PRECISION TOX

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

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CERJ
CENTRE FOR ENVIRONMENTAL RESEARCH AND JUSTICE

ASPIS Open Symposium

2 July 2026

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No. 965406

The 3 Pillars of PrecisionTox

PRECISION TOX

Phylotoxicology

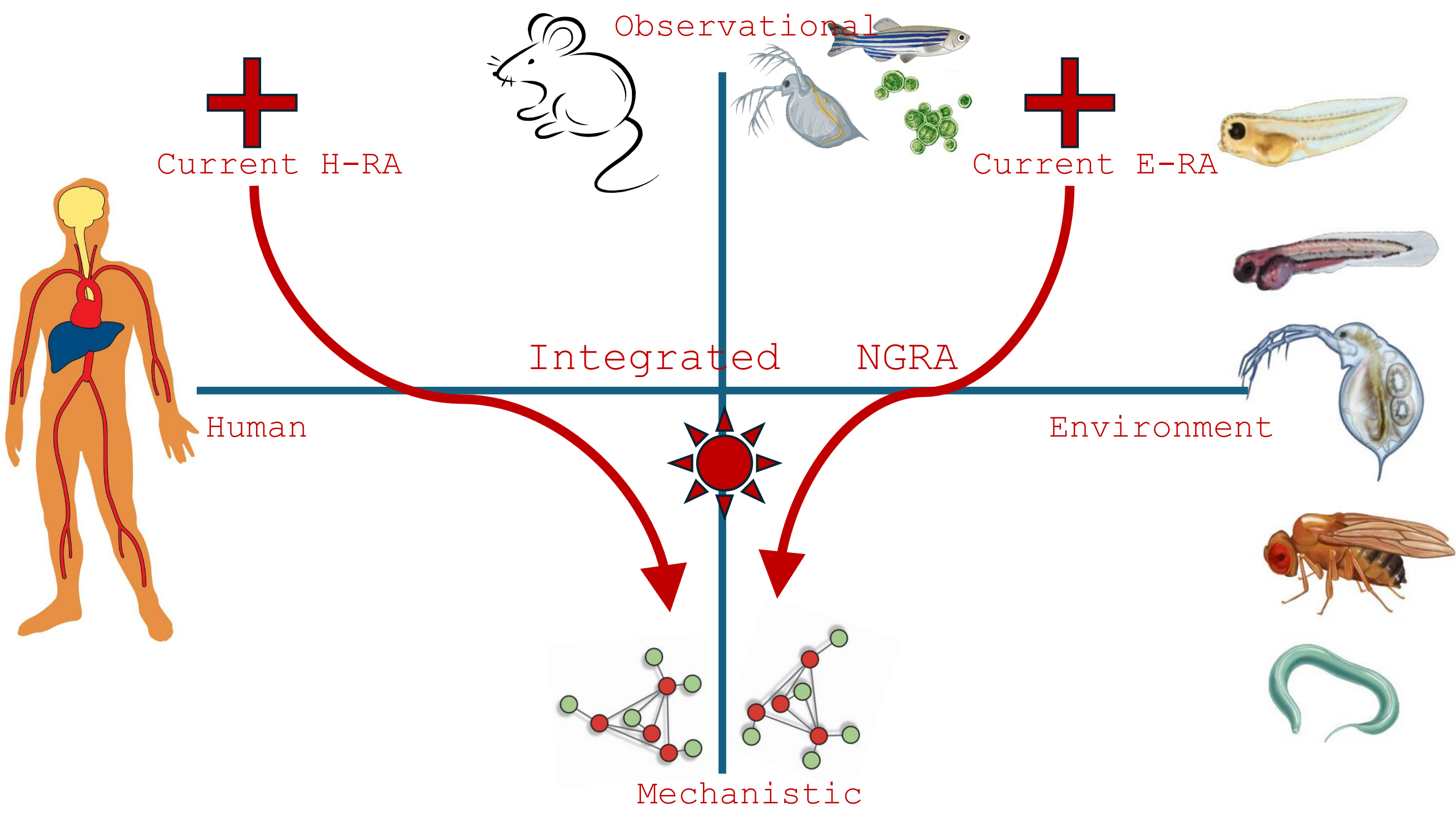
Replace traditional animal testing with an evolutionarily diverse suite of biomedical model organisms from multiple branches of the tree of life.

Variation in Susceptibility

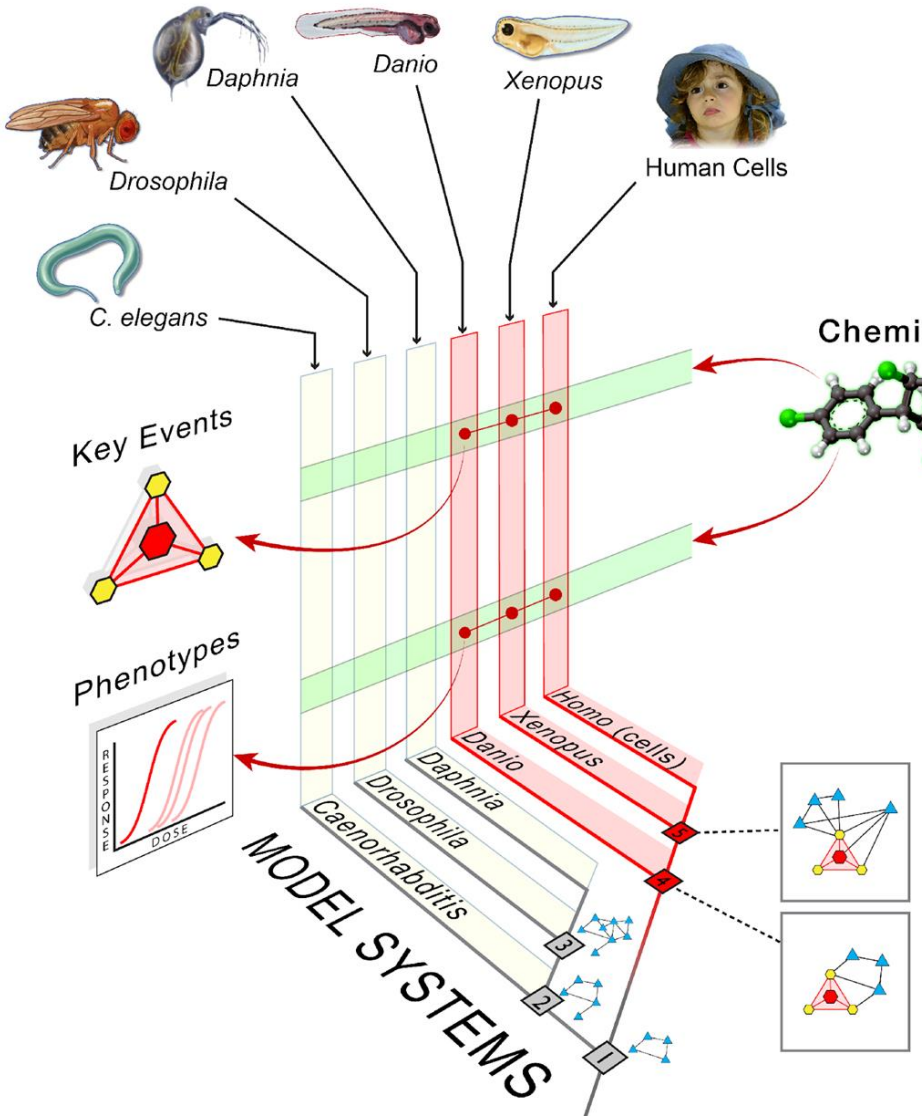
Determine safe levels of exposure to chemicals based on genetic variation.

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.


