Computational Toxicology and Exposure Communities of Practice

Sharing research and promoting collaboration

Thursday, November 14, 11 AM-12 PM ET

Agenda:

- **Introduction: Sammy Hanf**
  Communications Specialist, ORD Center for Computational Toxicology and Exposure
- **Presenter: Grace Patlewicz**
  Chemist in the Center for Computational Toxicology and Exposure (CCTE)
- **Q&A**
- **Closing remarks: Sammy Hanf**

Development of Chemical Categories for Per- And Polyfluoroalkyl Substances (PFAS) and The Proof-Of-Concept Approach to the Identification

Per- and Polyfluoroalkyl substances (PFAS) are a class of manufactured chemicals that are in widespread use and many present concerns for persistence, bioaccumulation, and toxicity. While a handful of PFAS have been characterized for their hazard profiles, the vast majority have not been extensively studied. In response, the EPA published the EPA National PFAS Testing Strategy in October 2021 which describes EPA's approach to developing categories of PFAS and identifying substances for further data collection efforts. In September 2024, EPA scientists published a paper that outlines the development of these PFAS categories and the proof-of-concept approach to the identification of potential candidates for tiered toxicological testing and human health assessment.

Upcoming Webinars

EPA hosts webinar series dedicated to delivering the latest information and training on our cutting-edge research addressing environmental and public health issues.

If you are interested in upcoming webinars, stay up-to-date with email notifications:

Webinar dates and topics are subject to change.

Air, Climate, and Energy Research

November 19: *Airborne Survey - Methane from U.S. Landfills*

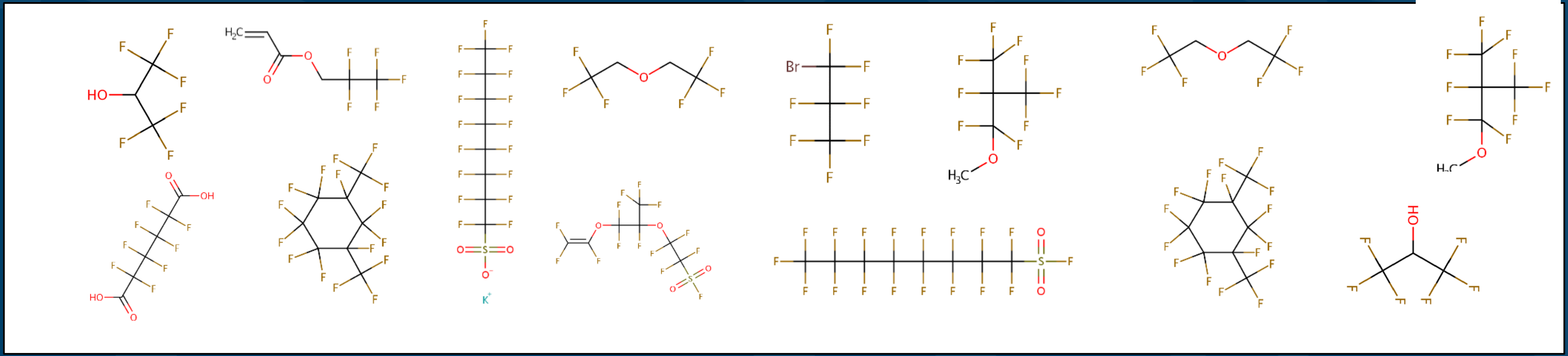
Registration and Additional Information Coming Soon!

Computational Toxicology and Exposure Communities of Practice

December 12: Updates to the Web-based Interspecies Correlation Estimation (Web-ICE) application

Registration and Additional Information Coming Soon!

Towards the development of chemical categories for Per- and polyfluoroalkyl substances (PFAS)



14th November 2024

Grace Patlewicz
Center for Computational Toxicology and Exposure
Office of Research and Development

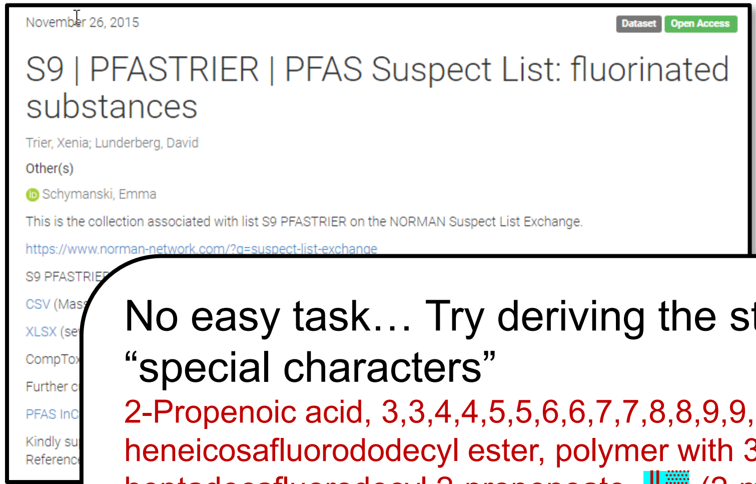
Outline

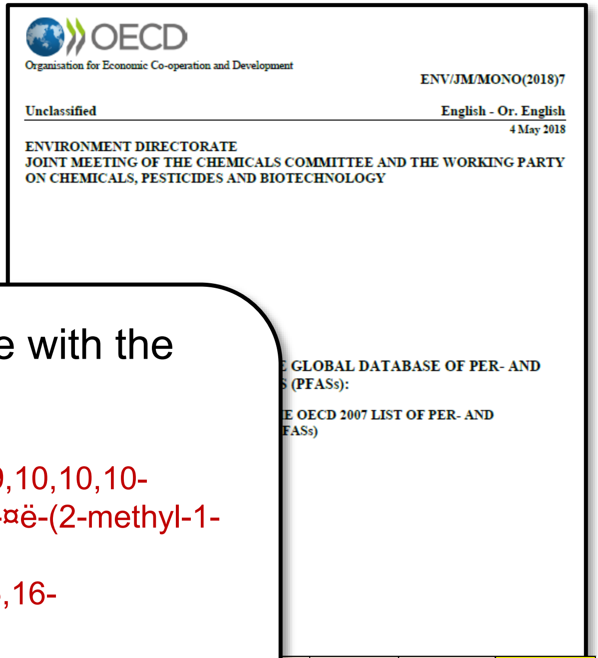
- Part 1: Foundations
- Part 2: EPA National Testing Strategy for PFAS
  - Devising a chemical categorisation approach
- Part 3: Updates to the categorisation approach
- Part 4: Operationalising the categorisation approach
- Summary
- Acknowledgements

Part 1: Foundations

- Establish a PFAS Testing Library
- Devise a set of PFAS structural categories to help select ~150 PFAS for testing
- Prompted new research to make category profiling more objective and scalable
- *In vitro* and toxicokinetic testing initiated

….Curating the Chemistry…Names, Structures, and Identifiers





No easy task… Try deriving the structure for this one with the "special characters"

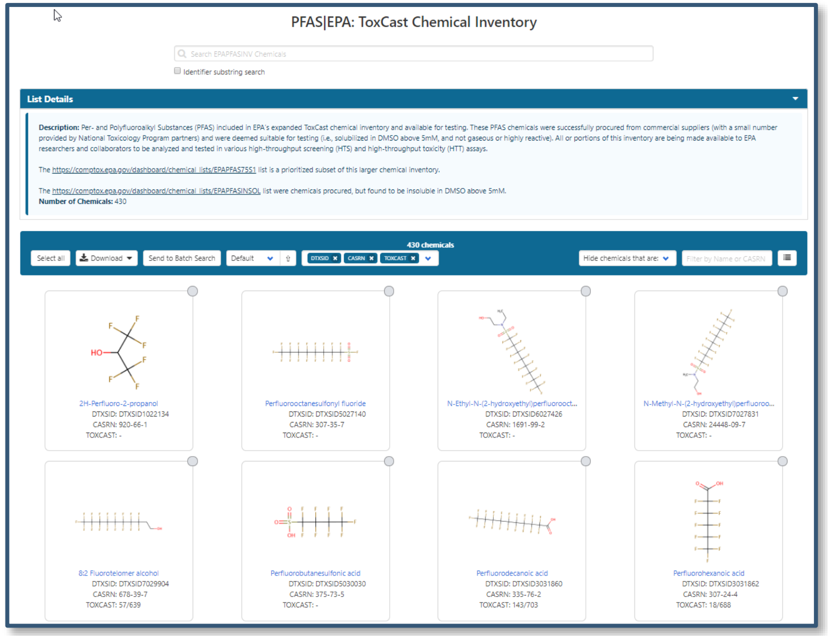
2-Propenoic acid, 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-heneicosafluorododecyl ester, polymer with 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl 2-propenoate, [illegible]-(2-methyl-1-oxo-2-propenyl)-¤ë-(2-methyl-1-oxo-2-propenyl)oxypoly(oxy-1,2-ethanediyl), 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,14,14,15,15,16,16,16-nonacosafluorohexadecyl 2-propenoate, octadecyl 2-propenoate and 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,14,14,14-pentacosafluorotetradecyl 2-propenoate

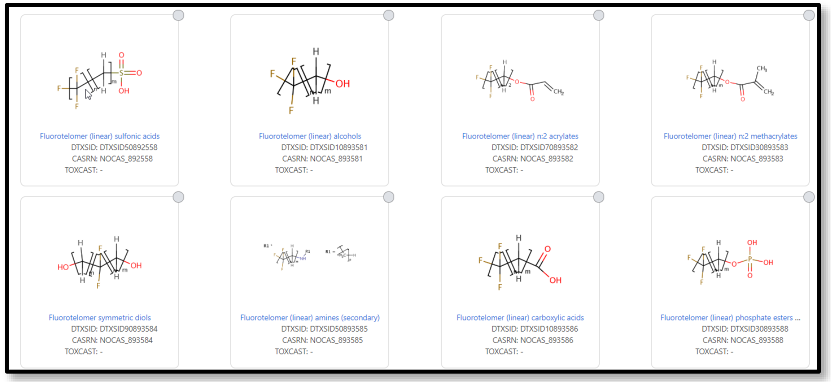
				Source_CASRN (incorrect or invalid)	Source_Acronym (incorrect or ambiguous)	Unique_Acronym
[illegible]	[illegible]	[illegible]	[illegible]	914637-49-3	5:3 acid	5:3 PFOA
[illegible]	[illegible]	[illegible]	…oethanol		NMeFOSE, MeFOSE	NMeFOSE
DTXSID10892352	Perfluoro-2-{[perfluoro-3-(perfluoroethoxy)-2-propanyl]oxy}ethanesulfonic acid	749836-20-2	Ethanesulfonic acid, 2-[1-[difluoro(1,2,2,2-tetrafluroroethoxy)methyl]-1,2,2,2-tetrafluoroethoxy]-1,[illegible]tetrafluoro	749836-20-2	PFESA Byproduct 2	PFESA Byproduct 2
DTXSID70892479	Perfluoro[illegible]	[illegible]-36-9	Perfluoro[illegible]sulfonate	[illegible]	[illegible]	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
DTXSID60873015	Perfluorobutanesulfonate	45187-15-3	Perfluorobutanesulfonate	375-73-5	PFBS	PFBS_ion
DTXSID3040148	Perfluorodecanesulfonic acid	335-77-3	Perfluorodecanesulfonic acid		PFDS	PFDS
DTXSID00873014	Perfluorodecanesulfonate	126105-34-8	Perfluorodecanesulfonate	335-77-3	PFDS	PFDS_ion
DTXSID60892443	Sodium perfluorodecanesulfonate	2806-15-7	Sodium perfluoro-1-decanesulfonate		PFDS	PFDS-Na

