

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

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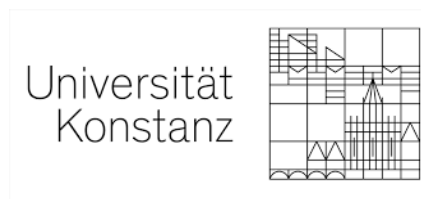


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DNT IVB Contractors



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

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

IATA case studies to exemplify different regulatory needs



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



toxics

Impact Factor 3.9
CiteScore 4.5
Indexed in PubMed
ISSN 2305-6304

ENV/CBC/MONO(2022)26

English - Or. English
1 September 2022

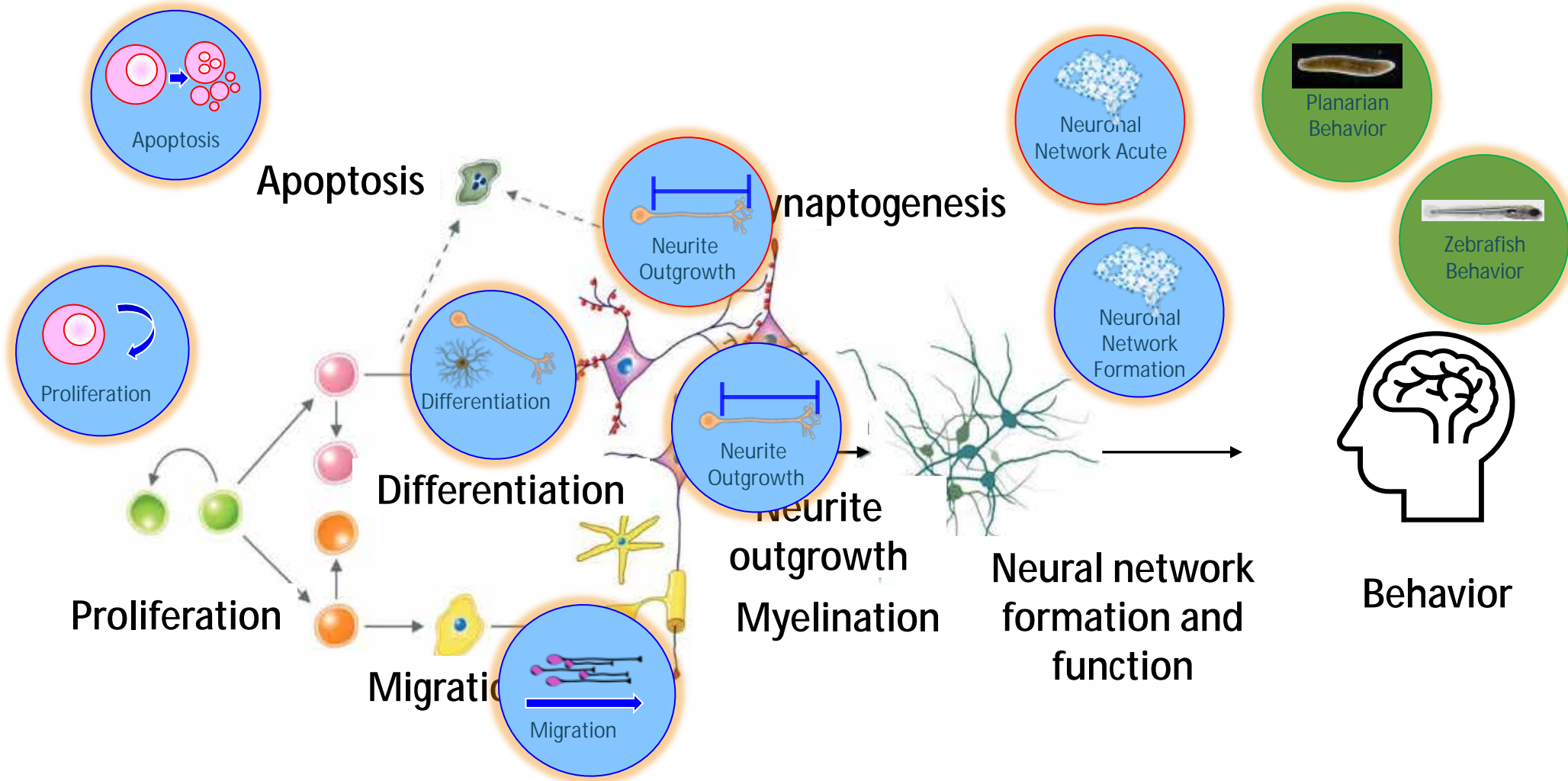
IATA for DNT to Prioritize Aromatic Organophosphorus Flame Retardants

