Integrating Screening Level Developmental Neurotoxicity (DNT) Information of Chemicals In a New Approach Methods (NAMs) Battery to Identify Compounds for Future Study

Christopher McPherson, PhD

NIEHS/DTT

SACATM
Bethesda, MD
September 17-18, 2024

Developmental Neurotoxicity Health Effects Innovation (DNT HEI)

Program objectives

1) Generate screening level information using New Approach Methodologies (NAMs) as an interim means to evaluate hazard and prioritize further evaluation

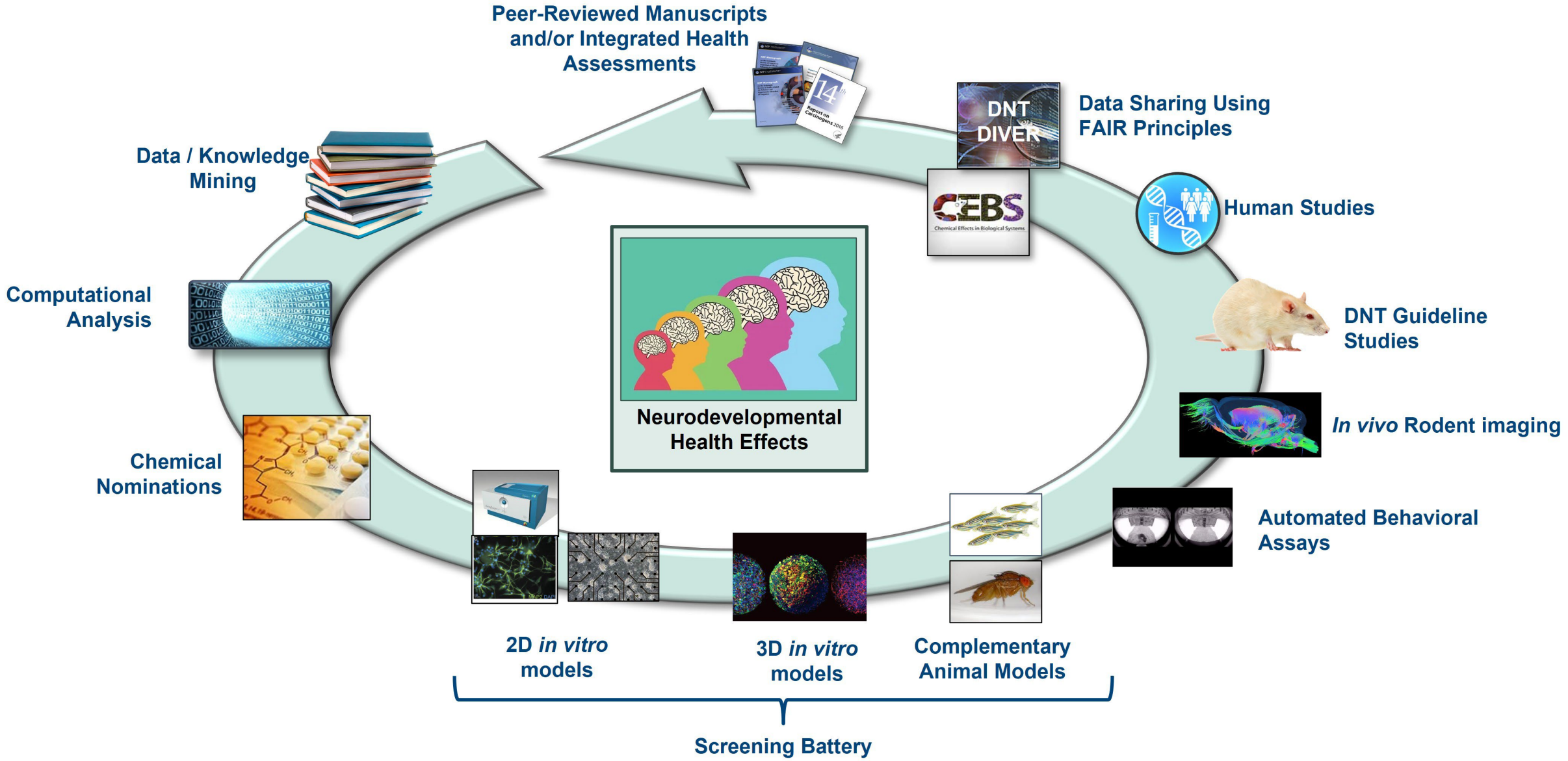
2) Incorporate human-relevant mechanistic, behavioral, and brain network assessments to address complex neurodevelopmental issues.

3) Contextualize in vitro and in vivo findings with human exposure using IVIVE and in silico approaches

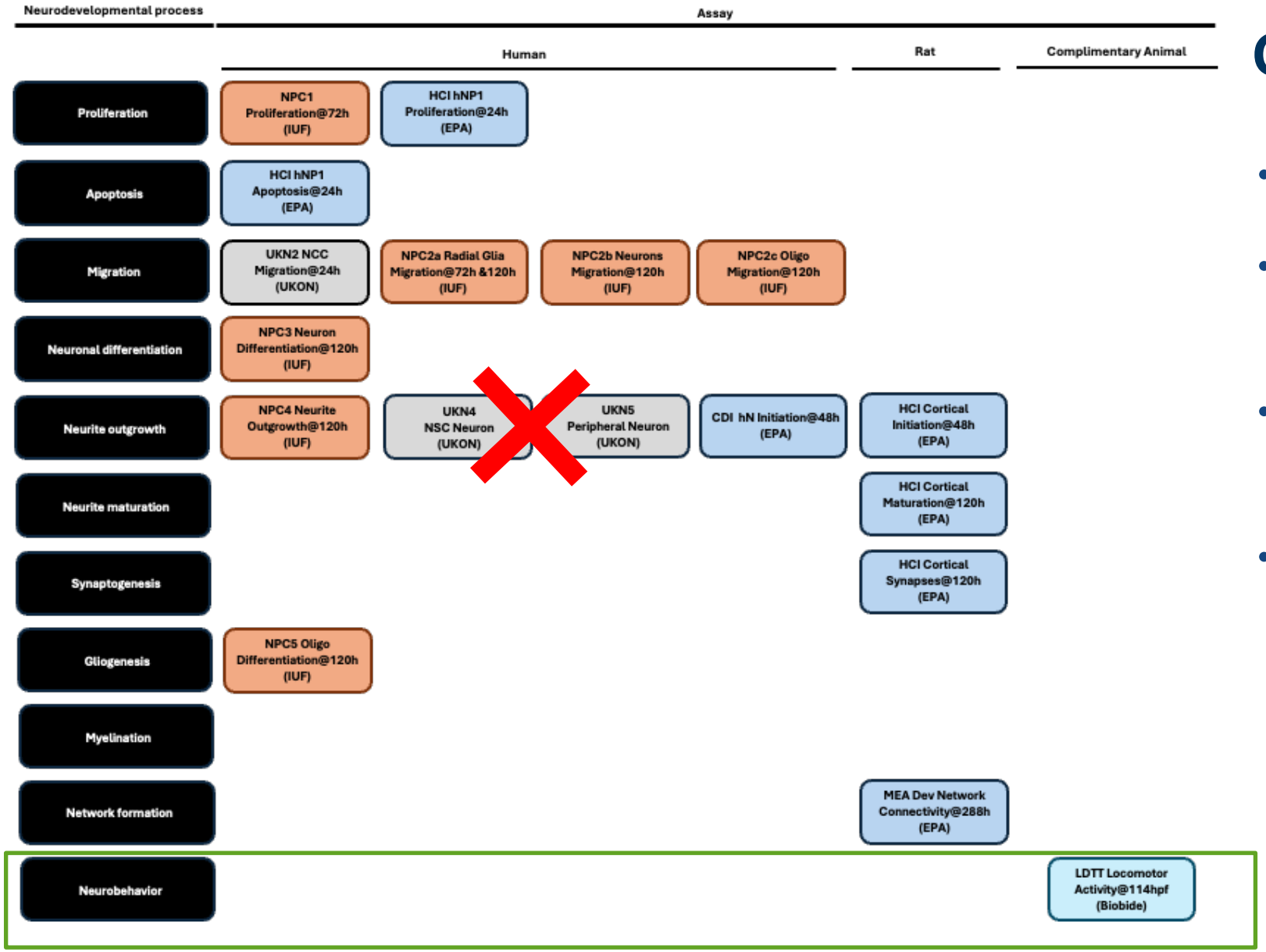
4) Establish communication pipelines with stakeholders to allow for concerted global progress of DNT

