Progress on Related EPA PFAS Research Activities

OCSPP Stakeholder PFAS Workshop

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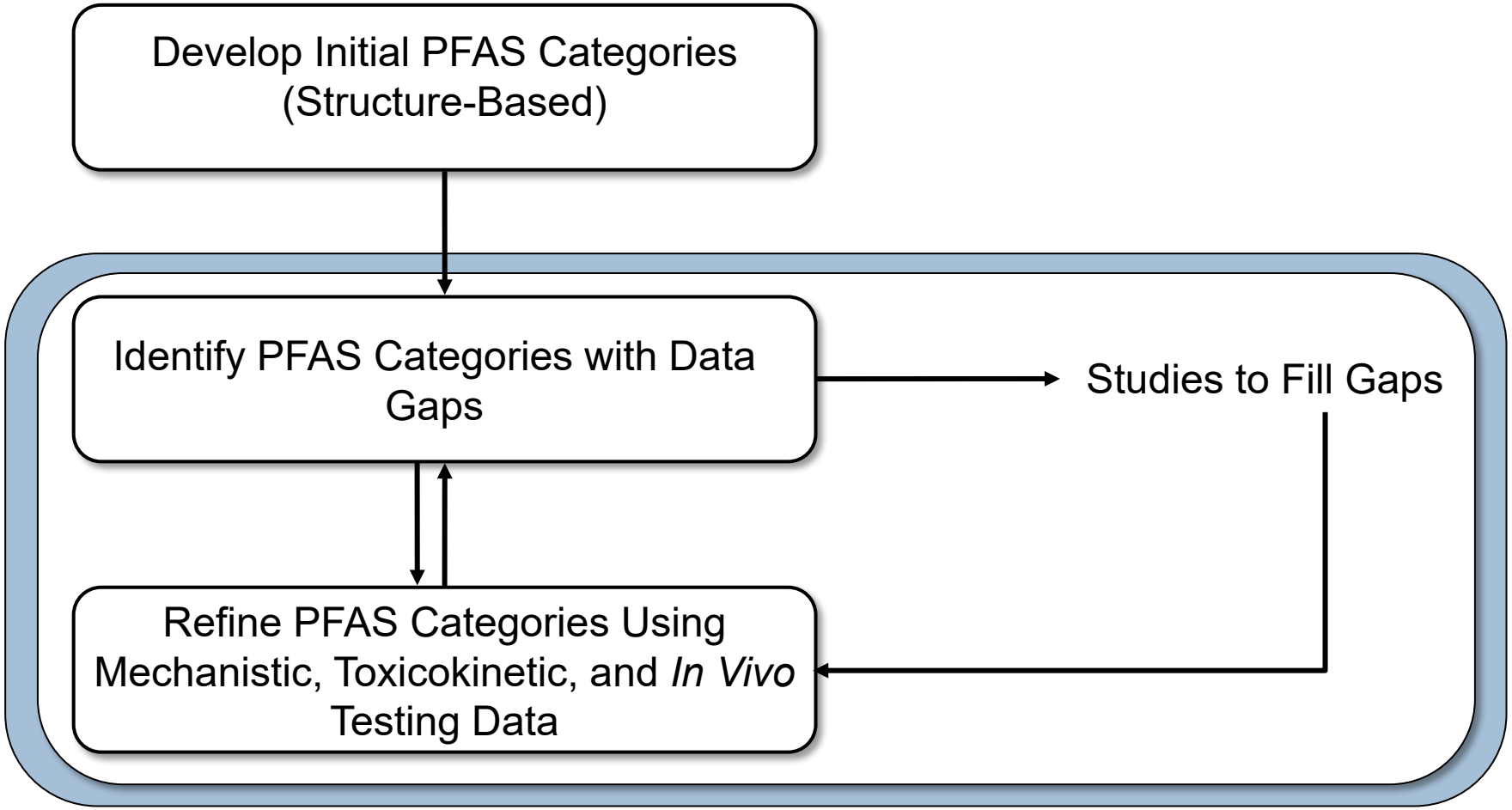
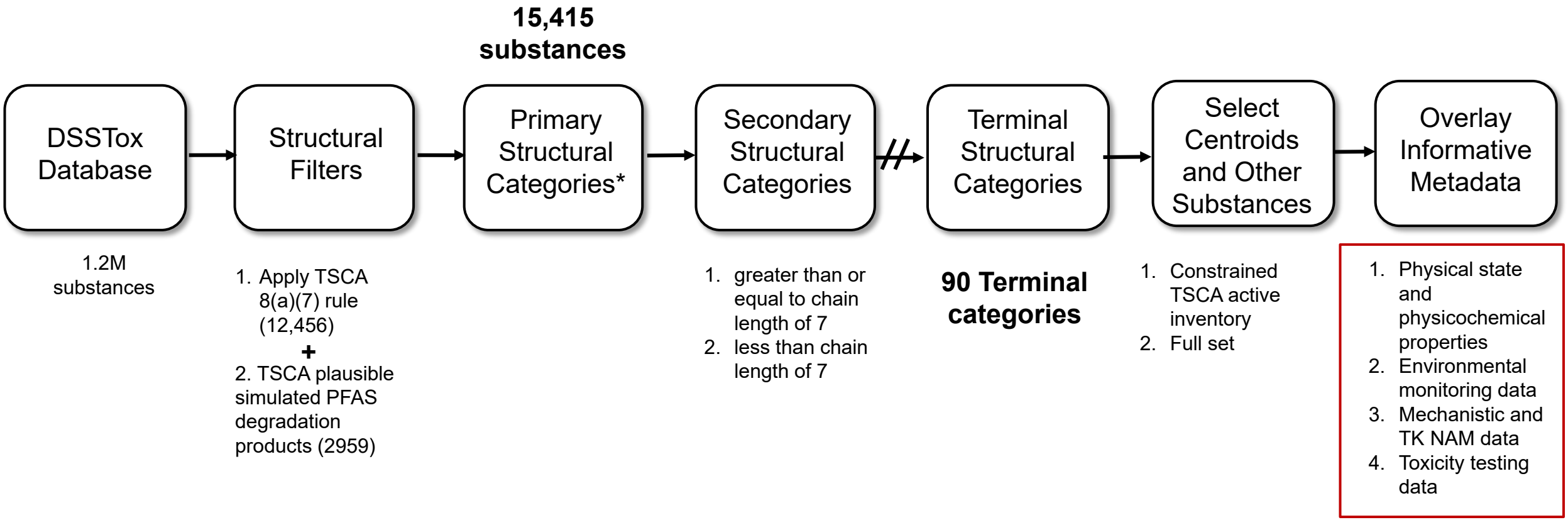
A Key Aspect of the PFAS National Testing Strategy is the Iterative Refinement Based on Ongoing Research