Volume 12 - Issue 6 July 2024

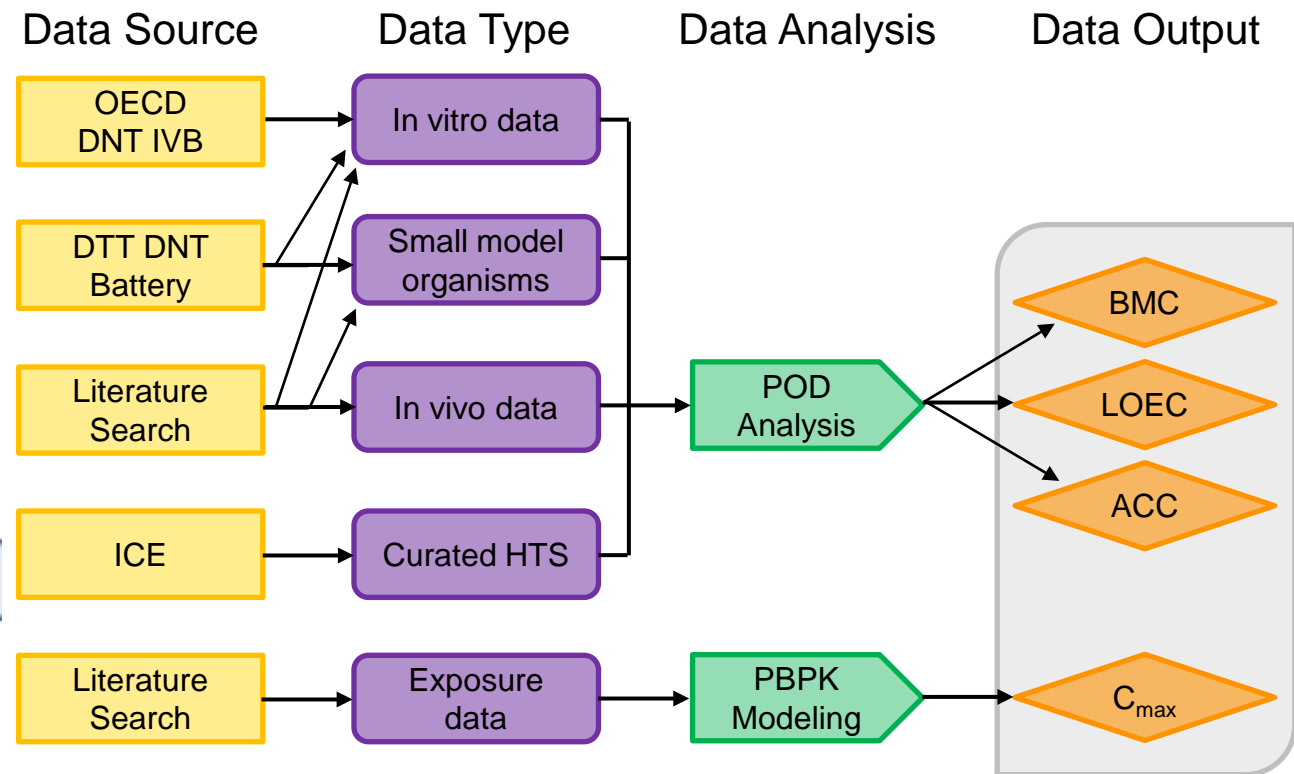
