



Comparative Toxicology as the Basis for an Integrated Human Health-Environmental NGRA Framework

John Colbourne with Isabelle Kavanagh & Xiaojing LI



University of Birmingham

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The 3 Pillars of PrecisionTox



Phylotoxichology

Replace traditional animal testing with an evolutionarily diverse suite of biomedical model organisms from multiple branches of the tree of life.



Variation in Susceptibility

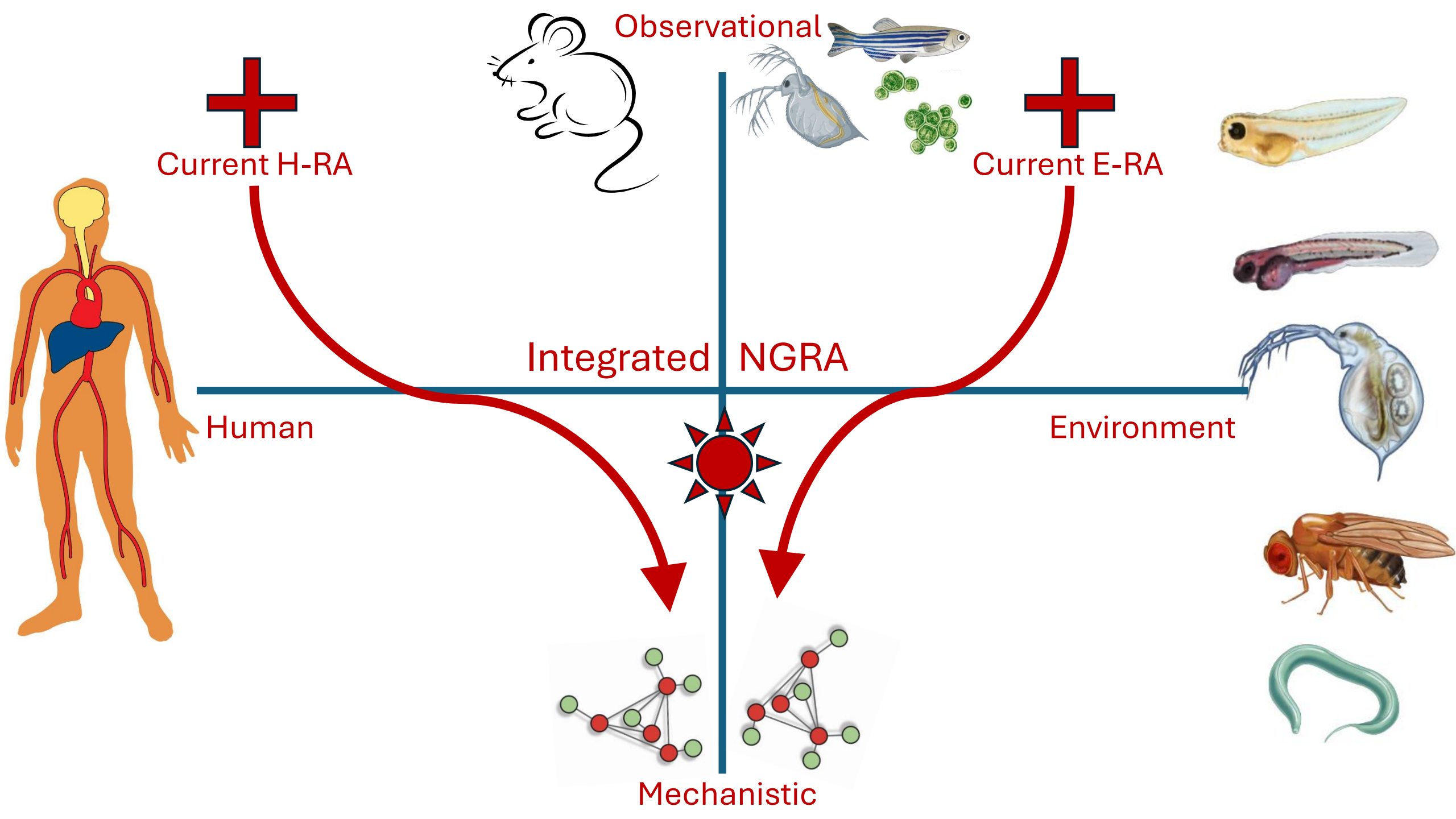
Determine safe levels of exposure to chemicals based on genetic variation.



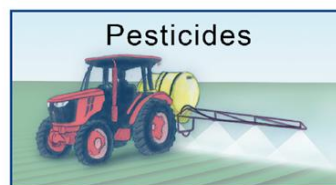
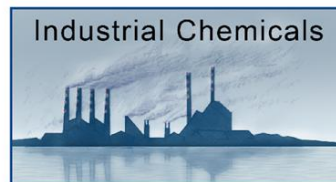
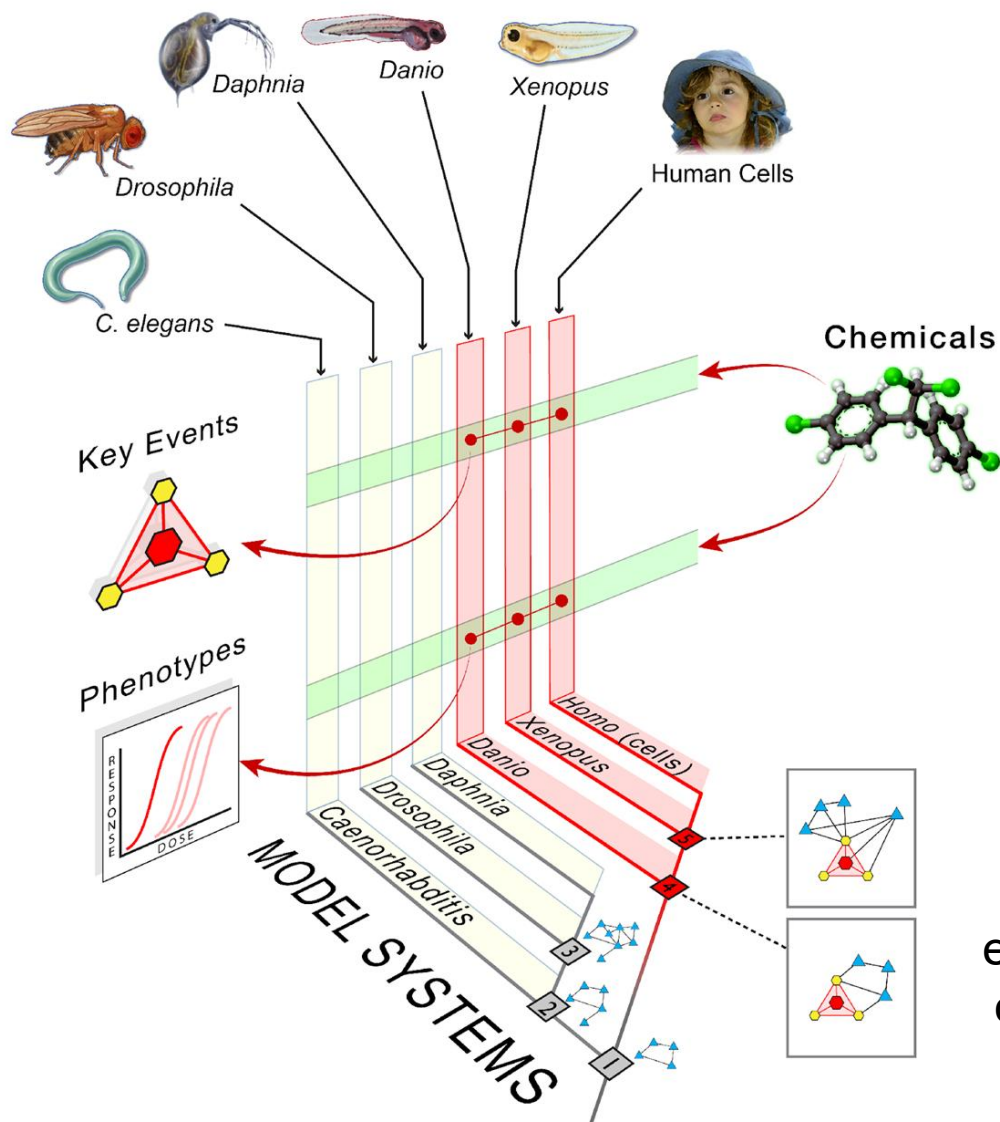
Embedded Translation

Collaborate with regulators and other key stakeholders in project planning, selection of chemicals for investigation, and case studies for applying Precision Toxicology in policy and law.