Many Lists from EPA Regulatory Offices and Regions

'The Chemistry Curation Team'

Assembled a PFAS Chemical Library for Research and Methods Development





- Attempted to procure ~3,000 based on chemical diversity, Agency priorities, and other considerations
- Obtained 480 total unique chemicals
  - 430/480 soluble in DMSO (90%)
  - 54/75 soluble in water (72%) (incl. only 3 DMSO insolubles)
- A number of issues encountered with sample stability and volatility

Selecting a Subset of PFAS for Tiered Toxicity and Toxicokinetic Testing

EPA United States Environmental Protection Agency

ehp Environmental Health Perspectives

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Brief Communication — Open Access

A Chemical Category-Based Prioritization Approach for Selecting 75 Per- and Polyfluoroalkyl Substances (PFAS) for Tiered Toxicity and Toxicokinetic Testing

Grace Patlewicz, Ann M. Richard, Antony J. Willia
Jason Lambert, Pamela D. Noyes, Michael J. DeV
Annette Guiseppi-Elie, and Russell S. Thomas

Published: 11 January 2019 | CID: 014501 | ht

ELSEVIER — Computational Toxicology, Volume 24, November 2022, 100250

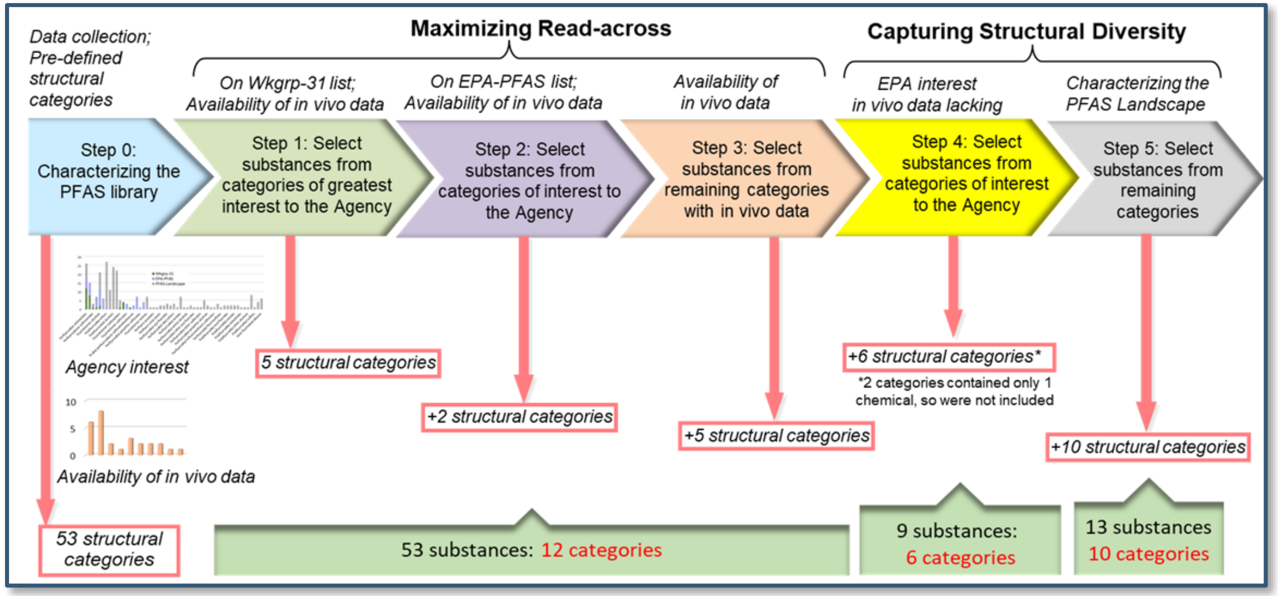
Towards reproducible structure-based chemical categories for PFAS to inform and evaluate toxicity and toxicokinetic testing

Grace Patlewicz, Ann M. Richard, Antony J. Williams, Richard S. Judson, Russell S. Thomas

Goals:

- Generate data to support development and refinement of categories and read-across evaluation
- Incorporate substances of interest to Agency
- Characterise mechanistic and toxicokinetic properties of the broader PFAS landscape

- Selected 150 PFAS in two phases representing 83 different structural categories
- These structural categories evolved over time..
    - Initially we used Buck et al terminology, CCTE Markush, OECD categories



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In Vitro Toxicity and Toxicokinetic Testing

Toxicological Response	Assay	Assay Endpoints	Purpose
Hepatotoxicity	2D HepaRG assay	Cell death and transcriptomics	Measure cell death and changes in important biological pathways
Developmental Toxicity	Zebrafish embryo assay	Fertilisation, lethality, and structural defects	Assess potential teratogenicity
Immunotoxicity	Bioseek Diversity Plus	Protein biomarkers across multiple primary cell types	Measure potential disease and immune responses
Mitochondrial Toxicity	Mitochondrial membrane potential (HepaRG)	Mitochondrial membrane potential	Measure mitochondrial health and function
Developmental Neurotoxicity	Microelectrode array assay (rat primary neurons)	Neuronal electrical activity	Impacts on neuron function
Endocrine Disruption	ACEA real-time cell proliferation assay (T47D)	Cell proliferation	Measure ER activity
General Toxicity	Attagene cis- and trans-Factorial assay (HepG2)	Nuclear receptor and transcription factor activation	Activation of key receptors and transcription factors involved in hepatotoxicity
	High-throughput transcriptomic assay (multiple cell types)	Cellular mRNA	Measures changes in important biological pathways
	High-throughput phenotypic profiling (multiple cell types)	Nuclear, endoplasmic reticulum, nucleoli, golgi, plasma membrane, cytoskeleton, and mitochondria morphology	Changes in cellular organelles and general morphology

Toxicokinetic Parameter	Assay	Assay Endpoints	Purpose
*Intrinsic hepatic clearance	Hepatocyte stability assay (primary human hepatocytes)	Time course metabolism of parent chemical	Measure metabolic breakdown by the liver
Plasma protein binding	Ultracentrifugation assay	Fraction of chemical not bound to plasma protein	Measure amount of free chemical in the blood

*Assays being performed by NTP and EPA

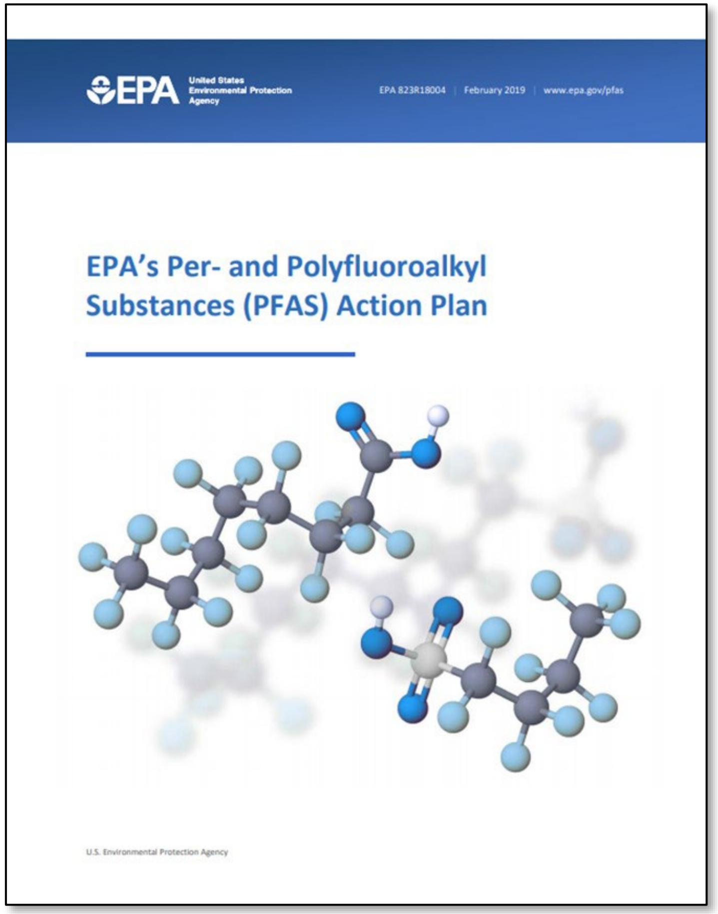
In Vitro Toxicity and Toxicokinetic Testing

EPA United States Environmental Protection Agency

- Aimed to inform
  - Chemical Category and Read-across approaches
  - Bioactive Dose Level (BDL) Approach (*in vitro* to *in vivo* extrapolation to define administered dose equivalent (ADE) values)
- Initially use structural categories to evaluate the degree of concordance in NAM results (per technology) within categories and across categories*

