Integrated Approaches to Testing and Assessment (IATA) Case Study for DNT

Helena Hogberg

NICEATM

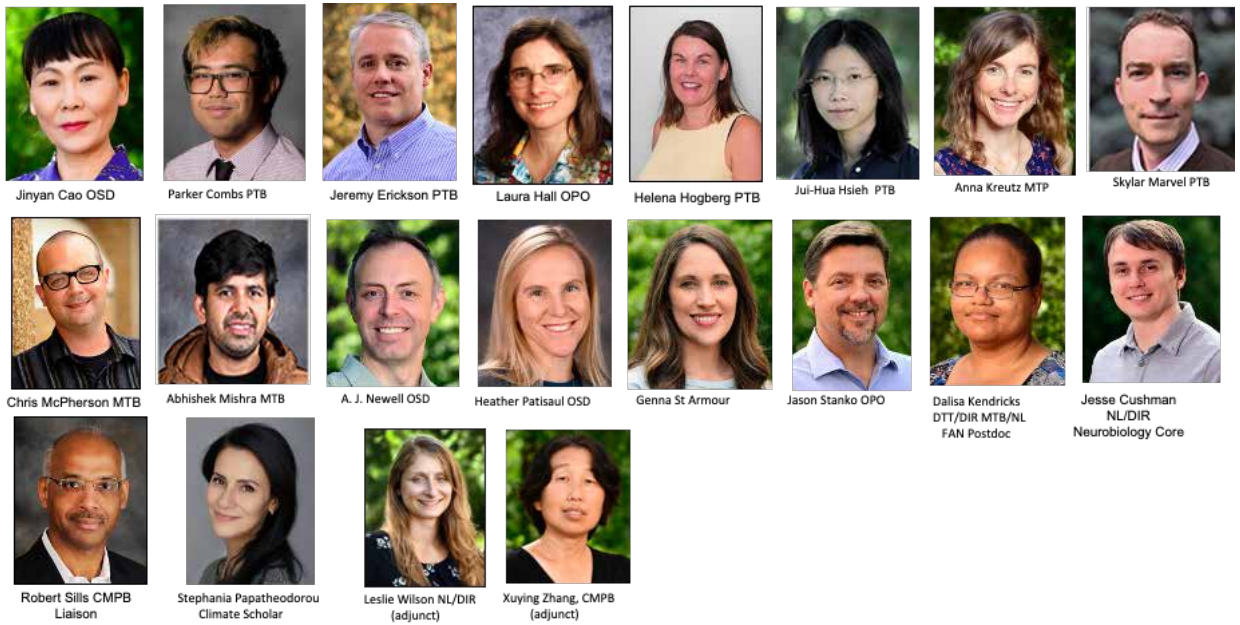
SACATM September 2024

Contact information:
helena.hogberg-durdock@nih.gov

Acknowledgments

NICEATM Team

DNT HEI Team



DNT IVB Contractors

Universität Konstanz

IUF
LEIBNIZ-INSTITUT FÜR UMWELT-MEDIZINISCHE FORSCHUNG

United States Environmental Protection Agency

biobide
Your Zebrafish Partner

Integrated Approaches to Testing and Assessment (IATA) Case Study Led by DTT

Guidance document to inform on the DNT IVB, its usage and interpretation

OECD
Organisation for Economic Co-operation and Development

ENV/CBC/MONO(2023)13

Unclassified — English - Or. English
10 July 2023

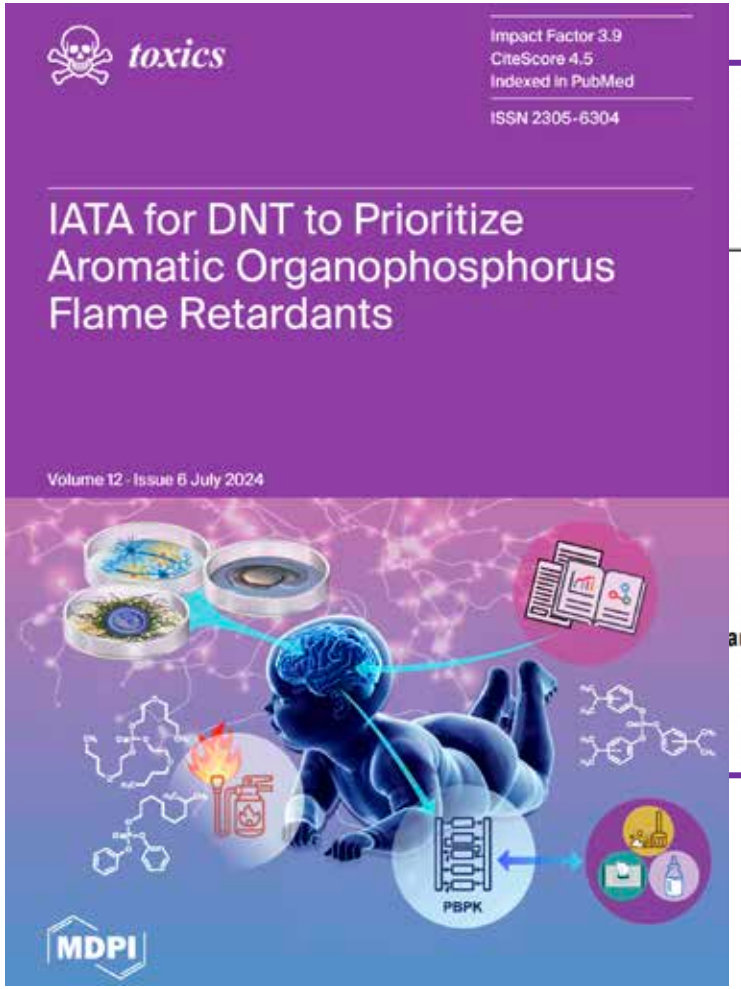
ENVIRONMENT DIRECTORATE
CHEMICALS AND BIOTECHNOLOGY COMMITTEE

Cancels & replaces the same document of 4 July 2023

Initial Recommendations on Evaluation of Data from the Developmental Neurotoxicity (DNT) In-Vitro Testing Battery