Mechanistic and evolutionary toxicology

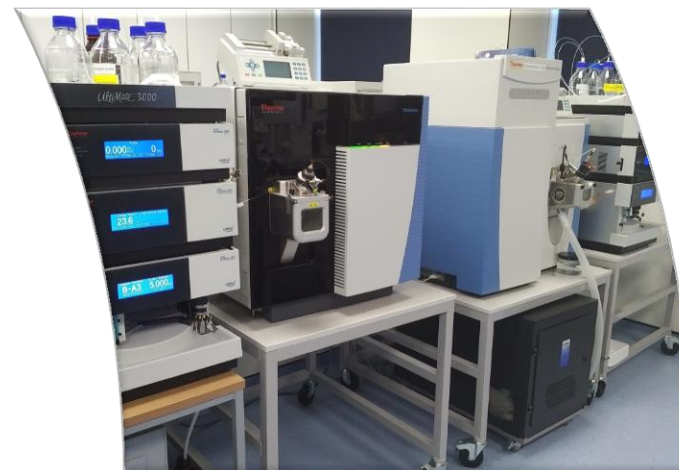


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Map of the
evolutionary origins
of the pathways to
toxicity

precisiontox.org

Comparative Metabolomics



Comparative Transcriptomics

The PrecisionTox chemicals library


CHEMICAL LIBRARY
[PrecisionTox](#)
[About](#)

[Network](#)
[List](#)

Select chemical classification:

 Use
  Toxicity

Focus on chemical:

[Reset View](#)

[Download Snapshot](#)

54

Pesticide

87

Pharmaceutical

5

Food and other consumption

31

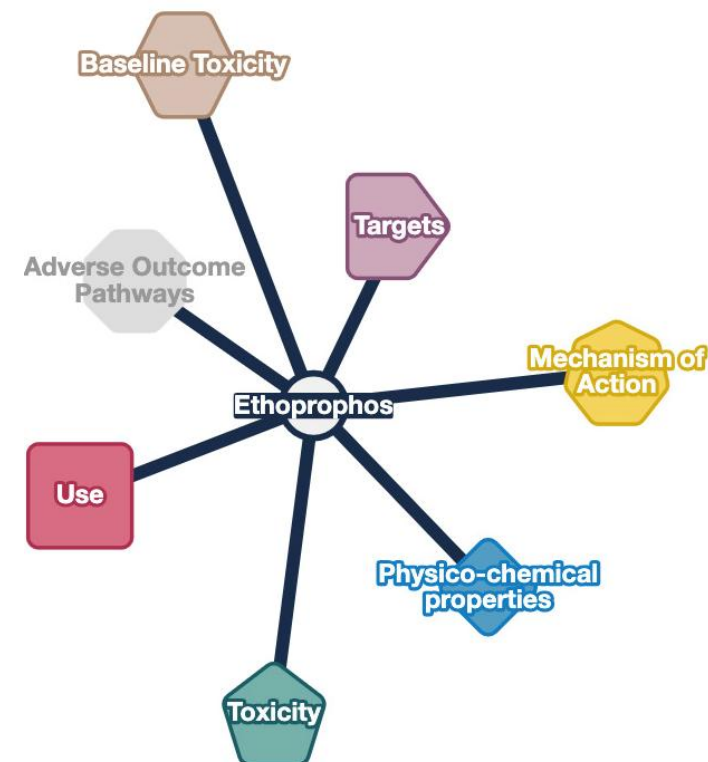
Industry and consumer goods

10

Personal care products

11

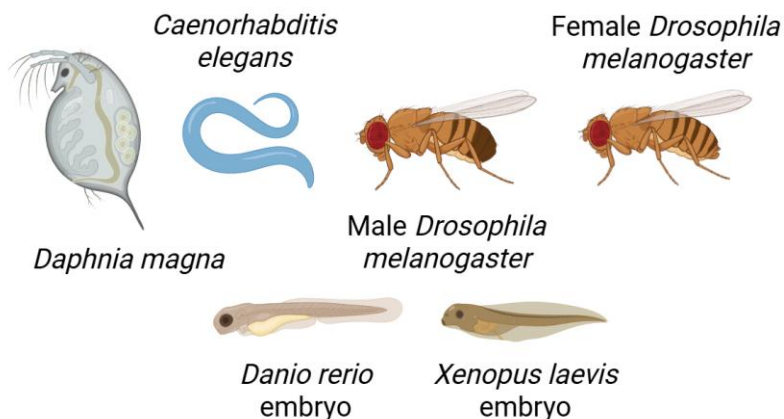
Endogenous



54 Cardiotox – 110 Hepatotox – 53 Nephrotox – 85 Genotox
 94 Neurotox – 11 Ototox – 40 Immunotox – 12 Hematotox

Comparing species sensitivities

PrecisionTox Dataset



80 chemicals
(subset)

Endpoints:
Immobilisation &
Mortality

48-hour exposure



Shao & Shapiro (2018)

MCMC Sampling

Non-informative priors

8 Dose-Response Models

Produces
posterior
distributions
of **BMD₁₀**
estimates

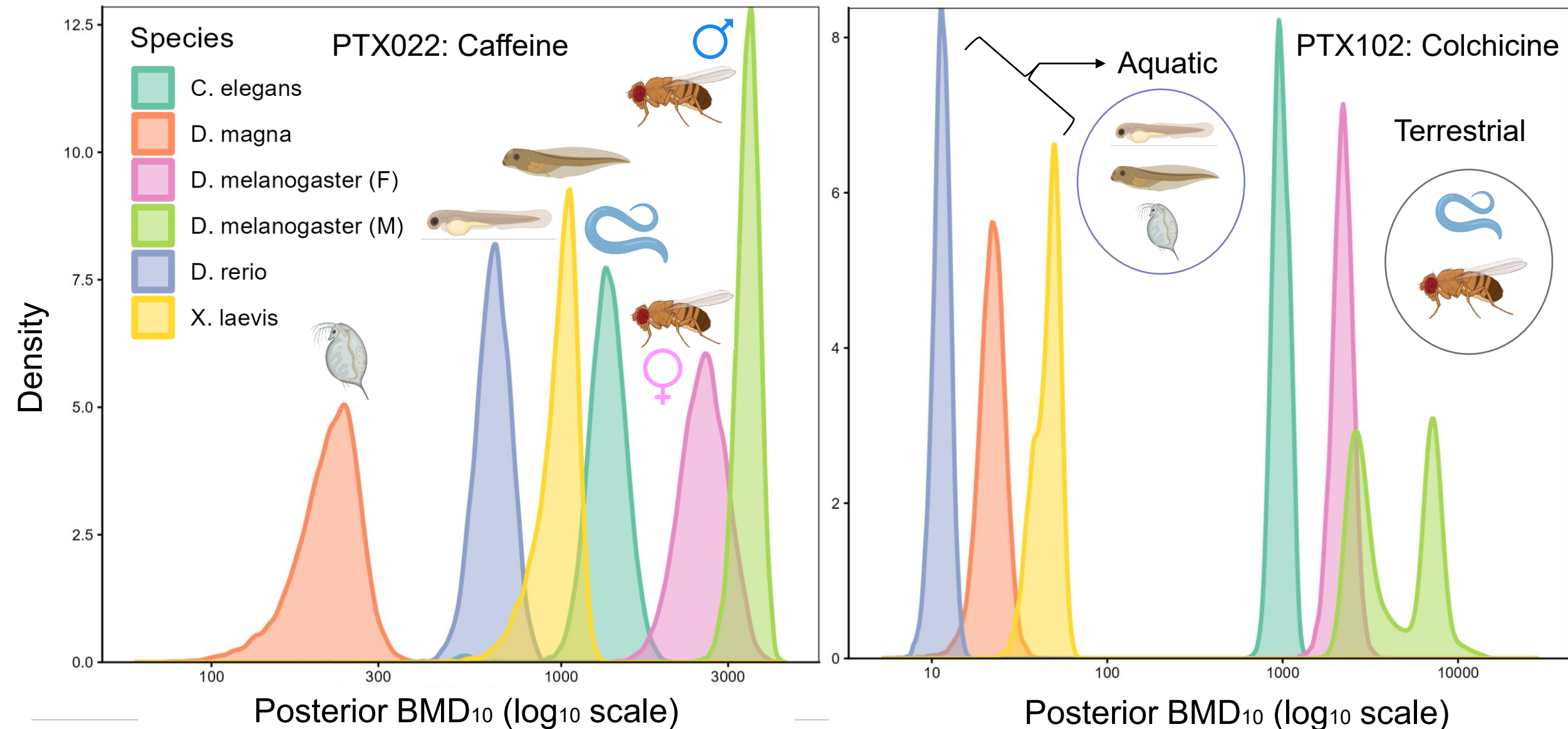
**Bayesian Model
Averaging**

Benchmark
Response = **10%**
Extra Risk

Model Diagnostics

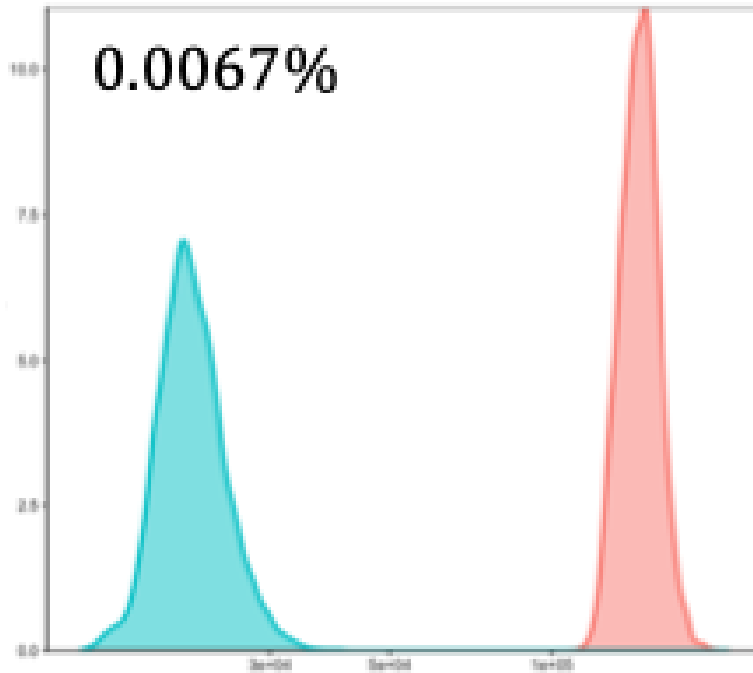
- Convergence
- Effective Sample Size
- Model Fit