*results & data published across multiple publications

Using New Approach Methods (NAMs) to Help Fill Information Gaps



***Research Area 1:** What are the human health and ecological effects of exposure to PFAS?*

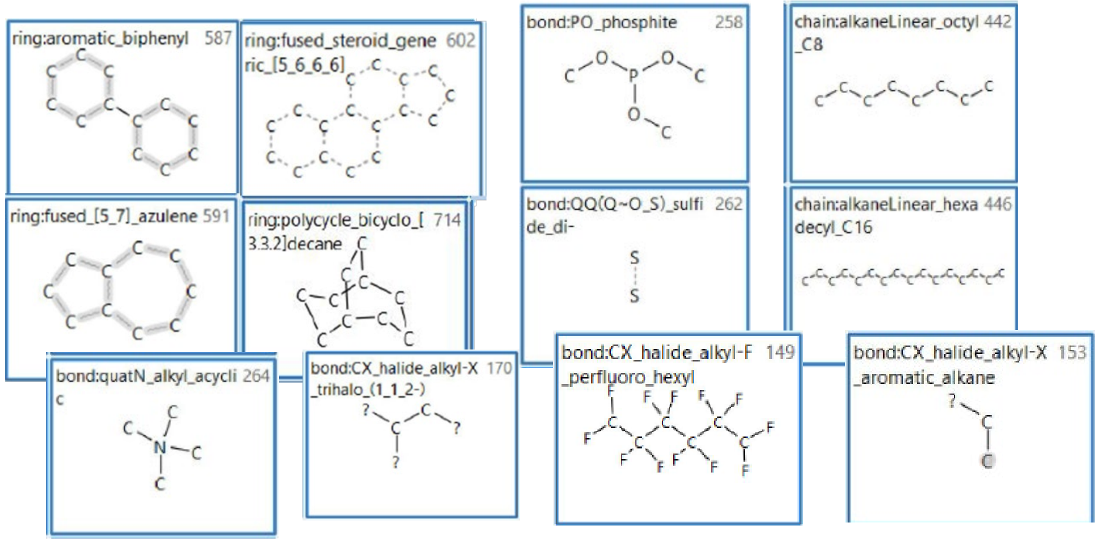
- Using computational toxicology approaches to fill in gaps. For the many PFAS for which published peer-reviewed data are not currently available, the EPA plans to use new approaches such as high throughput and computational approaches to explore different chemical categories of PFAS, to inform hazard effects characterization, and to promote prioritization of chemicals for further testing. These data will be useful for filling gaps in understanding the toxicity of those PFAS with little to no available data. ***In the near term***, the EPA intends to complete assays for a representative set of 150 PFAS chemicals, load the data into the CompTox Chemicals Dashboard for access, and provide peer-reviewed guidance for stakeholders on the use and application of the information. ***In the long term***, the EPA will continue research on methods for using these data to support risk assessments using New Approach Methods (NAMs) such as read-across and transcriptomics, and to make inferences about the toxicity of PFAS mixtures which commonly occur in real world exposures. The EPA plans to collaborate with NIEHS and universities to lead the science in this area and work with universities, industry, and other government agencies to develop the technology and chemical standards needed to conduct this research.

Characterising PFAS into categories

- Structural categories were assigned by visual inspection and whilst nominally consistent since only one individual was making the assignments, the approach was prone to error and not easily reproducible.
- The assignments provided by OECD were similar in their genesis – they were manually assigned by the same person.
- Indeed, authors of many of the published literature studies on PFAS have often end up deriving bespoke naming conventions for categories which has led to "the generation of a lot of parallel nomenclature that differs, creating unintended barriers to effective communication among scientists"
- There was an urgent need existed to develop a reproducible & objective means of developing structure-based categories

PFAS Structure-based Categorisation: ToxPrints

- Publicly available tools exist to generate & download ToxPrints e.g. ChemoTyper, CompTox Chemicals Dashboard
- Provides excellent coverage of PFAS chemical space
- Nested, hierarchical nature lends itself to creating flexible categories tailored to problem at hand, i.e., "fit for purpose"
- Can augment with computed structure properties (s.a., MW, size, etc.)
- Intuitive, easy to work with



ToxPrints:

- ✓ *729 chemical features*
- ✓ *Chemically interpretable*
- ✓ *Coverage of diverse chemistry*
- ✓ *Includes scaffolds, functional groups, chains, rings, bonding patterns, atom-types*

→ Clear, reproducible means for defining regions of local chemistry, i.e. categories!!

PFAS Structure-based Categorisation

United States Environmental Protection Agency

- Reconcile the different structural categories schemes initially used – by creating a harmonised set of structure-based categories
- Category assignments should be computationally generated from structure only → reproducible, transferable, standardised, extendable
- Permits nested & overlapping categories such that categories can be tailored to different datasets and decision contexts
- ToxPrints were used to develop 34 structural categories (TxP Cats) which covered >90% of the different PFAS testing inventories…
- But their ability to capture the diversity of much larger inventories (~1000s of PFAS) was a shortcoming which prompted further research to develop PFAS ToxPrints (Richard et al., 2023)

Side note – These TxPs have since been implemented in the CIM and for a limited set of PFAS in GenRA Version 3.3

Chemical Research in Toxicology > Vol 36/Issue 3 > Article

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ARTICLE | March 2, 2023

A New CSRML Structure-Based Fingerprint Method for Profiling and Categorizing Per- and Polyfluoroalkyl Substances (PFAS)

Ann M. Richard*, Ryan Lougee, Matthew Adams, Hannah Hidle, Chihae Yang, James Rathman, Tomasz Magdziarz, Bruno Bienfait, Antony J. Williams, and Grace Patlewicz

Open PDF | Supporting Information (1)

Part 1: Foundations

- Established a PFAS Testing Library
- Devised a set of PFAS structural categories to help select ~150 PFAS for testing
- New research lead to the development of ToxPrint PFAS categories and custom PFAS fingerprints to facilitate more efficient category profiling
- *In vitro* testing and toxicokinetic data generated for ~150 PFAS

Part 2: EPA's National Testing Strategy (NTS) for PFAS

- The EPA needs to evaluate a large number of PFAS for potential human and ecological effects.
- Most PFAS have limited or no toxicity data.
- There was emerging consensus on the need to use category/grouping-based approaches to evaluate PFAS for a range of decision contexts.
- In a category/grouping approach, one or more data rich analogues is used to read-across toxicity values for the remaining data poor substances within the group.
- Historically, for human health assessment within EPA, PFAS analogues and/or groups had been based on a combination of chain-length and functional groups.

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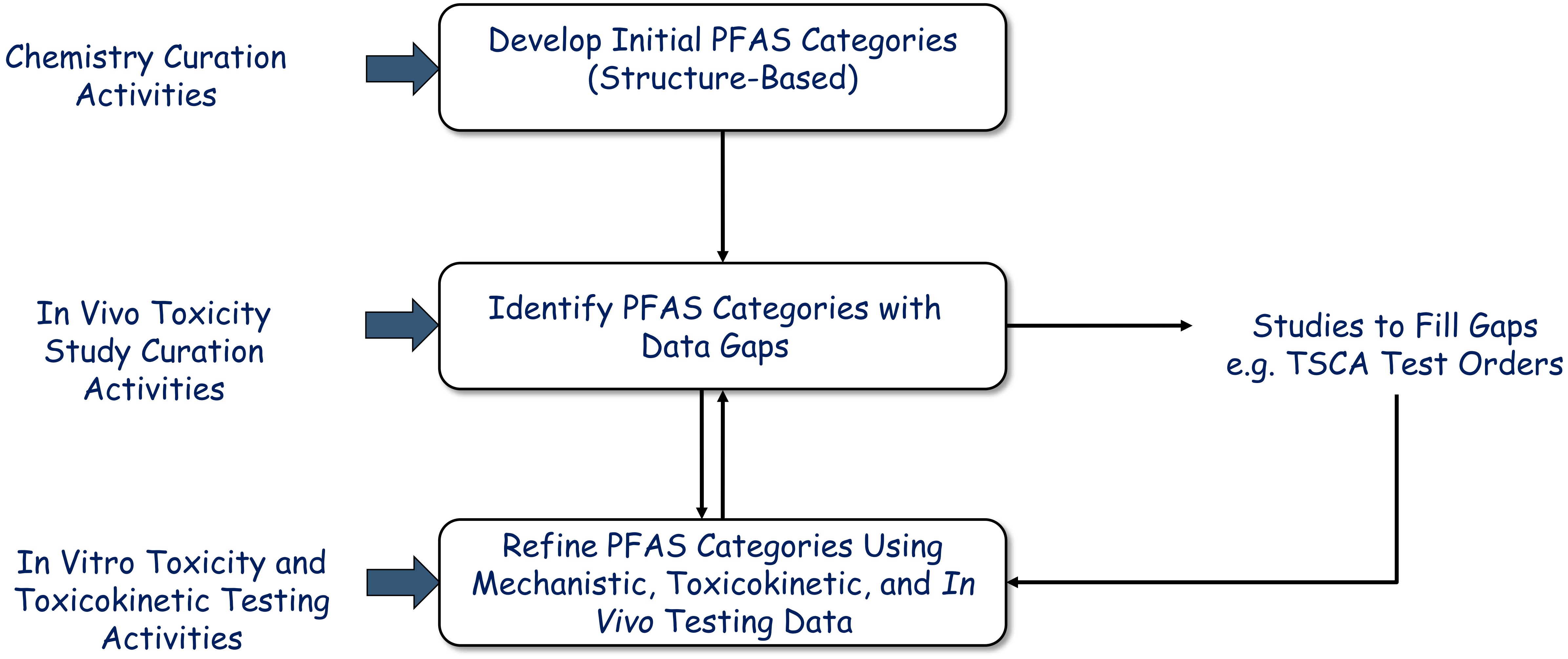
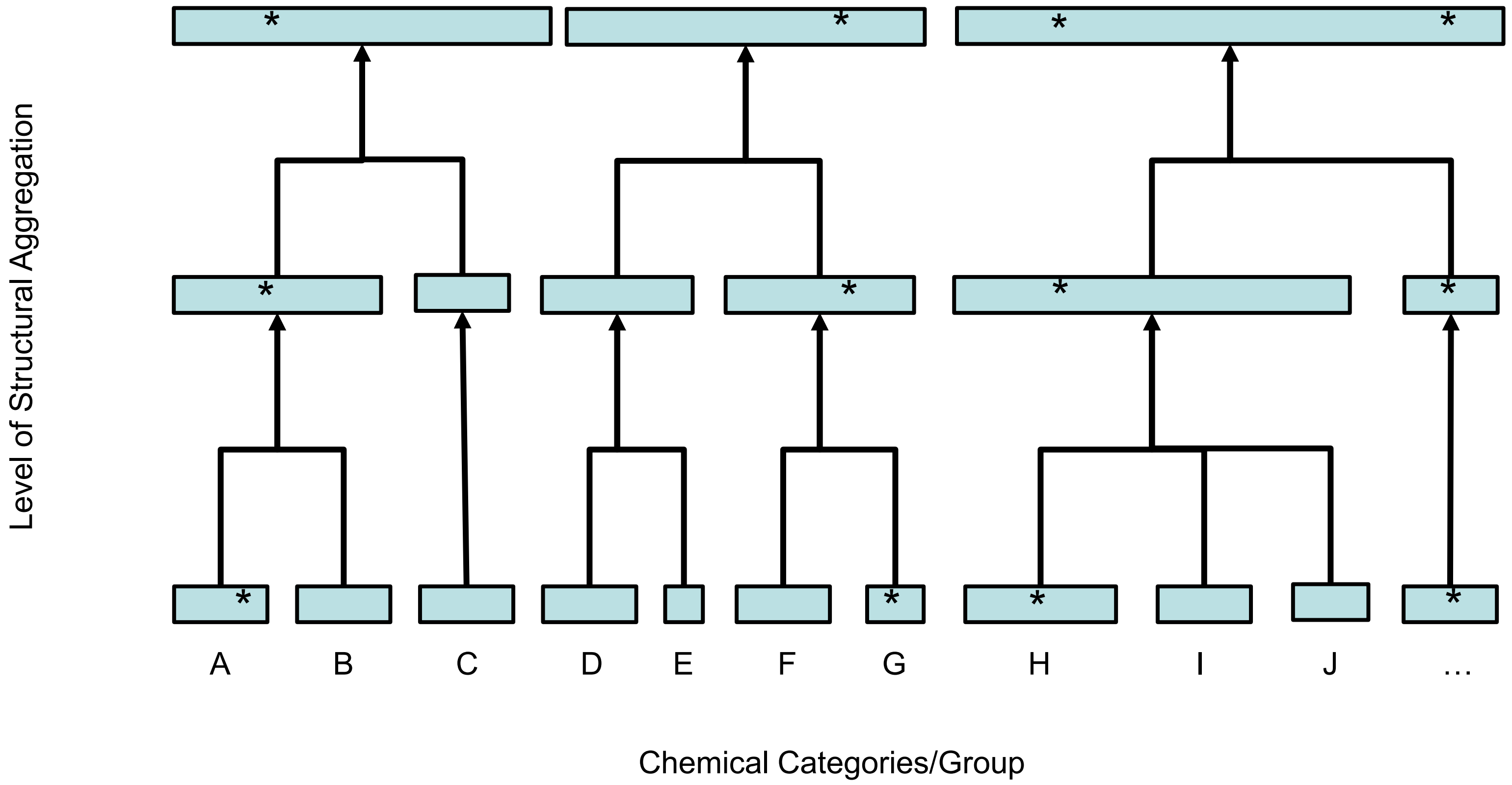
Developing and Refining PFAS Categories