Series on Testing and Assessment
No. 377

IATA case studies to exemplify different regulatory needs

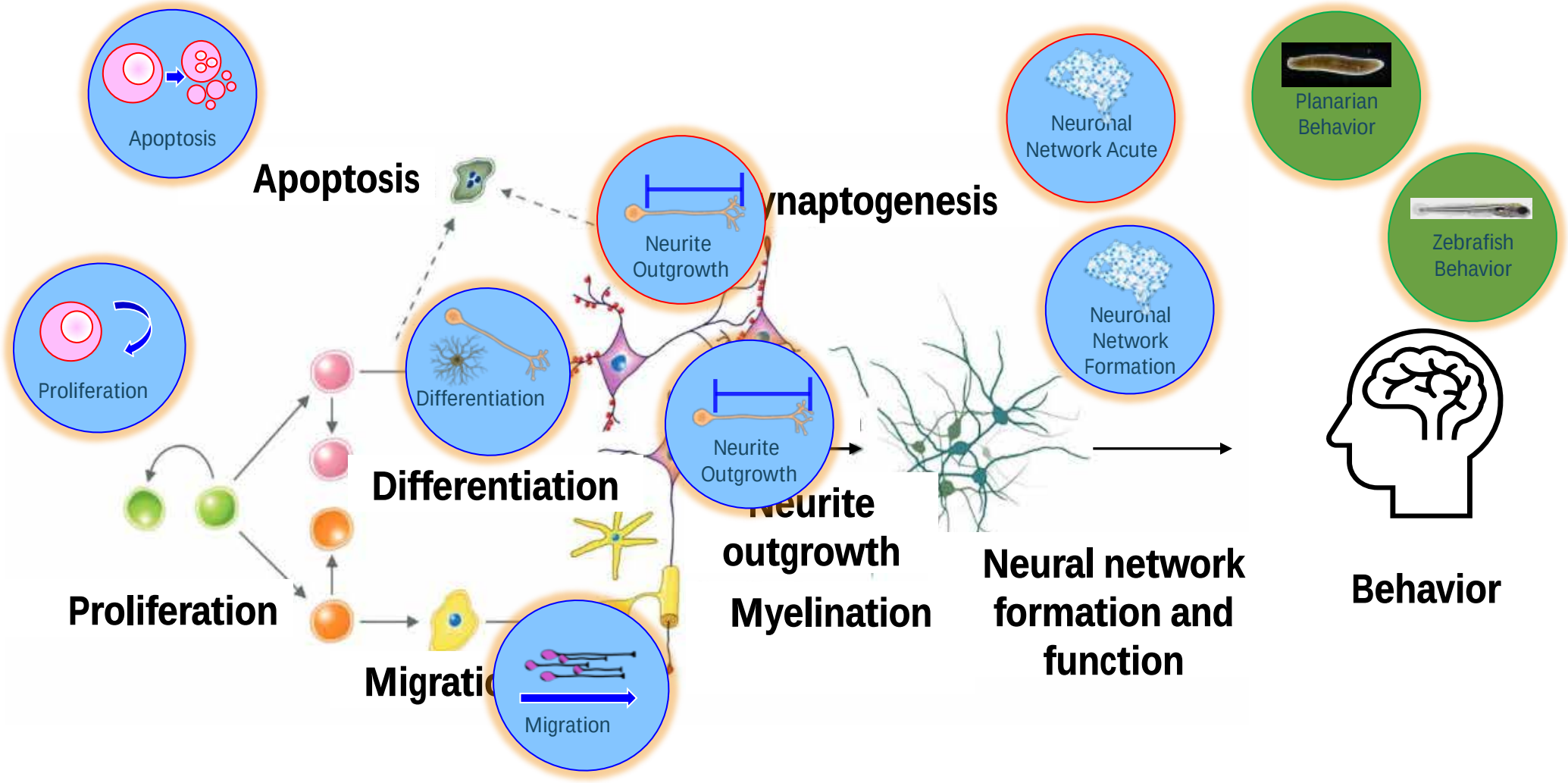


ENV/CBC/MONO(2022)26

English - Or. English
1 September 2022

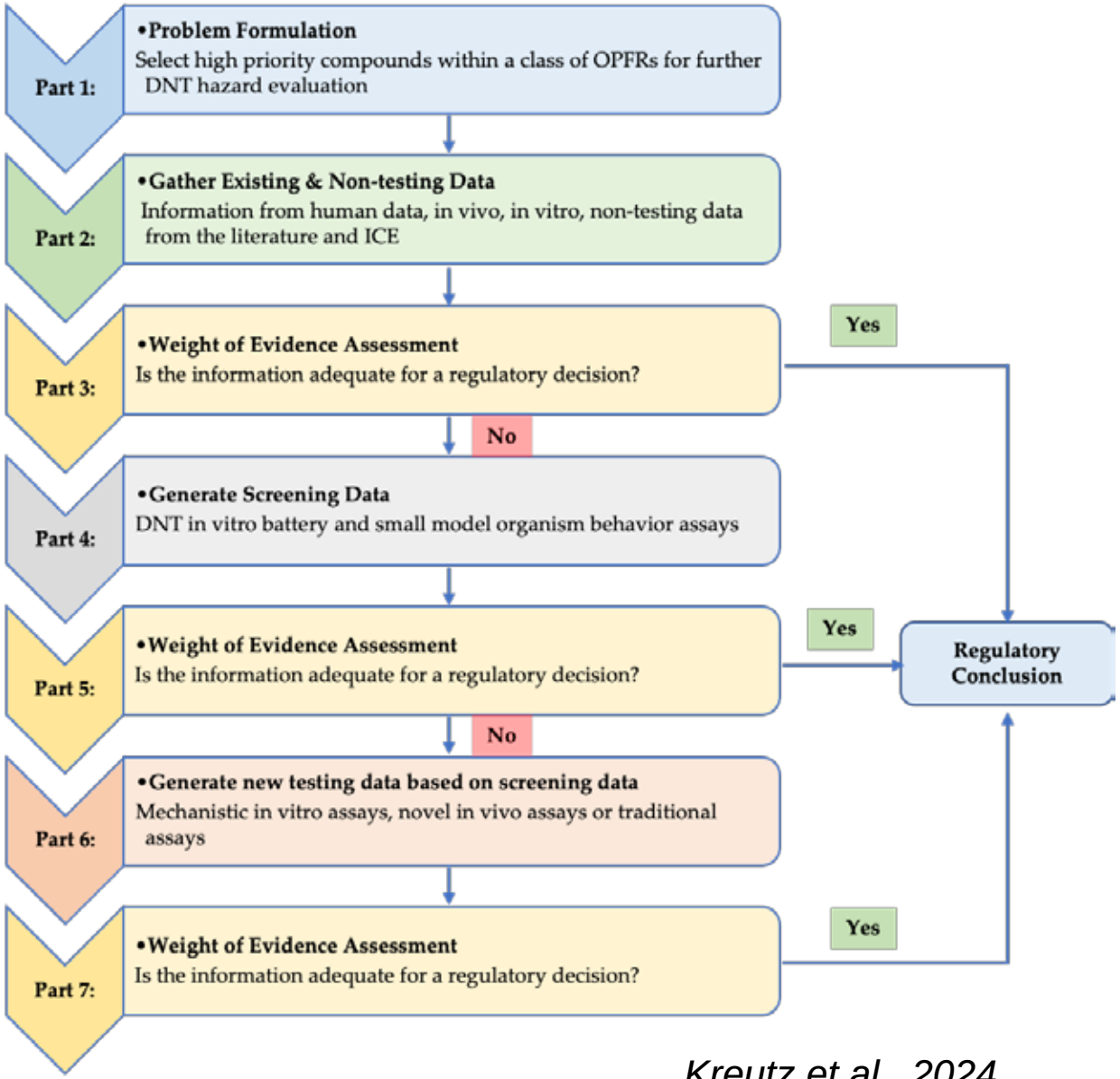
and Assessment for DNT to

DNT Battery in the DTT IATA Case Study



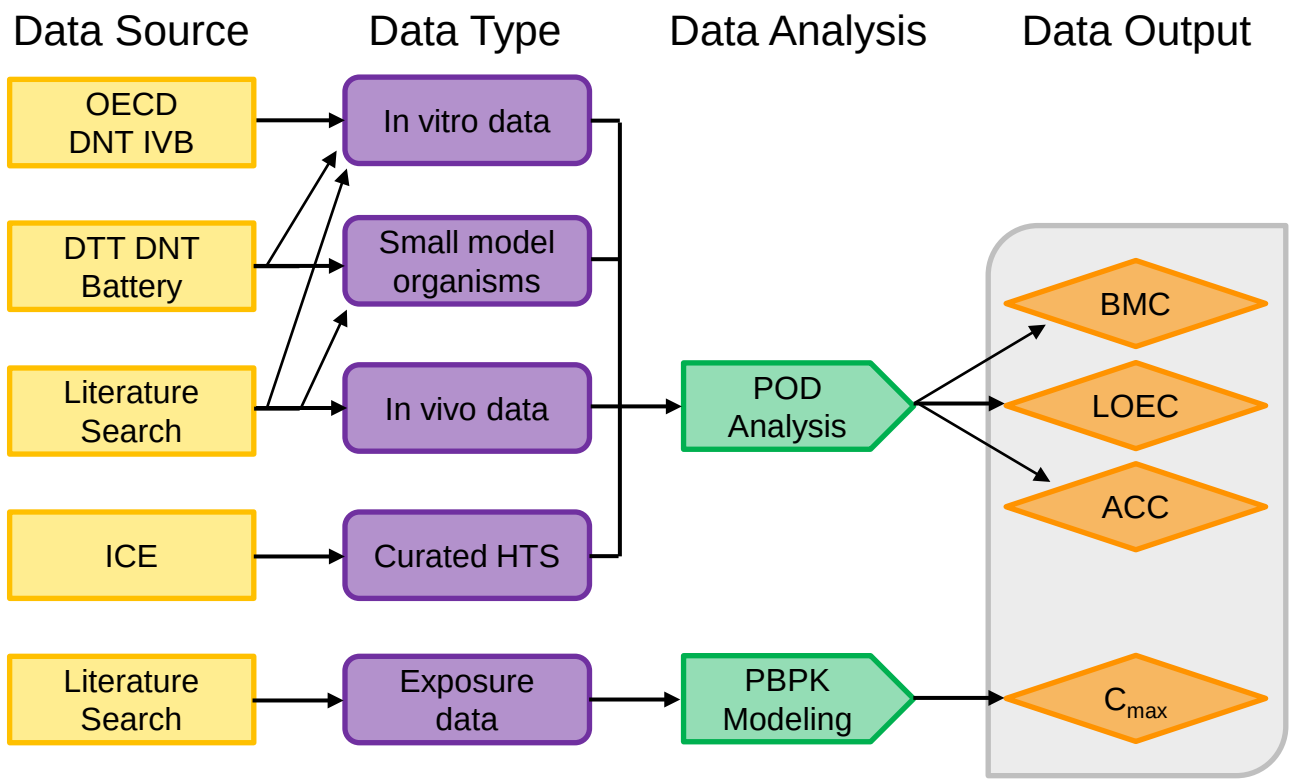
Adapted from OECD Guidance Document
https://one.oecd.org/document/ENV/CBC/MONO(2023)13/en/pdf

IATA Case Study for Prioritization



Kreutz et al., 2024

Workflow for collection of data



