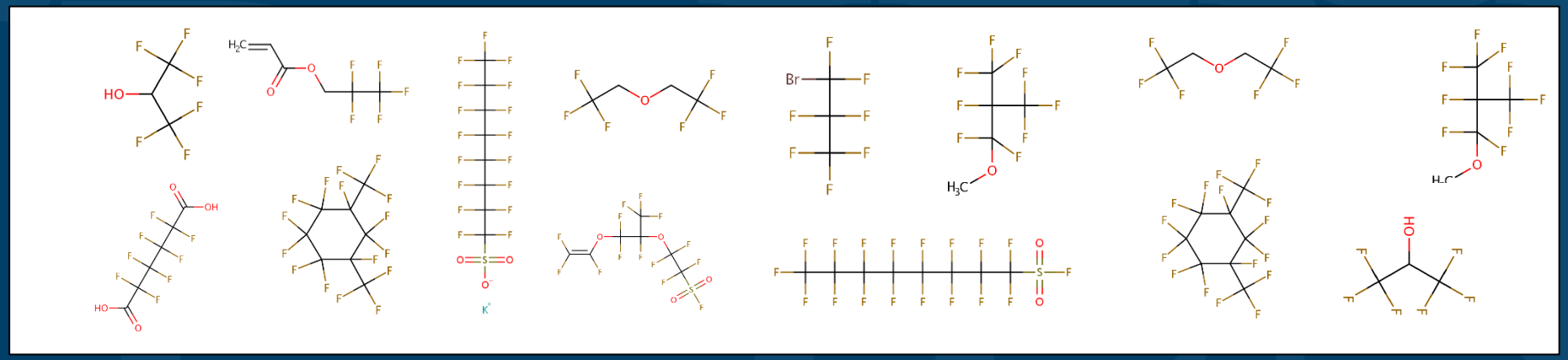
Updated PFAS Categorisation



February 14, 2024

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

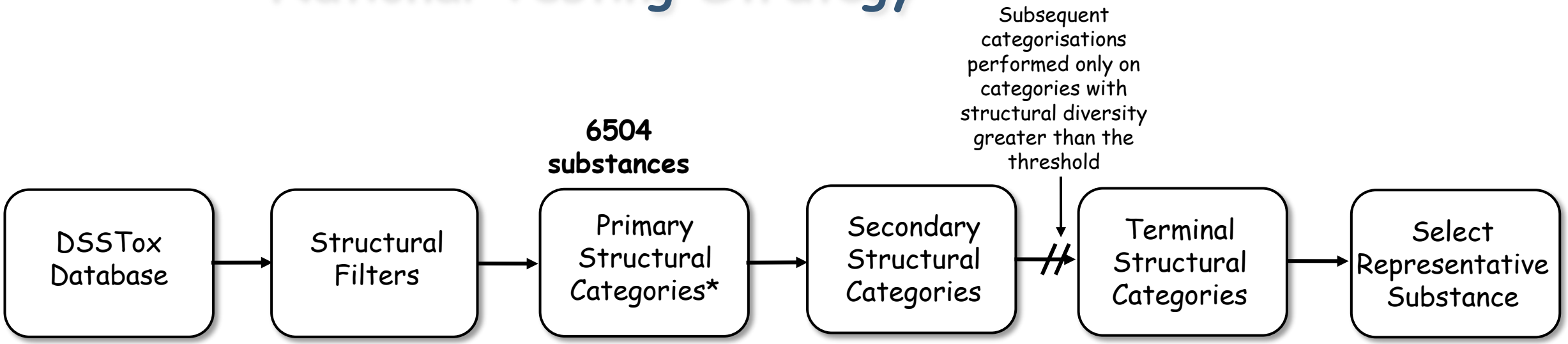
Disclaimer

- The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the U.S. EPA

- Slides represent analysis that is currently unpublished. Please do not cite or quote.