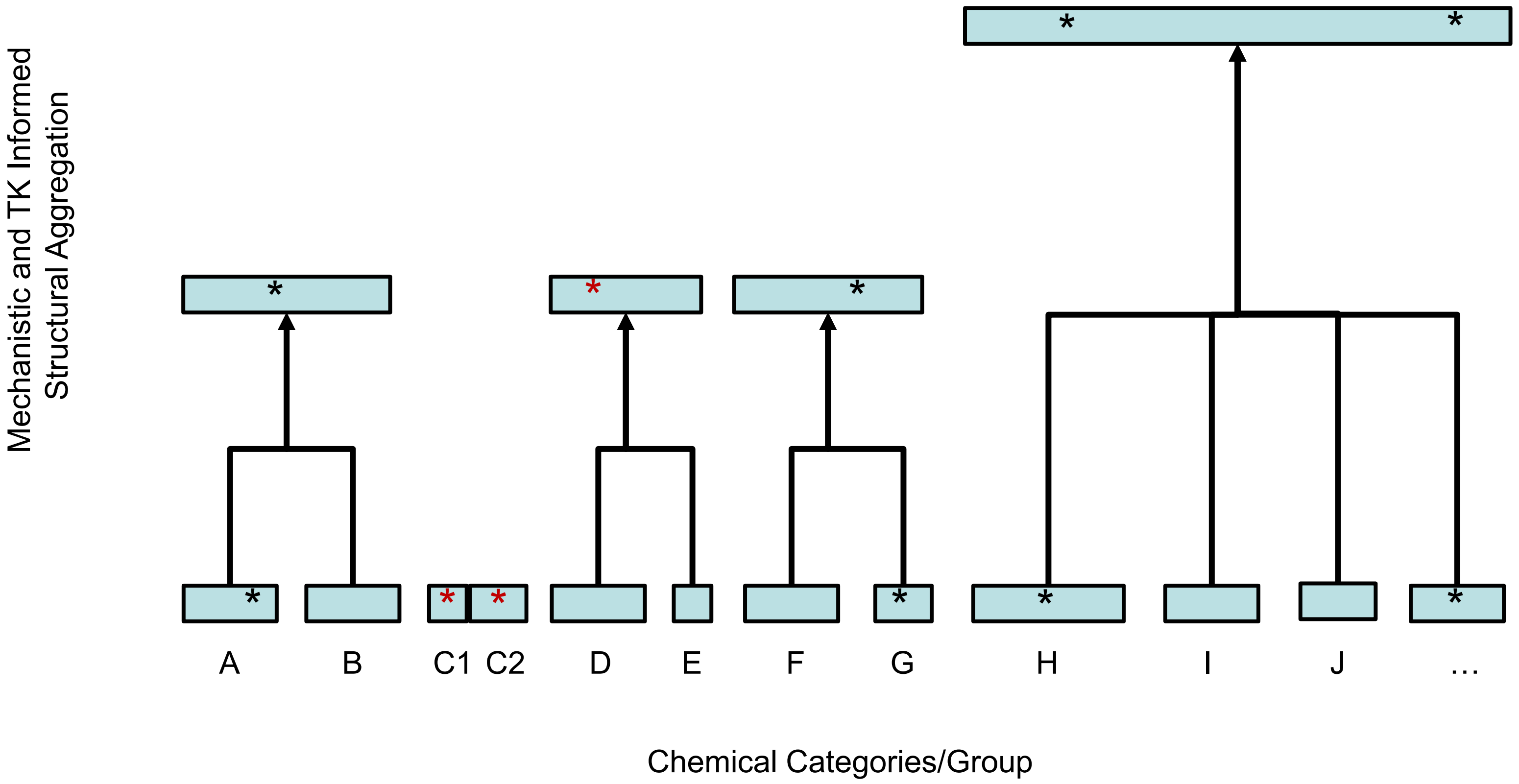
Hierarchical approach to PFAS structural categories



Followed a goldilocks principle

*Available source *in vivo* tox study

PFAS Category Aggregation that incorporates Structural, Mechanistic and Toxicokinetic Data



*Needed *in vivo* tox study *Available source *in vivo* tox study

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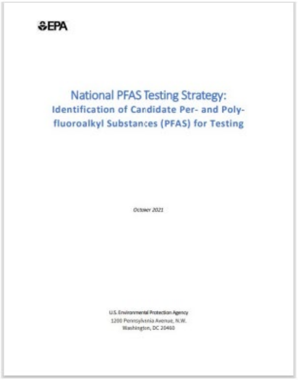
Initial PFAS Structural Categories for Hazard Assessment


National PFAS Testing Strategy:
Identification of Candidate Per- and Poly-fluoroalkyl Substances (PFAS) for Testing

October 2021

U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

DSSTox Database → **Structural Filters** → **Primary Structural Categories*** → **Secondary Structural Categories** → // → **Terminal Structural Categories** → **Select Representative Substance**

DSSTox Database

~906K substances

Structural Filters

1. Contains -CF2
2. Apply 'OPPT working definition'
3. Remove radicals, charge imbalanced
4. Remove specific types of 5 and 6 membered rings (aromatic, containing double bonds, heterocycles)

Primary Structural Categories*

6504 substances

1. PFAS derivatives
2. PFAAs
3. Perfluoro PFAA precursors
4. Non-PFAA Perfluoroalkyls
5. FASA-based PFAA Precursors
6. Fluorotelomer PFAA precursors
7. Silicon PFAS
8. Side-chain fluorinated aromatic PFAS
9. Other aliphatic PFAS

Secondary Structural Categories

1. Volatile (>100 mmHg vapour pressure)
2. Non-volatile with greater than or equal to 8 carbons
3. Non-volatile with less than 8 carbons

Subsequent categorisations performed only on categories with structural diversity greater than the threshold

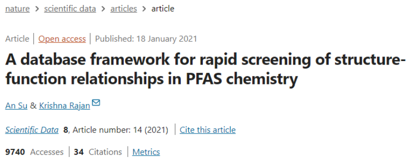
Terminal Structural Categories

70 Terminal categories

Select Representative Substance

A structure that contains the unit R-CF_2-CF(R')(R''), where R, R', and R'' do not equal "H" and the carbon-carbon bond is saturated

Chemicals with at least two adjacent carbon atoms, where one carbon is fully fluorinated and the other is at least partially fluorinated


nature › scientific data › articles › article

Article | Open access | Published: 18 January 2021

A database framework for rapid screening of structure-function relationships in PFAS chemistry