Observational
Current H-RA
Current E-RA
Integrated
NGRA
Human
Environment
Mechanistic

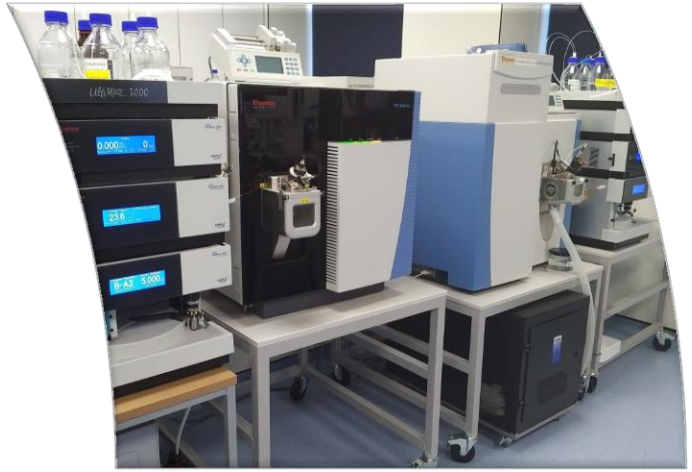
Mechanistic and evolutionary toxicology



Map of the evolutionary origins of the pathways to toxicity

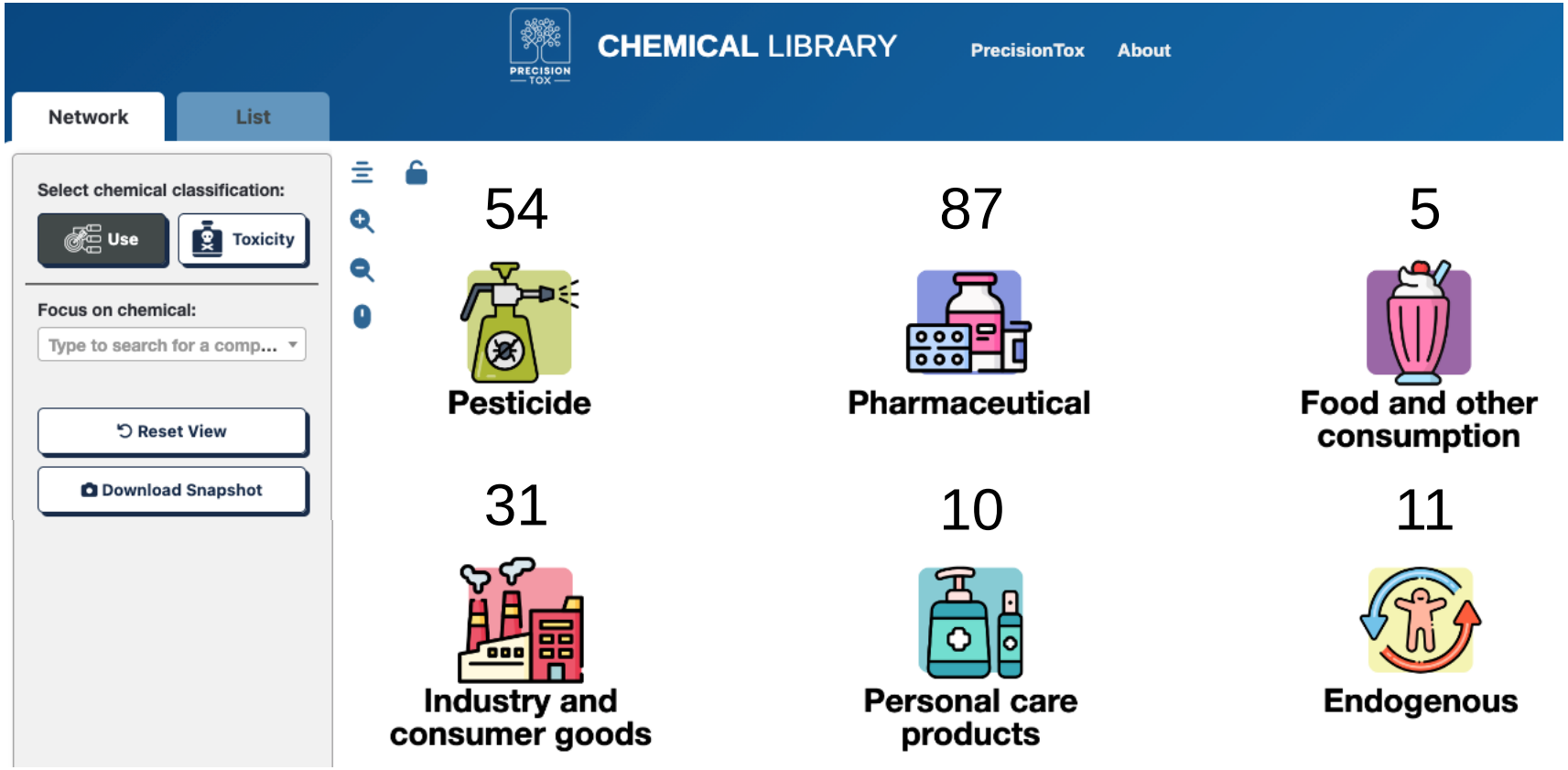
precisiontox.org

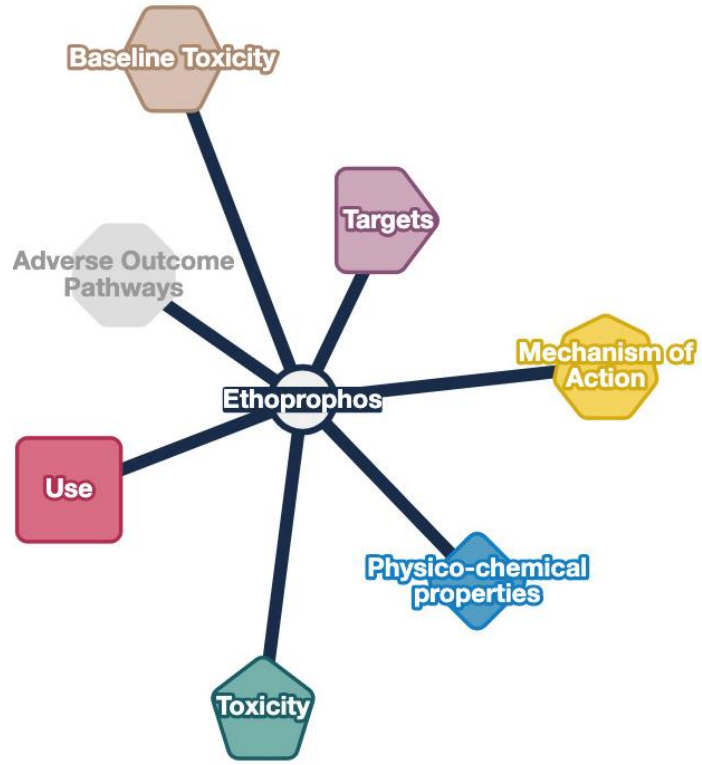
Comparative Metabolomics



Comparative Transcriptomics

The PrecisionTox chemicals library

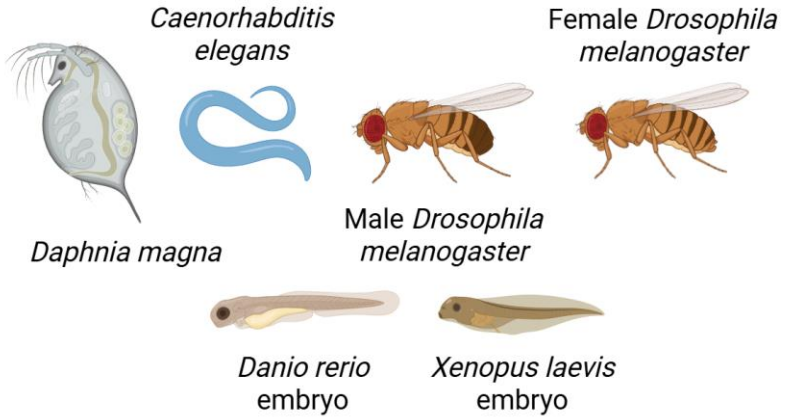




54 Cardiotox – 110 Hepatotox – 53 Nephrotox – 85 Genotox
94 Neurotox – 11 Ototox – 40 Immunotox – 12 Hematotox

Comparing species sensitivities

PrecisionTox Dataset



80 chemicals
(subset)

Endpoints:
Immobilisation &
Mortality

48-hour exposure

BBMD®
BAYESIAN BENCHMARK DOSE MODELING SYSTEM

Shao & Shapiro (2018)