Density plots of species sensitivity



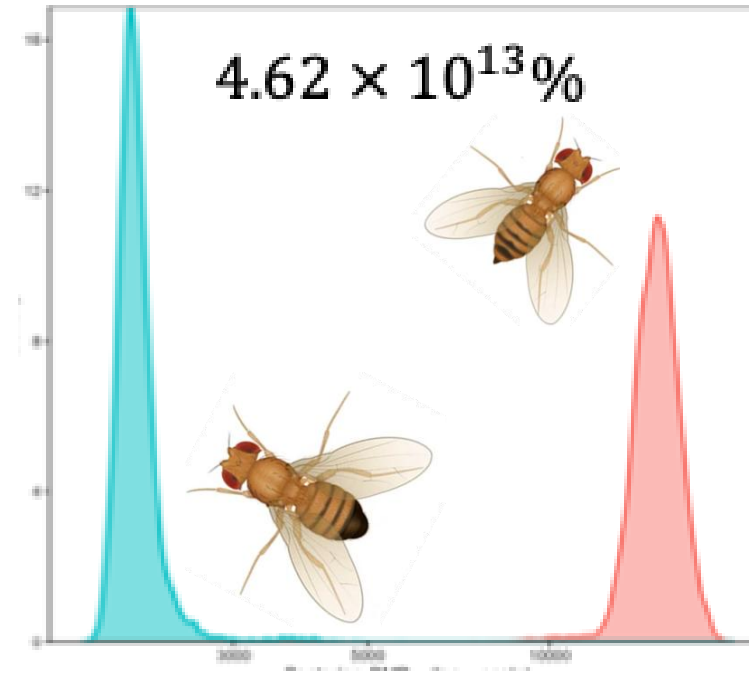
How well do we understand biology?

PTX059 - N,N-Dimethylacetamide



Posterior BMD₁₀ (log₁₀ scale)

PTX075 - 1-ethyl-1H-imidazole



Posterior BMD₁₀ (log₁₀ scale)

Overlap Coefficient %



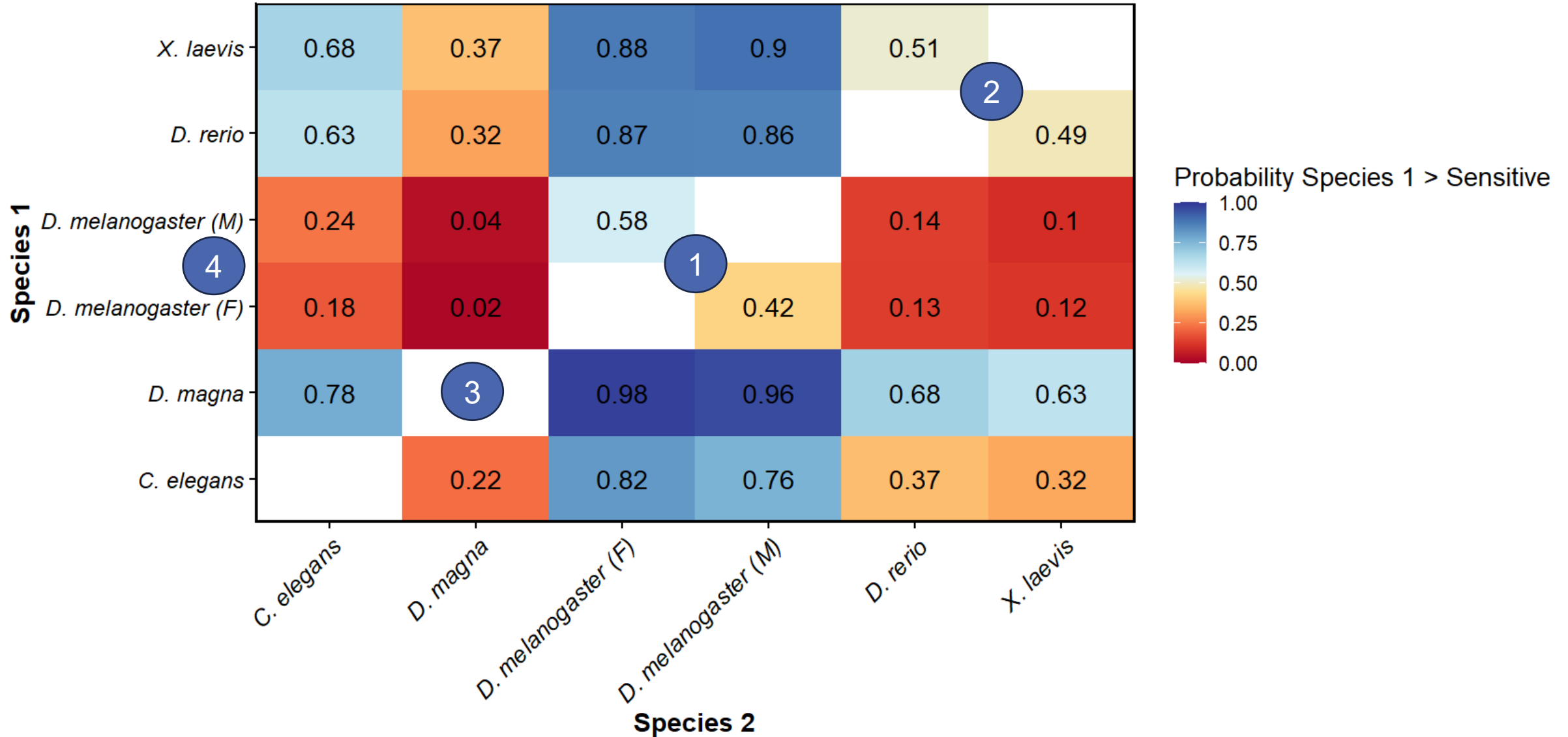
Drosophila female



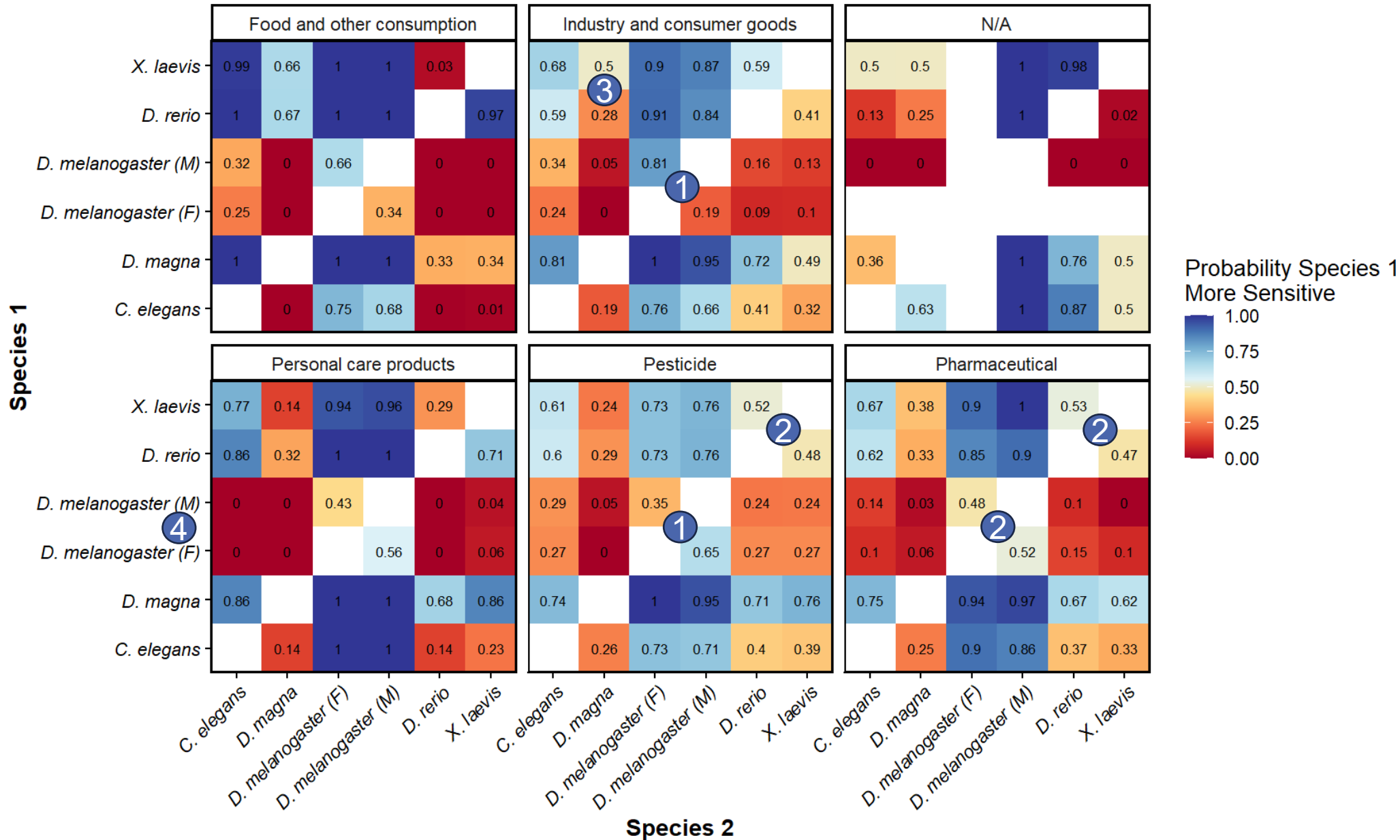
Drosophila male

Male & female responses show **>50% overlap** in just **17.24%** of chemical comparisons

