New Approach Methods - Toxicity

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Goals

- Use new approach methods (NAMs) to broadly characterize the mechanistic and phenotypic responses across a structurally diverse set of PFAS
- Refine structural categories based on mechanistic and phenotypic responses for grouping and read across
- Curate legacy *in vivo* toxicity data to identify data gaps in PFAS categories and guide selection of next PFAS compounds to test *in vivo*

Approach

Toxicological Response	Assay	Assay Endpoints	Purpose
Developmental Toxicity	Zebrafish embryo assay	Lethality, hatching status and structural defects	Assess potential teratogenicity
Immunotoxicity	Bioseek Diversity Plus	Protein biomarkers across multiple primary cell types	Measure potential disease and immune responses
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

In Vivo PFAS Data Collection

- Public data collected into ToxValDB from multiple sources
  - ATSDR, ECHA/REACH, ECOTOX, EFSA, HESS, EPA PPRTV, ToxRefDB, open literature
  - Total of 59 of 6558 PFAS have at least one study
- QA process being developed
  - Literature records – CPHEA staff and contractors use systematic literature review process to extract and QA data
  - For other records with available source documents, 100% QA of key fields will be performed using custom application
  - For remaining records (mostly ECHA / REACH), 10% QA will be performed to check for systematic software data transfer issues

Current Status

- Public comparator *in vivo* data is collected
  - Registrant data from OPPT still being compiled
  - All data undergoing QA
- NAM data collection largely complete, but delayed by Covid-19
- Analysis still in progress
- EPA ORD Whitepaper in progress
- Team has been supporting EPA PFAS National Testing Strategy

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