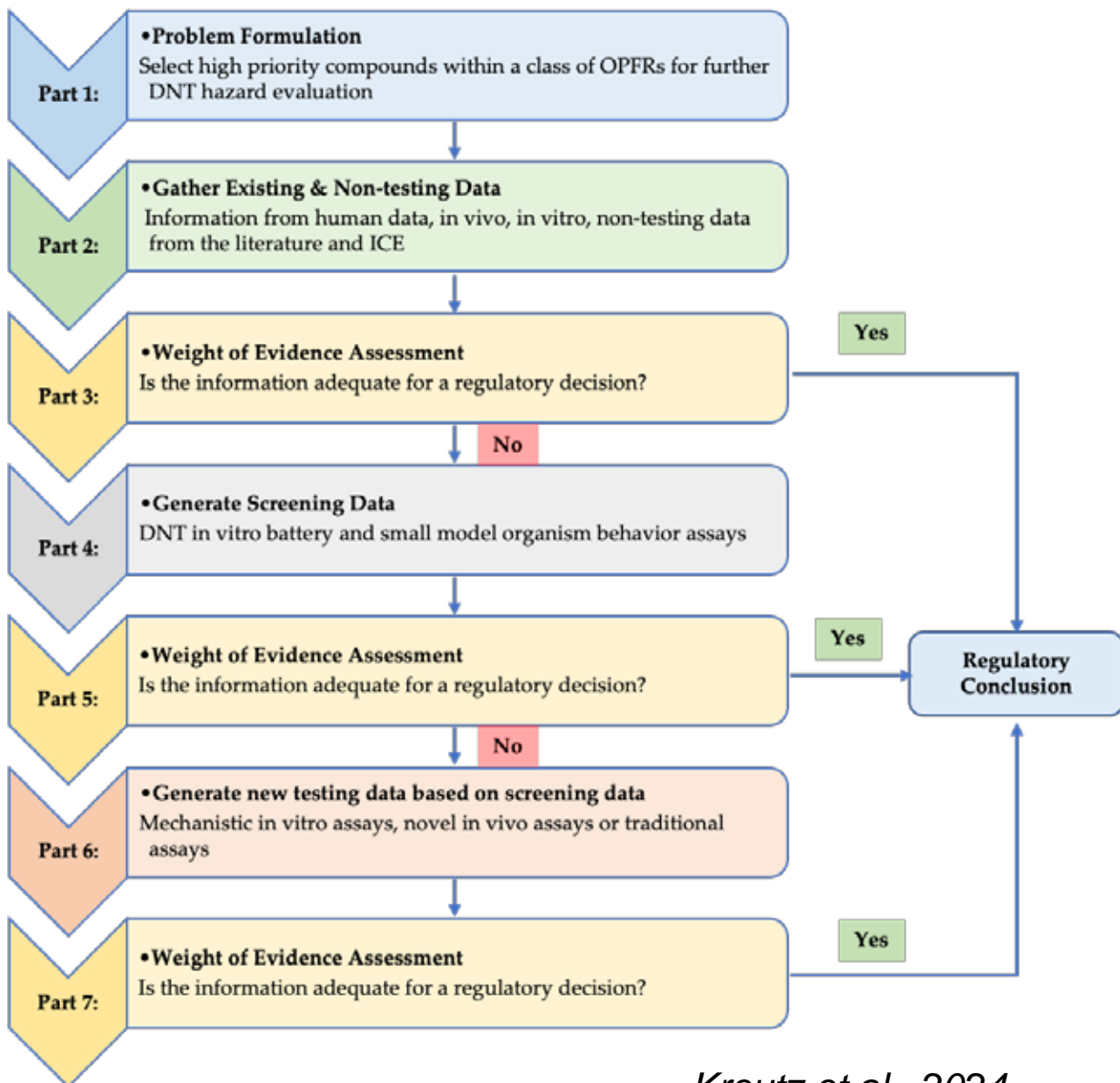
and Assessment for DNT to

