Expanding PFAS Grouping Matrix to Incorporate Toxicity Mode of Action Information

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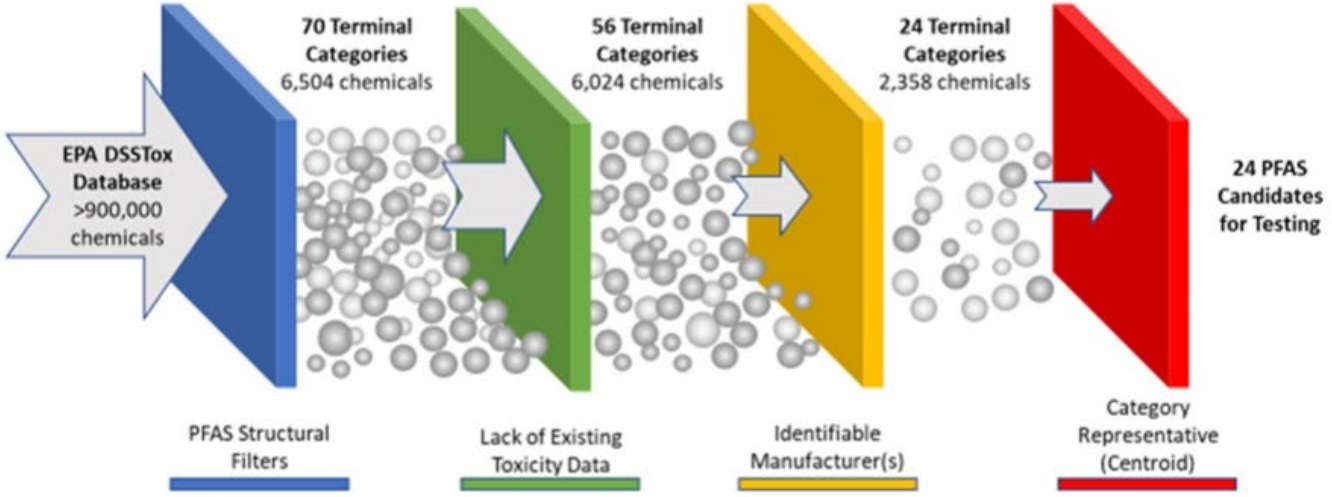
NTS Screening Prioritizes Structure and Non-Toxicity Related Factors

- Nine structure-based categories identified based on structure
- Additional screening factors relate to data gaps and manufacturers to participate in testing – as shown in NTS Figure 6
- Not capitalizing on available toxicity (potency and mechanism) information



USEPA 2021. National PFAS Testing Strategy: Identification of Candidate Per- and Poly-fluoroalkyl Substances (PFAS) for Testing. https://www.epa.gov/system/files/documents/2021-10/pfas-natl-test-strategy.pdf