Chemicals Assessed

Comparison of novel OPFRs to phased-out and well-studied BFRs

Chemical	Chemical Name	Class
BDE-47	2,2'4,4'-Tetrabromodiphenyl ether	Brominated
TBBPA	3,3',5,5'-Tetrabromobisphenol A	
TDCIPP	Tris(1,3-dichloro-2-propyl)phosphate	OPFRs, Aliphatic halogenated
TCEP	Tris(2-chloroethyl) phosphate	
TPHP	Triphenyl phosphate	OPFRs Aromatic
IPP*	Phenol, isopropylated, phosphate (3:1)	
EHDP*	2-Ethylhexyl diphenyl phosphate	
TMPP*	Tricresyl phosphate	
IDDP*	Isodecyl diphenyl phosphate	
BPDP*	tert-Butylphenyl diphenyl phosphate	

**representative isomer in mixture is shown as structure*

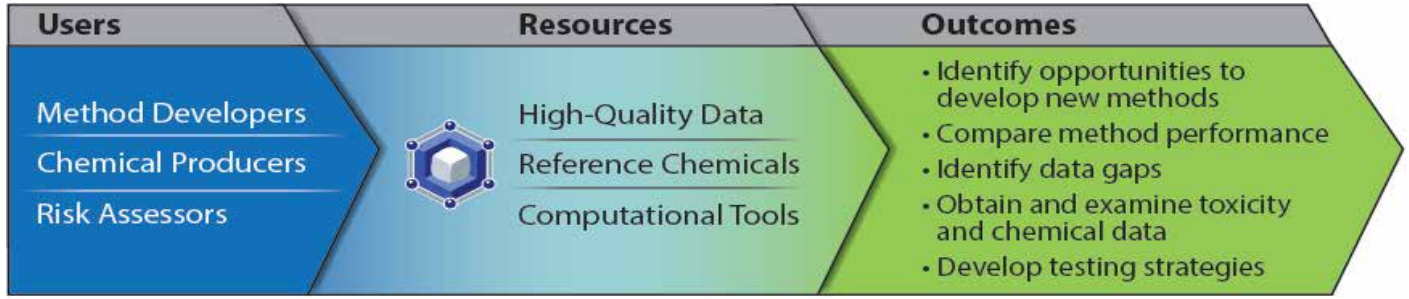
The concerns:

- Continual rise in use and increase in human exposure
- Resemble the structure of organophosphorus pesticides known to be DNT/NT
- 20-50 compounds in class including commercial and isomeric mixtures
- Cannot test our way through all combinations using traditional animal guideline studies
- Need for rapid, human-relevant data

National Institute of Environmental Health Sciences
Division of Translational Toxicology