Many of These Research Efforts are Intended to Inform and Refine the PFAS Categories



Physical Chemical Properties are Important to Inform Environmental and Exposure Pathways of PFAS

Property	PFAS Experimental Data	All Chemical Experimental Data
HLC	32	1908
VP	101	3440
BP	260	6903
WS	81	9241
LogP	53	14545
MP	195	29052

HLC, Henry's Law Constant; VP, Vapor Pressure; BP, Boiling Point; WS, Water Solubility; LogP, Log Octanol-Water Partition Coefficient; MP, Melting Point

- Multiple research efforts have developed QSAR models to predict physical chemical properties of PFAS (e.g., Bhhatarai et al. 2011, Wang et al. 2011, Gramatica et al. 2014, Kim et al. 2015, Lampic et al. 2020, Sosnowska et al. 2023).
- Curated experimental data to inform development of QSAR models have been limited.
- Physical chemical data was compiled from multiple public sources and QCd to the data source.
- Two sets of consensus QSAR models were developed for each of the six physical chemical properties
  - PFAS only model
  - All chemicals model

Progress on the Development of Updated QSAR Models to Predict PFAS Physical Chemical Properties

QSAR Test Set Performance

	Trained to All Chemicals		Trained to PFAS	
Property	R^2	MAE	R^2	MAE
HLC	0.68	1.18	0.85	1.13
VP	0.97	0.55	0.93	0.63
BP	0.88	20.1	0.87	19.4
WS	0.65	0.83	0.57	0.83
LogP	0.59	0.91	0.47	1.07
MP	0.84	40.2	0.77	46.1

HLC, Henry's Law Constant; VP, Vapor Pressure; BP, Boiling Point; WS, Water Solubility; LogP, Log Octanol-Water Partition Coefficient; MP, Melting Point; MAE, Mean Absolute Error

- Consensus QSAR models trained on all chemical classes gave slightly better results for predicting physical chemical properties of PFAS that models trained only on PFAS.
- Model performance for PFAS is similar to CADASTER models, which were trained on PFAS substances.
- Additional QC of experimental data is on-going.
- Results expected to be published in Summer, 2024.