MDPI

DNT Battery in the DTT IATA Case Study



Workflow for collection of data



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

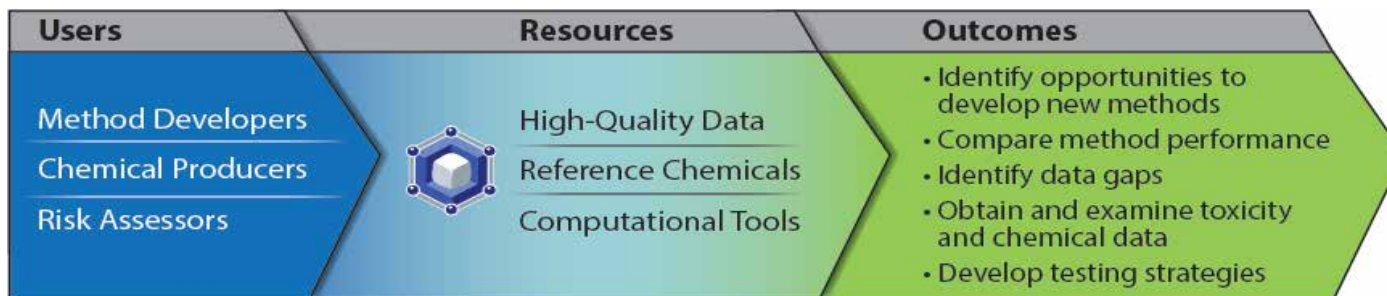
Chemical	Chemical Name	Class
BDE-47	2,2',4,4'-Tetrabromodiphenyl ether	Brominated
TBBPA	3,3',5,5'-Tetrabromobisphenol A	
TDCIPP	Tris(1,3-dichloro-2-propyl)phosphate	OPFRs, Aliphatic halogenated
TCEP	Tris(2-chloroethyl) phosphate	
TPHP	Triphenyl phosphate	OPFRs Aromatic
IPP*	Phenol, isopropylated, phosphate (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

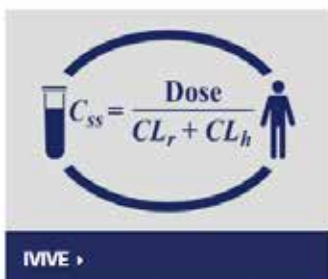
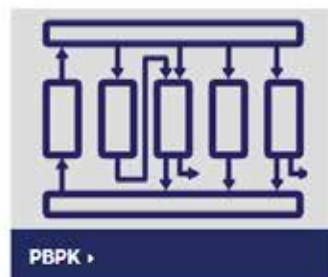
ICE v4.0.2
March 2024