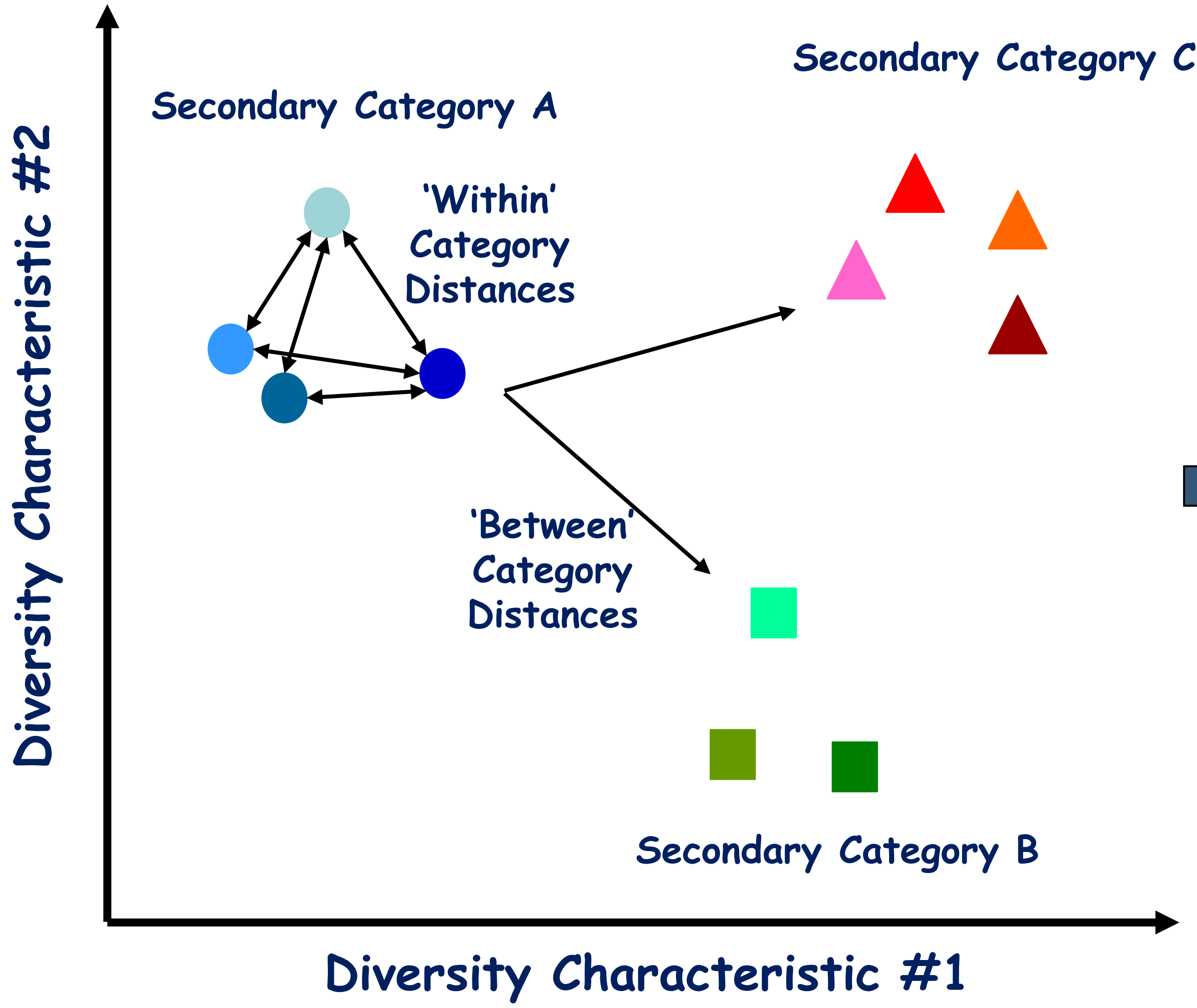
An Su & Krishna Rajan

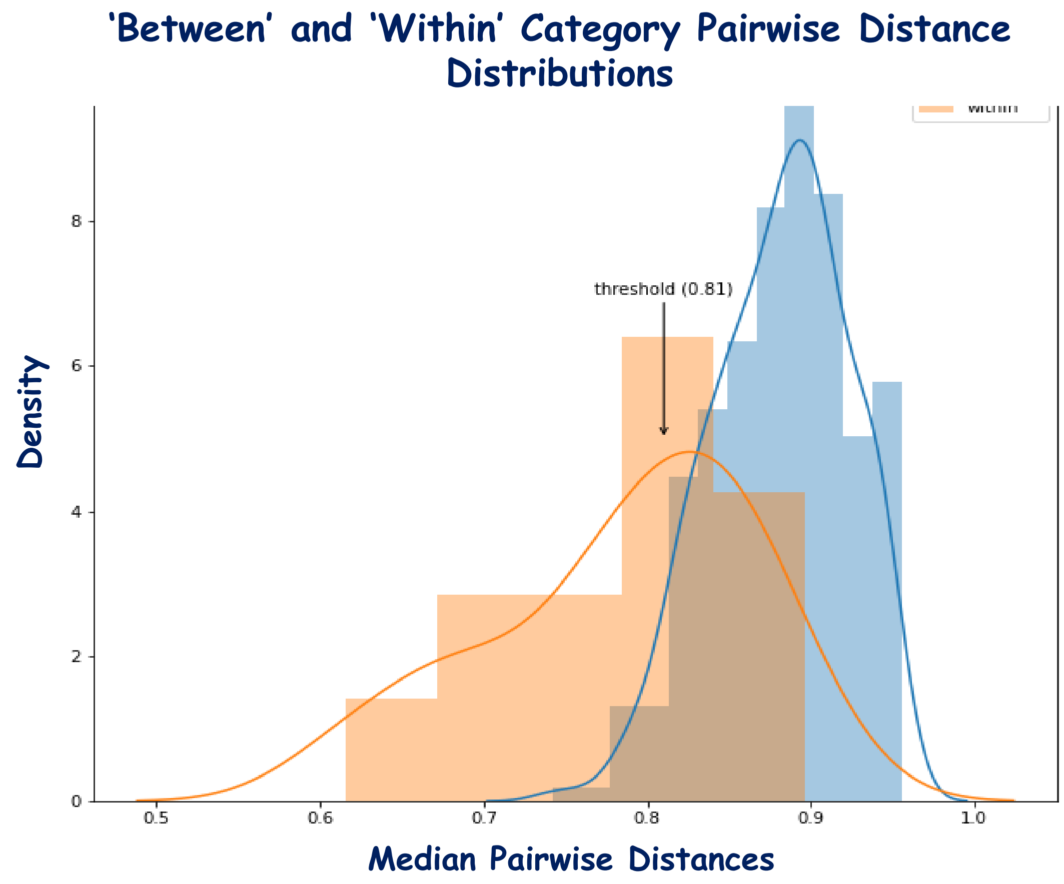
Scientific Data 8, Article number: 14 (2021) | Cite this article

9740 Accesses | 34 Citations | Metrics

*Based on Su and Rajan, 2021

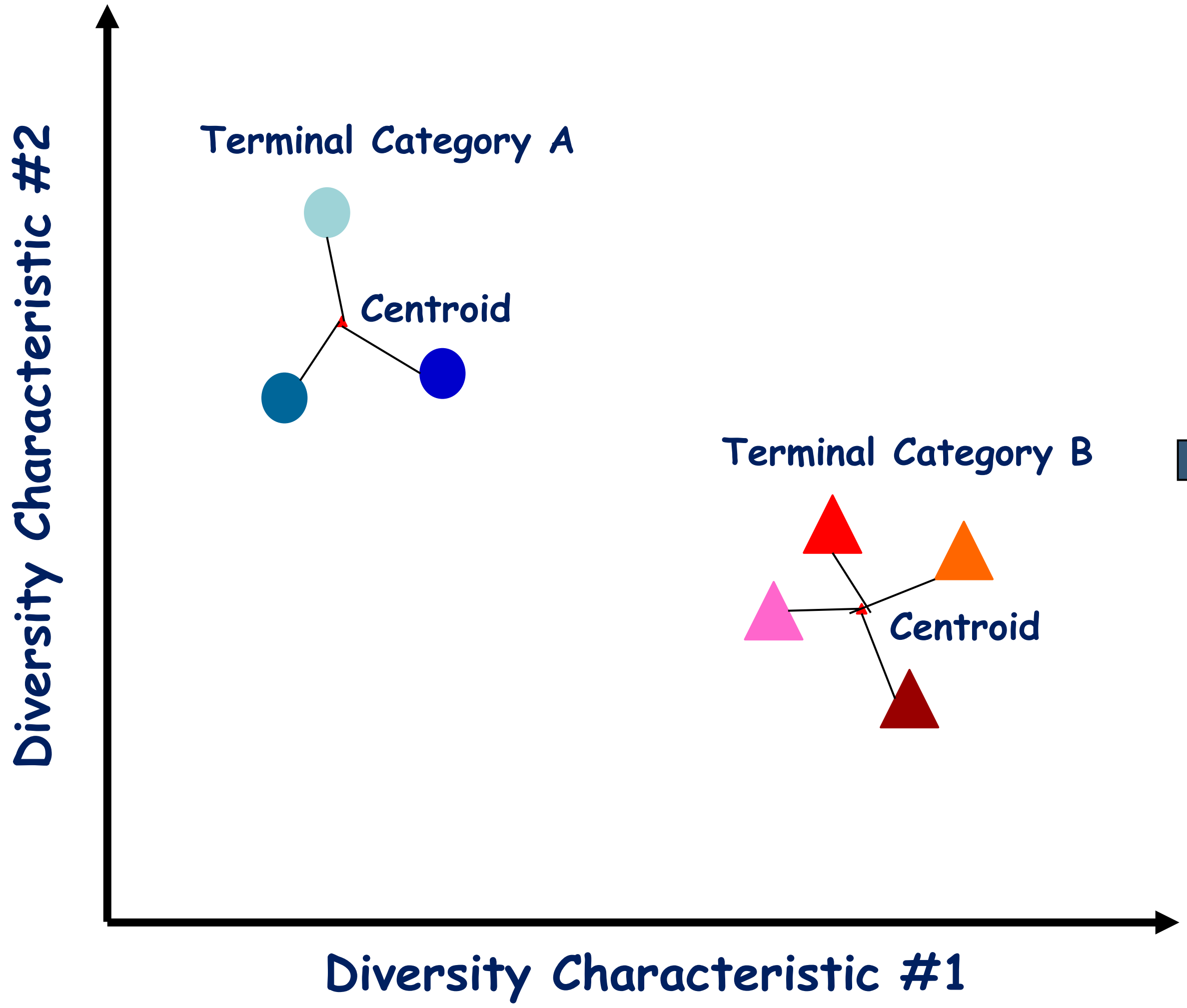
Structural Diversity 'Within' and 'Between' Secondary Categories Used to Set Diversity Threshold





Substances characterised by Morgan chemical fingerprints – Jaccard Pairwise distance

'Centroids' Calculated for Each Terminal Category to Help Select 'Most Representative' PFAS for Testing



Minimum pairwise distance in distance matrix used to identify the 'centroid'.

'Centroids' served as the most representative substance for the structural category

Part 3: Refinements

- Universe defined by the TSCA 8(a)(7) rule + plausible degradation products for those PFAS on the TSCA inventory (degradates met the same rule and were simulated using the Catalogic expert system by LMC)
- Updated primary categories based on revised OECD Category scheme as published by Su et al (2023) (replaces the Su and Rajan (2021) scheme)
- Changed secondary category criteria to a fully-fluorinated, consecutive chain length threshold of 7
  - Chain length threshold selected based on upper end as described in the EPA 2009 action plan
  - Replaced carbon number as a criteria
- Removed volatility (using 100 mm Hg threshold) as a criteria of secondary categorisation
- Consideration of physical state and physicochemical properties which could potentially inform toxicity testing, presence in environmental media, and exposure pathways

Cont..