Environmental Monitoring Data are Important to Help Prioritize PFAS Categories for Data Collection

EPA Regional-ORD Applied Research (ROAR) Project

ORD
Region 3
Region 5
Region 9

- Collaborative project focused on building state capacity to apply Non-Targeted Analysis (NTA) in their management of PFAS and other contaminants of emerging concern.
- Partner States/Regions involved:
  - R3/Maryland – NTA analysis of ~50 drinking water samples collected in relation to industrial release.
  - R5/Minnesota – NTA analysis of ~20 surface and groundwater samples related to two known PFAS point sources.
  - R9/California – NTA analysis of 9 well pilot study to inform large scale study of ~1,000 drinking water supply wells to support source and treatment investigation.
- EPA providing NTA knowledge and tools to standardize data processing and interpretation.
- NTA data will be released through state channels and within associated study time frames.

Mechanistic and Toxicokinetic Data are Intended to Help Refine PFAS Categories and Inform Study Needs

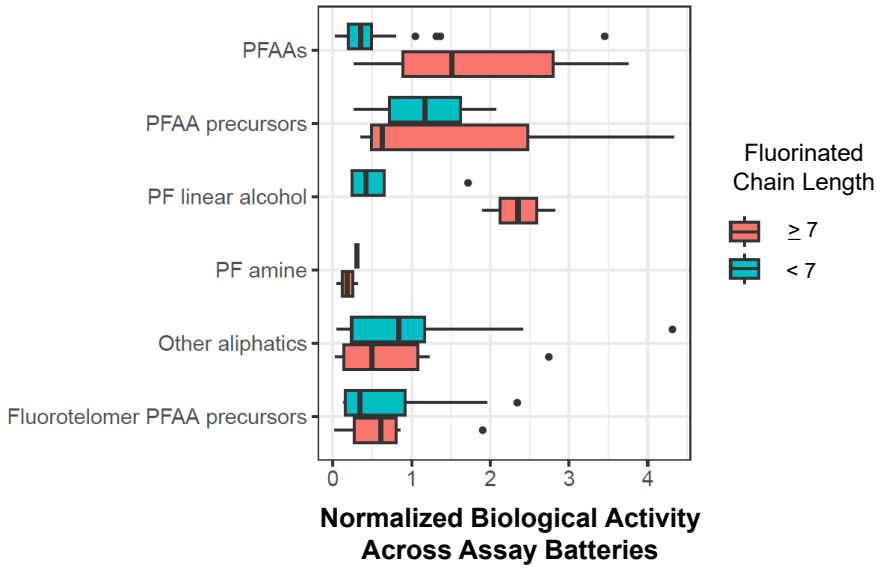
- ~150 PFAS from diverse structural classes were tested in 8 mechanistic and toxicokinetic assay batteries.
- Analytical QC was performed to detect presence and stability of each chemical.

Intended Endpoint	Assay	Purpose
Developmental Toxicity	Zebrafish embryo assay	Assess potential teratogenicity
Immunosuppression	Eurofins BioMAP Diversity PLUS Panel (previously BioSeek) (decreased T-cell proliferation, decreased IgG production and B-cell proliferation, decreased IL-10 production)	Measure potential disease and immune responses in human primary culture and co-culture models
Developmental Neurotoxicity	Microelectrode array assay (rat primary neurons) and High Content Imaging (CD1 and hNP1 cells)	Impacts on development of functional neural networks
Nuclear Receptor and Transcription Factor Activity	Attagene cis- and trans-Factorial assays (HepG2)	Activation of transcription factors involved in critical cell pathways and stress responses
Whole Transcriptome Gene Expression	High-throughput transcriptomic assay (multiple cell types)	Measures changes in important biological pathways
Cellular Phenotypic Response	High-throughput phenotypic profiling (multiple cell types)	Measure changes in cellular organelles and general morphology
Toxicokinetics	Intrinsic hepatic clearance and plasma protein binding	Metabolic breakdown and amount of free chemical in the blood