Integrated Chemical Environment



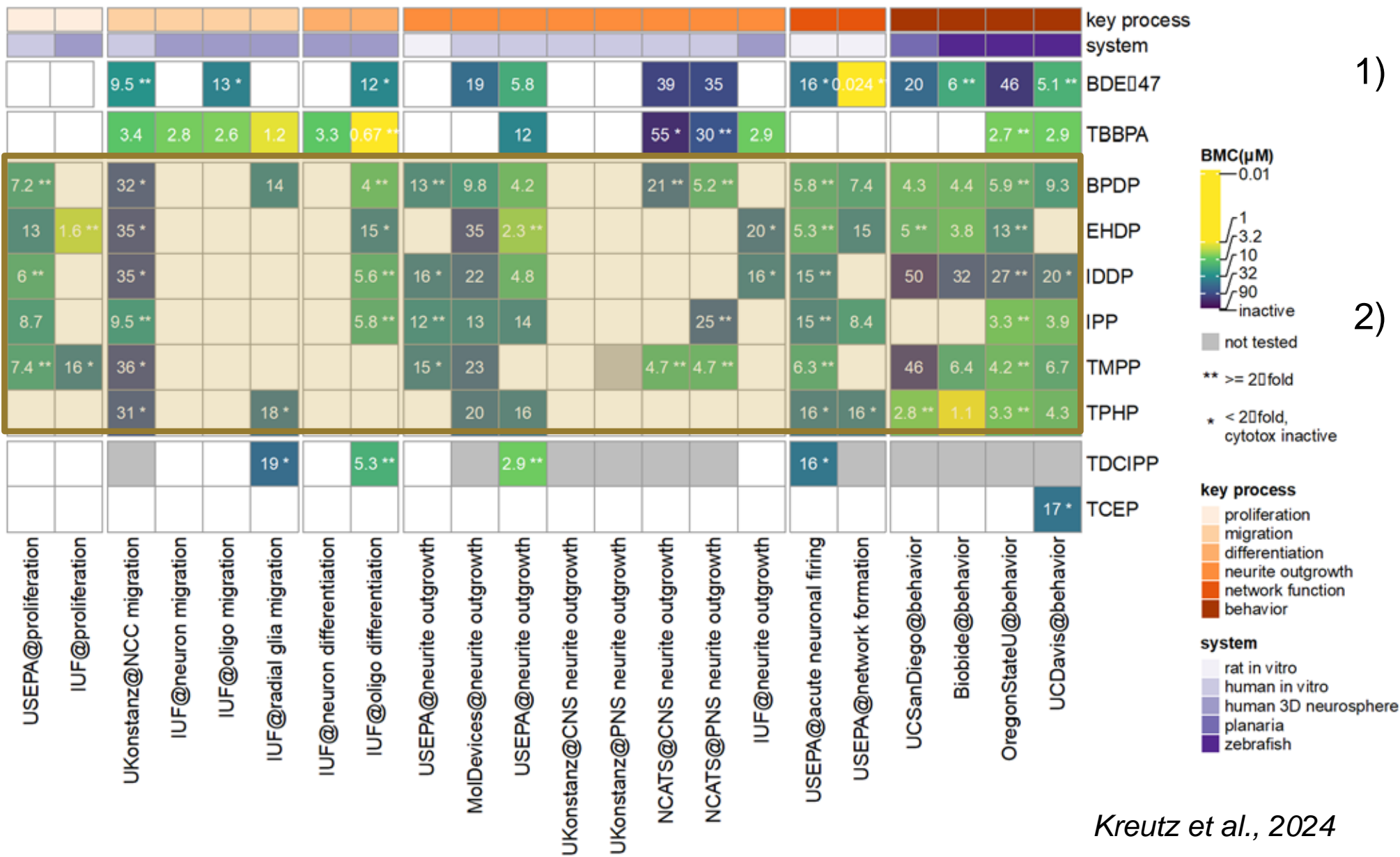
<https://ice.ntp.niehs.nih.gov/>



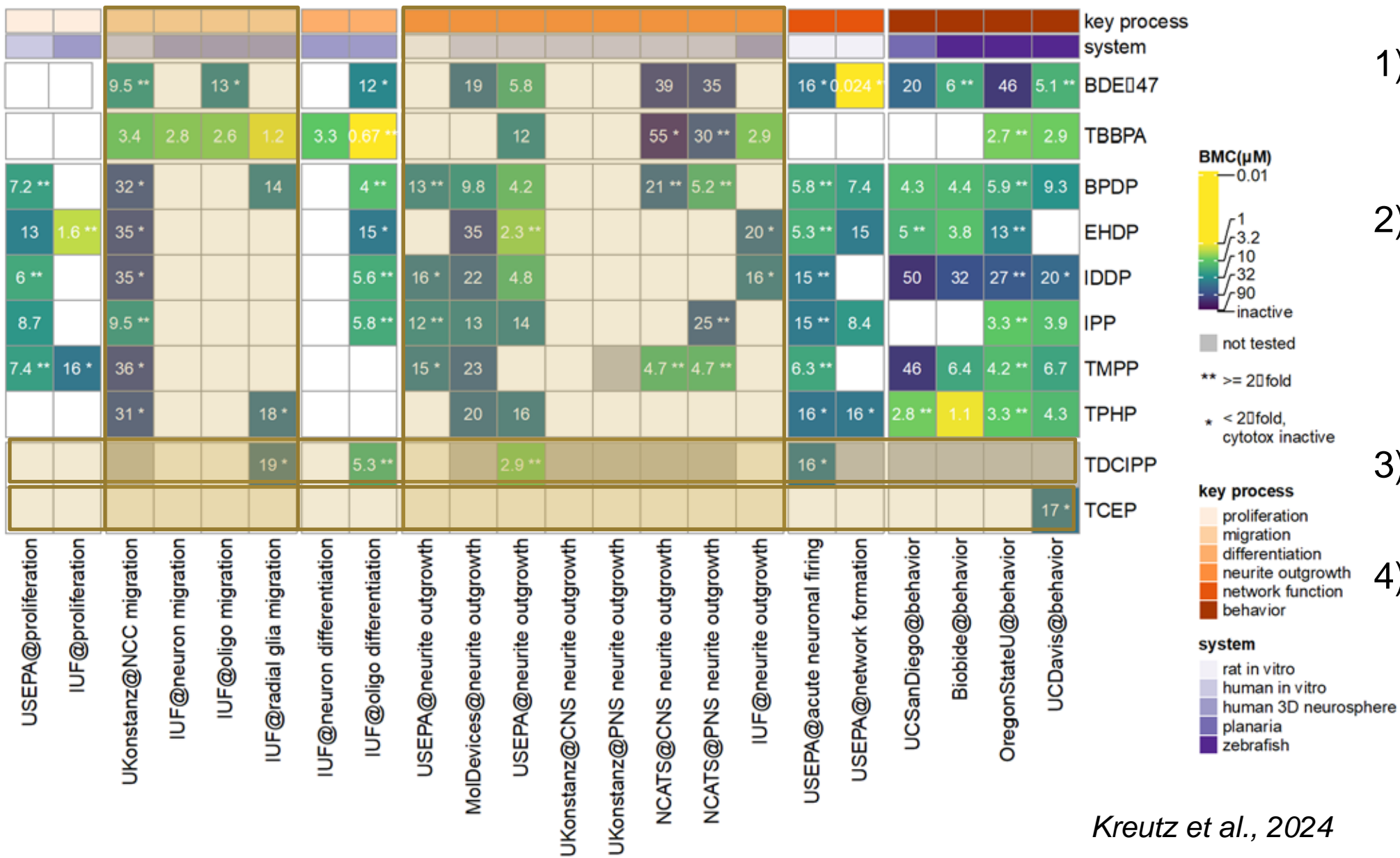
- **Integrated access to data**
 - Organized by toxicity endpoints and mechanisms
 - Interactive visualization
- **High quality, curated data**
 - Reference chemical lists with classifications and bioactivity
 - *In vitro* assays annotated with defined terminology
- **Computational models**
 - Chemical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