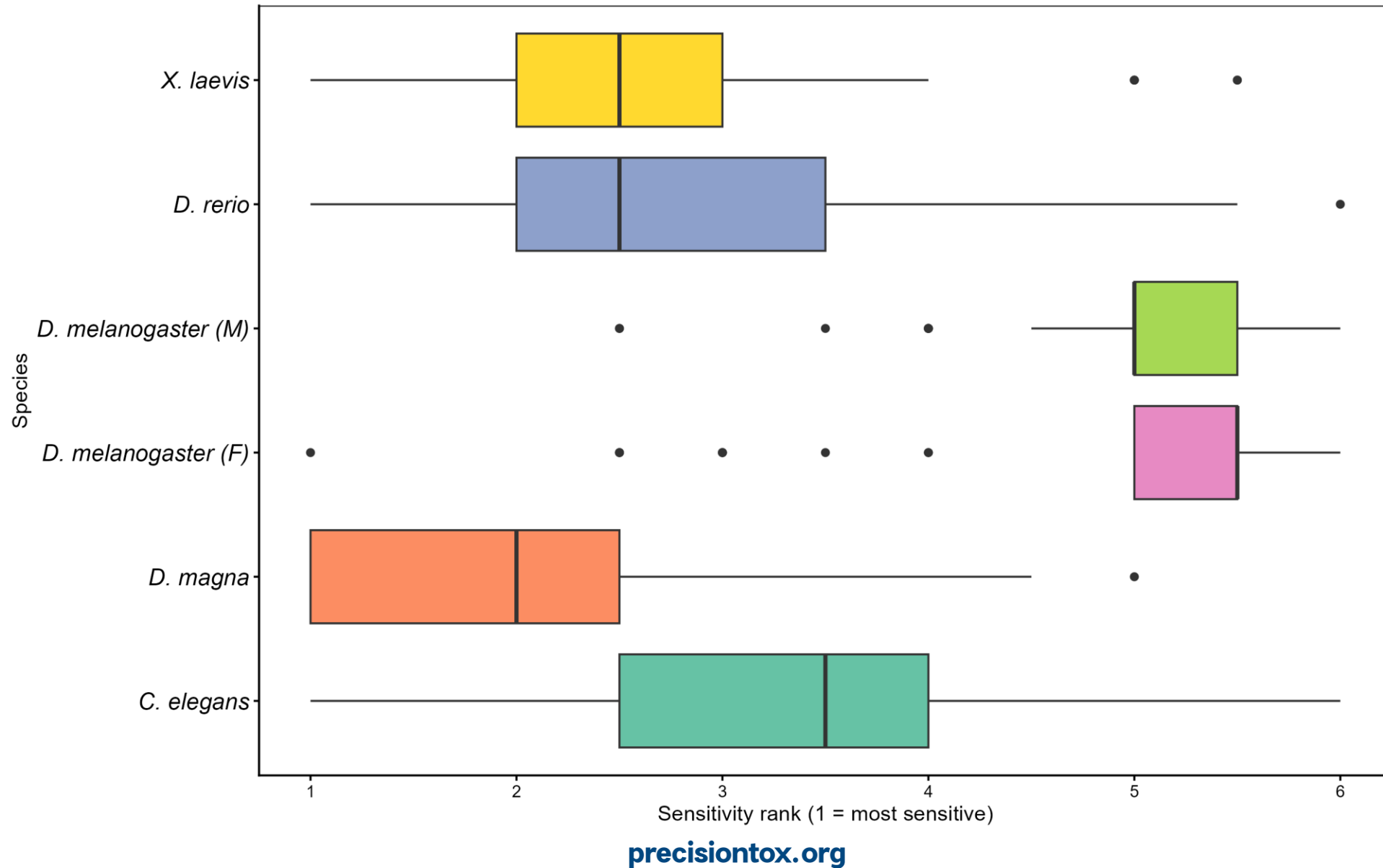
Probability of species sensitivity



Species sensitivity by chemical use



Phylogenetic replacement





Largest harmonised comparative toxicity dataset

[Home](#)[Explore](#)[Compare](#)[Experiments](#)[API](#)[Download](#)

PrecisionTox phenotype dashboard

Overview of phenotype data coverage across organisms, endpoints and chemicals.

Experiments

Browse experiment metadata, conditions and batch-level summaries.

Explore Endpoints

Inspect endpoint distributions, dose-response curves and raw records.

Compare Endpoints

Compare chemicals across endpoints with clustered heatmaps.

Data overview

Exposure Experiments

959

Exposure Conditions

129,459

Phenotype records

1,846,720

Phenotypic Endpoints

132

Organisms covered

5

Chemicals covered

204

Data composition

Summary of condition and experiment composition in the phenotype dataset.

Control conditions

21,217

Treatment conditions

108,242

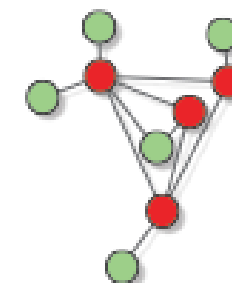
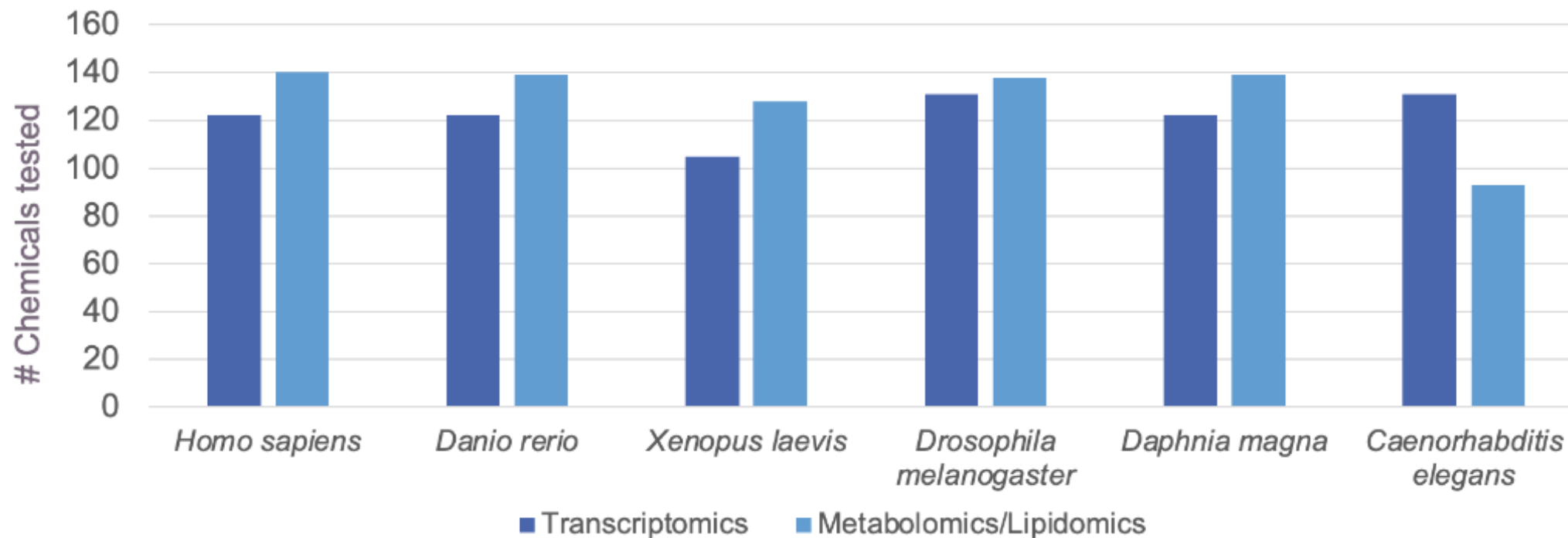
Aggregated experiments