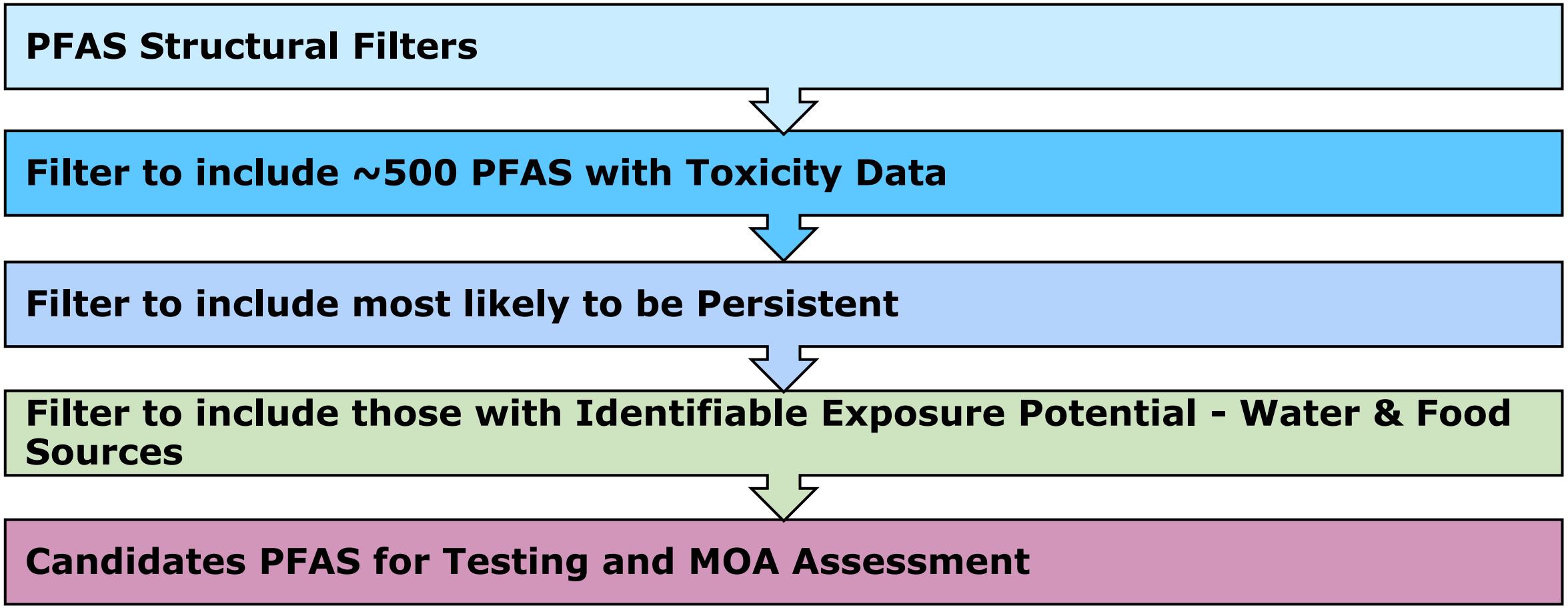
PFAS Health Effects Research Demonstrates Complexity/Variability

- Effects related to varied health effects reported for PFAS tested
  - Animal studies indicate various PFAS can cause effects associated with liver, endocrine, immunological, reproductive, developmental, and kidney toxicity
  - Most consistent epidemiological findings are increased cholesterol levels
  - Limited/inconsistent findings relate to birth weights, immune system effects, non-genotoxic cancer (for PFOA), thyroid hormone disruption (for PFOS)
- Research has prioritized PFAS based on persistence, releases to the environment and potential human exposure
- NTS should supplement strategy to take advantage of knowledge

Mode of Action & Exposure Potential Important for PFAS

- Epidemiological studies have revealed associations between exposure to specific PFAS and multiple non-cancer modes of action
- Animal and *in vitro* testing have demonstrated multiple and distinct modes of action for PFAS in the same structural group (e.g., perfluoroalkyl acids - PFAAs)
- Specific PFAS reported to occur in drinking water and food sources
- >500 PFAS have some have some available toxicity data

Parallel Screening Approach with Toxicity/Exposure Factors to Supplement Priorities



Value of Supplemental Toxicity/Mechanistic Evaluation to NTS

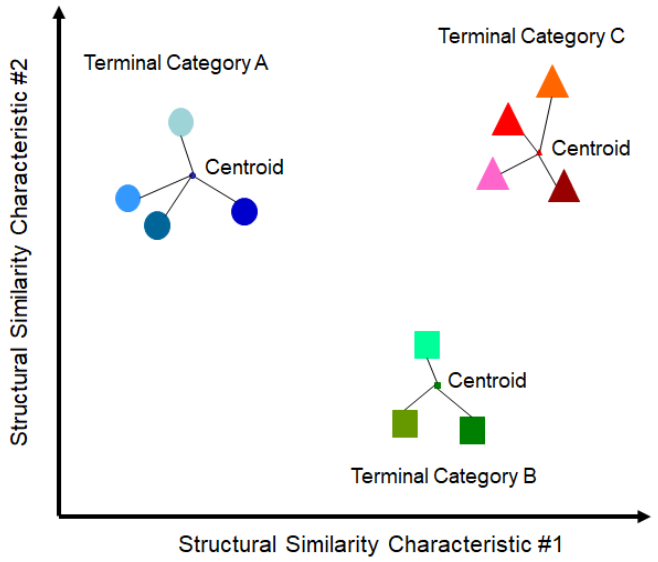
- Makes use of existing information to optimize testing
  - Specific tests for selected PFAS candidates can incorporate existing knowledge of modes of action
  - Mechanistic evaluations expand interpretation beyond toxicity test endpoints
- Makes use of recognized factor (varying and multiple modes of action among PFAS) to upgrade robustness of groupings
  - Structural similarities not consistently predictive of mechanistic similarity
  - Allows ranking/description of representatives for PFAS groups using decision matrix instead of one factor (structure)