PFAS Substances Demonstrated Broad Range of Mechanistic and Endpoint-Related Activities

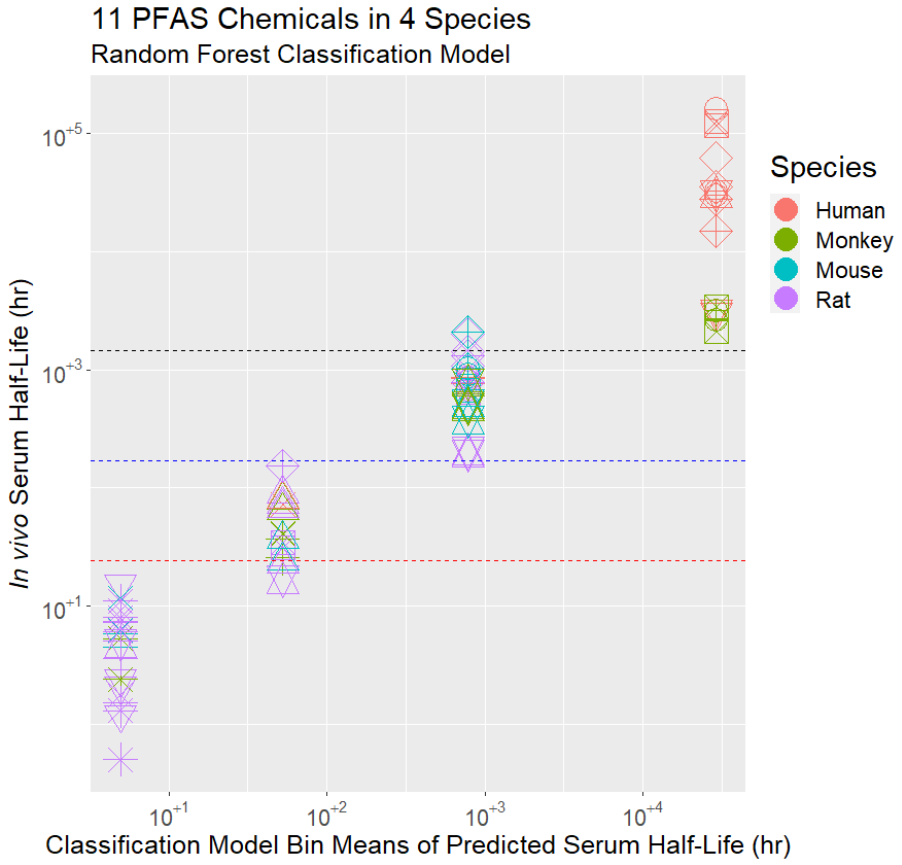
Predictive Performance of Enriched ToxPrints for Mechanistic Endpoints

	Balanced Accuracy	Sensitivity	Specificity
ER Activity	0.67	0.47	0.87
PPARa Activity	0.78	0.88	0.68
NRF2 Activity	0.82	1	0.64
PXR Activity	0.76	1	0.53
Z-Fish Dev Toxicity	0.66	0.59	0.74
DNT Activity	0.56	0.14	0.98
Immune Activity	0.55	0.1	0.99



- Some PFAS substances showed specific activities towards ERα, PPARα, PPARγ, RXRβ, PXR, and NRF2 receptors/ transcription factors (Houck et al., 2021).
- PFAS substances containing a perfluorinated carbon chain length ≥8, high C:fluorine ratio, or a carboxylic acid moiety were more likely to be bioactive in the developmental neurotoxicty-related assays (Carstens et al., 2023).
- A subset of PFAS substances demonstrated response profiles consistent with immunosuppression, but there was limited evidence for immunosuppression for PFOA and PFOS in the models employed (Houck et al., 2023).
- Structural alerts represented by enriched ToxPrints show mixed performance for predicting mechanistic activity of untested chemicals.
- Some structural categories show strong biological activity trends with chain length, while others do not.