553

Non-aggregated experiments

406

Largest multi-omics toxicological dataset



TRANSCRIPTOMICS

CHEMICALS WITH ANY DATA

131

CHEMICALS WITH DATA IN ALL 6 ORGANISMS

105

CONTRASTS

1,684

OBSERVATIONS

26,283,008

X 2 within 2 months from now

METABOLOMICS

CHEMICALS WITH ANY DATA

140

CHEMICALS WITH DATA IN ALL 6 ORGANISMS

86

CONTRASTS

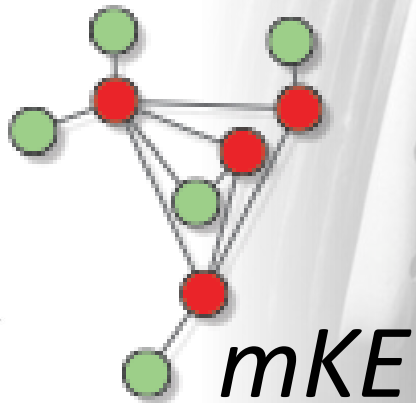
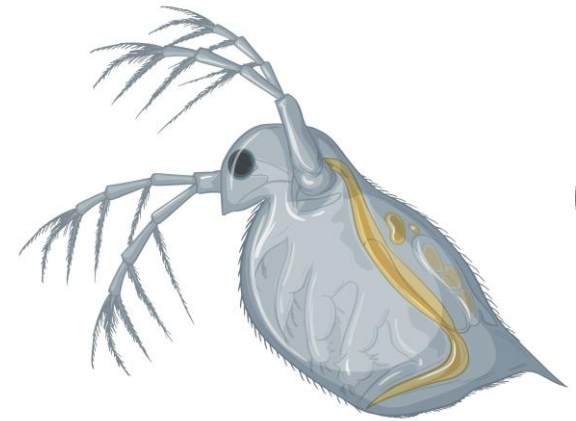
3,449

OBSERVATIONS

29,932,825

X 2 within 2 months, approx.

Biomolecular pathways as early warning systems (sentinels)



Integrated next-generation risk assessment (iNGRA)

Field sampling (Danube River)

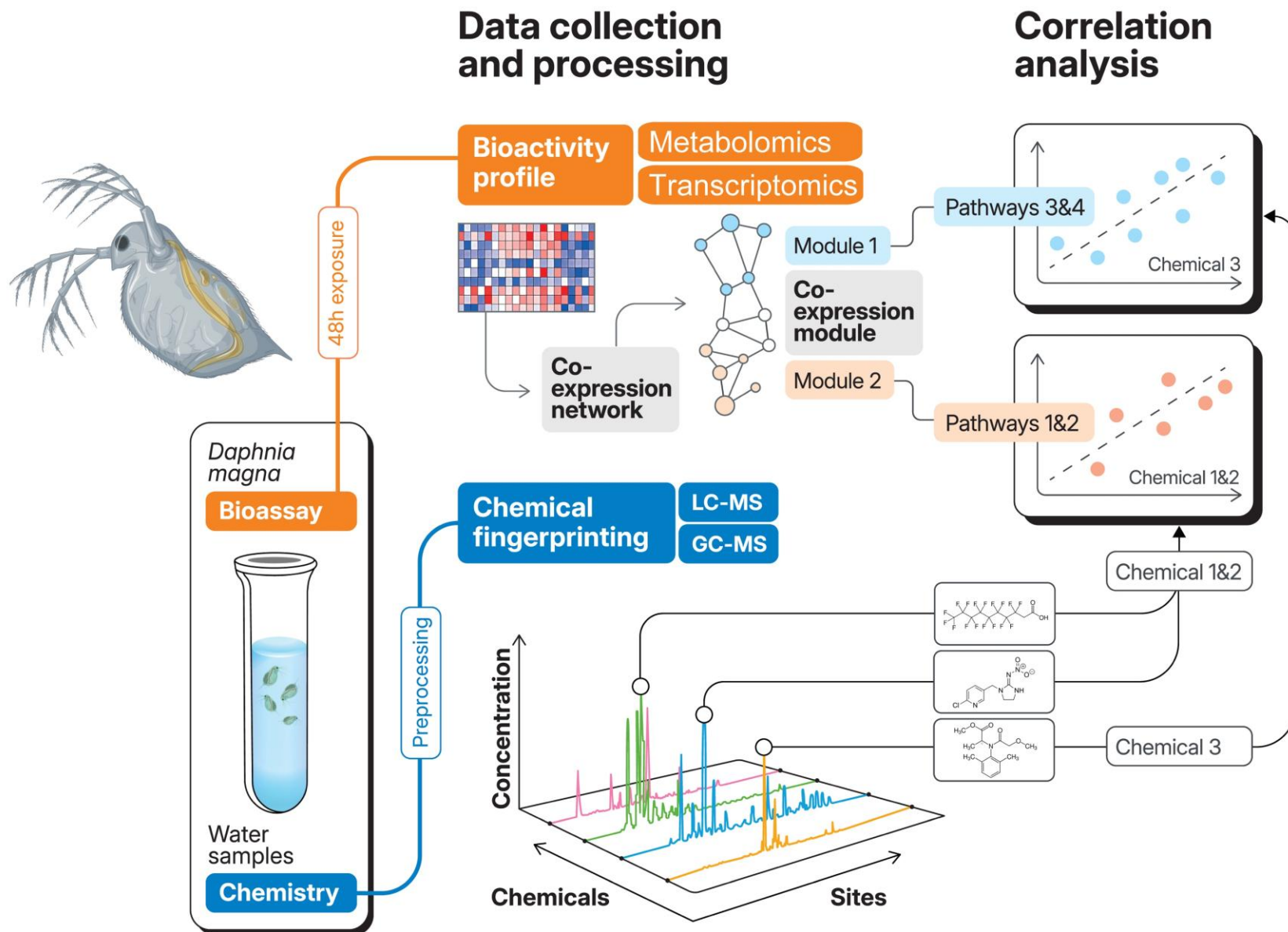
- 12 sampling sites collecting organic extracts and diluting back to original concentration

Chemical fingerprinting

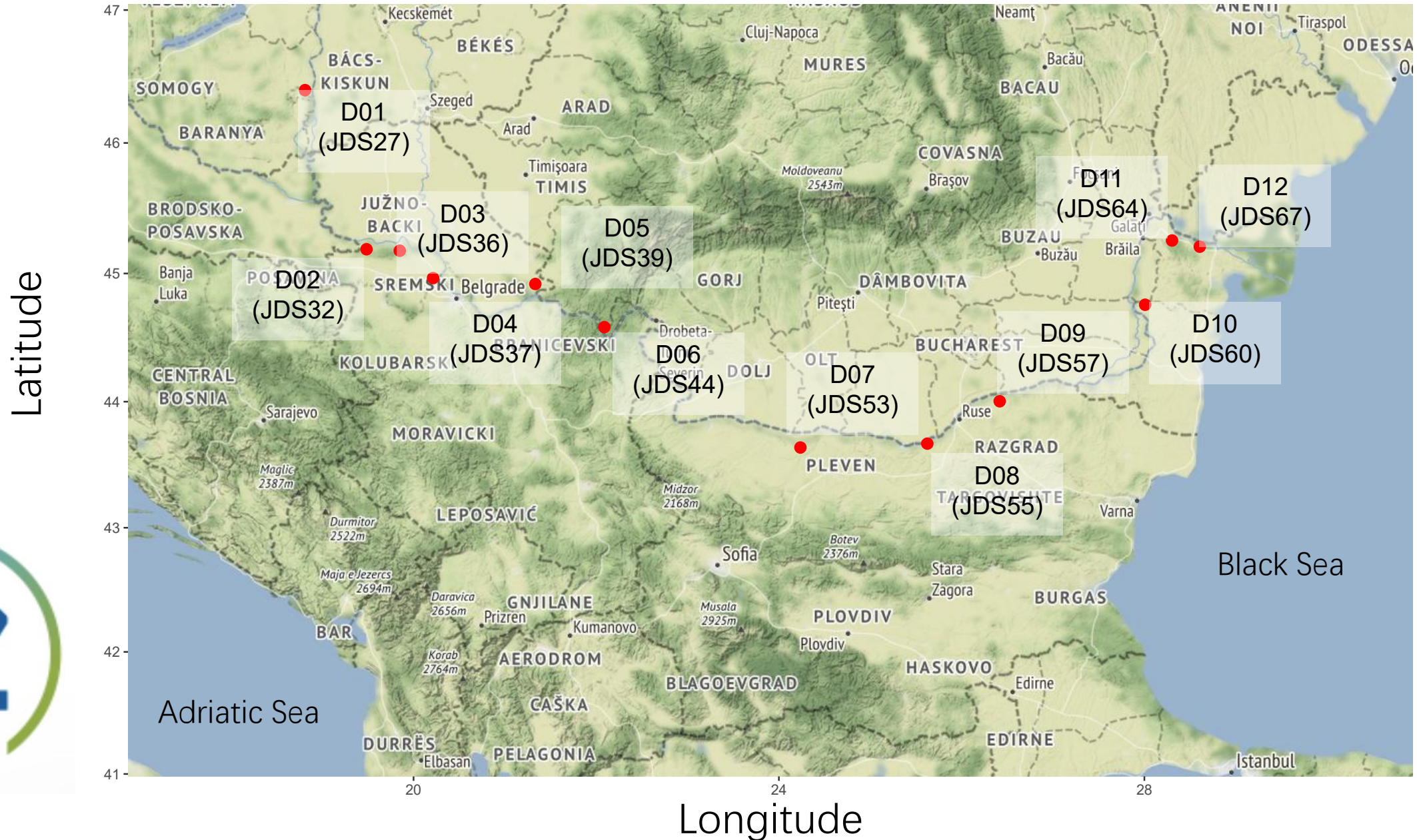
- Non-target screening (semi-quantification of 91 substances)