National Institute of Environmental Health Sciences
Division of Translational Toxicology

DNT HEI's Integrated Testing Framework

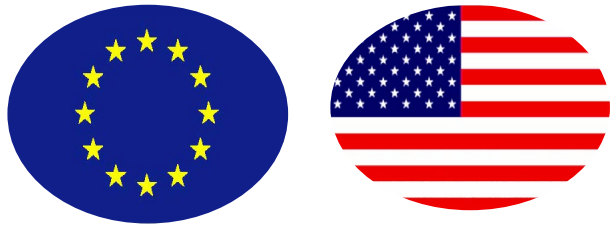


DNT Battery



OECD / DTT comparison

- US EPA (7assays)
- IUF Dusseldorf University (7 assays)
- Konstanz University (3 vs. 1 assays)
- DNT-HEI battery includes zebrafish neurobehavioral assays



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 & rep

Initial Recommendations on Eva
(DNT) In-Vitro Testing Battery

Series on Testing and Assessment
No. 377

Table 3.1. Examples of weight of evidence (WoE) limitations of the DNT IVB

• The lack of assays for several cellular processes and systemic processes known to be critical for normal neurological development (see Sections Developmental Neurotoxicity In Vitro Battery (description of assays) and evaluation of the DNT IVB for chemical testing).
• Need for development of additional AOPs to increase mapping of KEs covered in the DNT IVB.
• **Relatively limited number of tested chemicals as compared to current accepted batteries (e.g. ER activation).**
• Uncertainty in the overall specificity and sensitivity of the DNT IVB due to limited testing of DNT reference chemicals and comparison of results to curated in vivo developmental neurotoxicity database.
• A need for consensus-based and regulatory driven tiered testing strategy to be used in IATAs

Main Objectives of Screening Efforts

- Screen chemicals for DNT potential in a battery of assays that covers key neurodevelopmental events
- Evaluate assays in existing screening battery for redundancy
- Develop ranking methods to evaluate and compare chemicals for degree of DNT potential
- Prioritize chemicals for further testing in targeted studies
- Integrate data into DNT-DIVER to serve as a central repository to host DNT data (DTT and global) for the DTT and its stakeholders

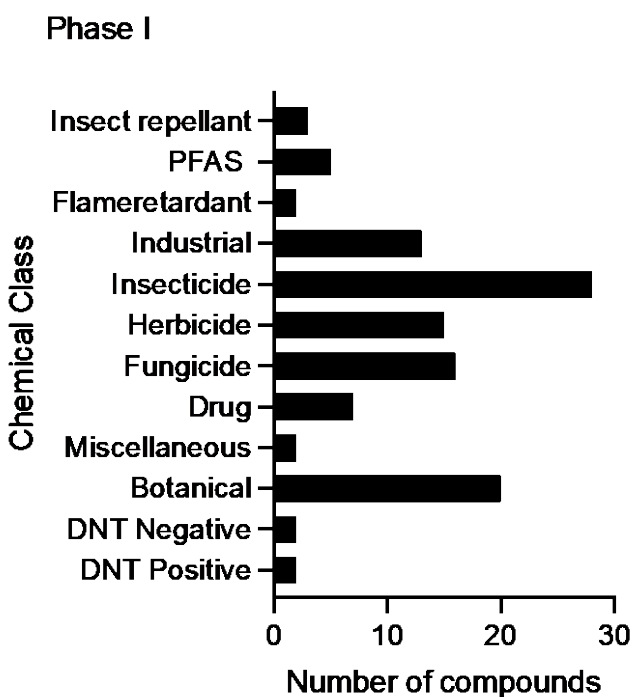
National Institute of Environmental Health Sciences
Division of Translational Toxicology

Stakeholder Nominated Chemical Libraries

Selection Criteria

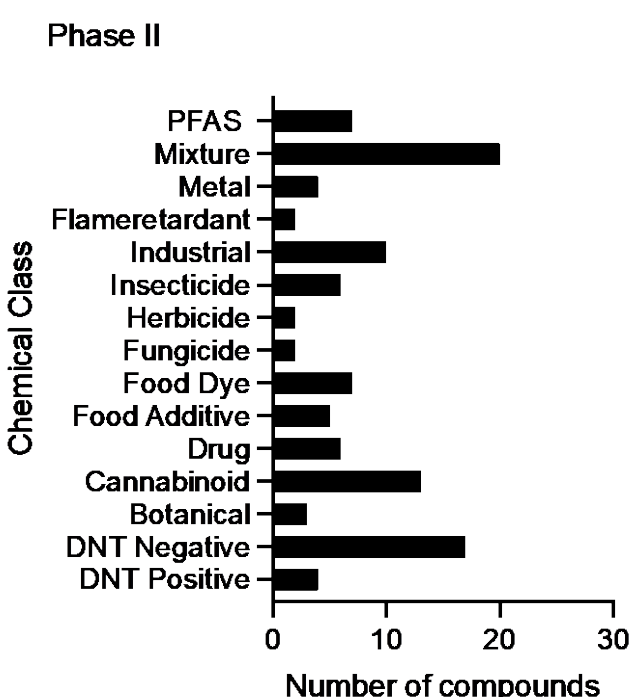
- Evidence of DNT *in vivo*
- Known human exposure
- Guideline study complete, lacking *in vitro*
- Incomplete in vitro battery data
- Suggested by multiple stakeholders

Phase I: 115 chemicals



COMPLETED

Phase II: 108 chemicals

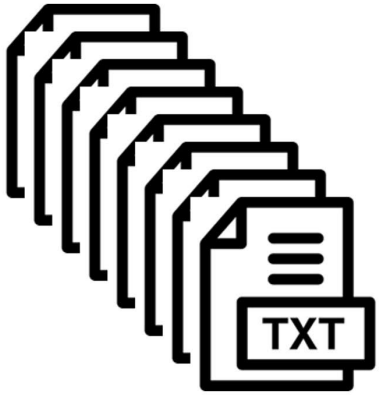


WORK IN PROGRESS

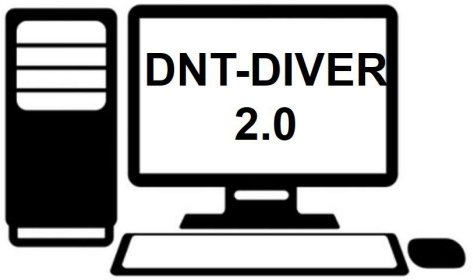
National Institute of Environmental Health Sciences
Division of Translational Toxicology