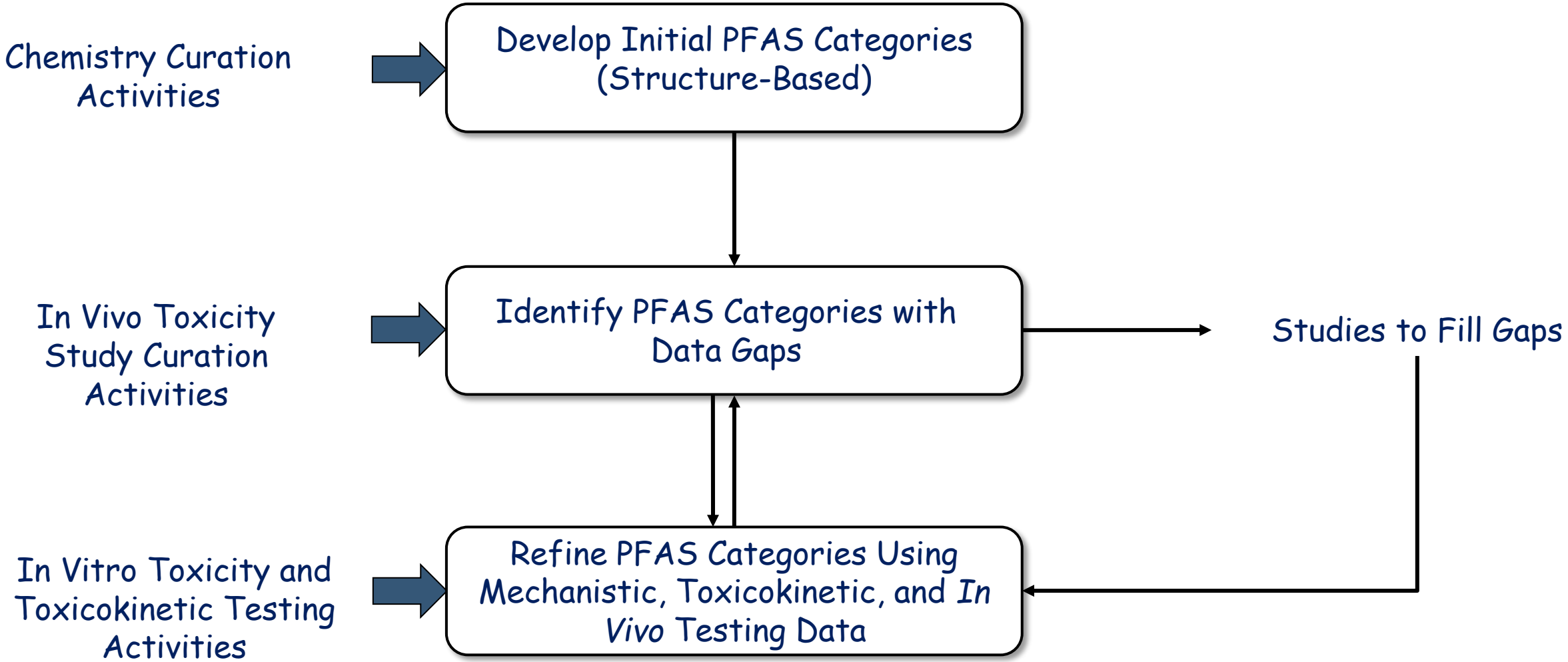
Initial PFAS Structural Categories for Hazard Assessment as published in the October 2021 National Testing Strategy