Bioactivity profiling

- RNAseq for transcriptome
- DIMS for metabolome (Polar positive, Polar negative)

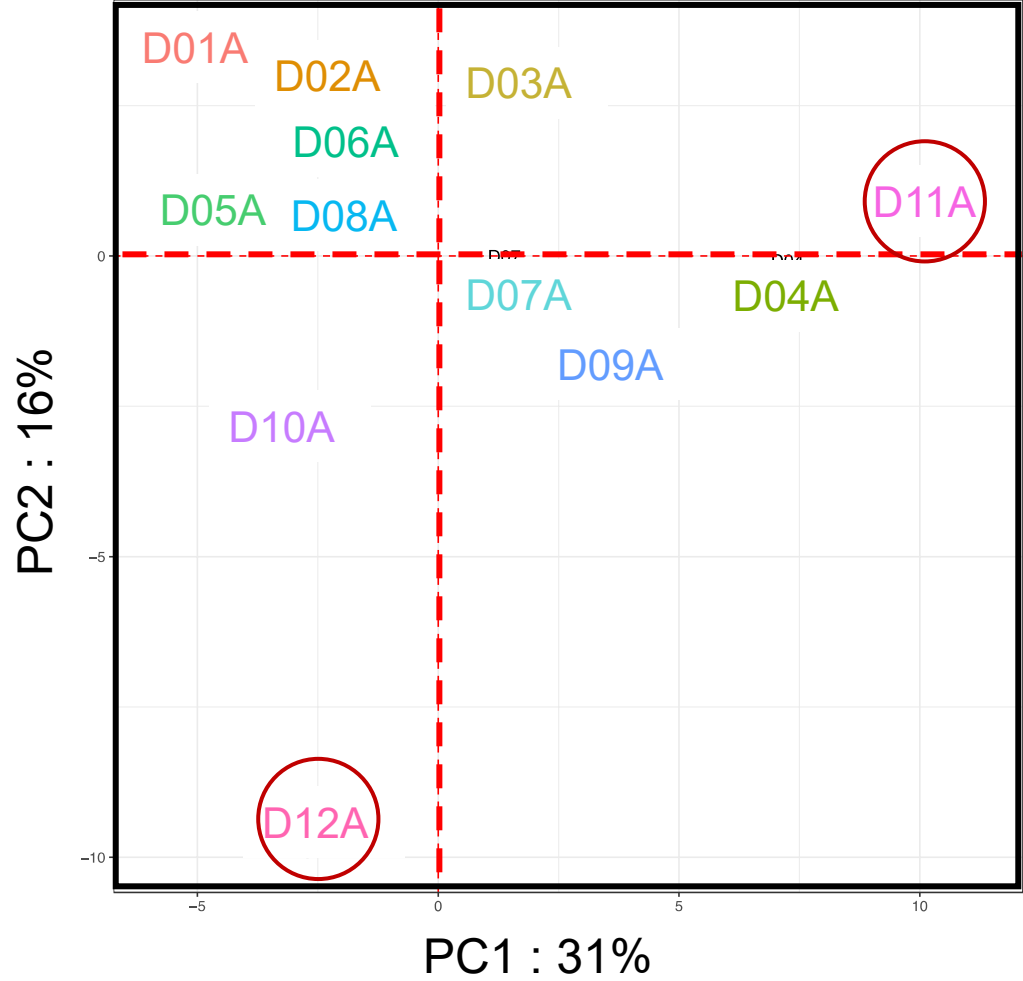


Case Study: sample sites along the Danube River

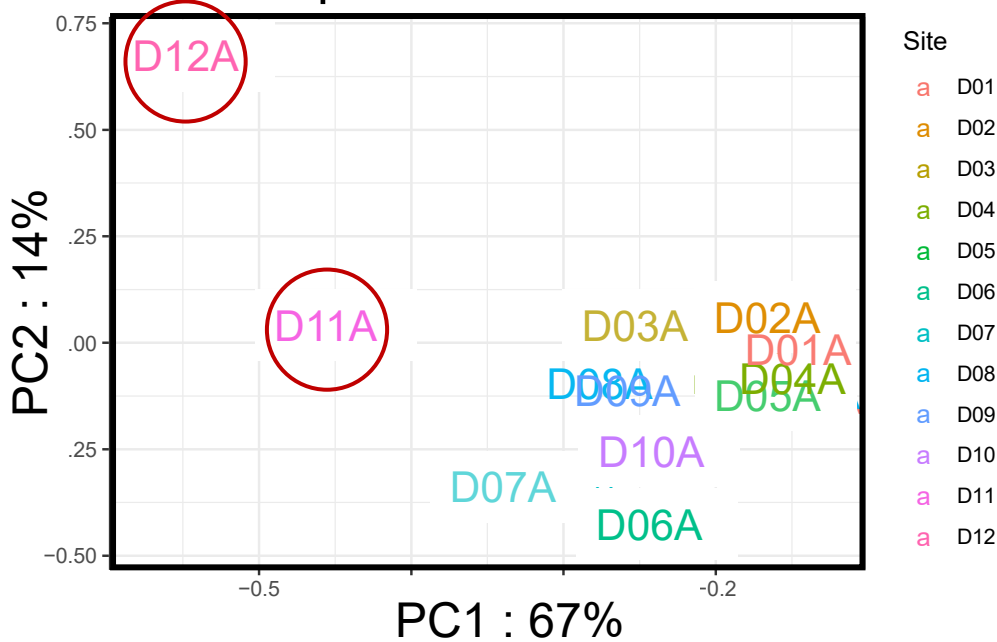


Data overview with PCA plots

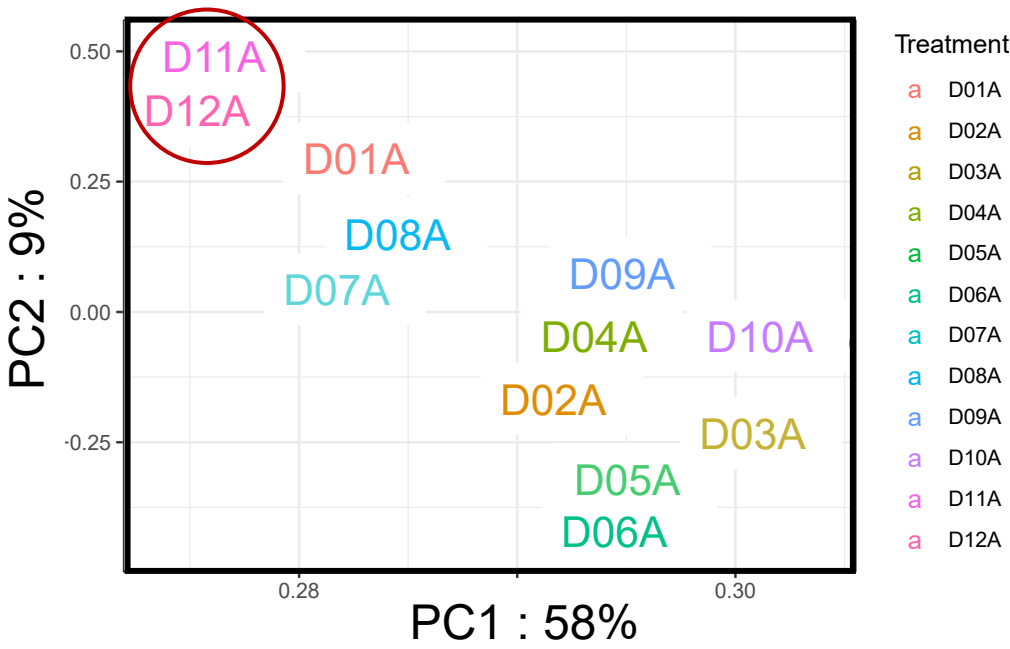
Chemical data



Transcriptomic data



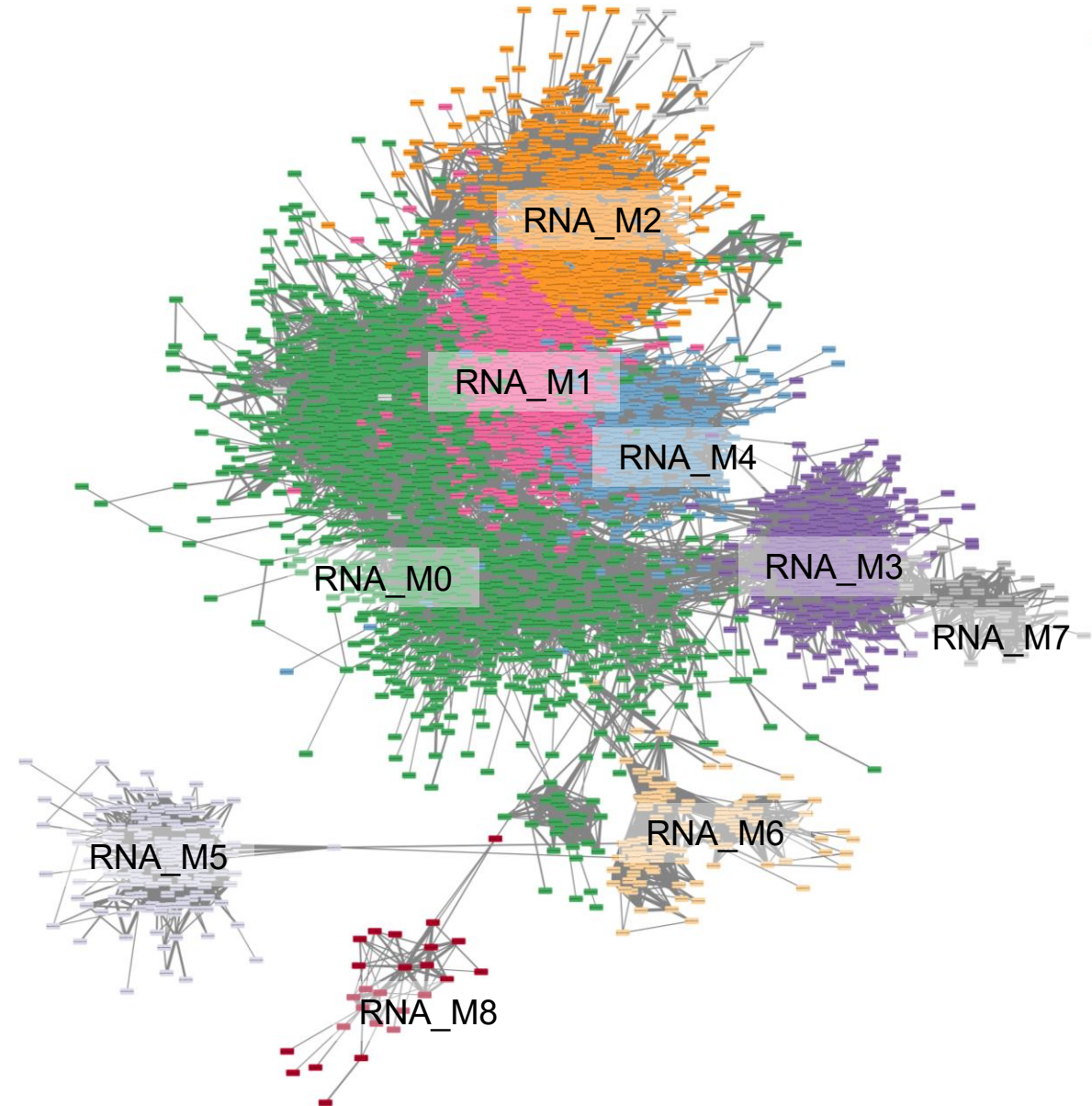
Metabolomic data



Putative *mKEs* by networks

Data set	# Feature	# Module	Max size	Min size
RNA	19549	11	1243	20
Polar positive	1285	19	98	10
Polar negative	2331	28	204	11

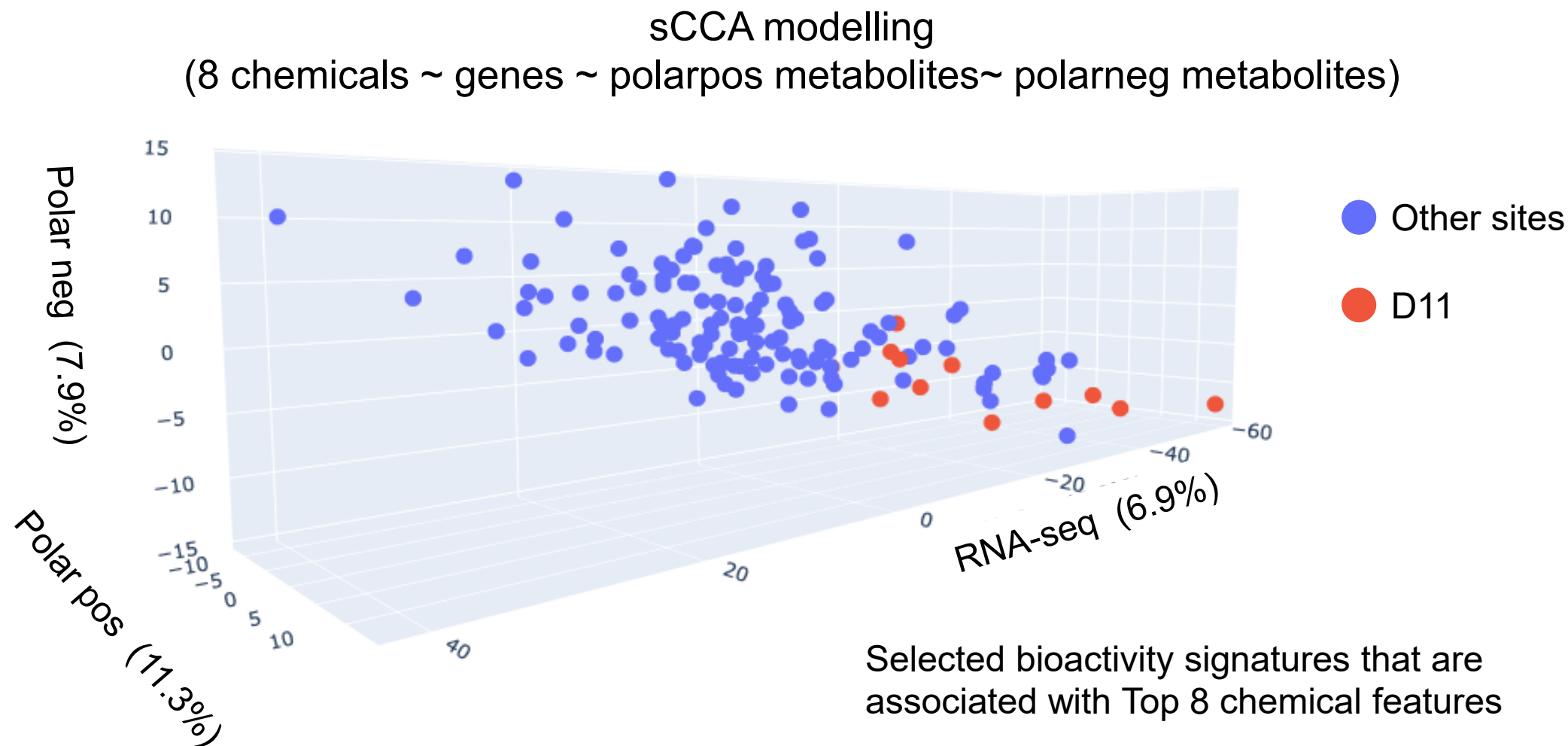
RNA co-expression network



Select chemical by MRMR/sCCA

D11

	Minimum redundancy maximum relevance	Pairwise correlation (feat Imp)	Sparse canonical correlation analysis	Joint correlation
herbicide	Metolachlor	0.94	Metolachlor	Explained variance: 53.3 % ; Correlation: 0.62
herbicide	Isoproturon	0.84	Isoproturon	
sweetener	Sucralose	0.82	Sucralose	
Pharmaceutical TPs	10,11-Dihydro-10,11- dihydroxy-carbamazepine	0.77	10,11-Dihydro-10,11- dihydroxy-carbamazepine	
Pharmaceutical TPs	10,11-Dihydro-10- hydroxycarbamazepine	0.76	10,11-Dihydro-10- hydroxycarbamazepine	
