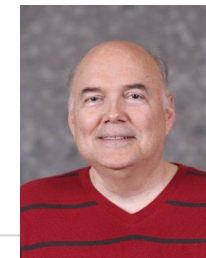
<http://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/>

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

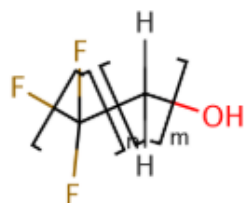
- 4730 PFAS in list
- 173 expert-assigned categories under 8 general headings (bold)
- Broad "catch-all" terms (in red)
- Structural elements, but NOT structure-based
- Requires expert to assign new chemicals to categories

perfluoroalkyl carbonyl compounds	CnF2n+1_C(O)_R
perfluoroalkyl carbonyl halides	R = F/Cl/Br/I
perfluoroalkyl carboxylic acids (PFCAs), their salts and esters	R = OH, ONa, OCH3, etc.
other perfluoroalkyl carbonyl-based nonpolymers	to be refined
perfluoroalkyl carbonyl amides / amido ethanols and other alcohols	R = NH2, NH(OH), etc.
perfluoroalkyl carbonyl (meth)acrylate	R = R'_OC(O)CH=CH2
perfluoroalkyl carbonyl (meth)acrylate polymers	
1-H perfluoroalkyl carboxylic acids	H(CF2)nCOOH
perfluoroalkane sulfonyl compounds	CnF2n+1_S(O)(O)_R
perfluoroalkane sulfonyl halides	R = F/Cl/Br/I
perfluoroalkane sulfonic acids (PFASs), their salts and esters	R = OH, ONa, OCH3, etc.
perfluoroalkane sulfonyl-based nonpolymers	
per- and polyfluoroalkyl ether-based compounds	CnF2n+1_O_CmF2m+1_R
per- and polyfluoro alkyl ether sulfonic acids (PFESAs), their salts and esters, as well as derivatives	CnF2n+1_O_CmF2m+1_SO3H
fluorotelomer-related compounds	
perfluoroalkyl iodides (PFAIs)	CnF2n+1_I
n:2 fluorotelomer-based non-polymers	CnF2n+1_C2H4_R, to be refined

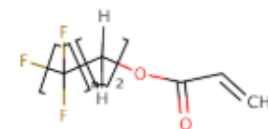
Markush Record Creation



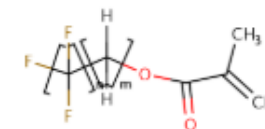
Fluorotelomer (linear) sulfonic acids
DTXSID: DTXSID50892558
CASRN: NOCAS_892558
TOXCAST: -



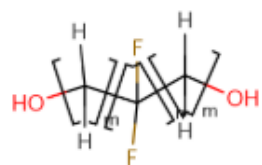
Fluorotelomer (linear) alcohols
DTXSID: DTXSID10893581
CASRN: NOCAS_893581
TOXCAST: -



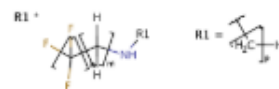
Fluorotelomer (linear) n:2 acrylates
DTXSID: DTXSID70893582
CASRN: NOCAS_893582
TOXCAST: -



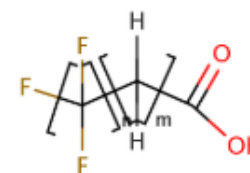
Fluorotelomer (linear) n:2 methacrylates
DTXSID: DTXSID30893583
CASRN: NOCAS_893583
TOXCAST: -



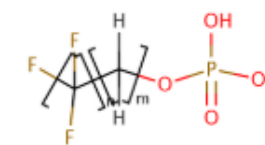
Fluorotelomer symmetric diols
DTXSID: DTXSID90893584
CASRN: NOCAS_893584
TOXCAST: -