MCMC Sampling

Non-informative priors

8 Dose-Response Models

Produces **posterior distributions** of **BMD_{10} estimates**

Bayesian Model Averaging

Benchmark Response = **10% Extra Risk**

Model Diagnostics
- Convergence
- Effective Sample Size
- Model Fit

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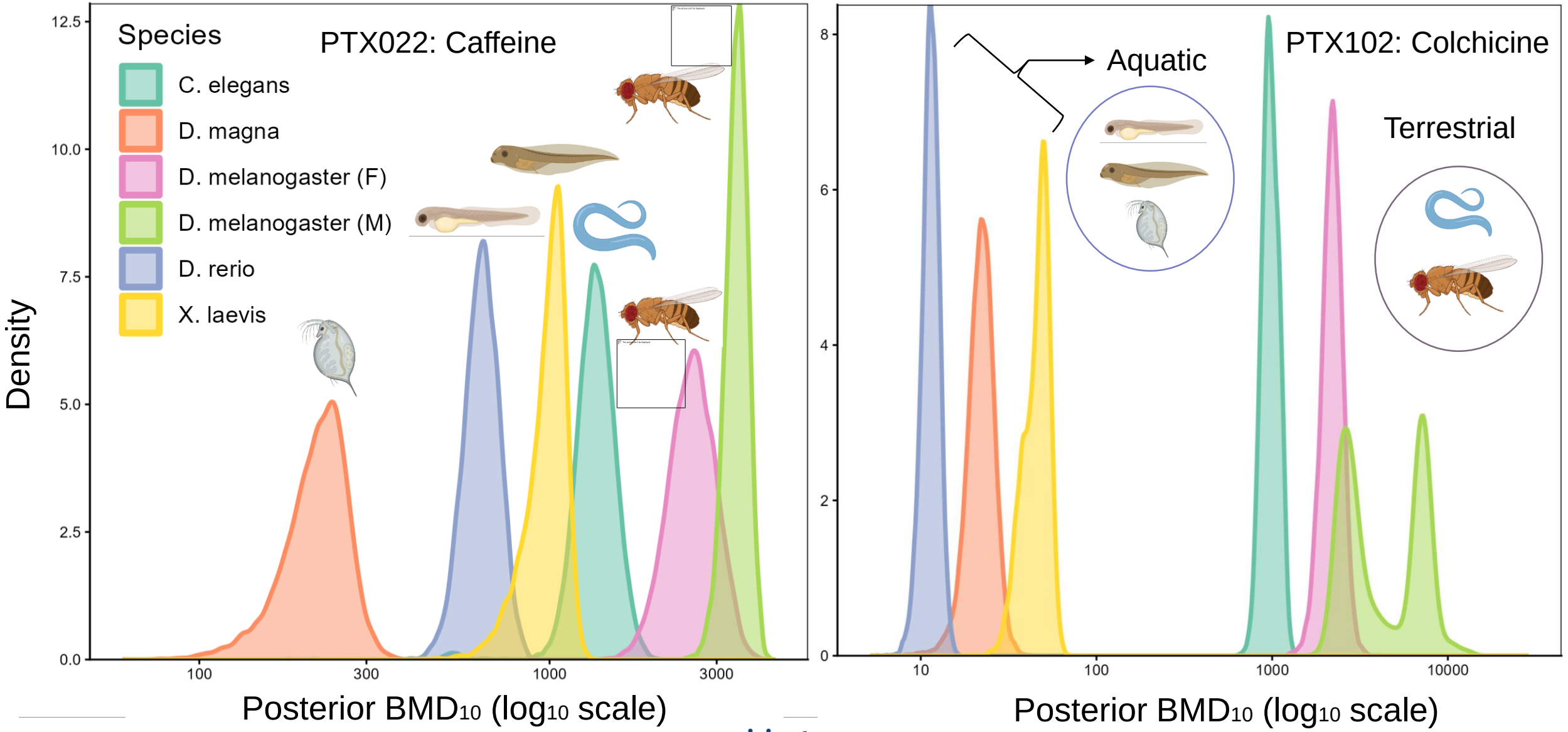
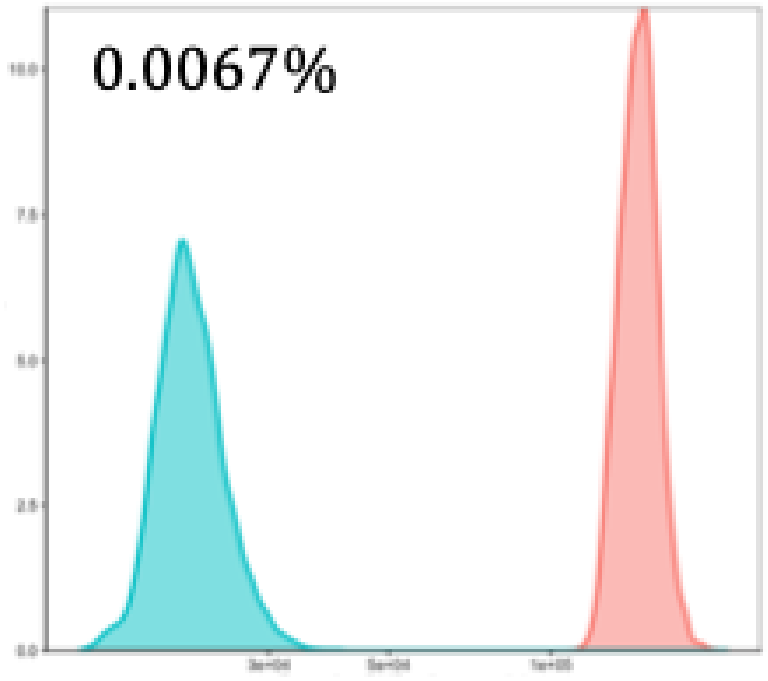
Density plots of species sensitivity



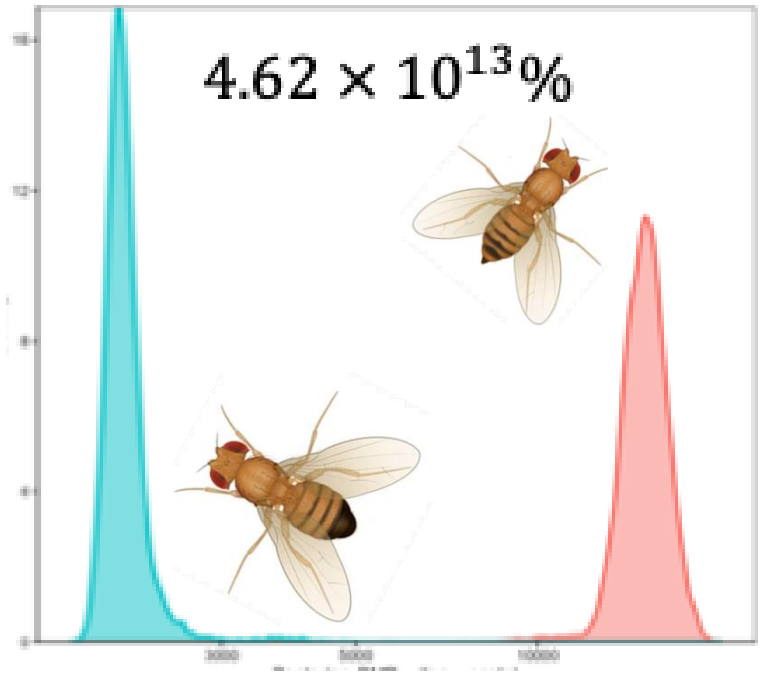
How well do we understand biology?

PTX059 - N,N-Dimethylacetamide



Posterior BMD_{10} (log_{10} scale)

PTX075 - 1-ethyl-1H-imidazole



Posterior BMD_{10} (log_{10} scale)