Data Analysis Pipeline

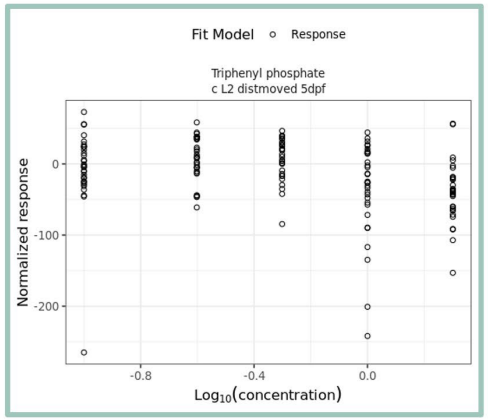
Raw data



Quality Check → Data Loading → Database Design → Data Analysis

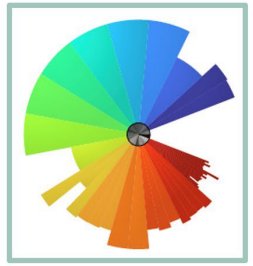


Data Analysis Pipeline

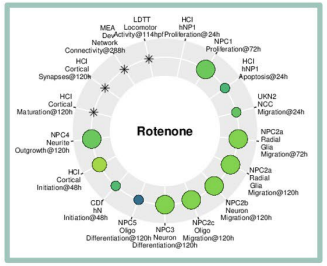


Concentration-response data

BMC Calculation → Selectivity Calculation → Activity summary → Compound prioritization



ToxPi

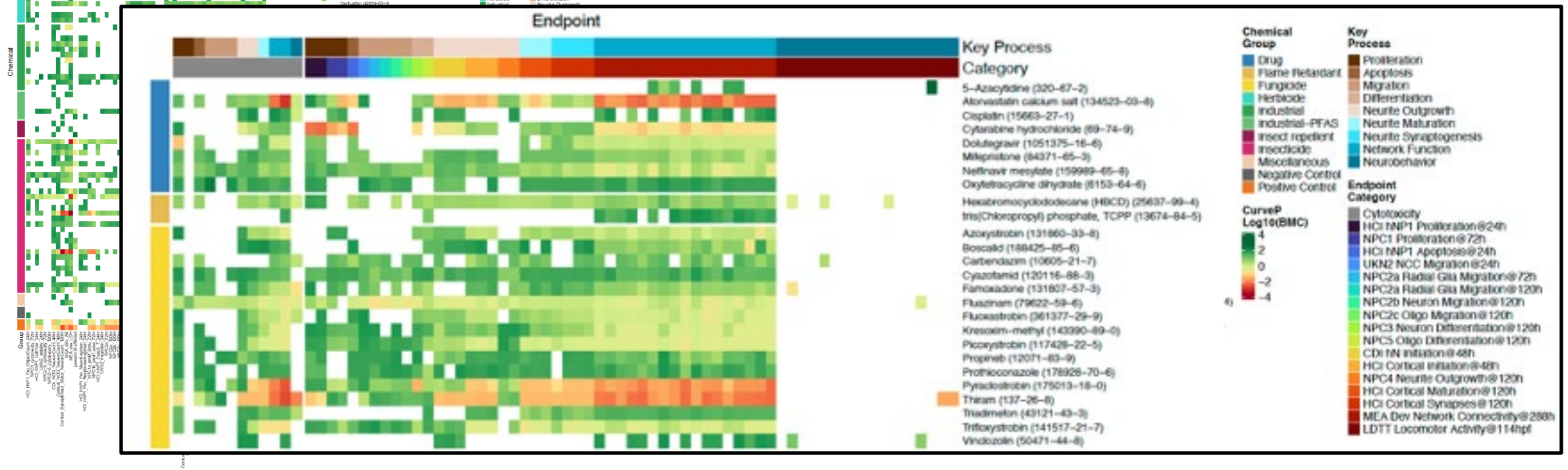


Pareto Front

National Institute of Environmental Health Sciences
Division of Translational Toxicology

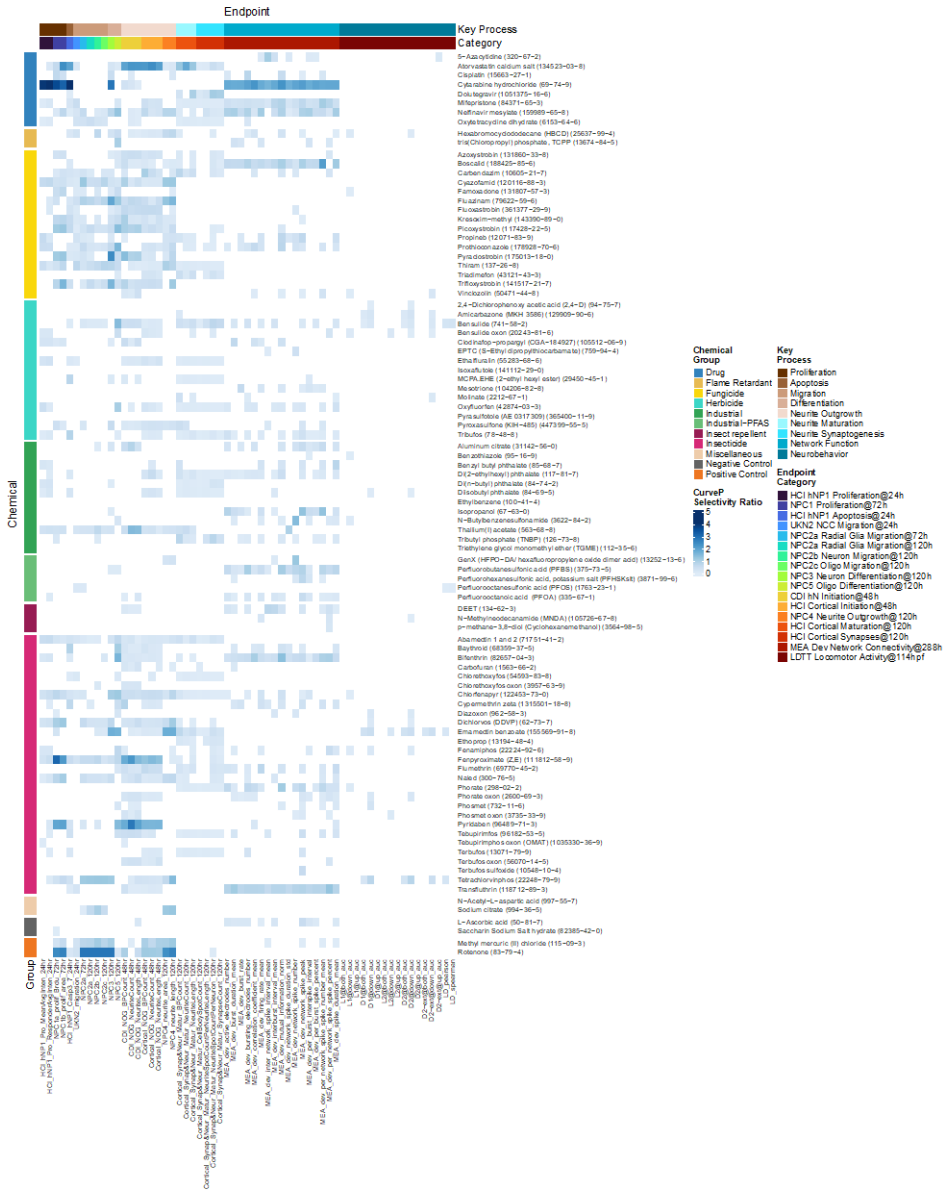
Summary of Benchmark Concentration (BMC) Values