EPA United States Environmental Protection Agency



*Based on Su and Rajan, 2021

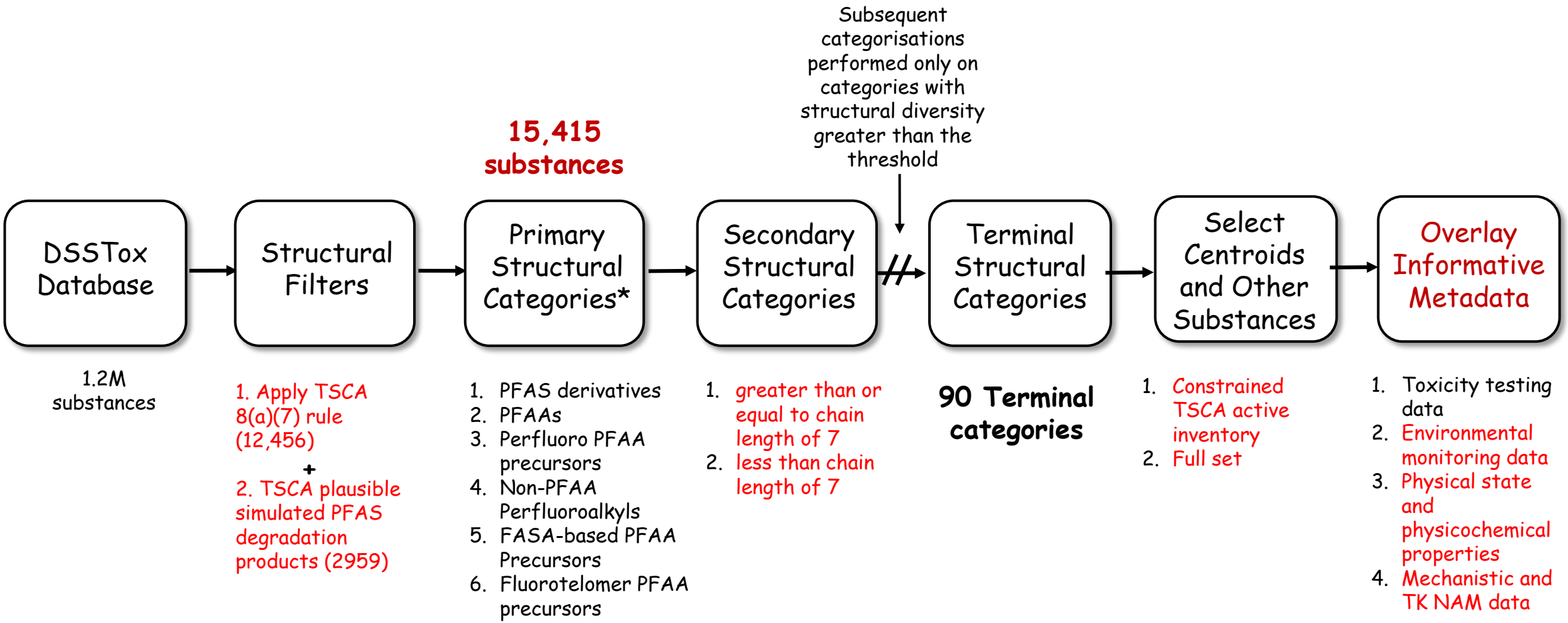
Developing and Refining PFAS Categories Was Intended to be an Iterative Process



Updated considerations

- Universe defined by the TSCA 8(a)(7) rule + plausible degradation products for those PFAS on the TSCA inventory
  - Enables potential linkage for assigning test orders to manufacturers
- Change 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
  - Replaces carbon number as a criteria
- Remove 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
- Include possibility to select more than 1 "representative" substance from a given terminal category based on maximal structural diversity (also called Max/Min)
- Enable selection of representative substances from both the full set of substances in a terminal category and the subset on the TSCA inventory
- Add flags on environmental monitoring/exposure, toxicokinetics, and mechanistic data (NAMs).