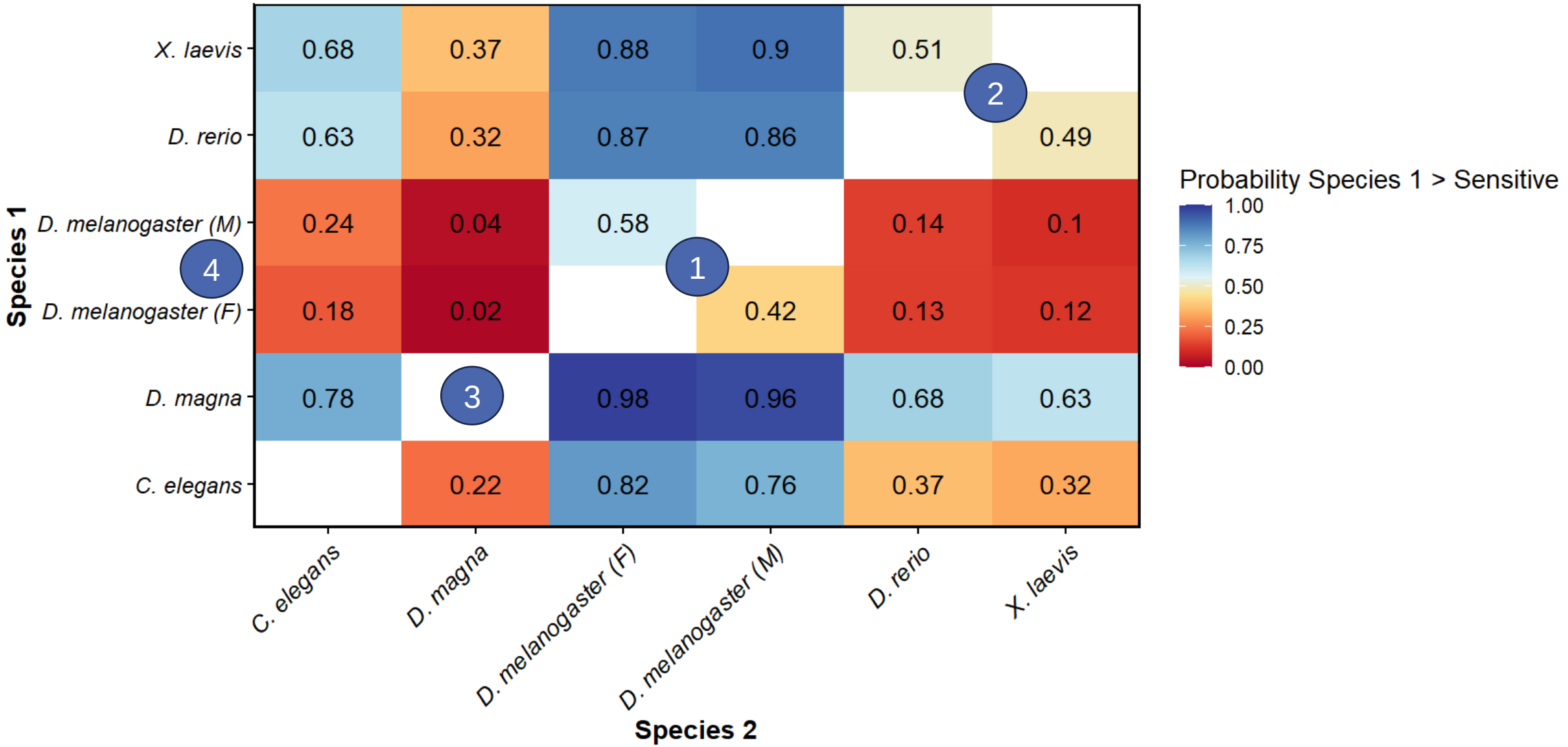
Overlap Coefficient %

Drosophila female

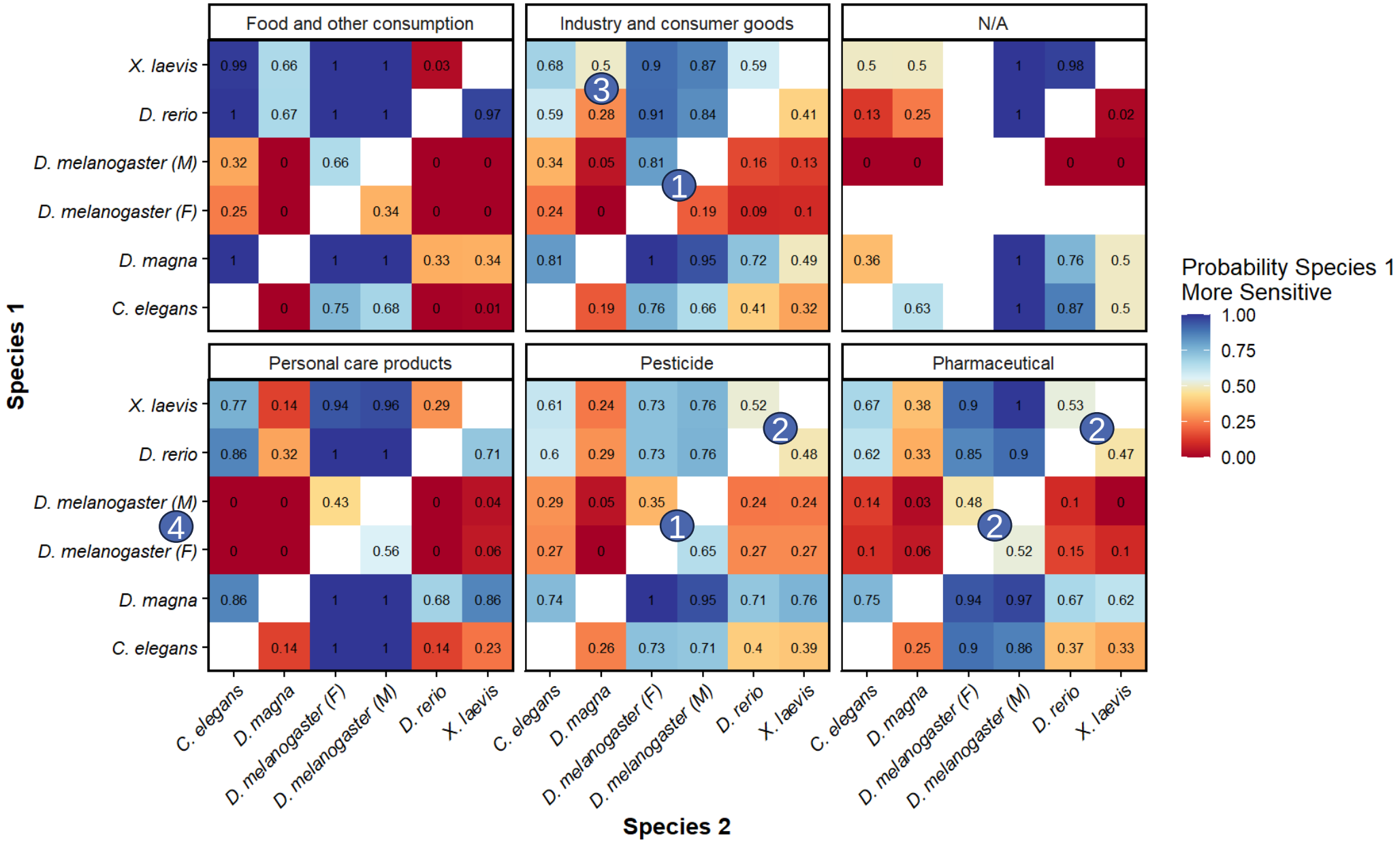
Drosophila male

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

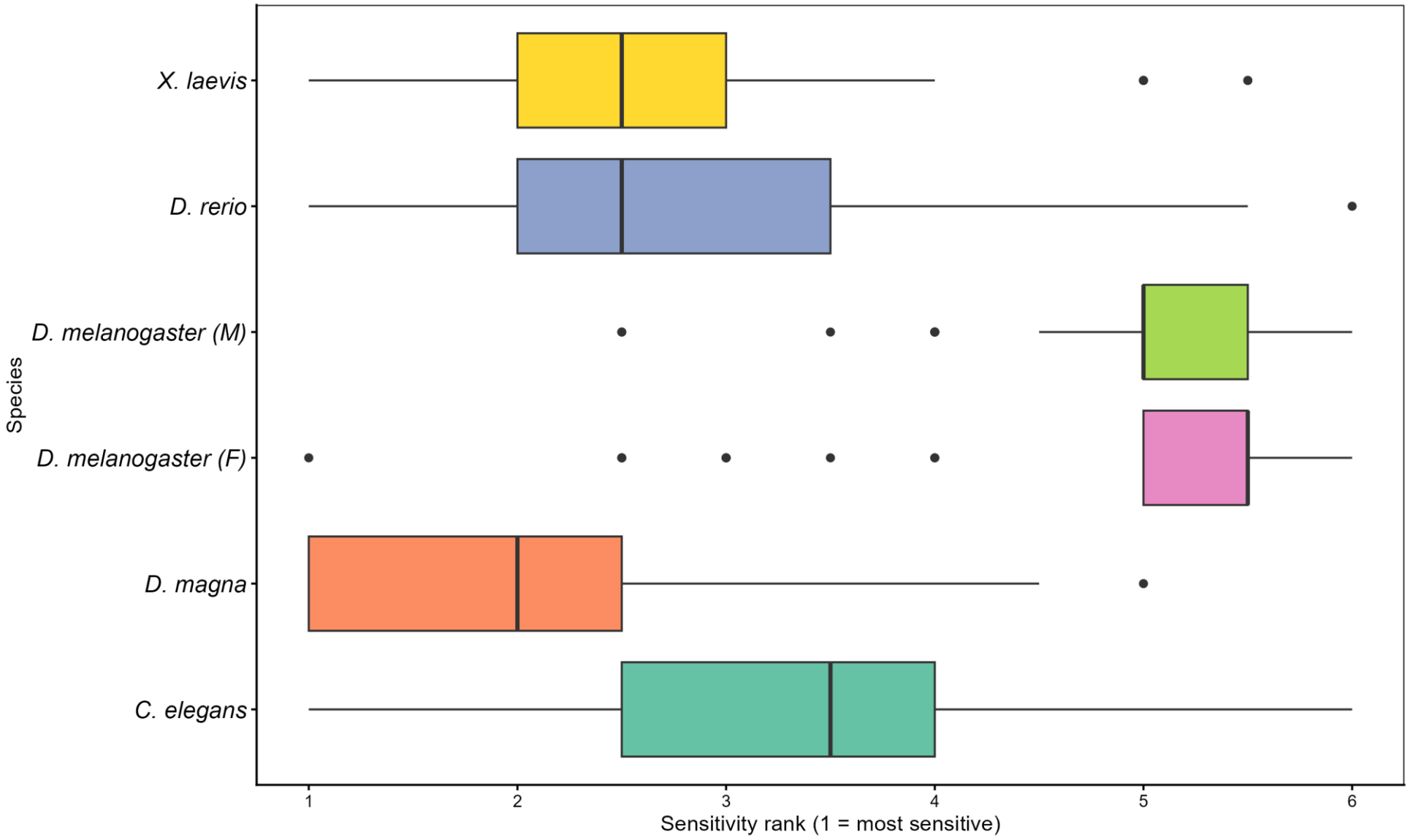
Probability of species sensitivity



Species sensitivity by chemical use



Phylogenetic replacement



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Largest harmonised comparative toxicity dataset