- Activity was observed in all use classes in the battery
- 99% of compounds were active in at least 2 experimental neurodevelopmental processes (e-NPs)
- Cytotoxicity observed in 99% of compounds

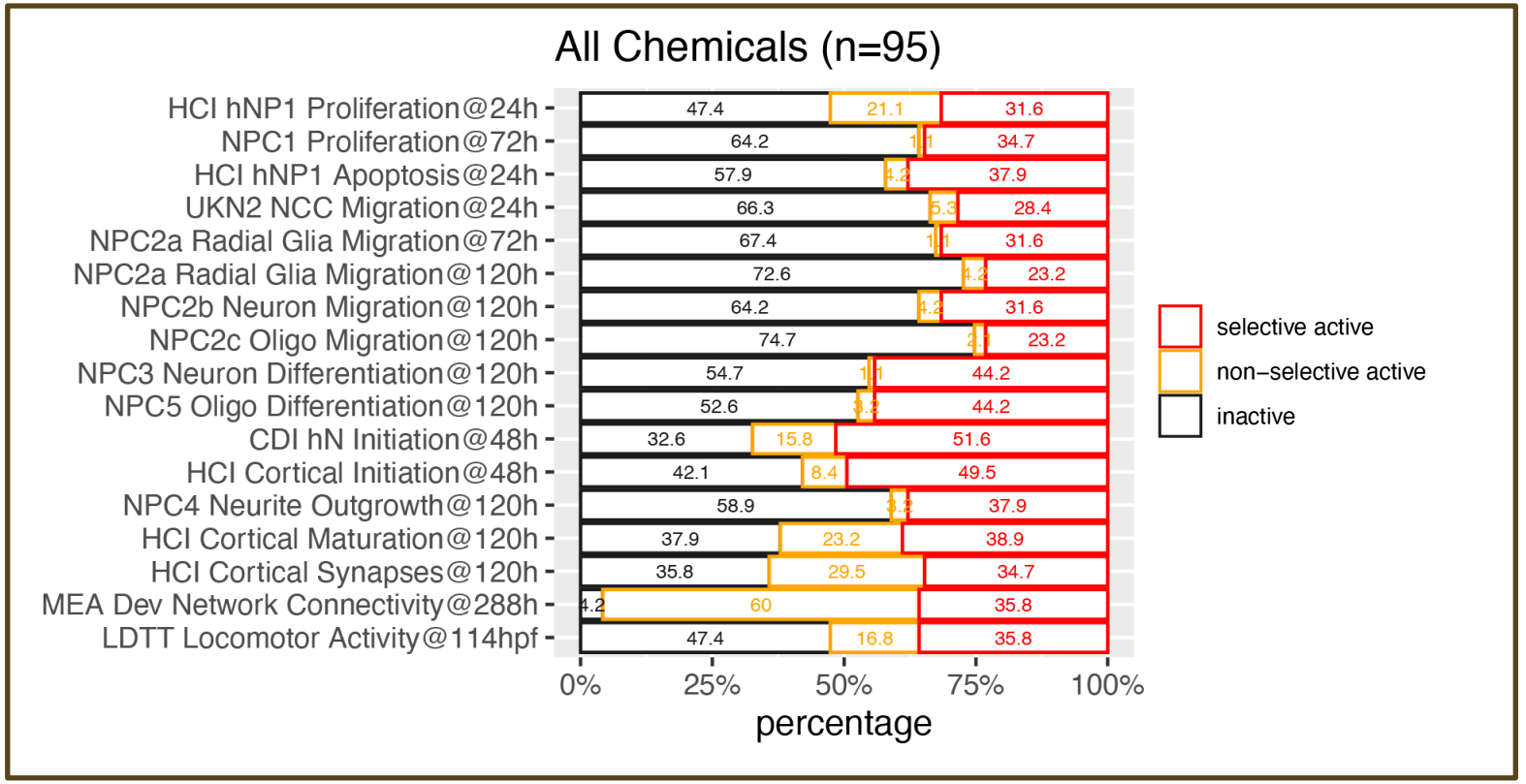


National Institute of Environmental Health Sciences
Division of Translational Toxicology