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: -

Name: C10-C18 alkyl alcohol

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

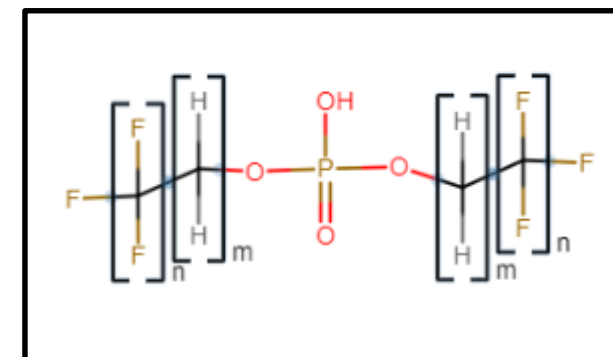
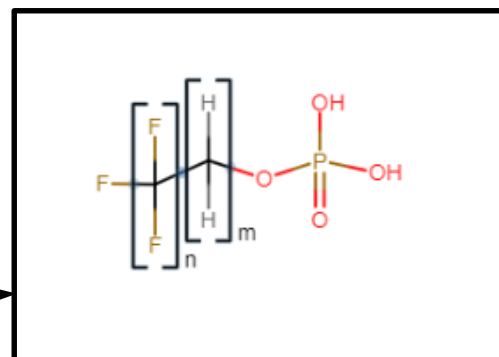
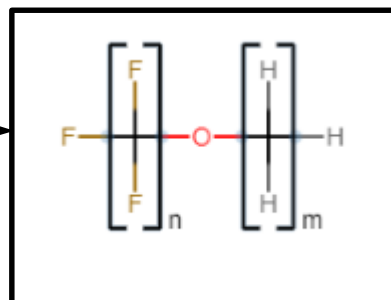
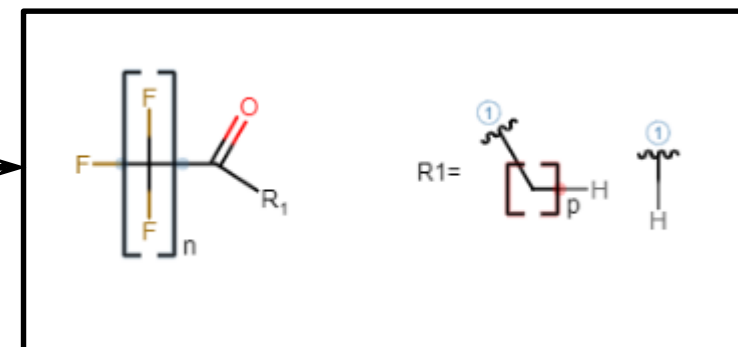
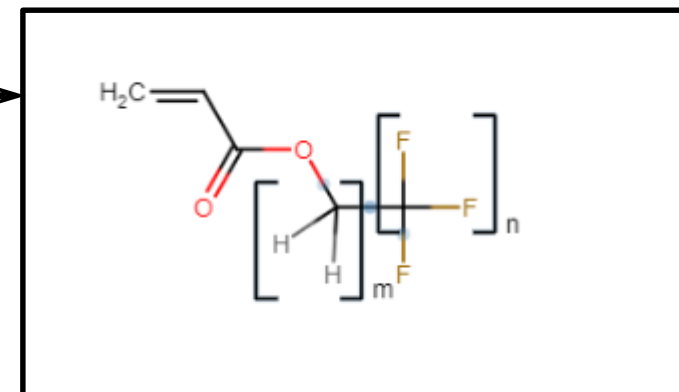
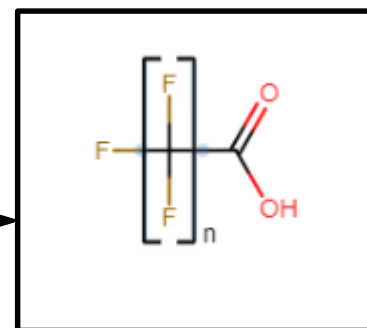
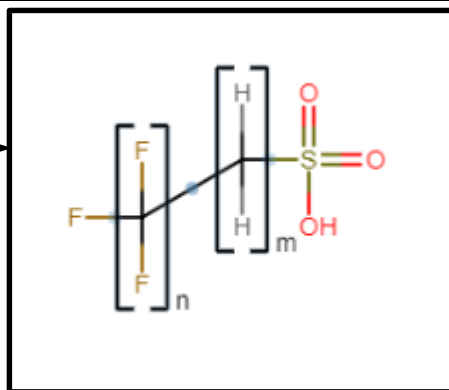
Perfluoroalkyl sulfonates