Updated PFAS Structural Categorisation Workflow



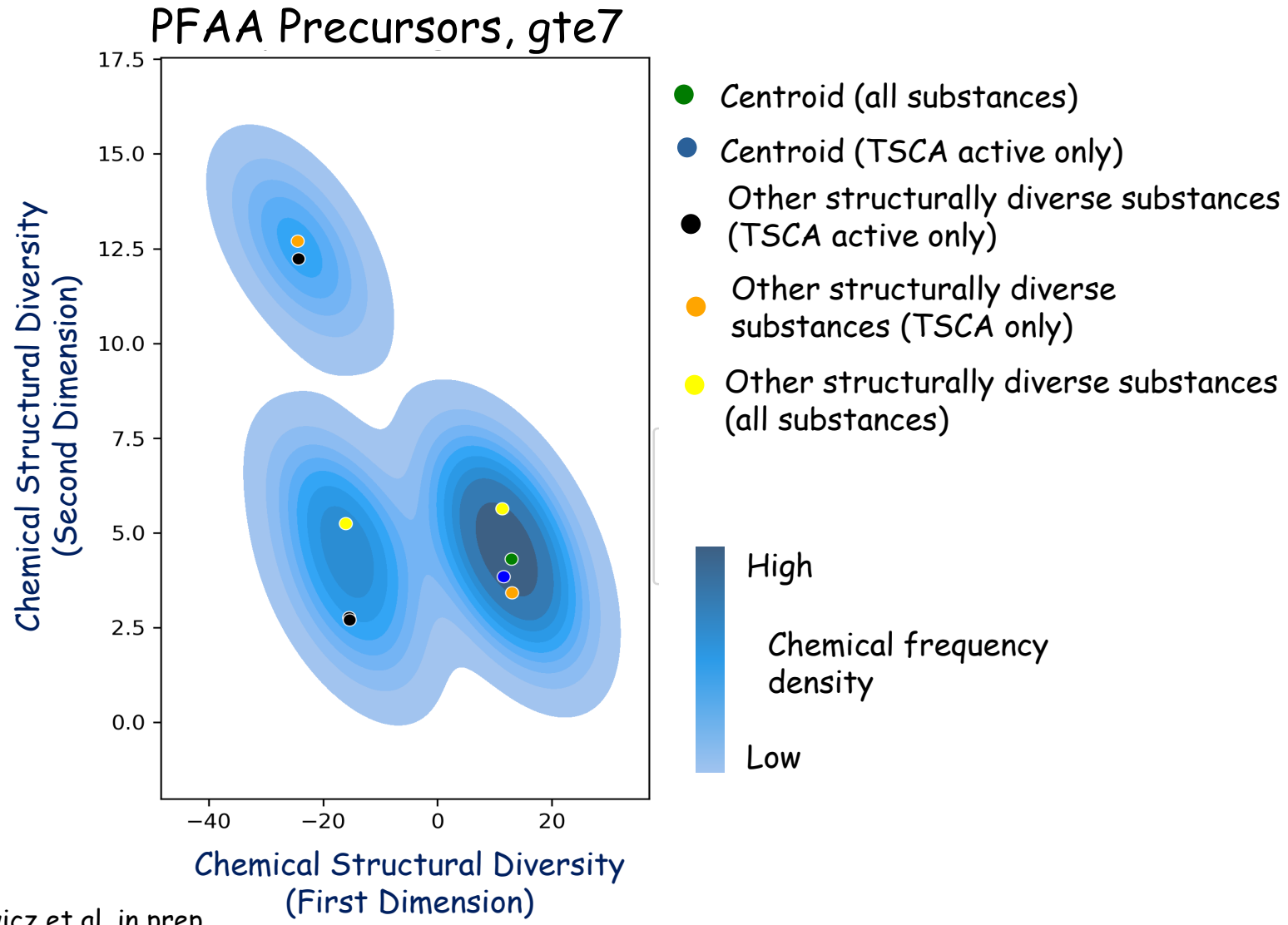
*Based on Su and Rajan, 2021

Patlewicz et al, in prep

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

- Presence on the TSCA inventory as surrogate for the ability to identify a manufacturer
  - 71 terminal categories with ≥1 substance on TSCA inventory
  - 57 terminal categories with ≥1 substance on TSCA active inventory
- Availability of repeated dose toxicity data
  - 58 data poor terminal categories (no repeated dose toxicity data by the oral route)
  - 39 data poor terminal categories with ≥1 substance on TSCA inventory
  - 25 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
  - 16 terminal categories that are data poor, have at least 1 substance on the TSCA inventory, and at least 1 substance on EM list.
  - 14 terminal categories that are data poor, have at least 1 substance on the TSCA active inventory, and at least 1 substance on EM list.
- Integrate information into a tiered prioritisation workflow for test order candidate identification and selection