Summary of Findings: DNT Battery

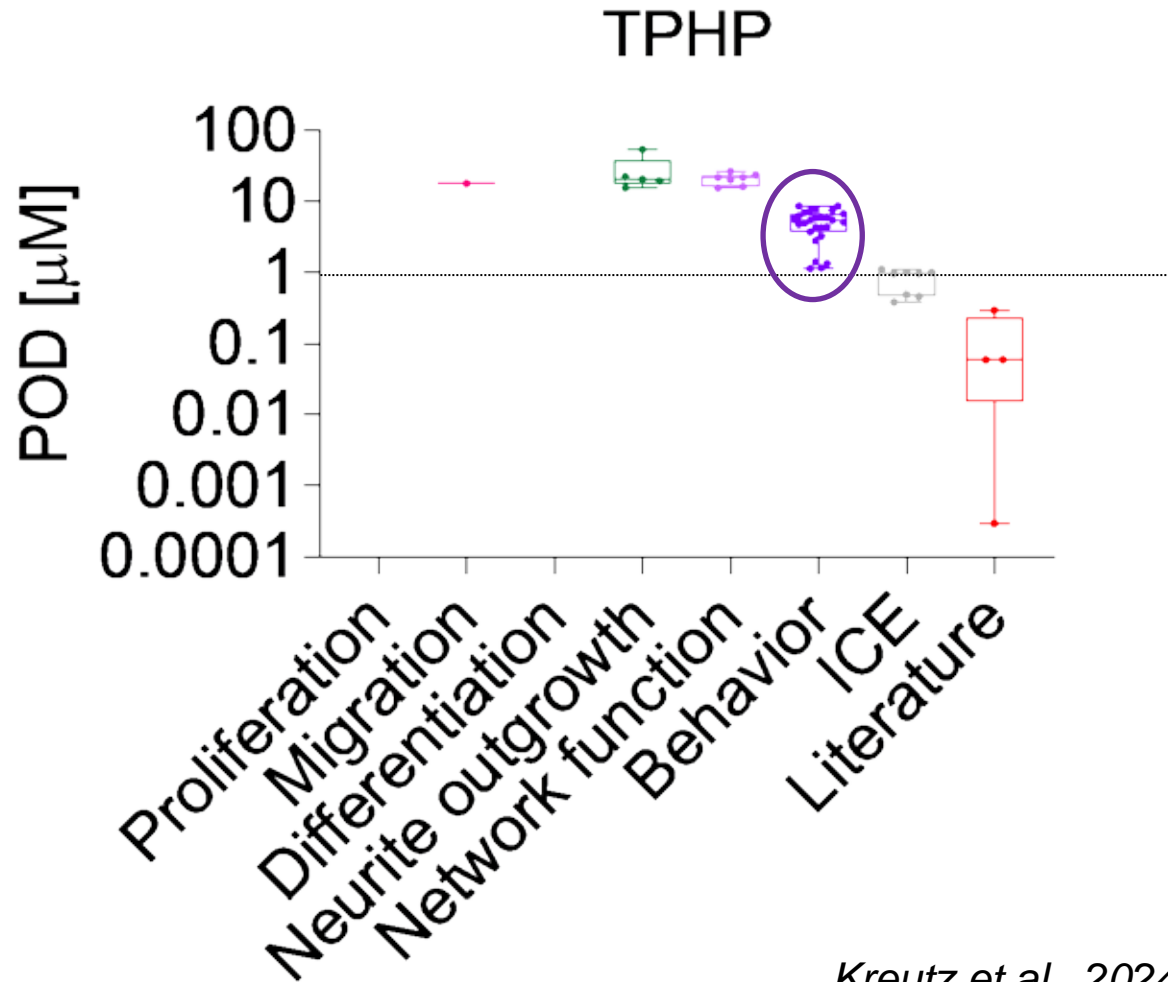
- 1) Overall, as a class the aromatic OPFRs appear to be active in a variety of DNT assays
- 2) Show comparable activity to other classes