- Included possibility to select more than 1 "representative" substance from a given terminal category based on maximal structural diversity (also called Max/Min). Important since some categories were particularly large and/or certain categories could be prioritised higher than others.
- Enabled selection of representative substances from both the full set of substances in a terminal category and the subset on the TSCA inventory
- Added qualitative flags for environmental monitoring/exposure, toxicokinetics,and mechanistic data (NAMs)
- Use human relevant benchmark dose based on Aurisiano et al (2023) approach in lieu of NOAELs/LOAELs for evaluating *in vivo* toxicity variability across categories
- Operationalise PFAS terminal categories into a predictive model to enable profiling of new PFAS

EPA United States Environmental Protection Agency

Updated PFAS Structural Categorisation Workflow

DSSTox Database → Structural Filters → Primary Structural Categories* → Secondary Structural Categories → // → Terminal Structural Categories → Select Centroids and Other Substances → Overlay Informative Metadata

Subsequent categorisations performed only on categories with structural diversity greater than the threshold

DSSTox Database

1.2M substances

Structural Filters

1. Apply TSCA 8(a)(7) rule (13,054)

\+

2. TSCA plausible simulated PFAS degradation products (2484)

Primary Structural Categories*

15,525 substances

1. PFAAs
2. PFAAs cyclic
3. PFAA precursors (+3)
4. PFAA precursors cyclic
5. Polyfluoroalkyl acids (+1)
6. Polyfluoroalkyl acids cyclic
7. Other PFAS (+4)
8. Other PFAS cyclic (+1)
9. Unclassified

Secondary Structural Categories

1. greater than or equal to chain length of 7
2. less than chain length of 7

Terminal Structural Categories

128 Terminal categories

Select Centroids and Other Substances

1. Constrained TSCA active inventory
2. Full set

Overlay Informative Metadata

1. Toxicity testing data
2. Environmental monitoring data
3. Physical state and physicochemical properties
4. Mechanistic and TK NAM data

Substances that meet any of the following criteria:

(i) $R-(CF_2)-CF(R')R''$, where both the CF_2 and CF moieties are saturated carbons

(ii) $R-CF_2OCF_2-R'$, where R and R' can either be F, O, or saturated carbons

(iii) $CF_3C(CF_3)R'R''$, where R' and R'' can either be F or saturated carbons

An Artificial Intelligence Platform for Automated PFAS Subgroup Classification: A Discovery Tool for PFAS Screening

16 August 2023, Version 1

Working Paper

An Su, Yingying Cheng, Chengwei Zhang, Yun-Fang Yang, Yuan-Bin She, Krishna Rajan

Show author details

*Based on the PFAS-Atlas scheme in Su et al, 2023

Incorporating TSCA Status, Toxicity Testing Data, and Environmental Monitoring Data

- Presence on the TSCA inventory as surrogate for the ability to identify a manufacturer
  - 80 terminal categories with ≥1 substance on TSCA inventory
  - 60 terminal categories with ≥1 substance on TSCA active inventory
- Availability of repeated dose toxicity data (ToxValDB)
  - 94 data poor terminal categories (no repeated dose toxicity data by the oral route)
  - 48 data poor terminal categories with ≥1 substance on TSCA inventory
  - 31 data poor terminal categories with ≥1 substance on TSCA active inventory
- Environmental monitoring (EM) lists – regions and states have undertaken environmental monitoring studies for selected PFAS and/or have identified PFAS of interest based on validated analytical methods
  - 21 terminal categories were data poor, had at least 1 substance on the TSCA inventory, and at least 1 substance on EM list.
  - 18 terminal categories were data poor, had at least 1 substance on the TSCA active inventory, and at least 1 substance on EM list.

EPA
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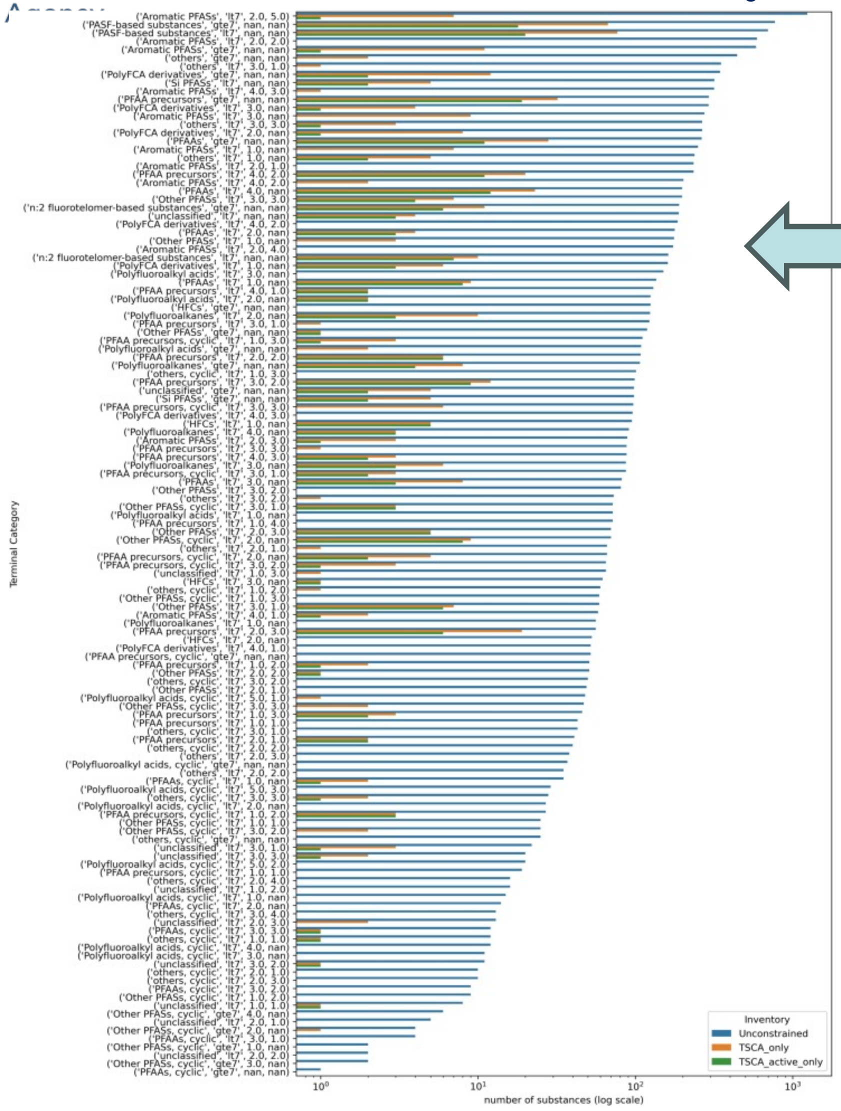
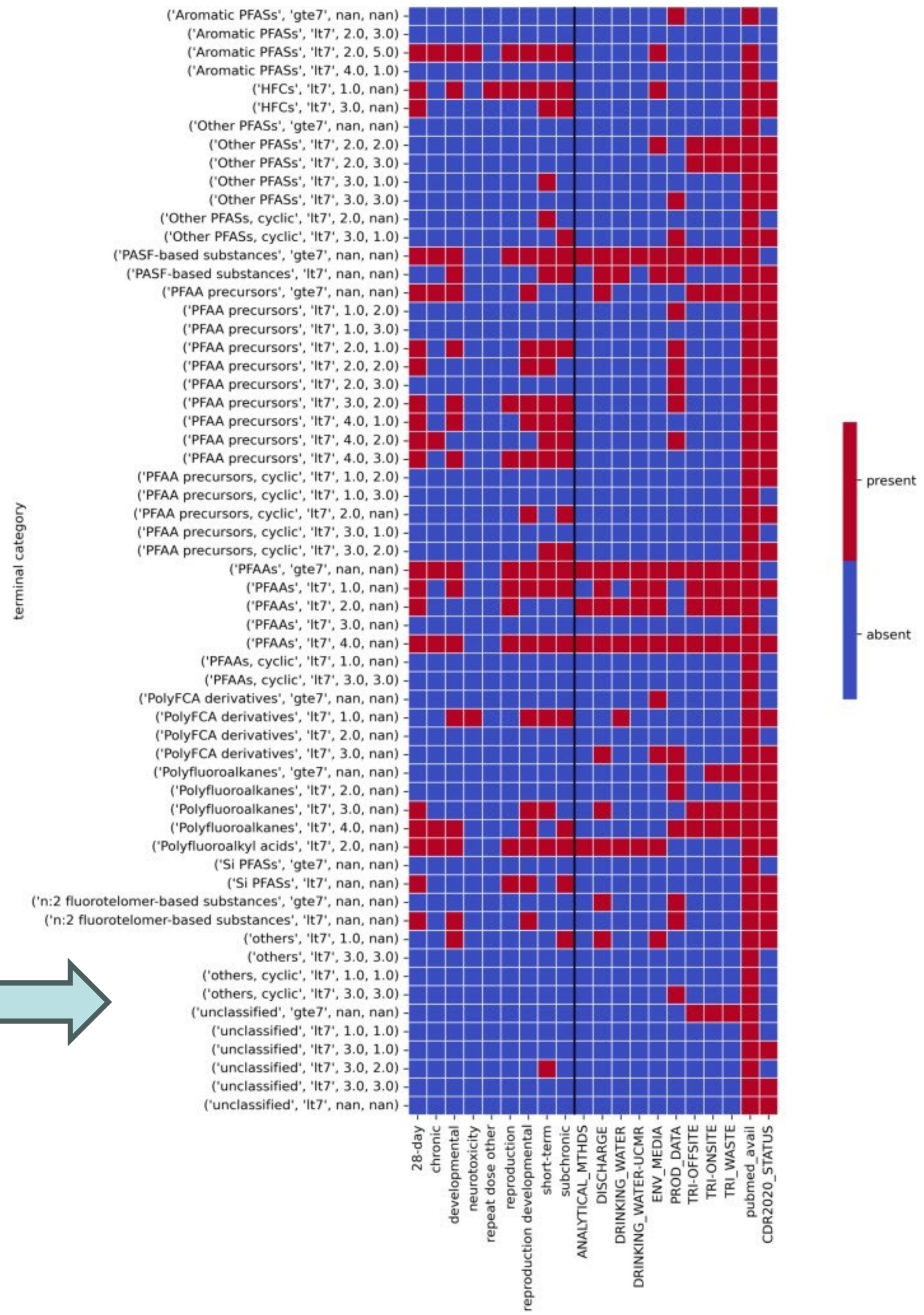
Agency