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	Exposure Conditions	Phenotype records	Phenotypic Endpoints	Organisms covered	Chemicals covered
959	129,459	1,846,720	132	5	204

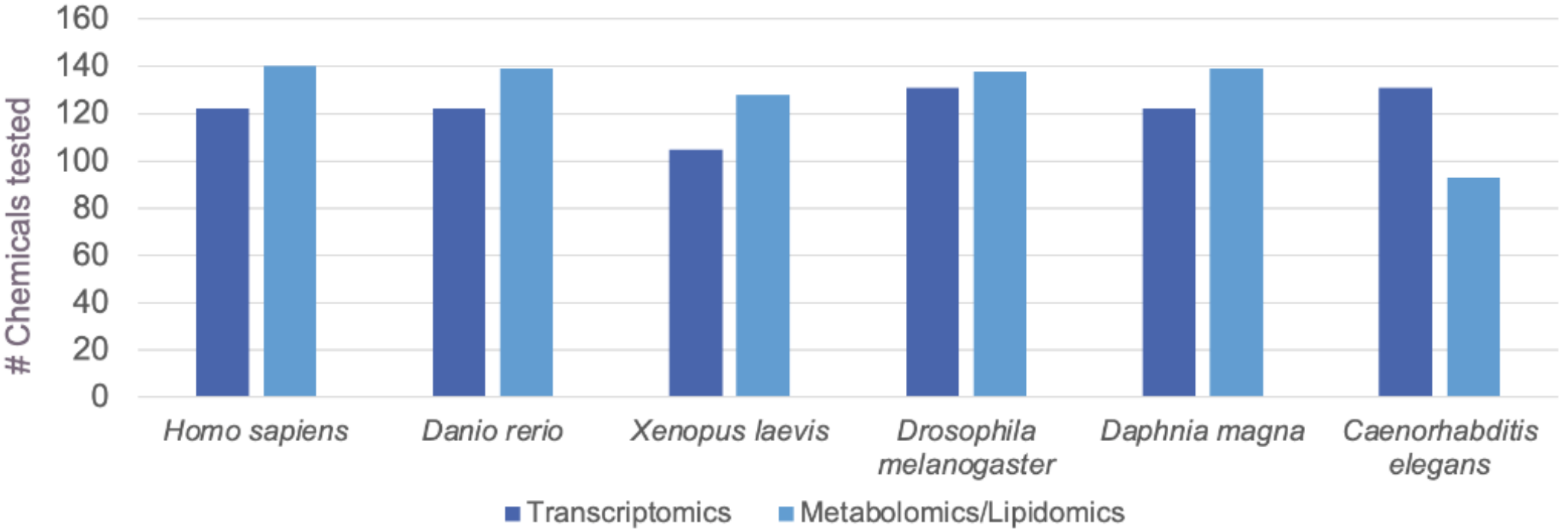
Data composition

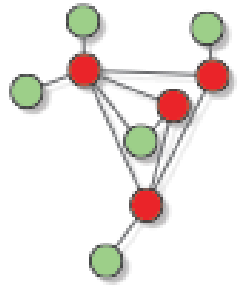
Summary of condition and experiment composition in the phenotype dataset.

Control conditions	Treatment conditions	Aggregated experiments	Non-aggregated experiments
21,217	108,242	553	406

precisiontox.org

Largest multi-omics toxicological dataset





TRANSCRIPTOMICS

CHEMICALS WITH ANY DATA	CHEMICALS WITH DATA IN ALL 6 ORGANISMS	CONTRASTS
131	105	1,684

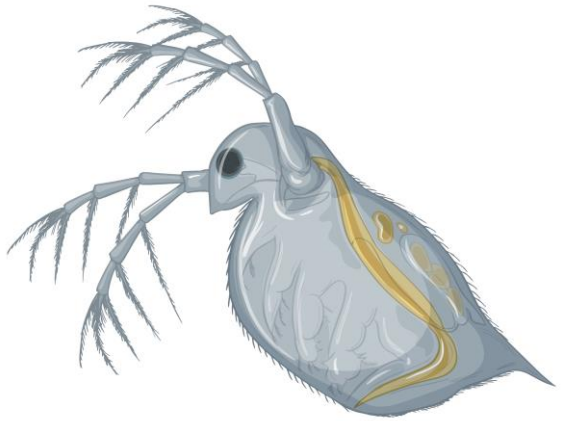
OBSERVATIONS
26,283,008 X 2 within 2 months from now

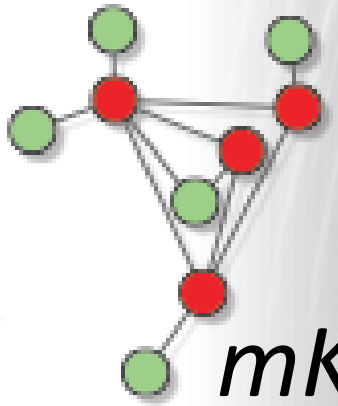
METABOLOMICS

CHEMICALS WITH ANY DATA	CHEMICALS WITH DATA IN ALL 6 ORGANISMS	CONTRASTS
140	86	3,449

OBSERVATIONS
29,932,825 X 2 within 2 months, approx.

Biomolecular pathways as early warning systems (sentinels)





mKE

Integrated next-generation risk assessment (iNGRA)

Field sampling (Danube River)

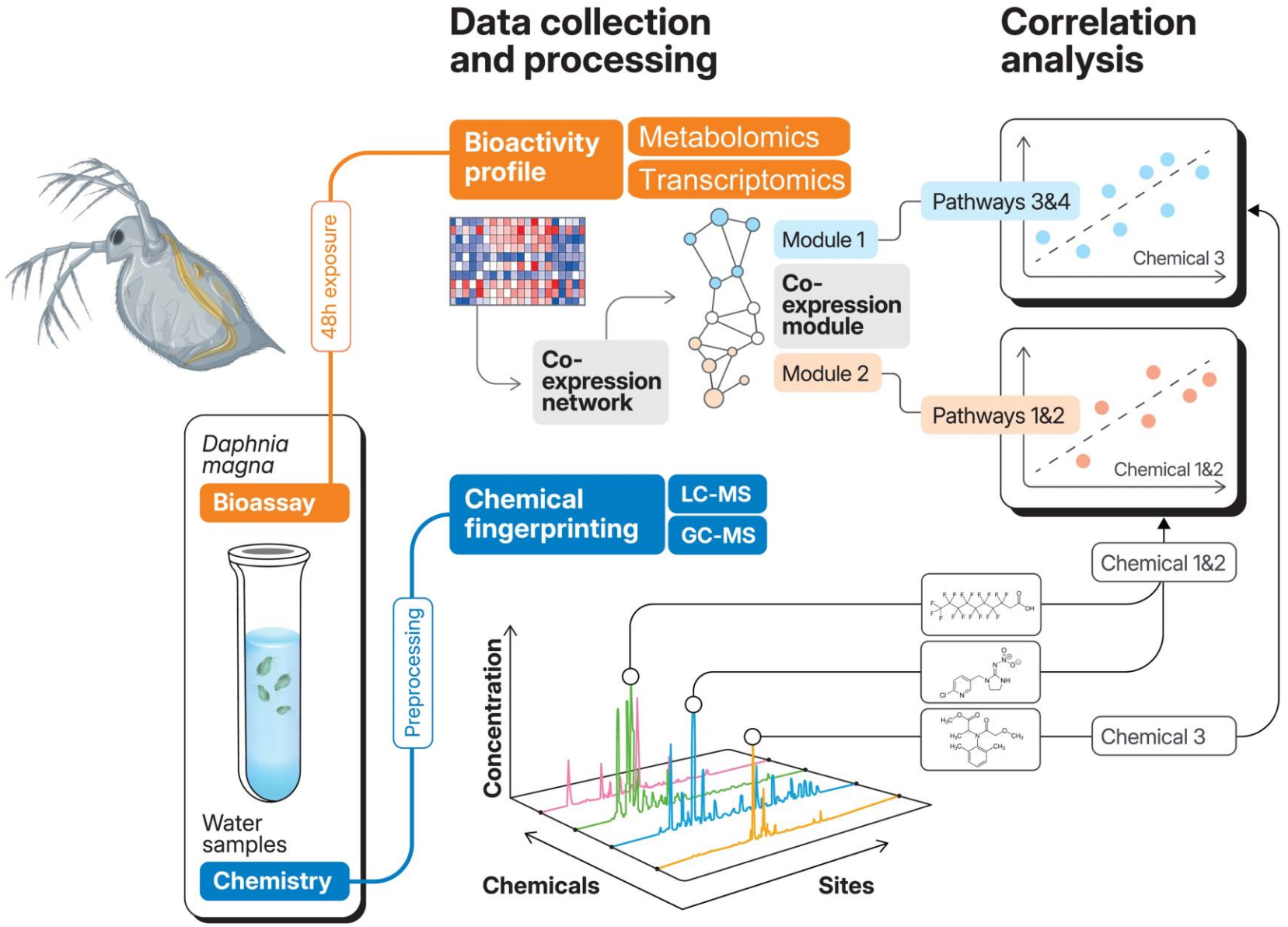
- 12 sampling sites collecting organic extracts and diluting back to original concentration