Pharmaceutical	Carbamazepine	0.72	Carbamazepine	
Pharmaceutical metabolite	N-Acetyl-4-aminoantipyrine	0.72	N-Acetyl-4-aminoantipyrine	
Pharmaceutical metabolite	2-Hydroxycarbamazepine	0.70	2-Hydroxycarbamazepine	
	Benzophenone-4	0.68	N-Formyl-4-aminoantipyrine	Top 8 chemical components that distinguish D11 from other sites (bi-class labels)
	Terbutylazine-2-hydroxy	0.64	Chloridazon	



mKE Effect by pathway analysis

Module ID	Module Size	With annotation	FDR q-value
RNA_M1	922	438	1.09E-105
RNA_M4	296	112	1.79E-08
RNA_M2	746	362	5.75E-94
Polarpos_M3	38	4	1.51E-07
Polarpos_M9	27	6	2.54E-02
Polarneg_M17	22	9	2.11E-02
Polarneg_M1	176	36	3.76E-10
Polarneg_M11	46	7	4.32E-07
Polarneg_M24	13	9	3.50E-02
Lipidpos_M4	128	43	6.66E-04

D11

Enriched Pathway	Module ID
Metabolism of xenobiotics by cytochrome P450	RNA_M1 & M2
Chemical carcinogenesis - DNA adducts	RNA_M1, M2, M4
Drug metabolism - cytochrome P450	RNA_M1 & M2
Nitrogen metabolism	RNA_M1 & M4
Drug metabolism - other enzymes	RNA_M1 & M2
PPAR signalling pathway	RNA_M1 & M2
ABC transporter	RNA_M2
Chemical carcinogenesis - receptor activation	RNA_M2
Glutathione metabolism	RNA_M1
Isoflavonoid biosynthesis	Polarneg_M1
One carbon pool by folate	Polarneg_M4