Landscape profile

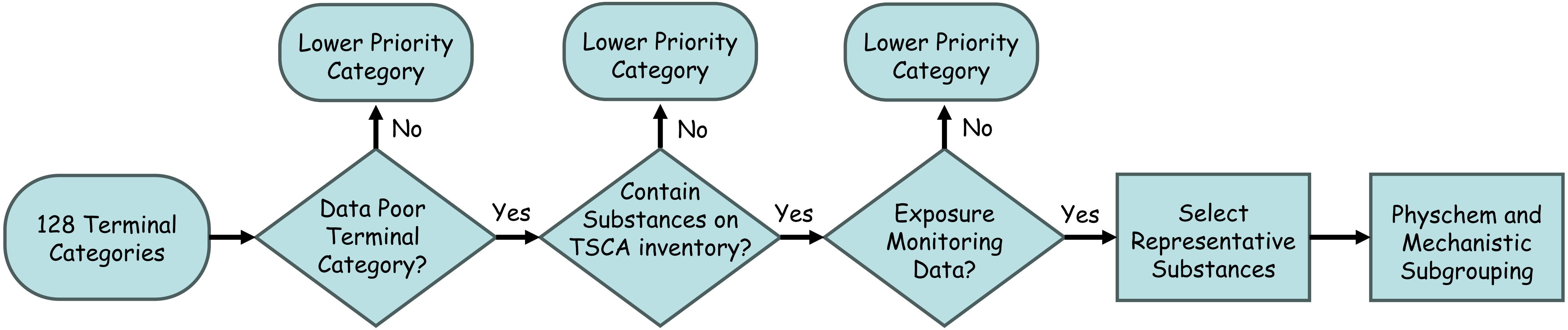


Comparison of categories across unconstrained and constrained landscapes

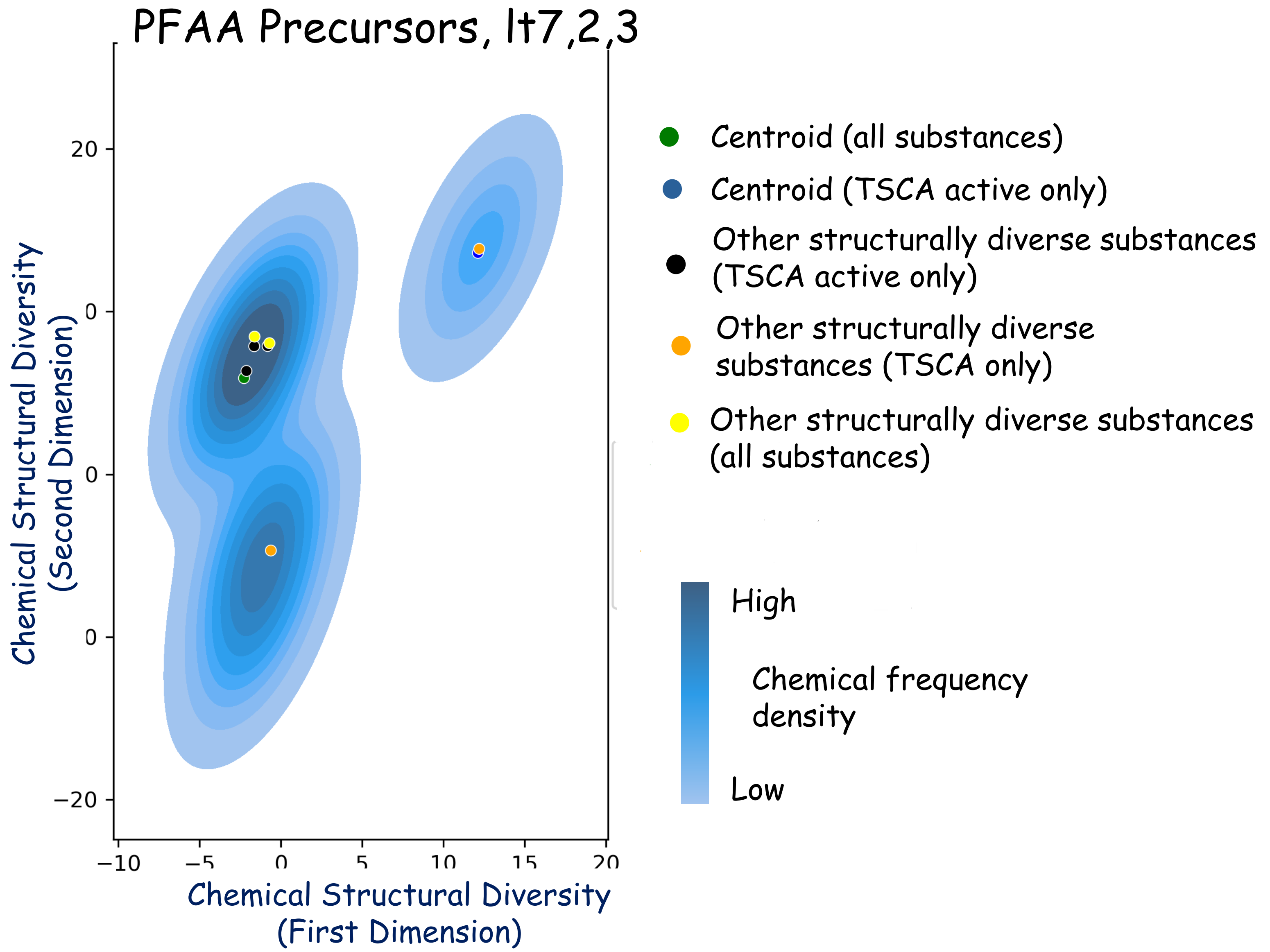
Data availability across TSCA active landscape to prioritise potential terminal categories



Integrate Information in Tiered Prioritisation Workflow for Candidate Identification



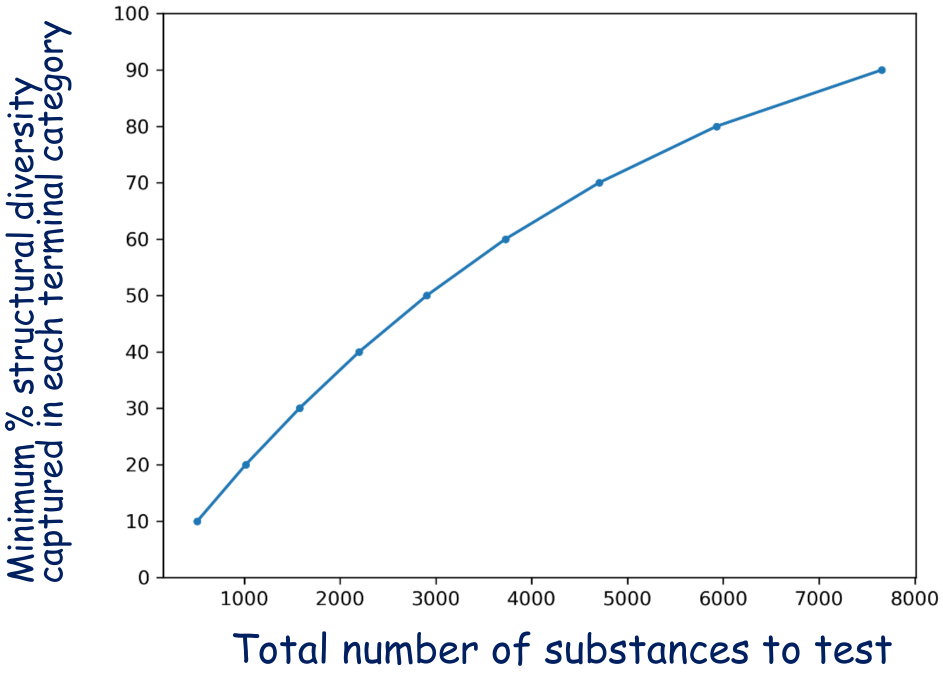
Selecting Representative Substances in an Illustrative Terminal Category



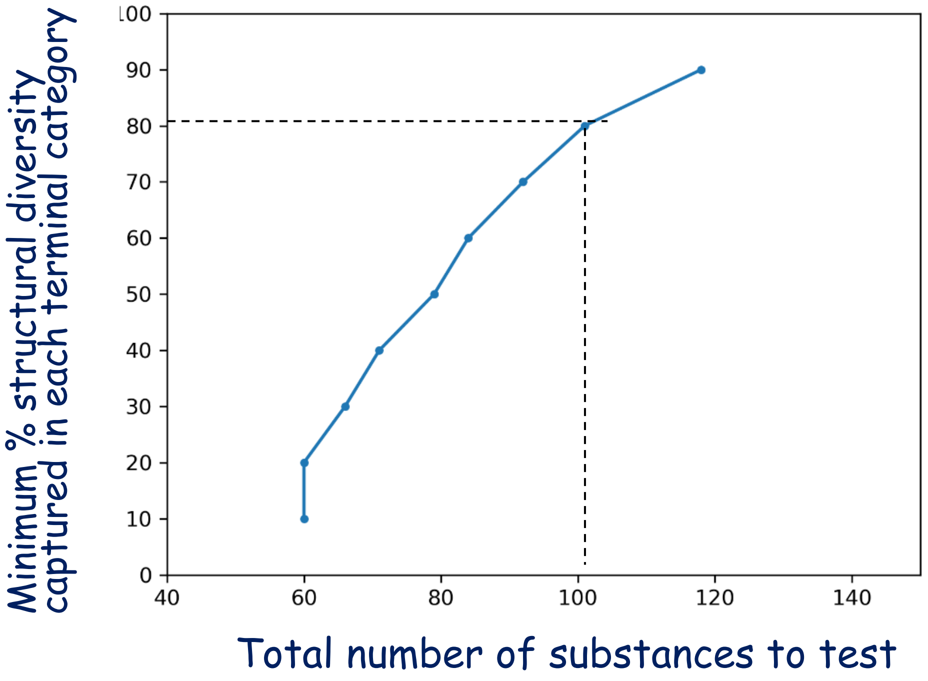
Illustrative terminal category that is data poor, has at least 1 substance on the TSCA active inventory, and at least 1 substance on the Environmental Monitoring list

How many representative substances are really needed?

Full landscape



TSCA constrained landscape



Depends on what proportion of structural diversity is desired to be captured and for which Landscape – the full landscape of ~15K substances or one constrained by the TSCA active inventory

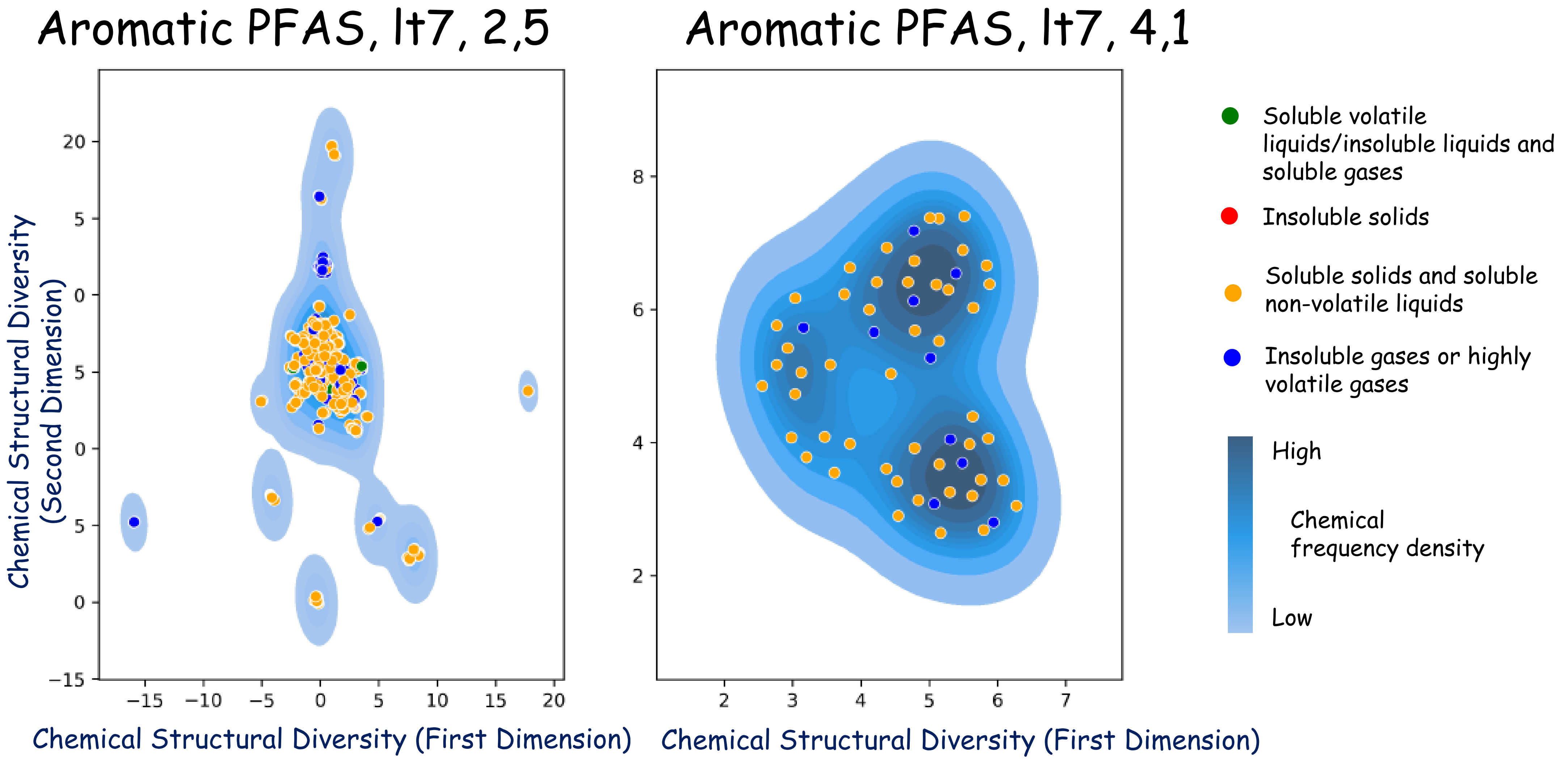
101 substances would be needed to capture 80% of structural diversity in the TSCA constrained inventory*