Perfluoroalkyl sulfonamido amines

Polyfluoroalkyl carboxylates

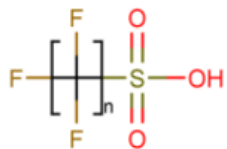
Perfluoroalkyl ethers

Fluorotelomer phosphates



Example of Markush representation

Searched Chemical

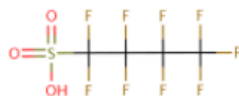


Perfluoroalkyl sulfonates

DTXSID: DTXSID70892979

CASRN: NOCAS_892979

markush



Perfluorobutanesulfonic acid

DTXSID: DTXSID5030030

CASRN: 375-73-5

markush



Perfluorooctanesulfonic acid

DTXSID: DTXSID3031864

CASRN: 1763-23-1

markush



Perfluorodecanesulfonic acid

DTXSID: DTXSID3040148

CASRN: 335-77-3

markush



Perfluorohexanesulfonic acid

DTXSID: DTXSID7040150

CASRN: 355-46-4

markush



Perfluoroheptanesulfonic acid

DTXSID: DTXSID8059920

CASRN: 375-92-8

markush



Perfluoropentanesulfonic acid

DTXSID: DTXSID8062600

CASRN: 2706-91-4

markush



Perfluorononanesulfonic acid

DTXSID: DTXSID8071356

CASRN: 68259-12-1

markush

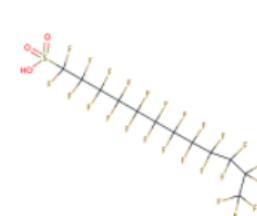


Perfluoropropanesulfonic acid

DTXSID: DTXSID30870531

CASRN: 423-41-6

markush



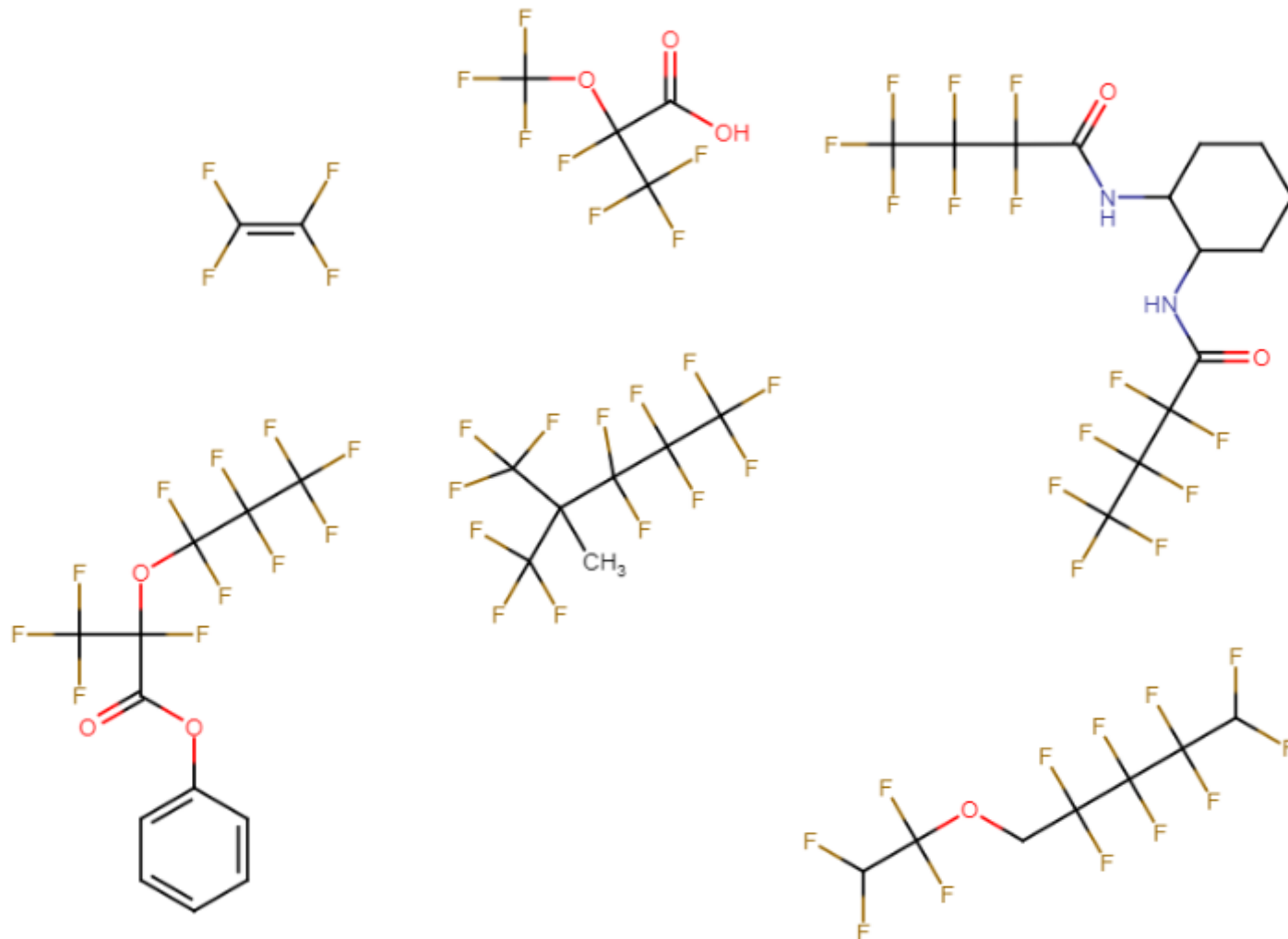
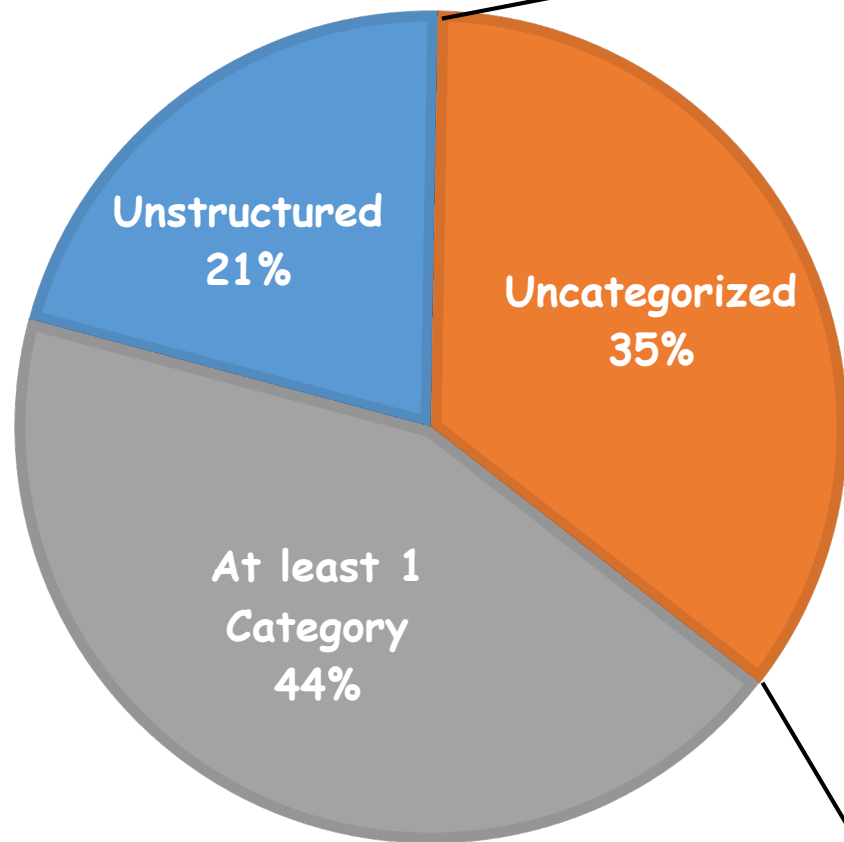
Perfluorododecanesulfonic acid (PFDOS)