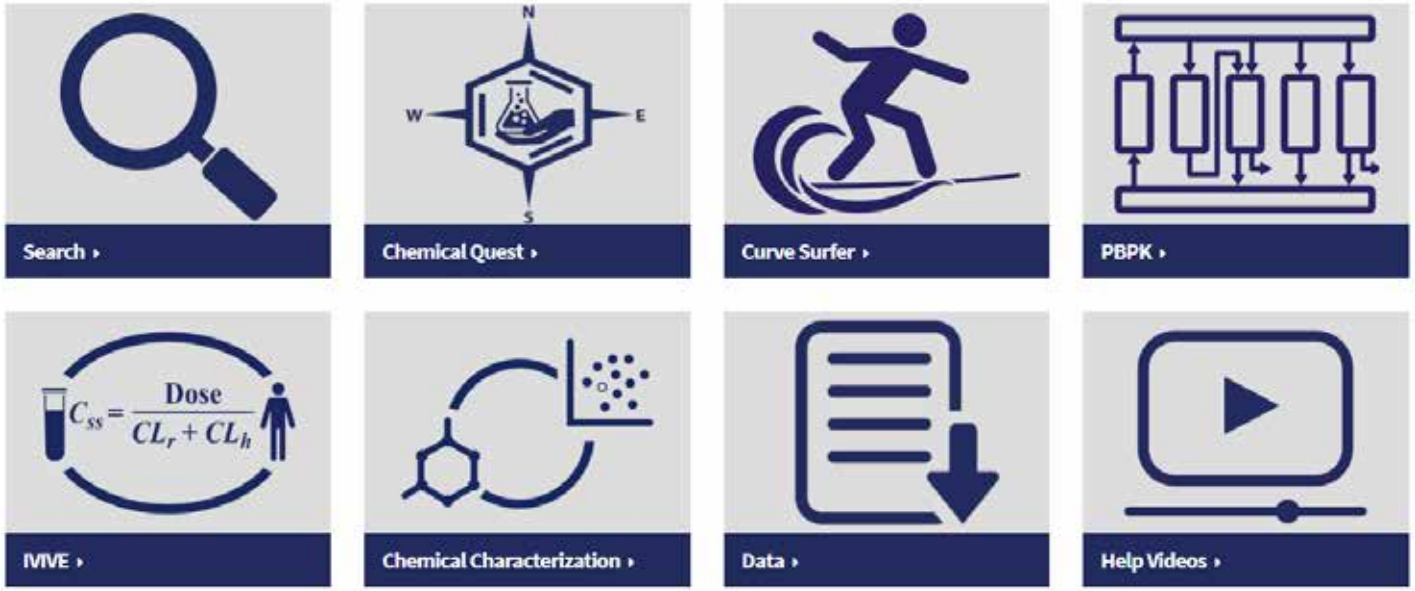
ICE: The Integrated Chemical Environment