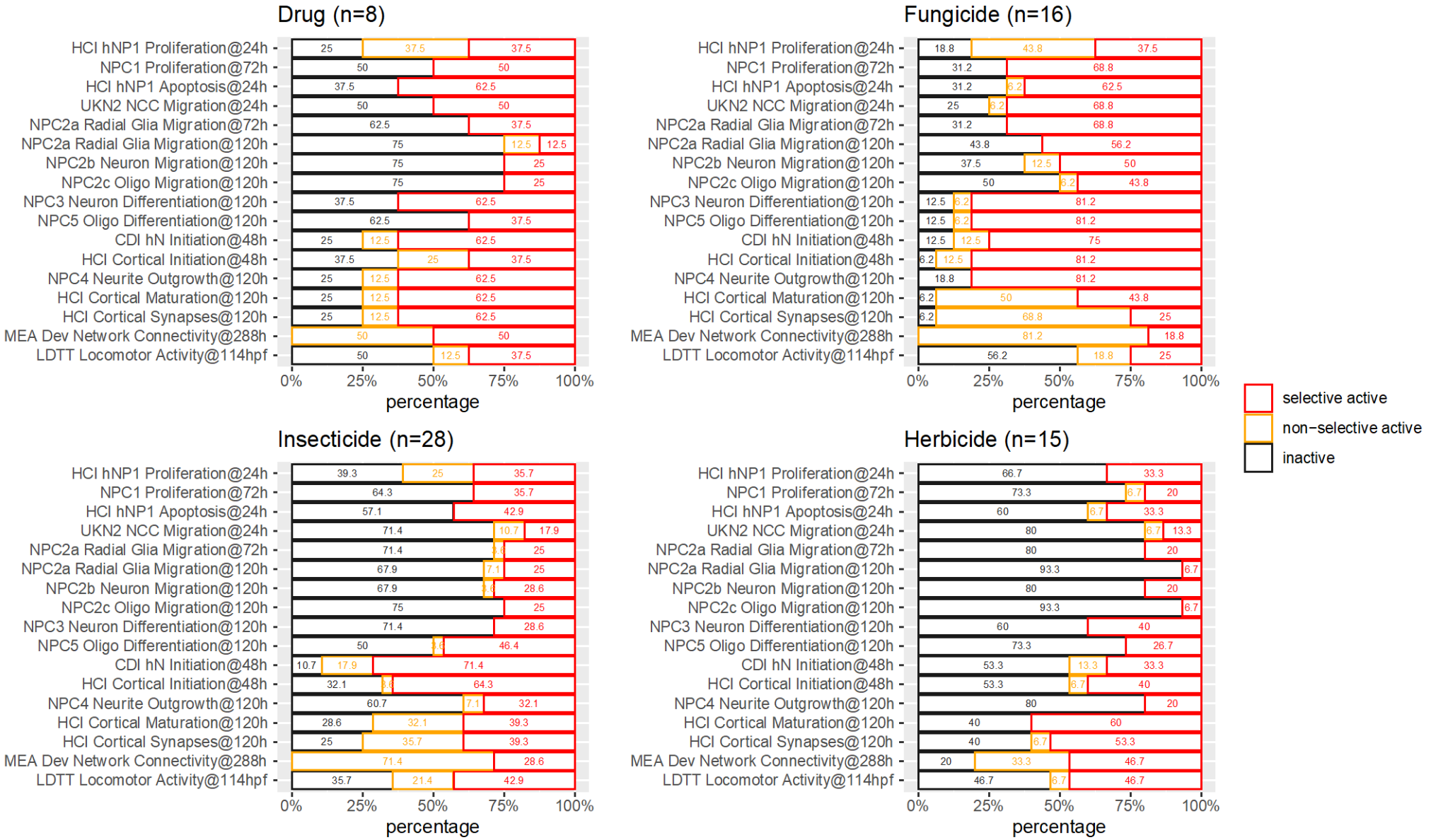
Summary of Selectivity Values



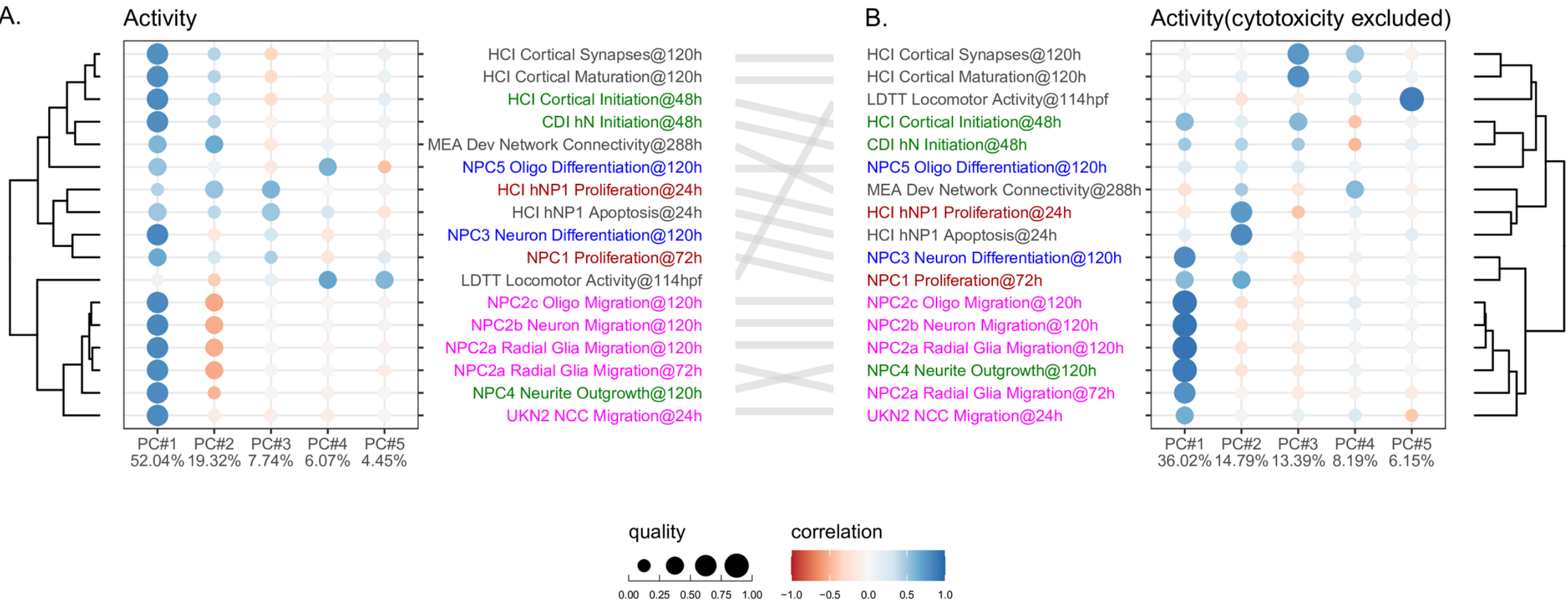
- Selective activity was observed across all e-NPs and chemical use classes



Summary of Selectivity Values (2)



