



New Approach Methods - Toxicity

Richard Judson, PhD

Center For Computational Toxicity and Exposure
Office of Research and Development

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- 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



Contributors – All ORD / CCTE

Grace Patlewicz
Richard Judson
Anthony Williams
Barbara Wetmore
Katie Paul Friedman
Garret Nelson
Russell Thomas
Joshua Harrill
John Wambaugh
Katherine Coutros
Timothy Shafer
John Cowden
Aswani Unnikrishnan
Colleen Elonen

Johanna Nyffeler
Taylor Wall
Stephanie Padilla
Keith Houck
Imran Shah
Logan Everett
Ann Richard
Todd Martin
Theresa Freudenrich
Kathleen Wallace
Seline Choo
Amy Carpenter
Kelly Carstens

Madison Feshuk
Clinton Willis
Richard Brockway
Megan Culbreth
Marci Smeltz
Matthew Scott Clifton
Matthew Henderson
Anna Kreutz
Evgenia Korol-Bexell
Larry McMillan
Lucas Albrecht
Matthew Phillips

Jon Haselman
Phil Degoe
Mike Hornung
Katy Britton
Kimberly Jarema
David Korest
Sig Degitz

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