Conclusion – *mKEs* of top 8 chemical components

D11

Two Herbicides, one sweetener, five pharmaceuticals

Chemical set

Metolachlor
Isoproturon
Sucralose
10,11-Dihydro-10,11-dihydroxy-carbamazepine
10,11-Dihydro-10-hydroxycarbamazepine
Carbamazepine
N-Acetyl-4-aminoantipyrine
2-Hydroxycarbamazepine

Association



mKEs

RNA_M1
RNA_M4
RNA_M2
Polarpos_M3
Polarpos_M9
Polarneg_M17
Polarneg_M1
Polarneg_M11
Polarneg_M24
Lipidpos_M4

Interpretation

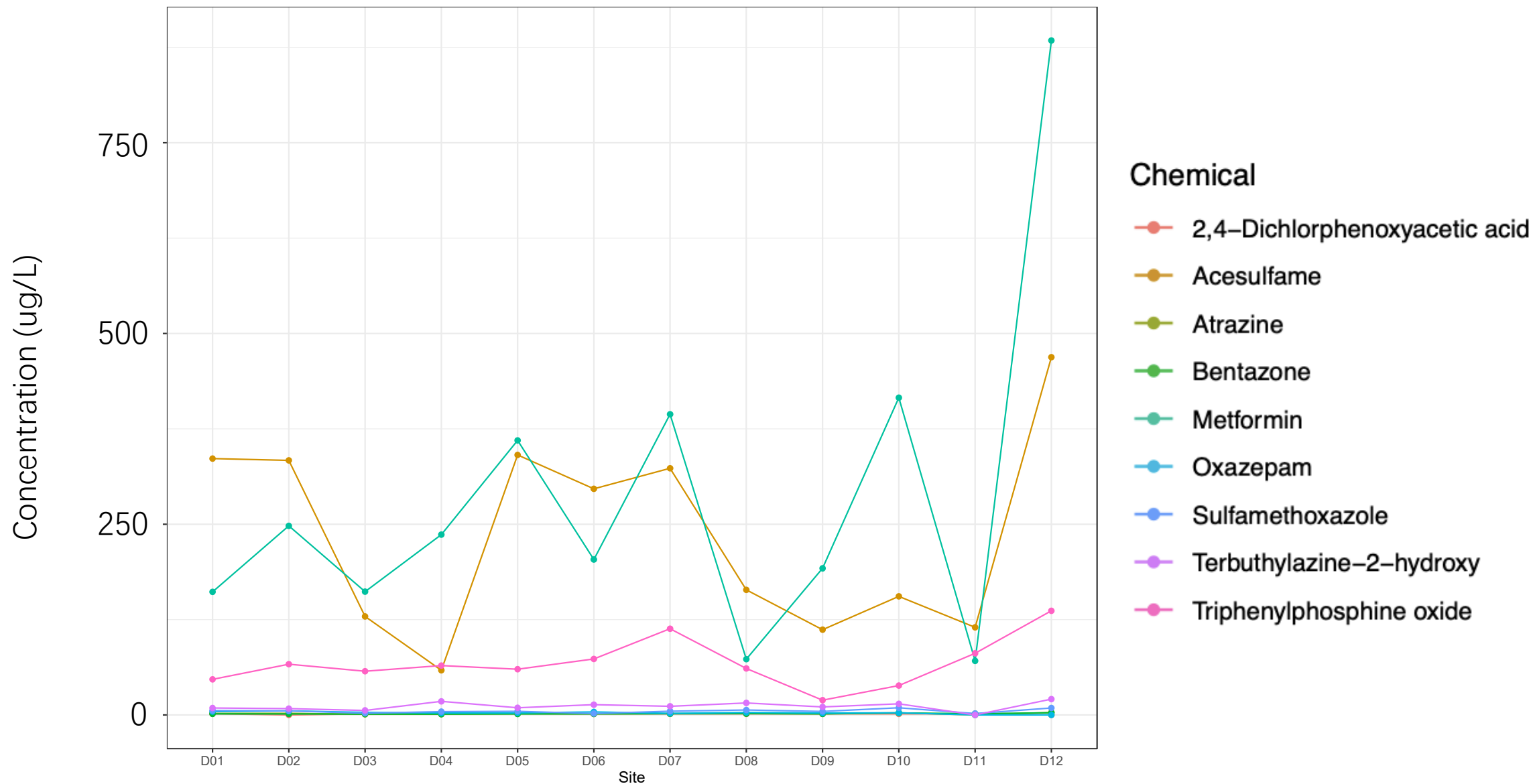


Pathway profile

Metabolism of xenobiotics by cytochrome P450
Chemical carcinogenesis - DNA adducts
Drug metabolism - cytochrome P450
Nitrogen metabolism
Drug metabolism - other enzymes
PPAR signalling pathway
ABC transporter
Chemical carcinogenesis - receptor activation
Glutathione metabolism
Isoflavonoid biosynthesis
One carbon pool by folate

D12

Top 9 Chemical components that distinguish D12 from the rest



Conclusion – *mKEs* of top 9 chemical components

D12

Chemical set

Metformin (PHAR)
Bentazone (HER)
2,4-Dichlorophenoxyacetic acid (HER)
Triphenylphosphine oxide (FR)
Atrazine (HER)
Acesulfame (SW)
Oxazepam (PHAR)
Terbutylazine-2-hydroxy (HER)
Sulfamethoxazole (PHAR)

mKEs

RNA_M1
RNA_M6
Polarpos_M3
Polarpos_M7
Polarneg_M27
Polarneg_M15
Polarneg_M3
Polarneg_M17
Polarneg_M24
Polarneg_M0
Polarneg_M1
Polarneg_M14
Polarneg_M13

Association



Interpretation



Pathway profile

Metabolism of xenobiotics by cytochrome P450
Chemical carcinogenesis - DNA adducts
Drug metabolism - cytochrome P450
Nitrogen metabolism
Drug metabolism - other enzymes
PPAR signalling pathway
Glutathione metabolism
Isoflavonoid biosynthesis

With reference to conserved biomolecular processes


PTox/DEx | PrecisionTox Data Explorer
Data
Downloads
About

Transcriptomics
Metabolomics
Chemicals
Orthologs
Functions
Log out

Explore Data
Metabolite Centric View
Compare Data

Choose organisms to compare:

C_elegans x
Danio_rerio x
Daphnia_magna x
Drosophila_melanogaster_female x
Xenopus_laevis x

Choose assay type:

All

Choose chemical:

Acrylamide

Choose dose:

BMD10

Choose timepoint (hours):

All

Choose direction of gene expression:

Both

Set p-value cutoff using:

☒ Raw p-value
 ☐ Adjusted p-value

0 0.025 0.05 0.075 0.1 0.125 0.15 0.175 0.2 0.225 0.25

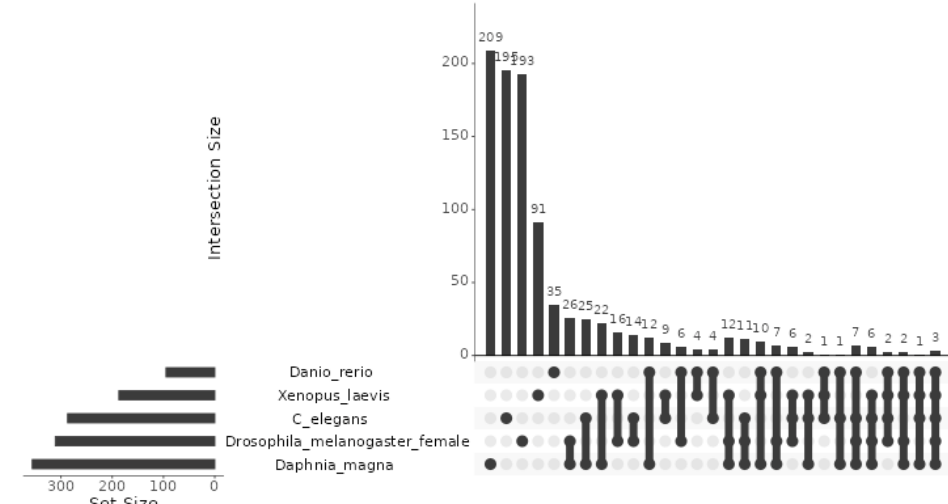
Log2FoldChange cutoff (in the direction chosen above)

0 1 2 3 4 5 6 7 8 9 10

Submit

Here you compare the metabolomics data across all species. Note: Click on the submit button only once, you might have to wait up to 15 seconds to get the results. The vertical bar plot (called an upset plot) shows the number of metabolites that are unique or overlap between the chosen species (overlap indicated by the points and connected lines). The horizontal bars on the left are the number of significant metabolites in each organism.

Upset Plot



Common chemicals

Show 10 entries CSV Excel Print Copy

Search:

Annotation	Structure	Found in	Inchikey	Pubchem ID	KEGG ID	Known links to genes in	In Mtox700
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Evolution-informed sentinel species for 1-Health Toxicology