Chemical fingerprinting

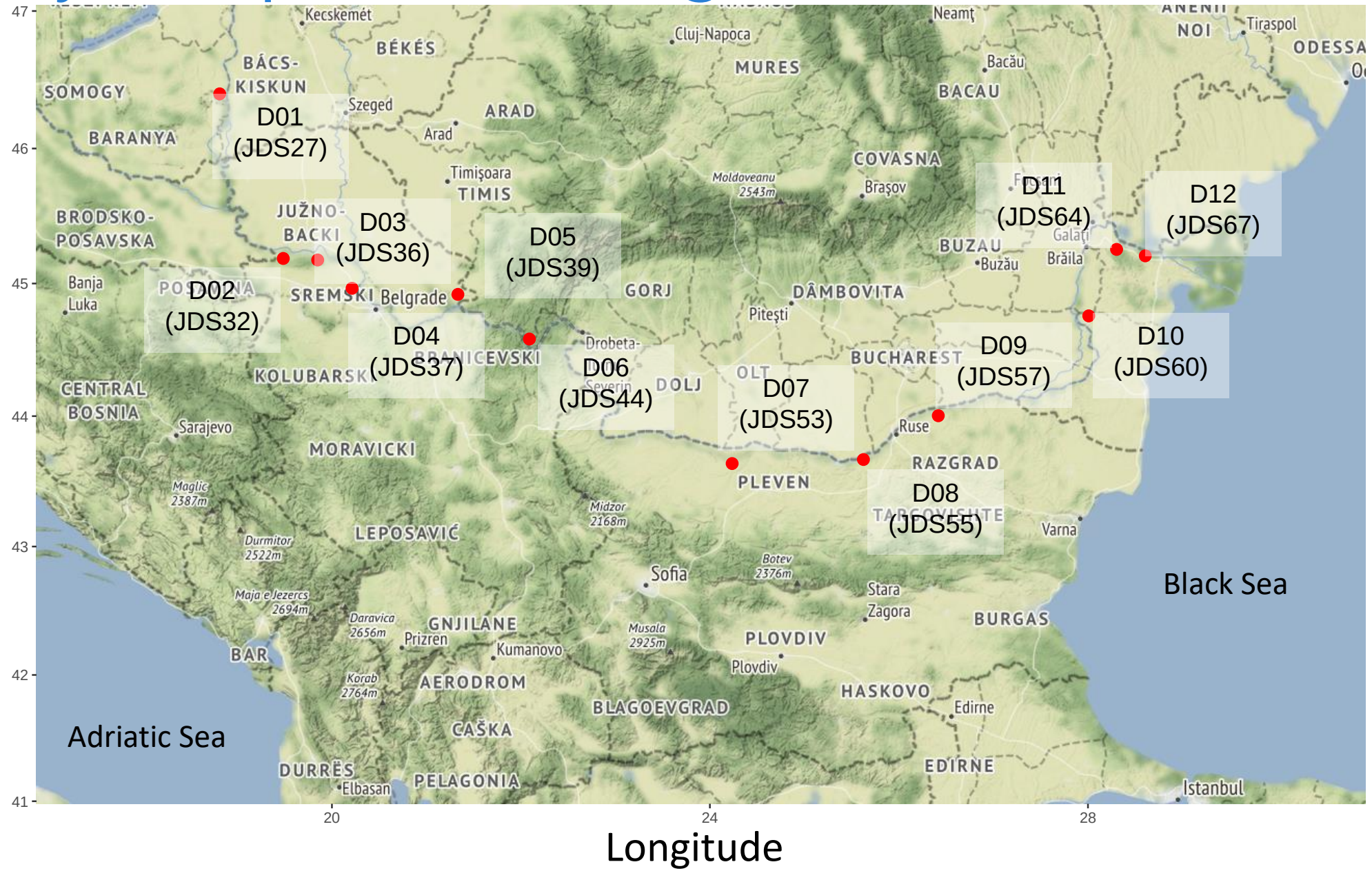
- Non-target screening (semi-quantification of 91 substances)