Sources of Uncertainty: DNT Battery



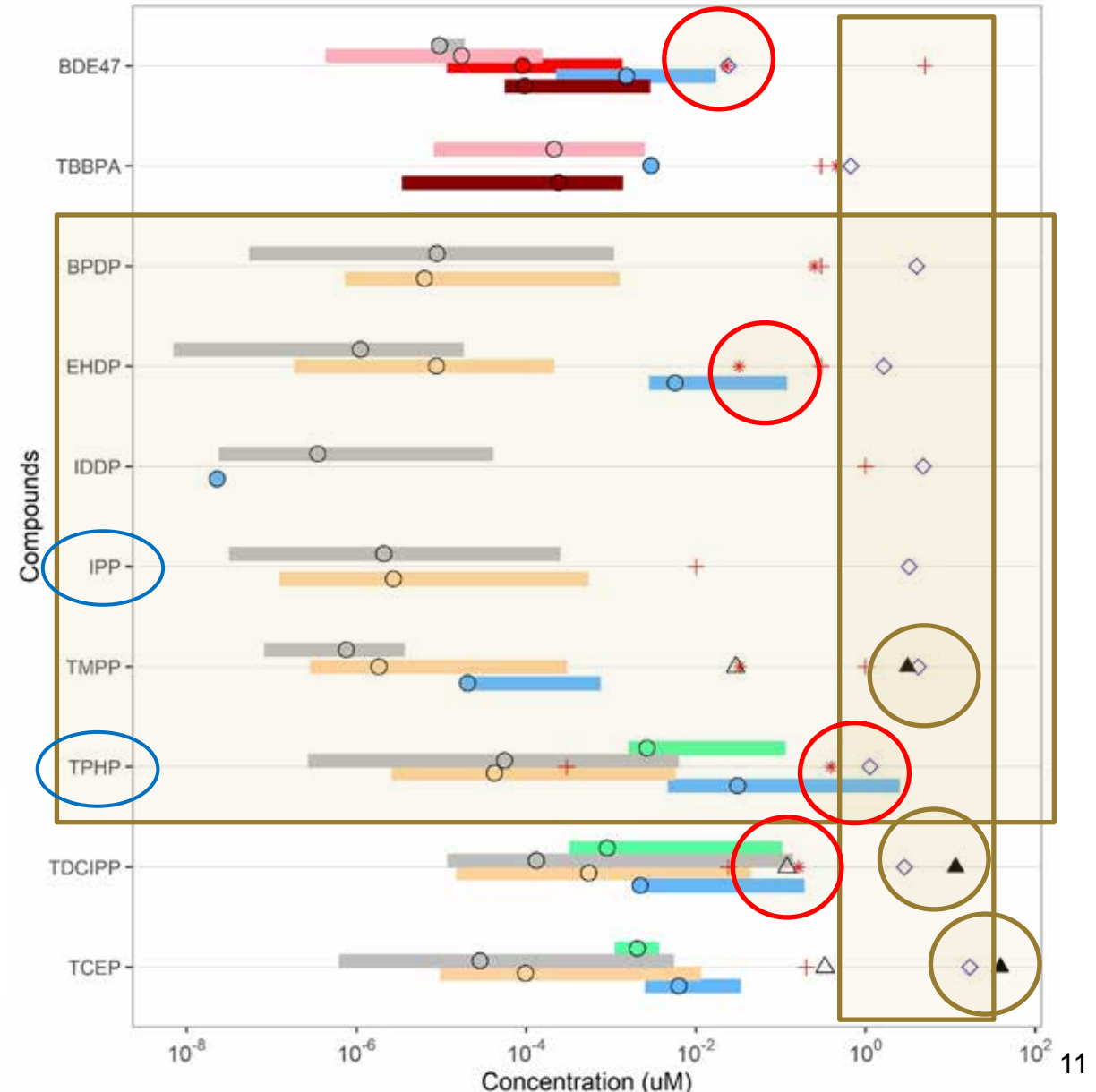
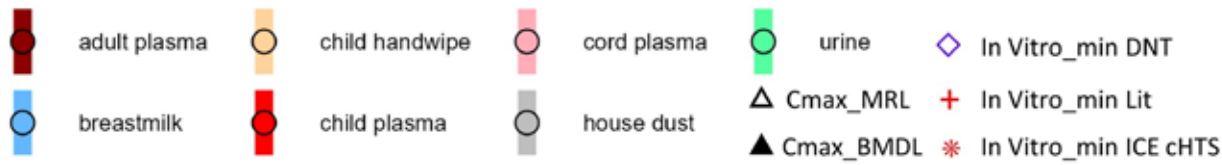
- 1) Lack of testing across assays (TDCIPP)
- 2) Lack of concordance between assays (neurite outgrowth, migration)
- 3) Number of hits (TCEP)
- 4) Mechanistic uncertainties



Kreutz et al., 2024

- 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

- 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



- 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

OECD 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 WHPA by the end of 2025