*25 of the 101 are associated with public toxicity data from EPA's ToxValDB

Physical state and physicochemical designations (PSPD)

Physical state and physicochemical designations	Full Landscape	TSCA active constrained Landscape
A (insoluble solids)	2060 (13%)	25 (12.6%)
B (soluble solids and soluble non-volatile liquids)	9824 (63%)	71 (35.7%)
C (soluble volatile liquids/insoluble liquids and soluble gases)	3115 (20%)	85 (42.7%)
D (insoluble gases or highly volatile gases)	95 (0.6%)	10 (5%)
No designation	431 (2.8%)	8 (4%)

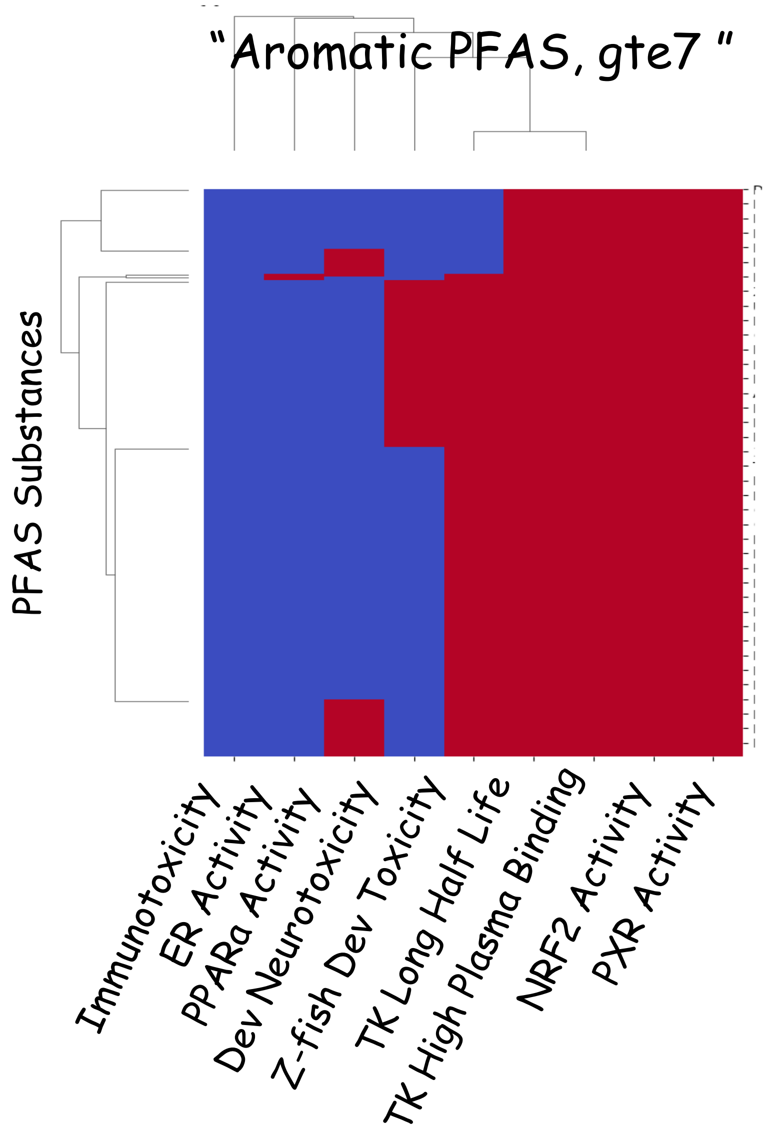
Distribution of PSPD Within Illustrative Terminal Categories

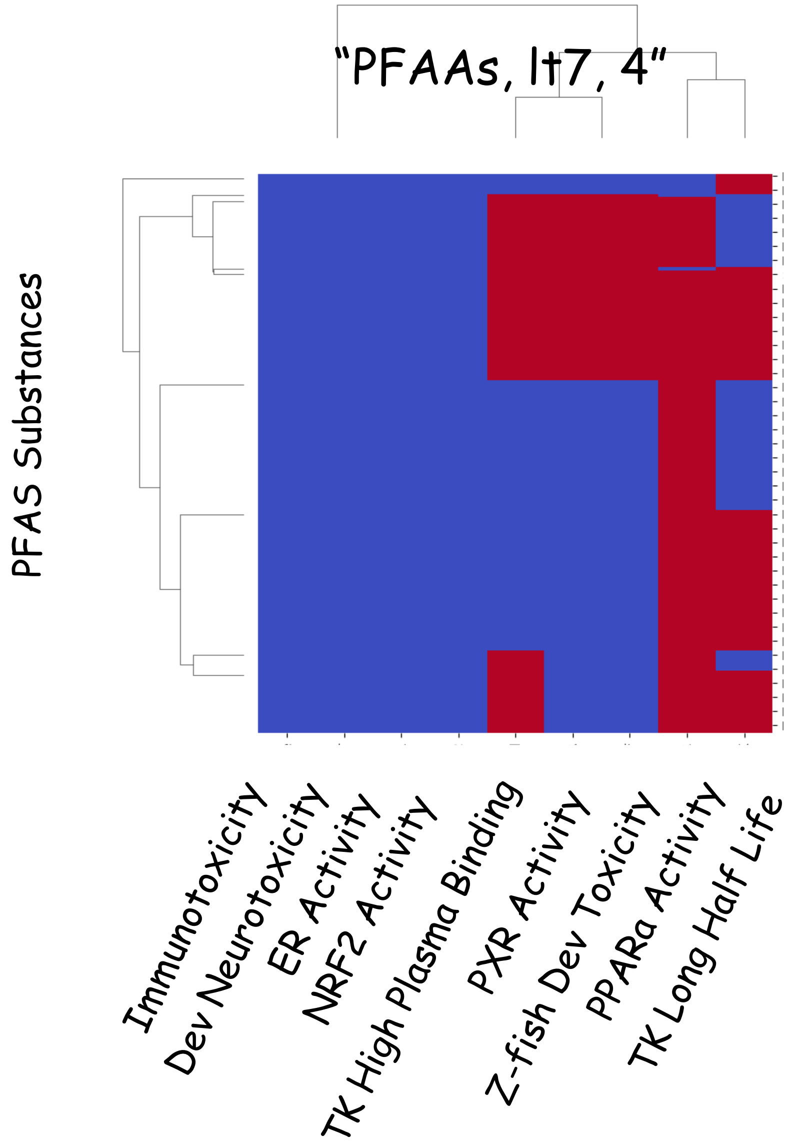


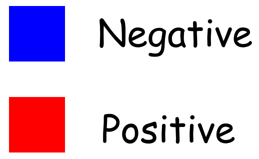
Incorporating Mechanistic and TK NAM Data

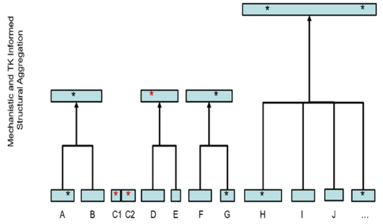
- NAM data has only been generated for only ~1% of the PFAS landscape which posed challenges in extrapolating to the larger PFAS landscape in a quantitative manner.
- Qualitative flags for each of the NAM data streams were created from which preliminary structural based alerts were derived as a means of providing indicators of potential mechanistic, toxicological and TK related concerns.
- TK half-life predictions were generated using the QSAR-based model developed by Dawson et al. (2023)
- Collectively these qualitative flags were used to facilitate evaluation of the mechanistic and TK consistency within a terminal category and informing what tests may be needed.

Illustrative Terminal Categories with Qualitative Mechanistic and TK Flags









Chapter 4: Operationalising Terminal Categories for Re-Use

- PFAS Landscape continually evolving as new PFAS are being identified
- Needed an efficient means of profiling new PFAS and assigning them into one of the 128 Terminal categories developed
- Built a random forest model that uses chemical structural features + primary category labels + chain length to predict most likely terminal category label
- Overall balanced accuracy* was 86% but this varied across terminal categories.

*Balanced accuracy is the arithmetic mean of sensitivity and specificity, i.e. the mean of how good you are at picking up the positives as a percentage of all positives and how good you are at picking up the negatives as a percentage of all negatives

Summary

- The PFAS Landscape was updated using the TSCA 8(a)(7) definition for a PFAS and incorporating plausible degradation products originating from PFAS on the TSCA inventory
- The updated PFAS Landscape was subcategorised into 128 terminal categories
- A conceptual workflow was defined to prioritise terminal categories based on whether they are data poor, contain members that are on the TSCA inventory and/or members that are under the purview of different State environmental monitoring efforts
- Potential test order candidates could be selected based on centroid and other structurally diverse picks from either terminal categories based on the full landscape or from categories constrained by TSCA (active) members only
- Mechanistic and toxicokinetic information was incorporated to inform testing requirements and provide confidence in category membership

Summary

Terminal categories were operationalised using a predictive model to facilitate prospective profiling of new PFAS

Next TSCA test orders are yet to be determined

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Full Length Article

Development of chemical categories for per- and polyfluoroalkyl substances (PFAS) and the proof-of-concept approach to the identification of potential candidates for tiered toxicological testing and human health assessment

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