Selecting Representative Substances in an Illustrative Terminal Category

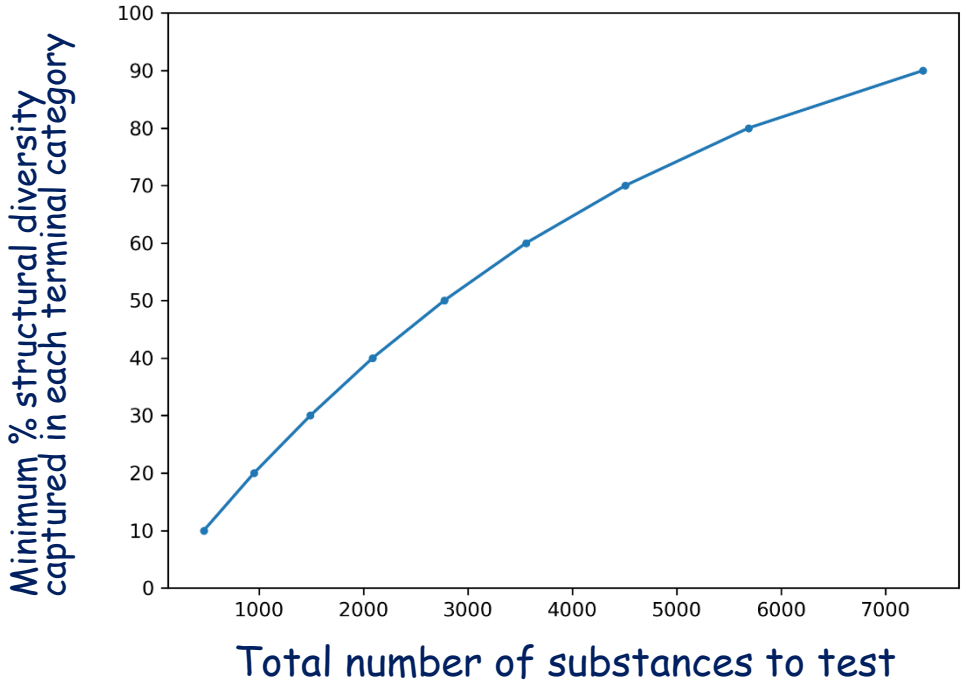


Illustrative terminal category that is data poor, has at least 1 substance on the TSCA active inventory, and at least 1 substance on the Environmental Monitoring list

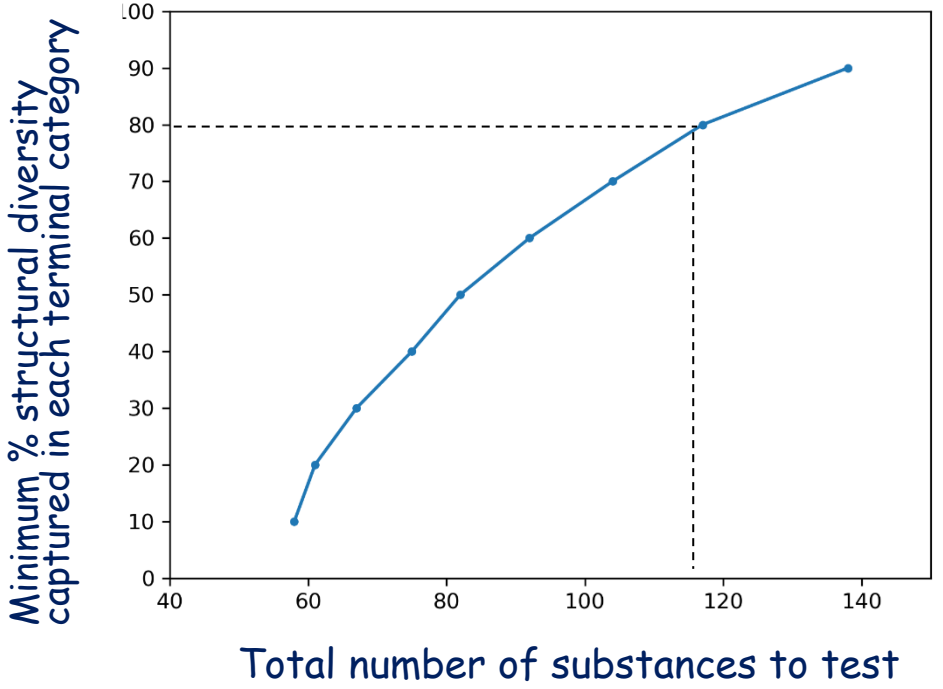
Patlewicz et al, in prep

How many representative substances are 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