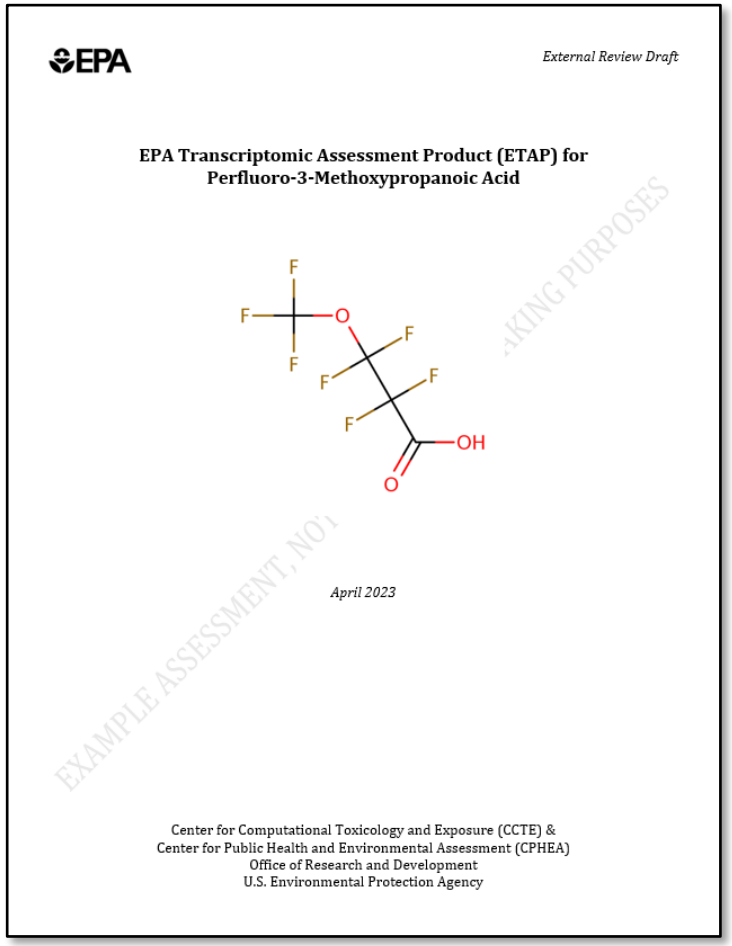
Toxicokinetic Data are Important for Interpreting Toxicological Responses From Animal Models



Dawson et al., 2023

- Cross-species toxicokinetic data are very limited with data available for 11 PFAS in four species (human, rat, money, and mice)(Lau et al., 2007, 2012, 2015, and 2021).
- A machine learning model was developed to predict half-lives ($t_{½}$) in one of four bins: 0–12 h, >12 h to 1 week, >1 week to 60 days, and >60 days.
- Chemical and physiological descriptors were used as potential predictors of half-life (with surrogates for active transport).
- Model accuracy was 86.4% compared to the no information rate of 27%.
- Additional data have been identified to incorporate into the model.

Novel Toxicity Testing Data May Help Fill Information Gaps and Anchor Data Poor Categories


EPA

External Review Draft

EPA Transcriptomic Assessment Product (ETAP) for Perfluoro-3-Methoxypropanoic Acid

April 2023

Center for Computational Toxicology and Exposure (CCTE) &
Center for Public Health and Environmental Assessment (CPHEA)
Office of Research and Development
U.S. Environmental Protection Agency

- ORD recently peer reviewed the EPA Transcriptomic Assessment Product (ETAP) designed for developing human health assessments for data poor chemicals in < 9 months.
- The new human health assessment product uses short-term *in vivo* transcriptomic studies to identify a point-of-departure with no coordinated transcriptional changes that would indicate a potential toxicity of concern.
- Transcriptomic reference values are derived using a standardized set of uncertainty factors due to the carefully prescribed design.
- Transcriptomic reference values with traditional reference doses demonstrated similar levels of protection.
- Anticipate releasing ETAP assessments beginning in mid 2024.

Summary

- The EPA National PFAS Testing Strategy was intended to be iteratively updated and refined based on on-going research and data collection activities.
- The on-going research effort includes:
  - Updated models for physical chemical properties to better inform environmental and exposure pathways.
  - Environmental monitoring using non-targeted methods to help prioritize data poor categories.
  - Mechanistic and toxicokinetic data to help refine PFAS categories and inform study needs.
  - Novel toxicity testing and human health assessment approach methods to more rapidly fill information gaps and anchor data poor categories.
- The integration of the PFAS categories and research activities provides a strategic approach to focus data collection activities under TSCA and other authorities.

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