ICE v4.0.2
March 2024



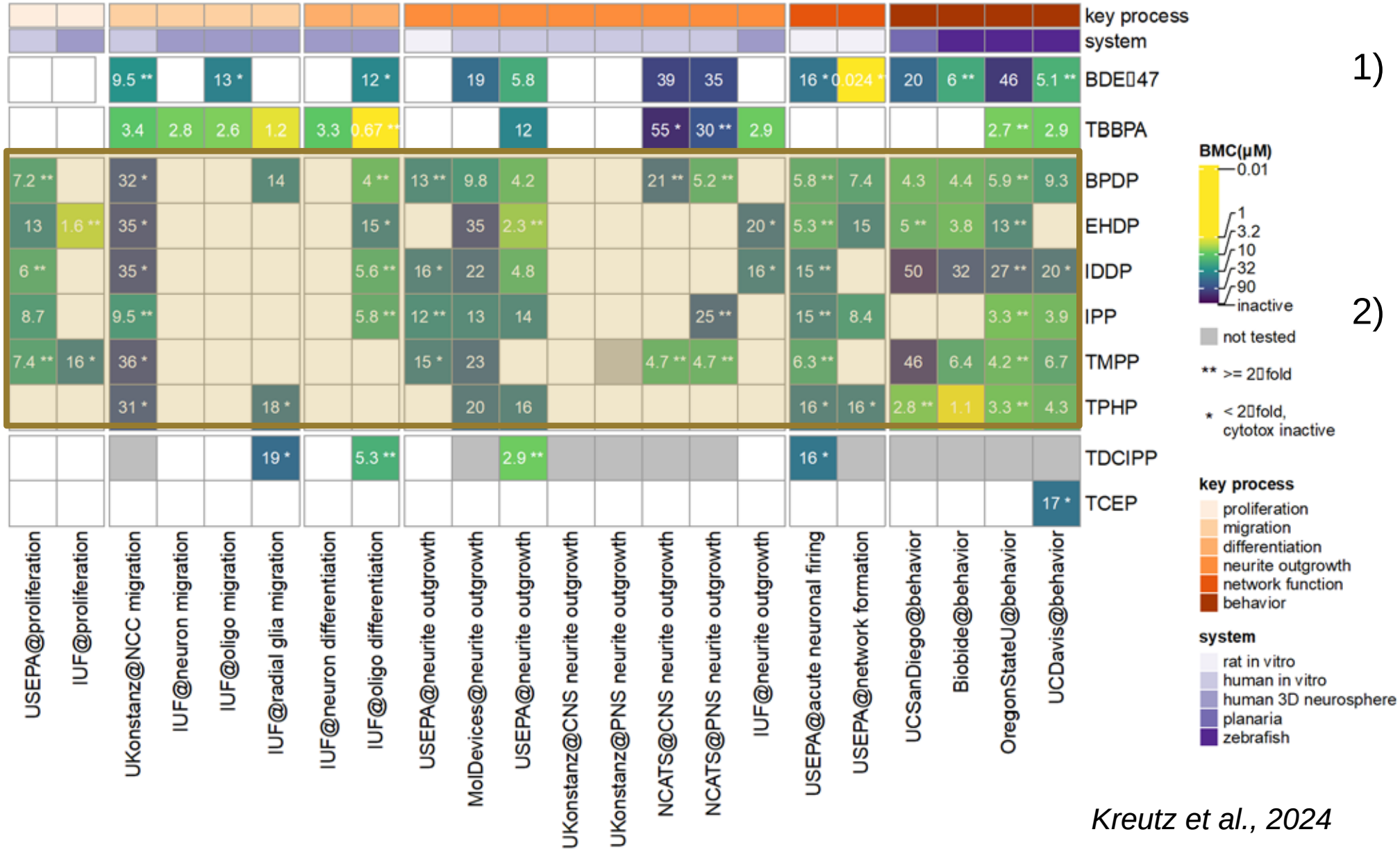
Integrated Chemical Environment

https://ice.ntp.niehs.nih.gov/



- **Integrated access to data**
  - Organized by toxicity endpoints and mechanisms
  - Interactive visualization
- **High quality, curated data**
  - Reference chemical lists with classifications and bioactivity
  - *In vitro* assays annotated with defined terminology
- **Computational models**
  - Chemical characterization and toxicity predictions
  - PBPK modeling and IVIVE of dosimetry

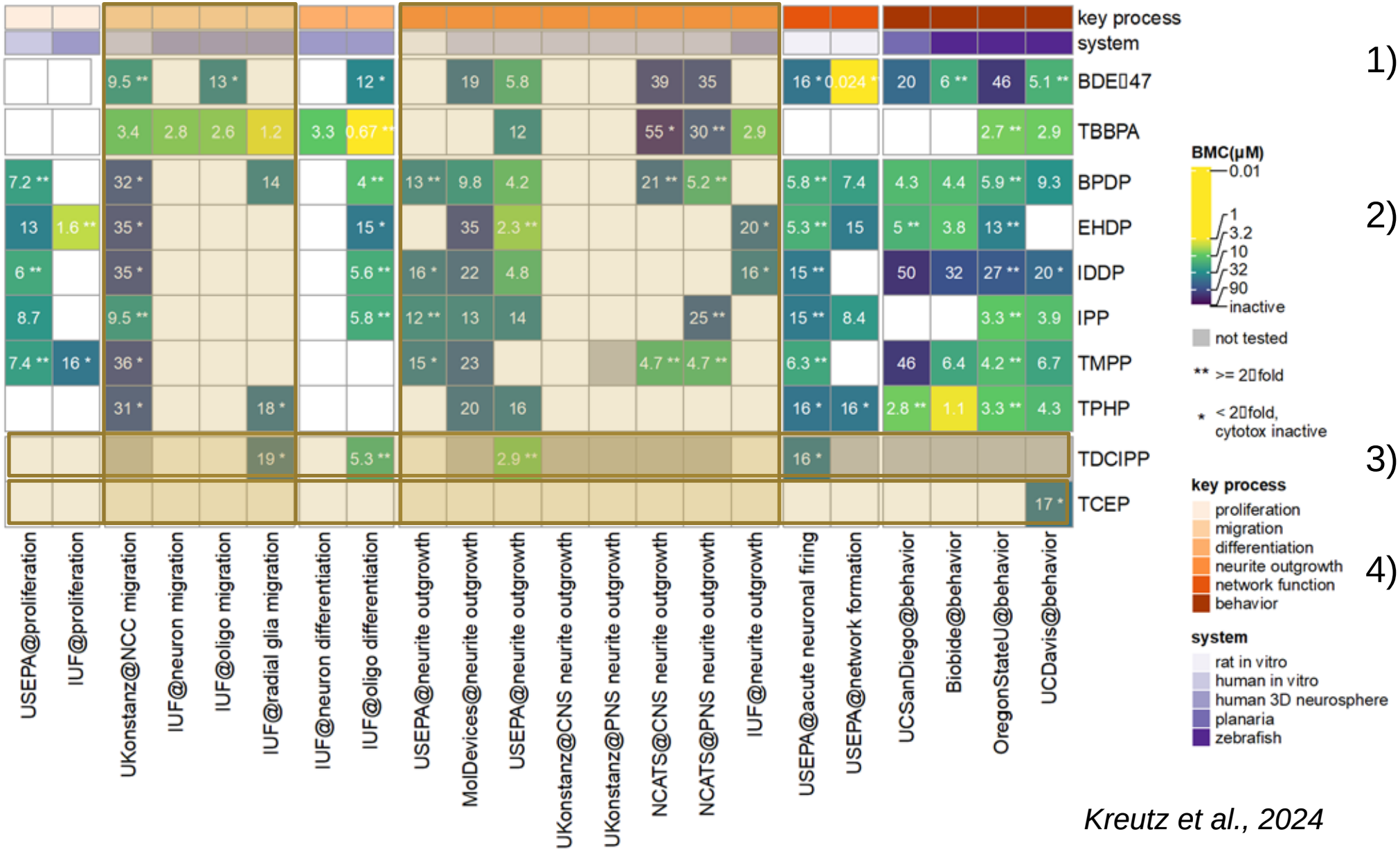
Summary of Findings: DNT Battery



1) Overall, as a class the aromatic OPFRs appear to be active in a variety of DNT assays
2) Show comparable activity to other classes