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

Patlewicz et al, in prep

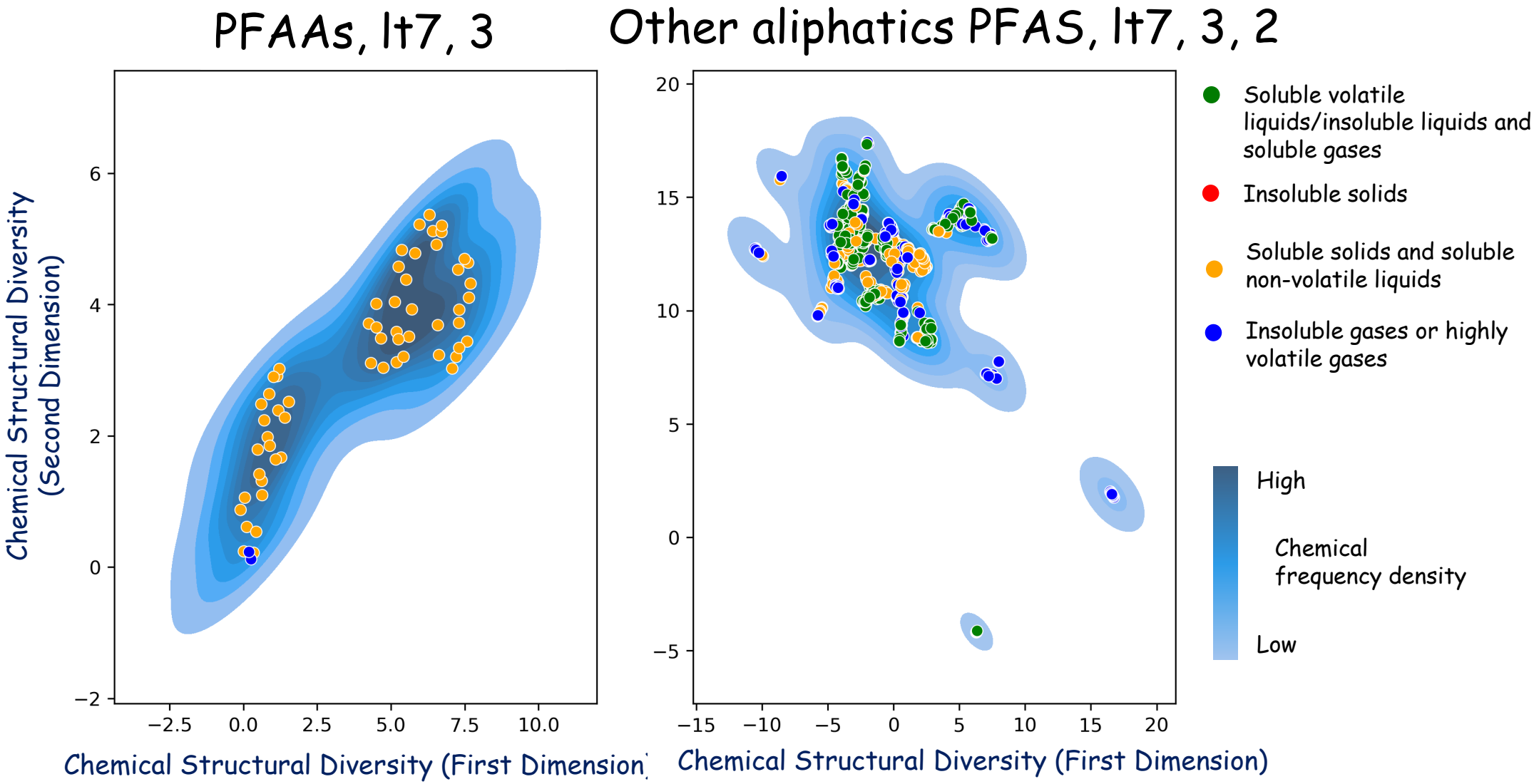
*29 of the 117 are associated with toxicity data

Physical state and physicochemical designations (PSPD)