PFAAs Illustrate Diversity of Modes of Action and Endpoints

- Diversity of reported endpoint effects for various PFAAs with shared, linear (alkyl) structure
  - Immunosuppression, hepatic/renal function, endocrine (thyroid), growth/developmental, male reproductive, non-genotoxic tumor formation
- Diversity of established MoA for PFAAs
  - Intracellular receptor binding/blocking, alterations of cell membrane and membrane-bound transport function (calcium), effects on cellular energetics (mitochondrial function), effects on circulatory transport processes/metabolism
- Takeaway: sensitive effects expected to vary depending by operative MoA for specific PFAS – should not be expected to be the same

Matrix Approach for Multi-Factor Grouping

- Upgrade 2-D clusters identified by structural similarity (NTS Figure 5) to 3-D "clouds" with MoA/endpoint findings on additional axis



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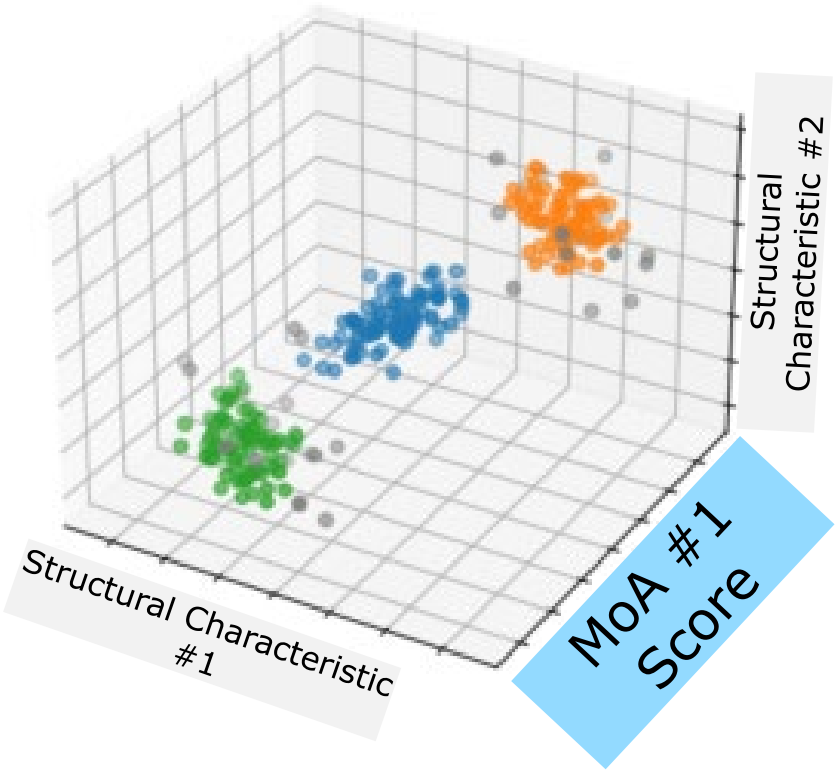

Preventing Regrettable Misgrouping

- Where indicated, mechanistic studies relatively inexpensive addition to testing programs – primarily *in vitro*
- Interpretive value high – mechanistic findings inform potentially relevant health endpoints for individual PFAS and optimized grouping
- Effective approach to limit misclassification/misgrouping of PFAS
  - Avoidance of misclassification enhances acceptance/credibility of testing interpretation and health-related target levels
  - Explaining determinations based on structure alone less convincing than inclusion of toxicological/health-related characteristics

Summary

- PFAS risks to human and environmental health determined by more than structural similarities
- NTS can build from available information to incorporate effective, relatively low-cost tests into set for representative candidates
- Mechanistic information expands basis for interpreting sets of results for individual PFAS; more likely to explain differences within groups
- Considering structure and mode of action together limits mischaracterization of potential health effects, optimizes groupings

Questions or Comments?

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