Kreutz et al., 2024

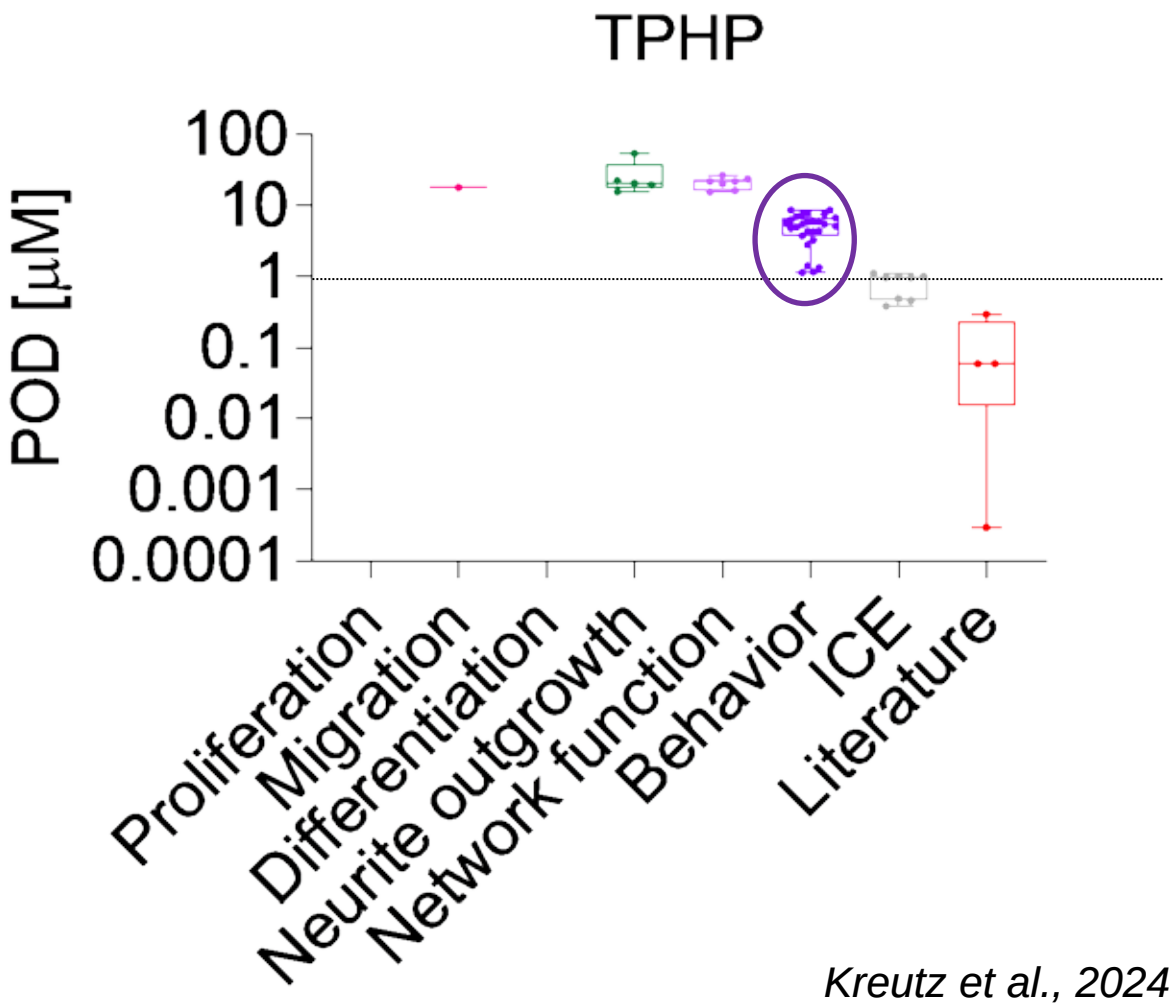
Sources of Uncertainty: DNT Battery



1) Lack of testing across assays (TDCIPP)
2) Lack of concordance between assays (neurite outgrowth, migration)
3) Number of hits (TCEP)
4) Mechanistic uncertainties