Redundancy Analysis of Assays

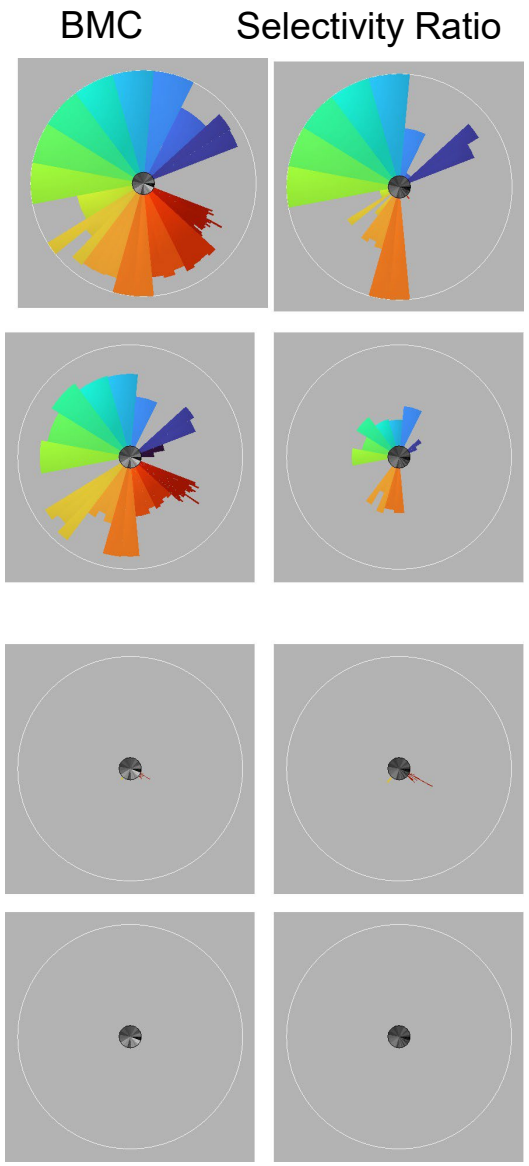


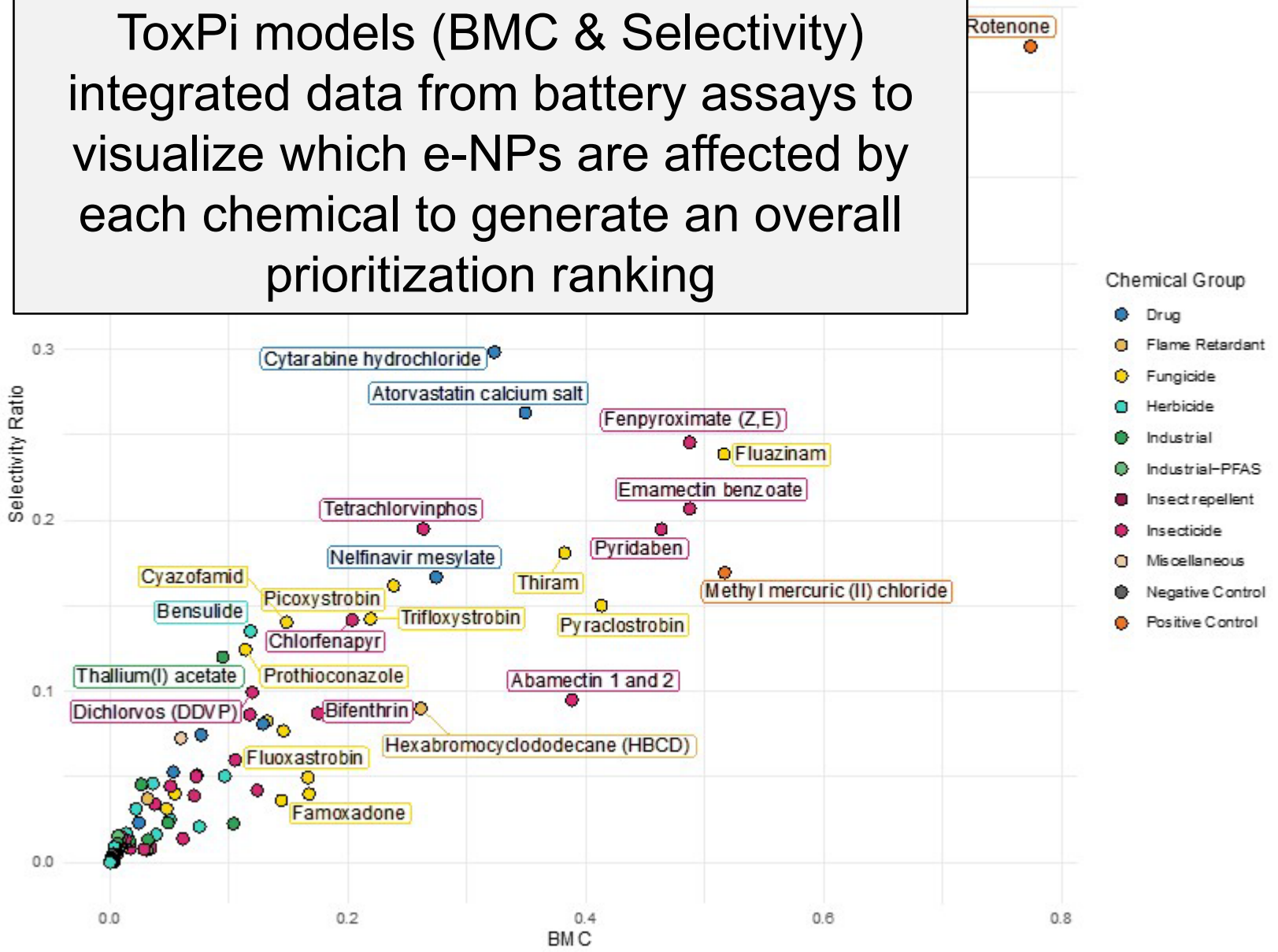
- Different assays provide complementary information that together offer a comprehensive picture of a chemical's neurodevelopmental toxicity.

National Institute of Environmental Health Sciences
Division of Translational Toxicology

Compound Prioritization Using Toxicological Prioritization Index (ToxPi)

ToxPi models (BMC & Selectivity) integrated data from battery assays to visualize which e-NPs are affected by each chemical to generate an overall prioritization ranking



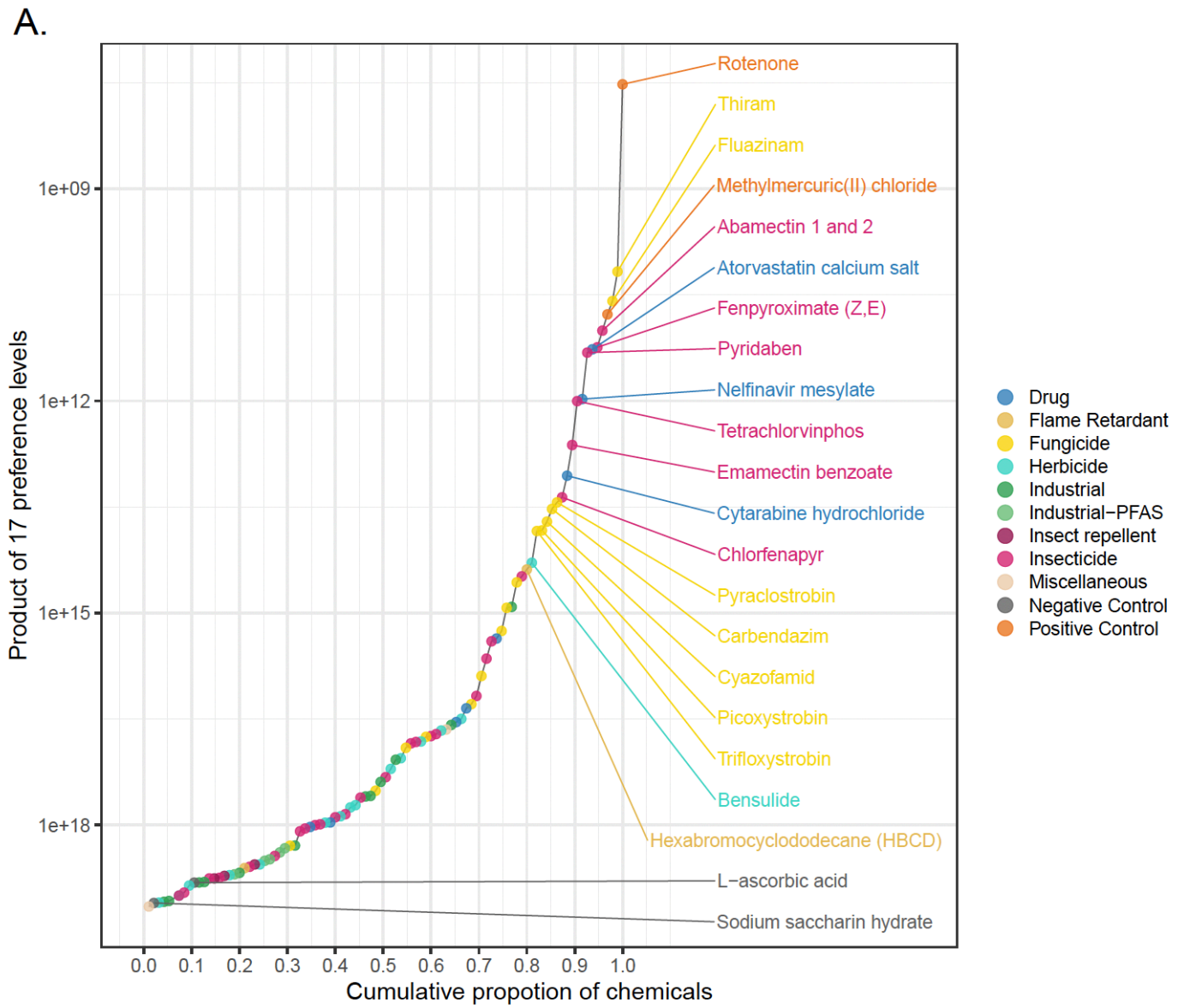


Compound prioritization using Pareto frontier rankings

Pareto ranking based on the following attributes:

1. Mean BMC from active endpoints
   Mean selectivity scores from active endpoints
2. Mean activity confidence scores from active endpoints
3. Fraction of active endpoints

- In this assessment, chemicals with higher potency and/or selectivity were considered to possess greater potential for developmental neurotoxicity and thus could be prioritized for further testing

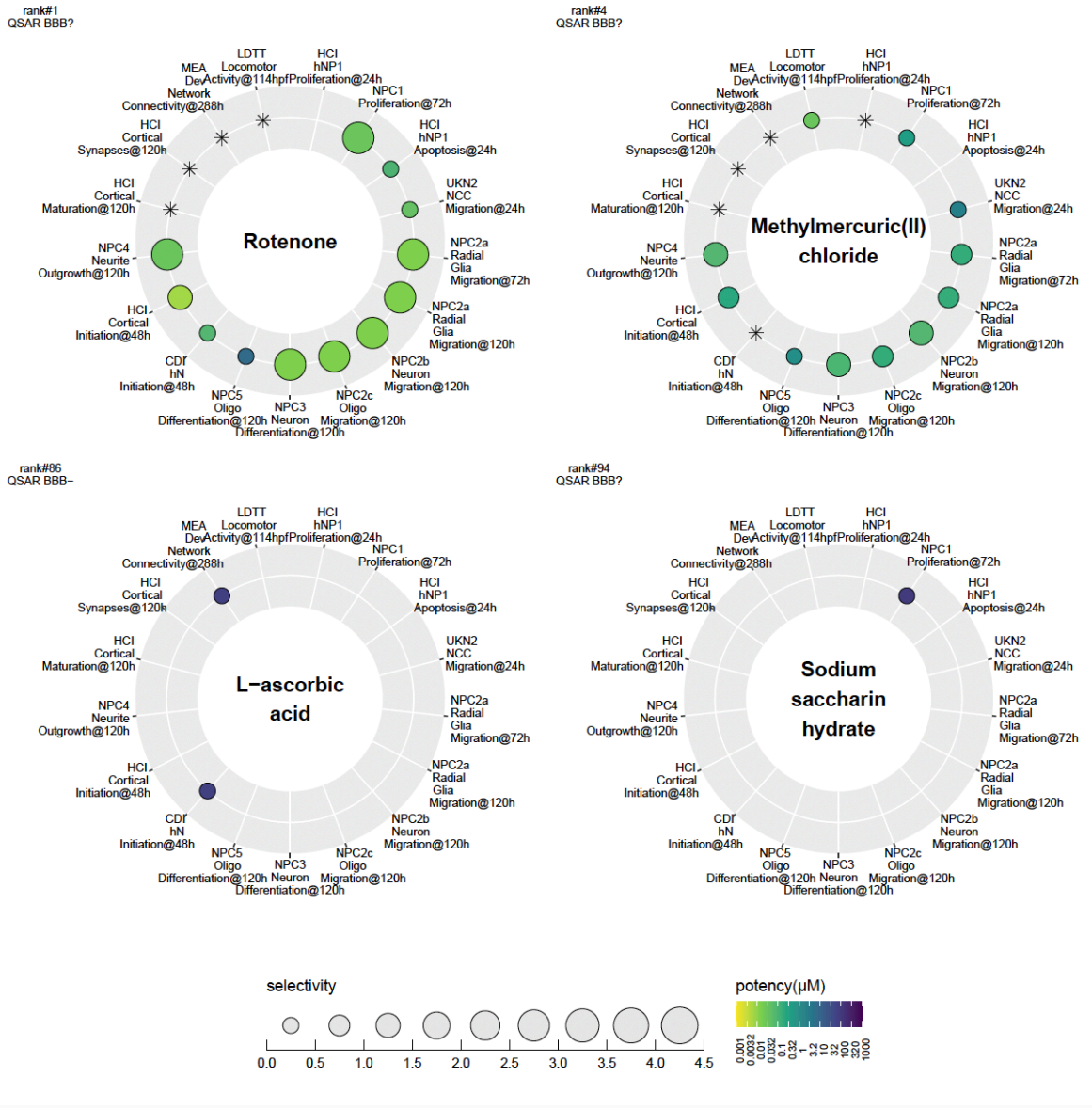


Compound prioritization using Pareto frontier rankings

Pareto ranking based on the following attributes:

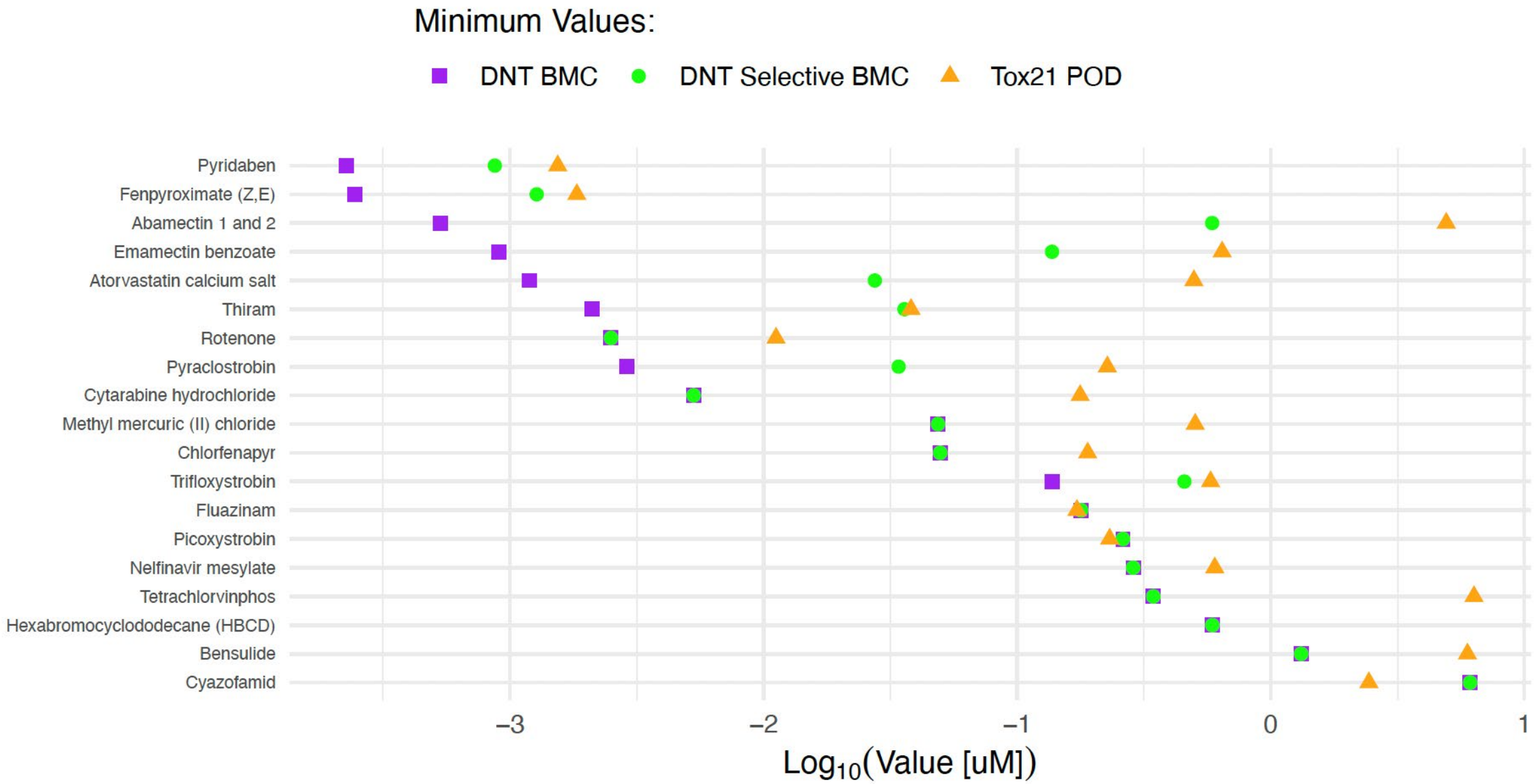
1. Mean BMC from active endpoints
   Mean selectivity scores from active endpoints
2. Mean activity confidence scores from active endpoints
3. Fraction of active endpoints