Bioactivity profiling

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

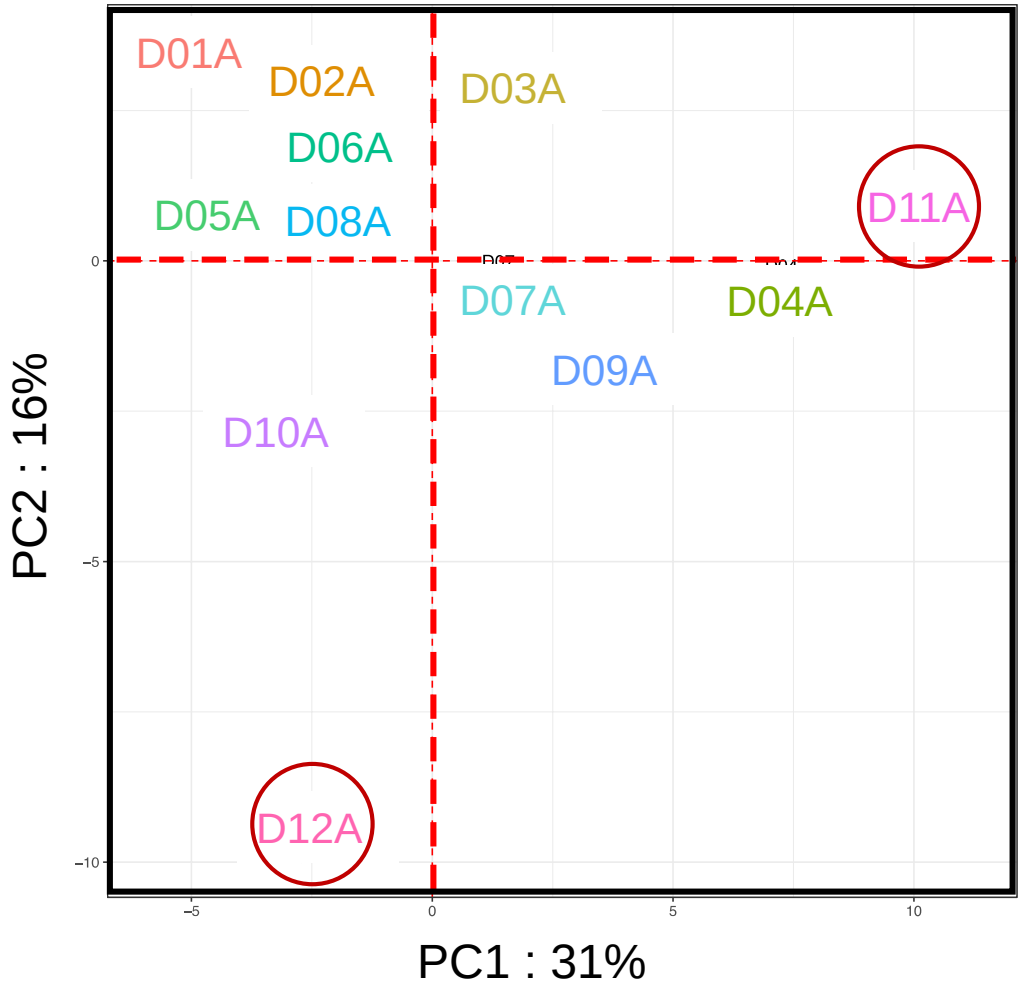


Case Study: sample sites along the Danube River

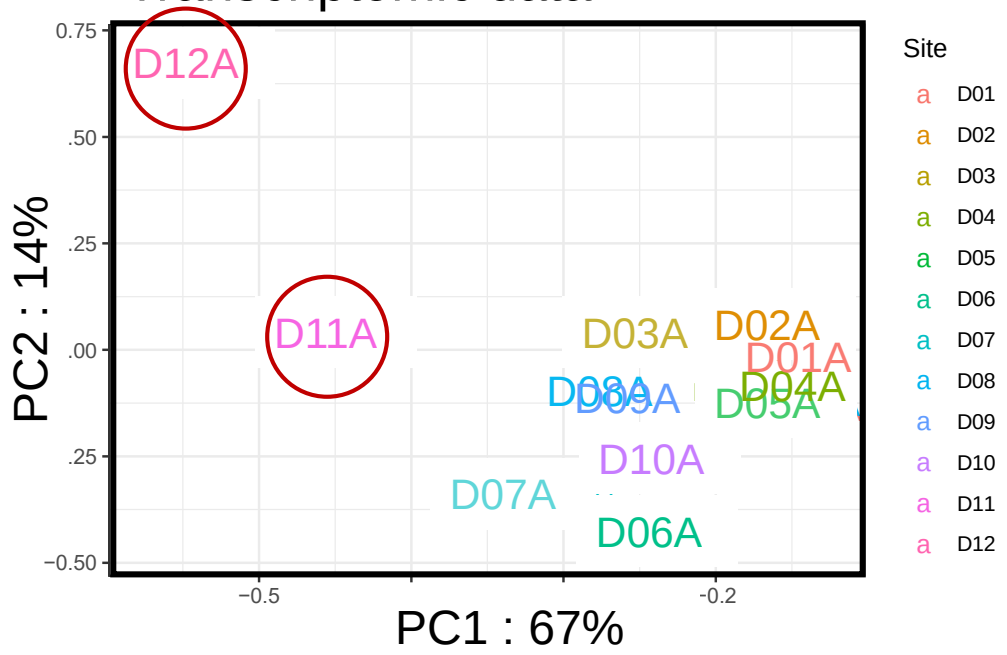


Data overview with PCA plots

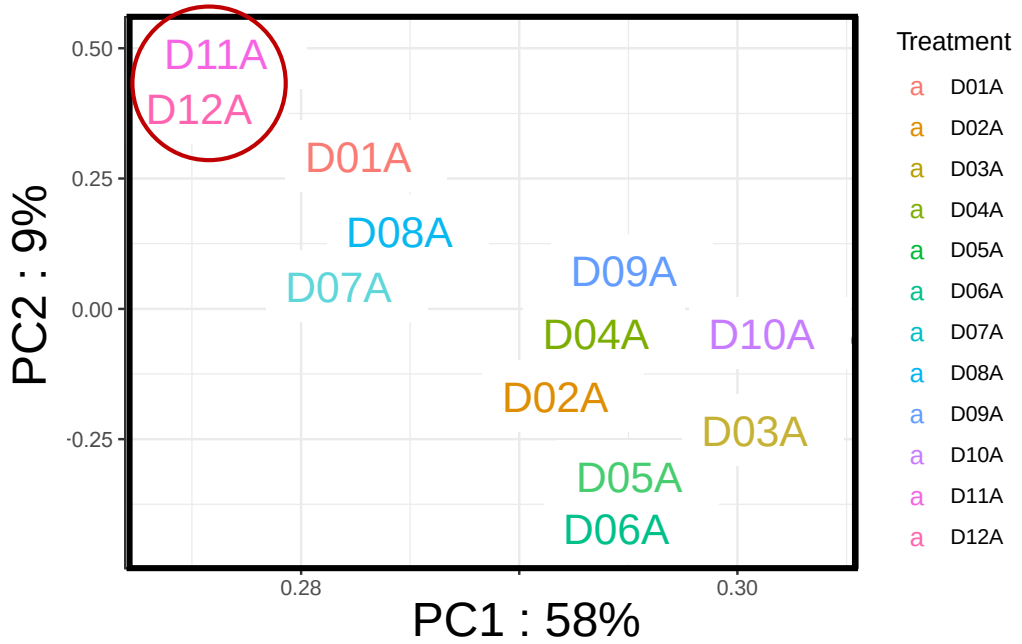
Chemical data



Transcriptomic data



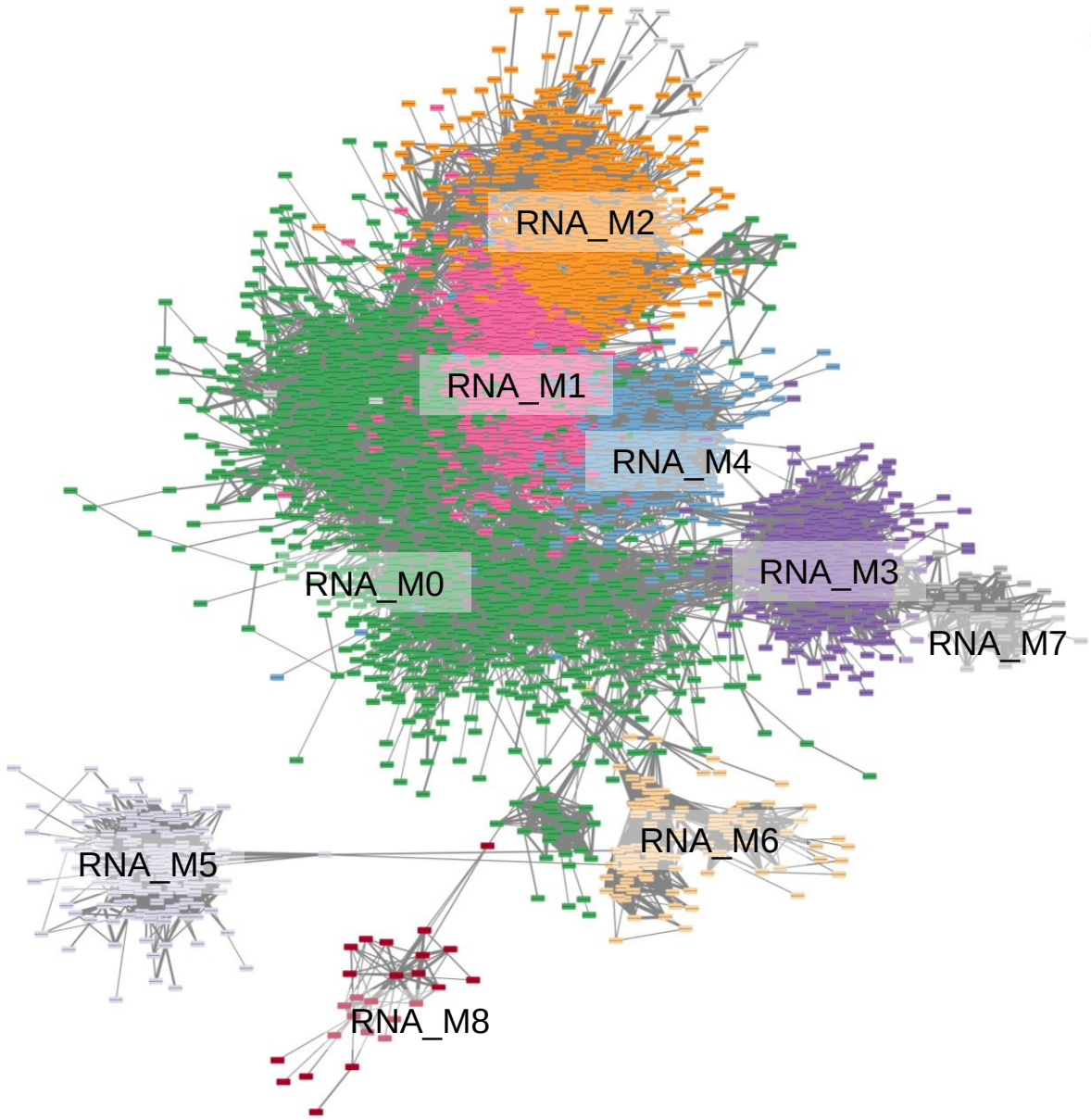
Metabolomic data



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

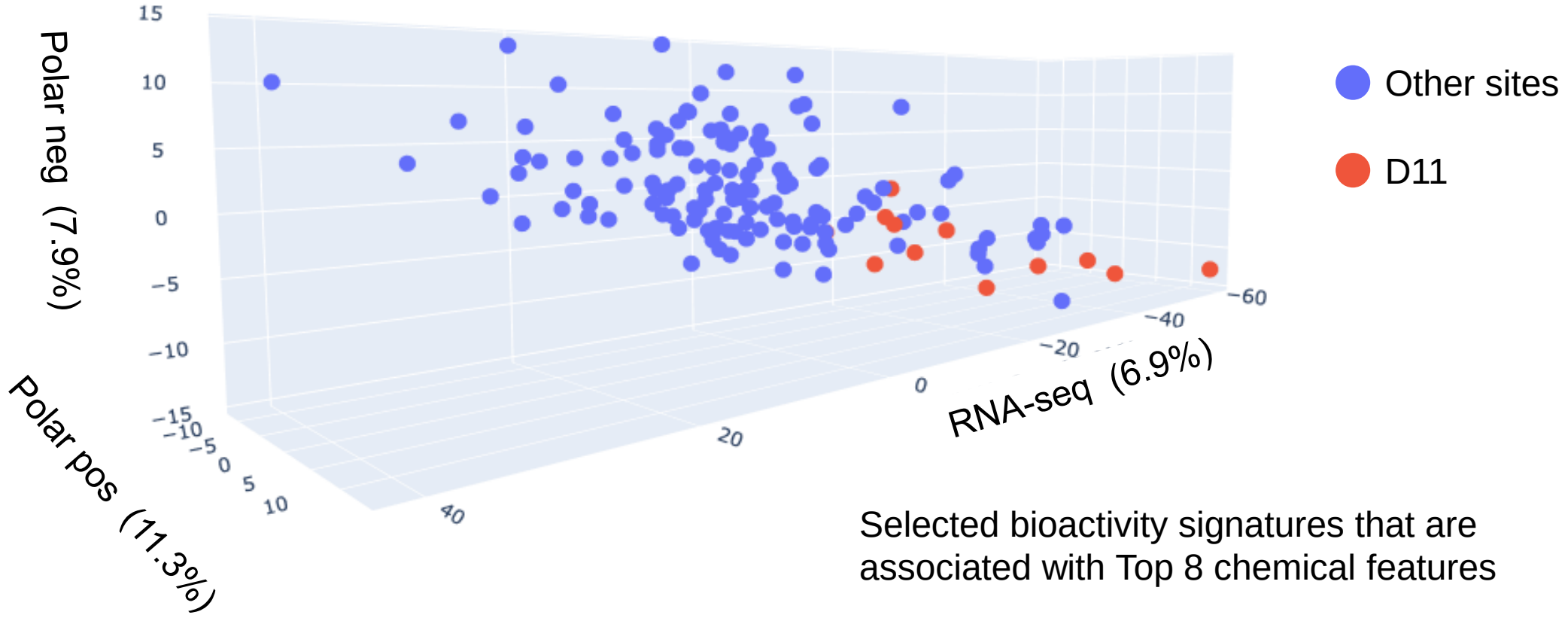
	Minimum redundancy maximum relevance	Pairwise correlation (feat Imp)	Sparse canonical correlation analysis	Joint correlation
herbicide	Metolachlor	0.94	Metolacholar	
herbicide	Isoproturon	0.84	Isoproturon	
sweetener	Sucralose	0.82	Sucralose	
Pharmaceutical TPs	10,11-Dihydro-10,11-dihydroxy-carbanazepine	0.77	10,11-Dihydro-10,11-dihydroxy-carbamazepine	
Pharmaceutical TPs	10,11-Dihydro-10-hydroxycarbamazepine	0.76	10,11-Dihydro-10-hydroxycarbamazepine	Explained variance: **53.3 %**; Correlation: **0.62**
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	