Kreutz et al., 2024

Data Integration from ICE and Literature

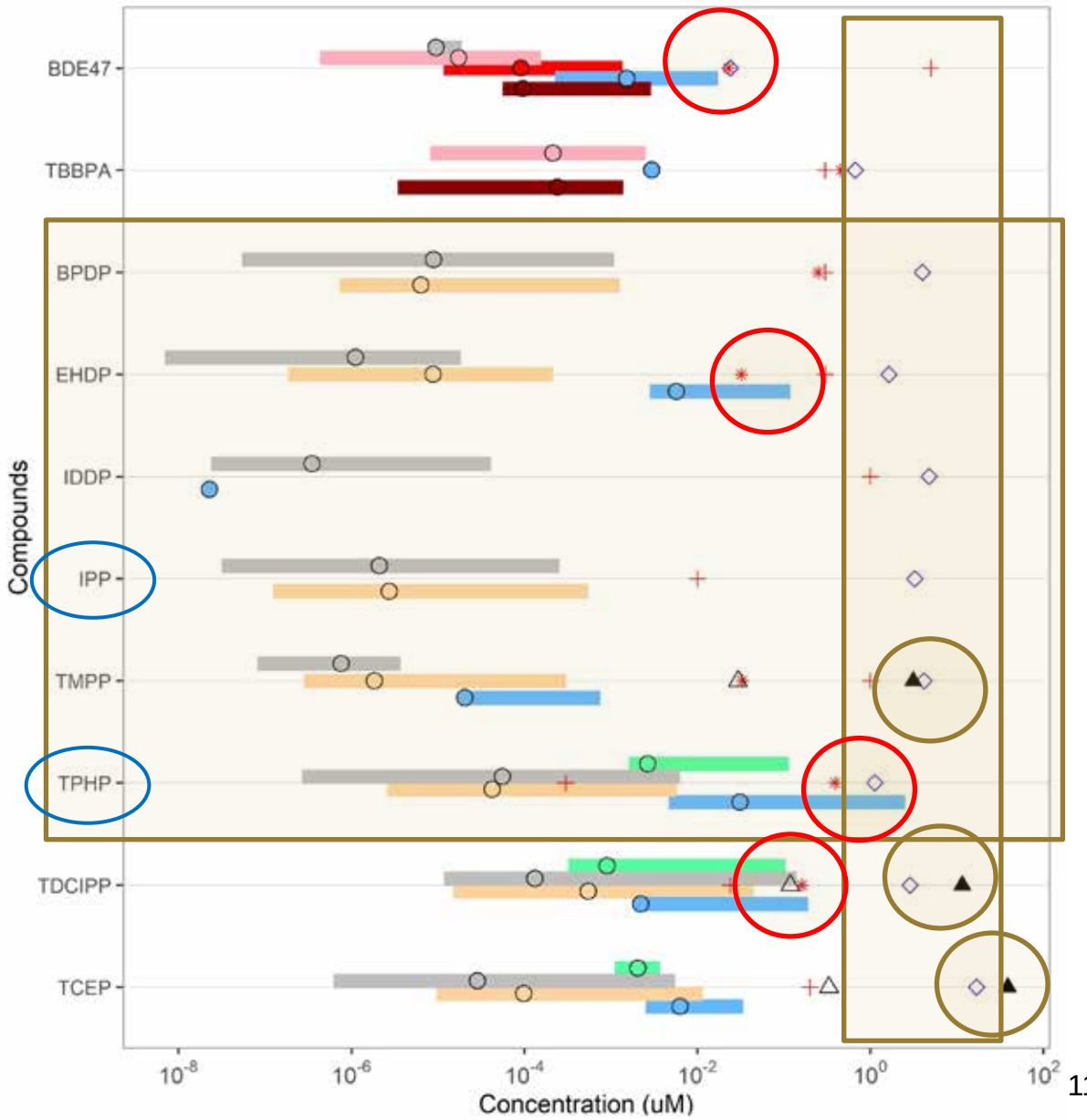


Kreutz et al., 2024

- Zebrafish behavior most sensitive DNT battery endpoint for several of the FRs
- The point of departure for some compounds was lowered by integrating data from ICE and the literature
- Majority of the most sensitive endpoints found in ICE and literature were annotated to glial differentiation, immune processes and the endocrine system
- Higher uncertainty with POD from literature data
- Integration of data from multiple sources increases confidence and can provide more mechanistic understanding

Relevance to Human Exposures

- Novel substitutes have comparable DNT battery activity to older FRs
- In vitro activity within order of magnitude of in vivo POD (when known)
- Human estimated exposure overlaps or approximates the lowest activity concentrations in vitro for several FRs
- DTT prioritized TPHP and IPP for tailored in vivo studies based on activity in the battery and chemical structure



Kreutz et al., 2024

Summary

- OPFRs (novel substitutes) have comparable in vitro activity to older FRs
- In vitro activity within order of magnitude of in vivo POD; usually more sensitive
- Activity concentrations in the IATA overlap with predicted human exposure for some OPFRs, indicating potential concern for human health
- Data from ICE and the literature identified other sensitive targets, such as endocrine disruption and the inclusion of astrocytes and microglial cell populations
- Integration of data from multiple sources reduce uncertainties and can provide mechanistic understanding
- The IATA suggest compounds such as TPHP to be prioritized for further testing

Next Steps To Expand the Regulatory Applicability for DNT

DNT IATA Framework Template and Guidance of Support

- EU (EFSA) and US (DTT, NICEATM) lead project, approved by WHPA in June 2024
- Develop an IATA framework template specific for DNT
  - Advance and provide guidance to address QIVIVE
  - Standardize uncertainty analyses for integration in WoE assessment
- Leverage on the existing and development of new DNT IATA case studies
- IATA framework template specific to the DNT regulatory endpoint
  - Several information sources
  - Multiple problem formulations
  - Consistent way to integrate data

Framework expected to be finalized and approved by WPHA by the end of 2025