- In this assessment, chemicals with higher potency and/or selectivity were considered to possess greater potential for developmental neurotoxicity and thus could be prioritized for further testing



National Institute of Environmental Health Sciences
Division of Translational Toxicology

Comparison of DNT-Specific Endpoints to Tox21 Cytotoxicity Endpoints

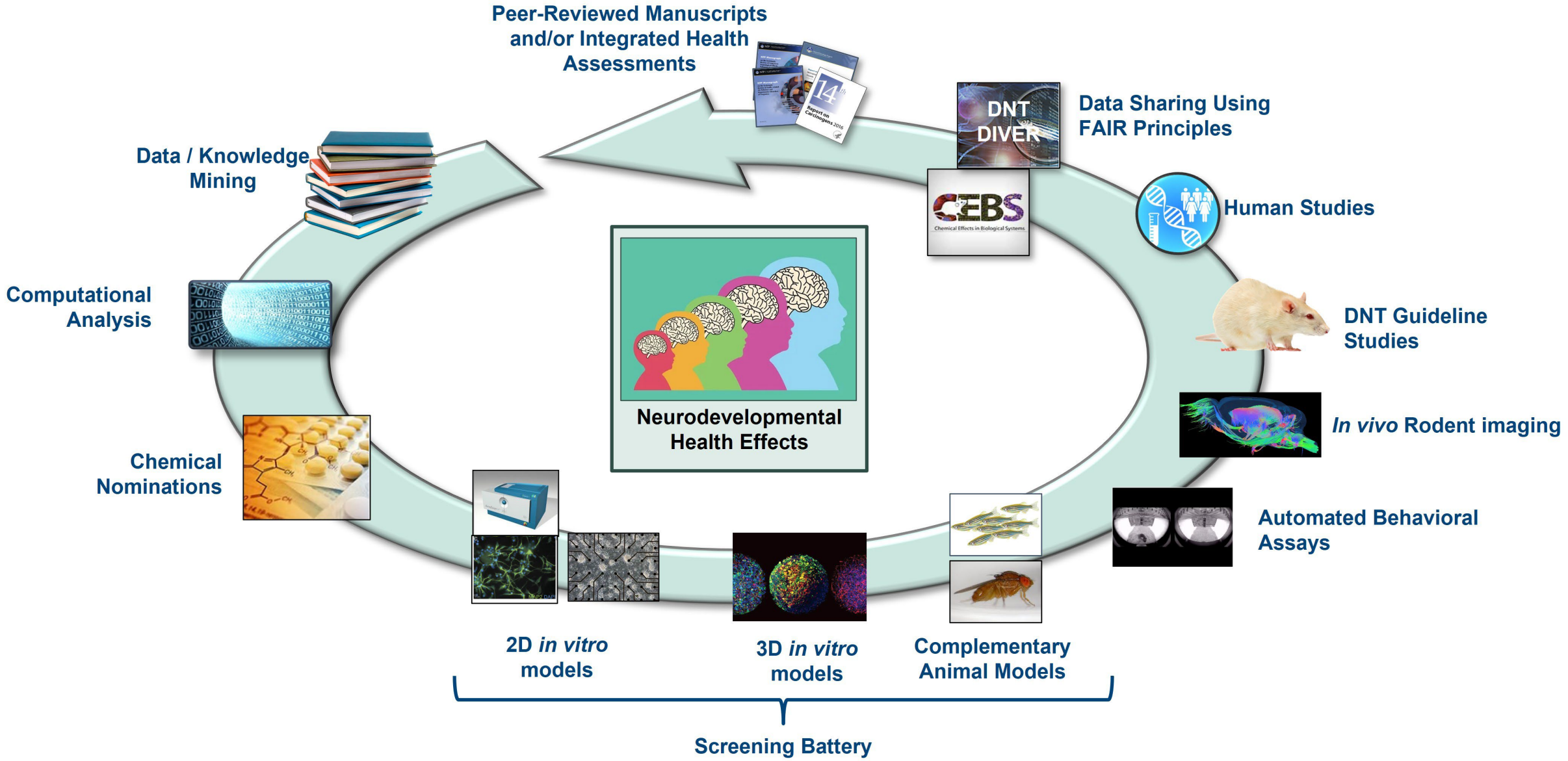


Summary of Screening Efforts To-Date

- **Summary**
  - Screening battery covers multiple endpoints, rapid, high-throughput and reproducible
  - Activity was observed with varying potency across all endpoints and chemical classes
  - The screening battery captures a wide range of potency/selectivity in the compounds we've tested.
  - It is well suited for screening and prioritization.

- **Lessons learned**
  - Current battery assays do not include all cell types necessary for neurodevelopment
  - In its current form not fit for purpose to elucidate mechanistic understanding
  - Narrow coverage of chemical universe

Future Directions



Current Team

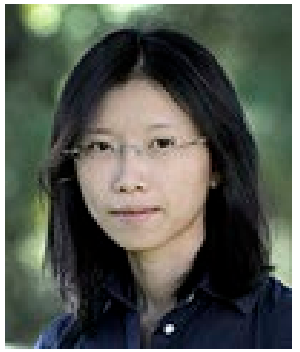

Jinyan Cao OSD


Parker Combs PTB


Jeremy Erickson PTB


Laura Hall OPO


Helena Hogberg PTB


Jui-Hua Hsieh PTB


Anna Kreutz MTP


Skylar Marvel PTB


Chris McPherson MTB


Abhishek Mishra MTB


A. J. Newell OSD


Heather Patisaul OSD


Genna St Armour


Jason Stanko OPO


Dalisa Kendricks
DTT/DIR MTB/NL
FAN Postdoc


Jesse Cushman
NL/DIR
Neurobiology Core


Robert Sills CMPB
Liaison


Stephania Papatheodorou
Climate Scholar


Leslie Wilson NL/DIR
(adjunct)


Xuying Zhang, CMPB
(adjunct)

Division of Translational Toxicoloty (DTT)
OPO (Office of Program Operations)
CMPB (Comparative & Molecular Pathogenesis Branch)
MTB (Mechanistic Toxicology Branch)
OSD (Office of the Scientific Director)
PTB (Predictive Toxicology Branch)

Division of Intramural Research (DIR)
NL (Neurobiology Laboratory)

National Institute of Environmental Health Sciences

Division of Translational Toxicology