DTXSID: DTXSID20873011

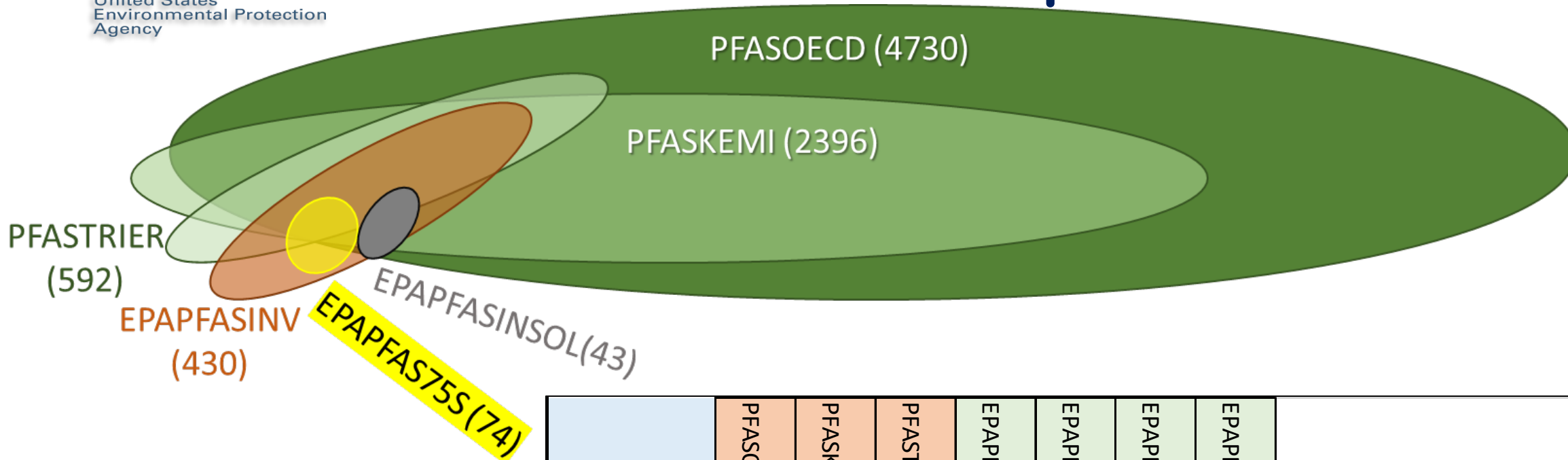
CASRN: 79780-39-5

PFASMASTER Markush Category Coverage

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

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