Physical state and physicochemical designations	Full Landscape	TSCA active constrained Landscape
A (insoluble solids)	6675 (43%)	78 (27%)
B (soluble solids and soluble non-volatile liquids)	4054 (26%)	66 (23%)
C (soluble volatile liquids/insoluble liquids and soluble gases)	4230 (27%)	120 (41%)
D (insoluble gases or highly volatile gases)	133 (0.8%)	22 (7.5%)
No designation	322 (0.02%)	7 (2%)

Patlewicz et al, in prep

Distribution of PSPD Within Illustrative Terminal Categories



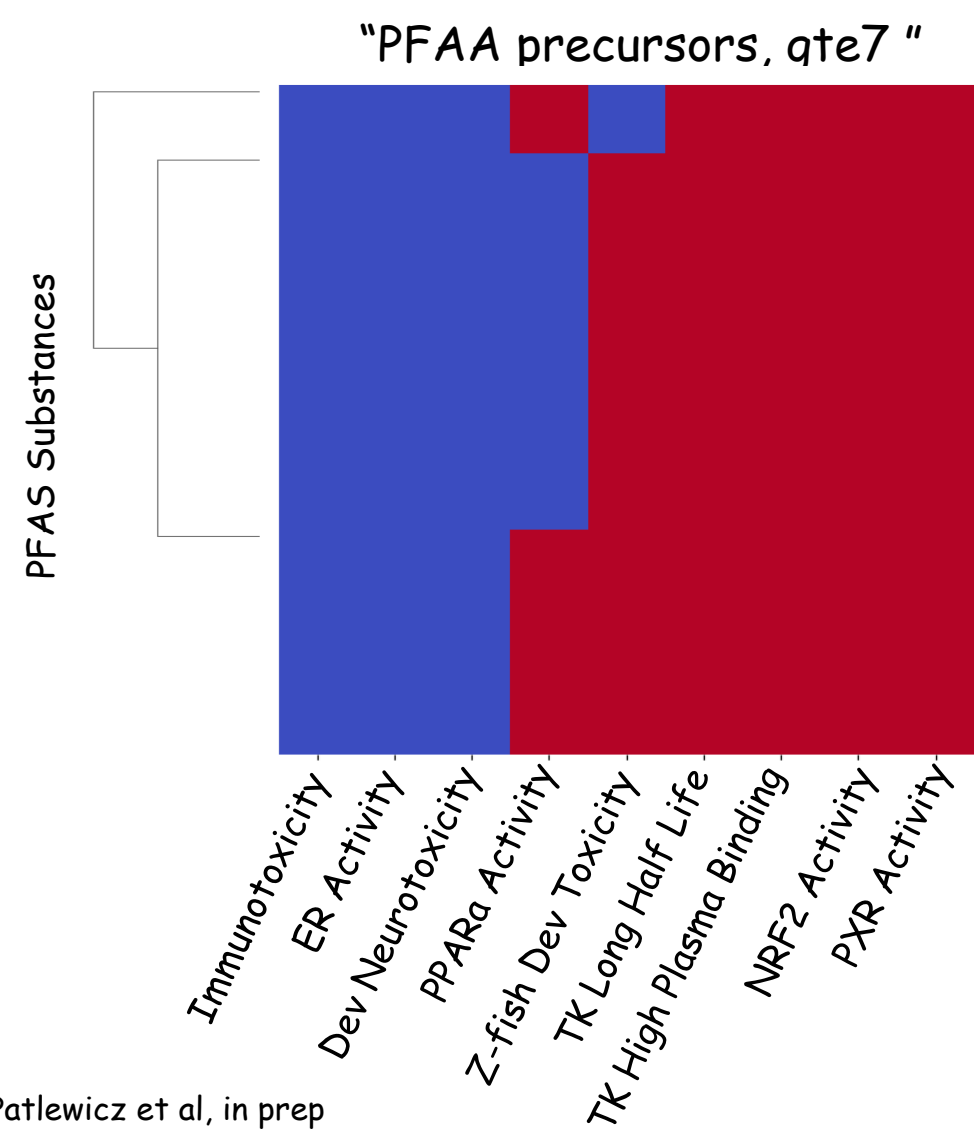
Patlewicz et al, in prep

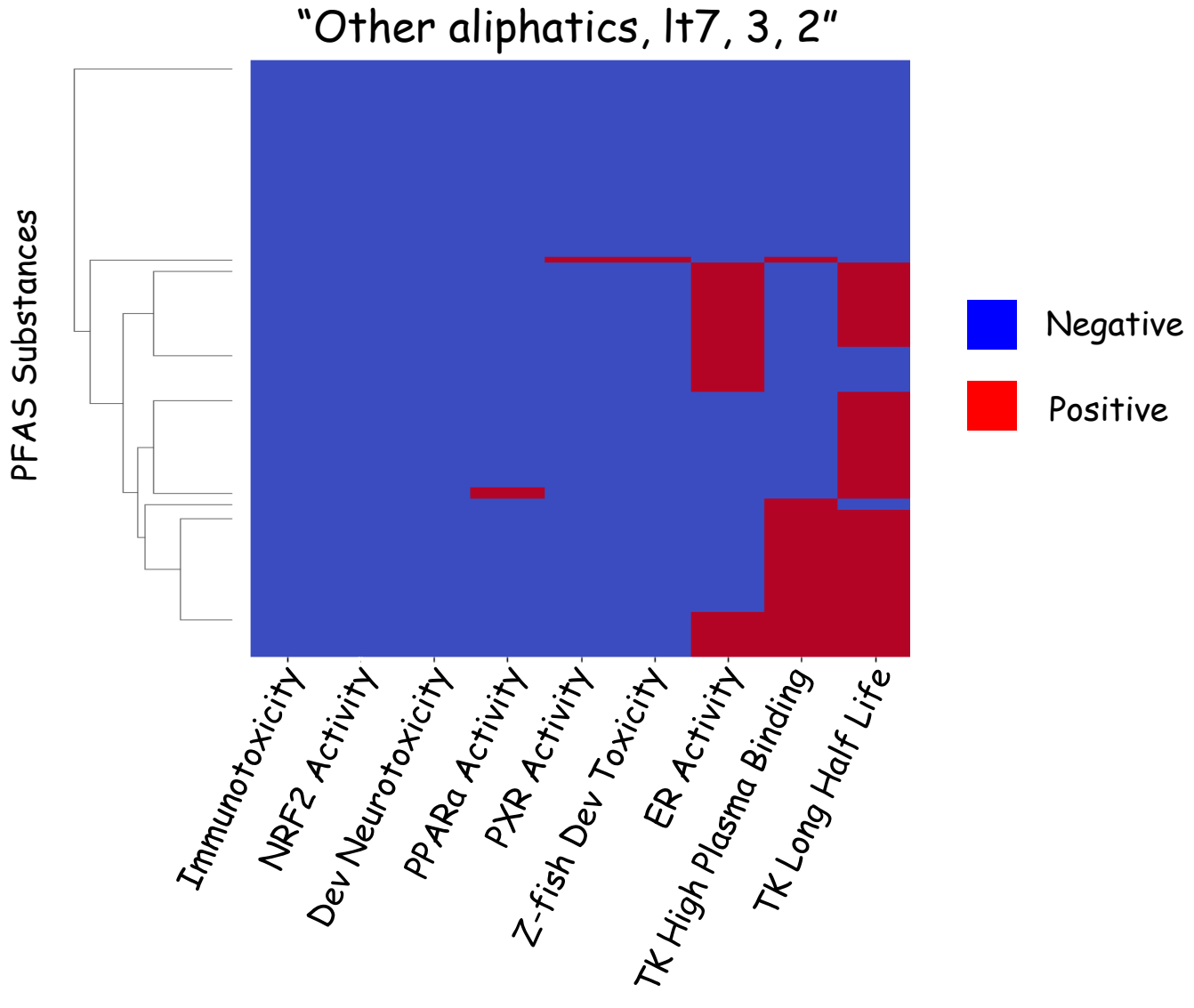
Incorporating Mechanistic and TK NAM Data

- NAM data has only been generated for only ~1% of the PFAS landscape which poses 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 can be used to facilitate evaluation of the mechanistic and TK consistency within a terminal category and informing what tests may be needed.

Patlewicz et al, in prep

Illustrative Terminal Categories with Qualitative Mechanistic and TK Flags





Patlewicz et al, in prep

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 90 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 can 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