	Terbuthylazine-2-hydroxy	0.64	Chloridazon	

Top 8 chemical components that distinguish D11 from other sites (bi-class labels)

Correlation analysis by sCCA

D11

sCCA modelling
(8 chemicals ~ genes ~ polarpos metabolites~ polarneg metabolites)



Selected bioactivity signatures that are associated with Top 8 chemical features

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-carbanazepine

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

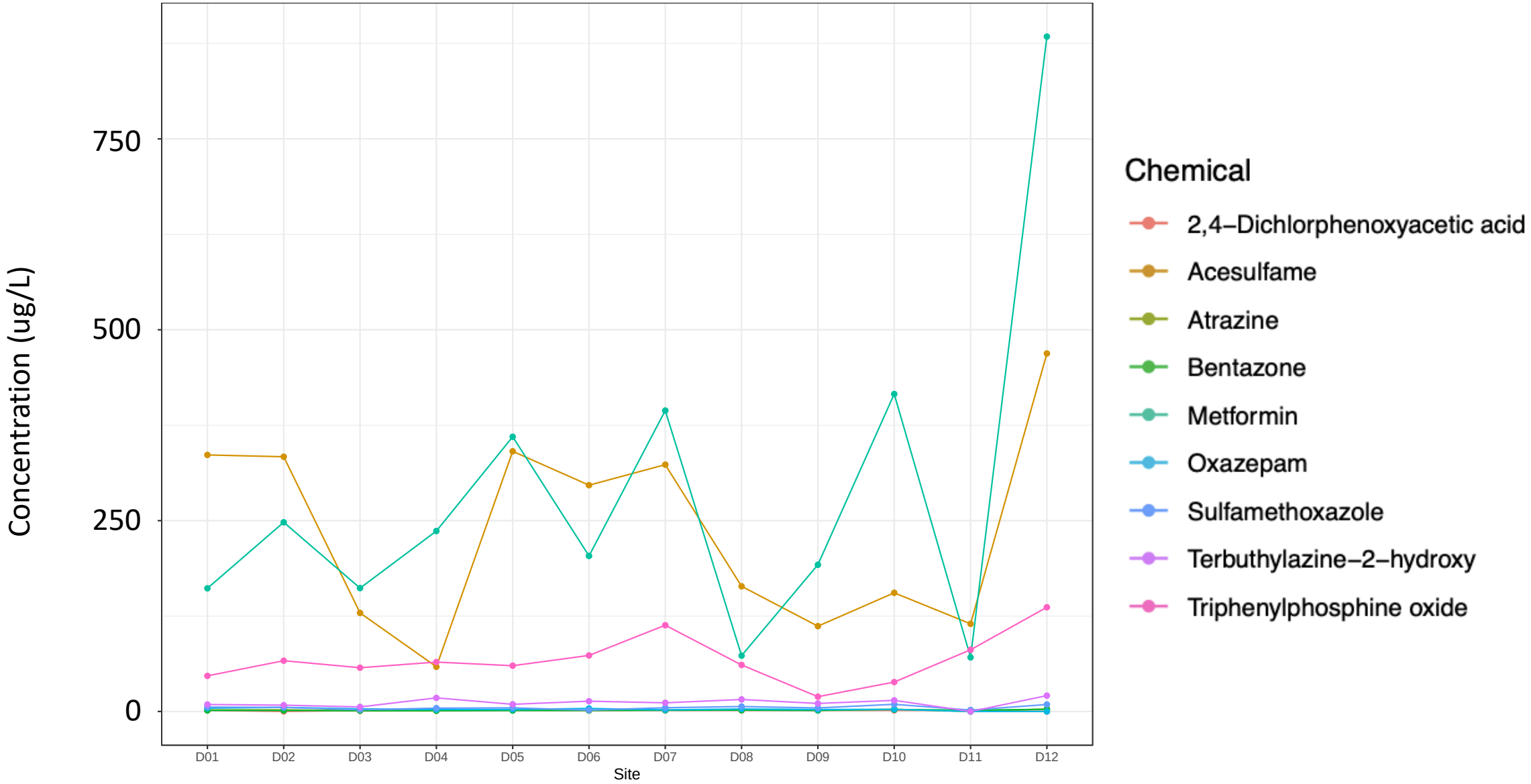
Glutathione metabolism

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-Dichlorphenoxyacetic acid (HER)

Triphenylphosphine oxide (FR)

Atrazine (HER)

Acesulfame (SW)

Oxazepam (PHAR)

Terbuthylazine-2-hydroxy (HER)

Sulfamethoxazole (PHAR)

Association

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

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 × Danio_rerio × Daphnia_magna × Drosophila_melanogaster_female × Xenopus_laevis ×

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 0.05 0.25

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)

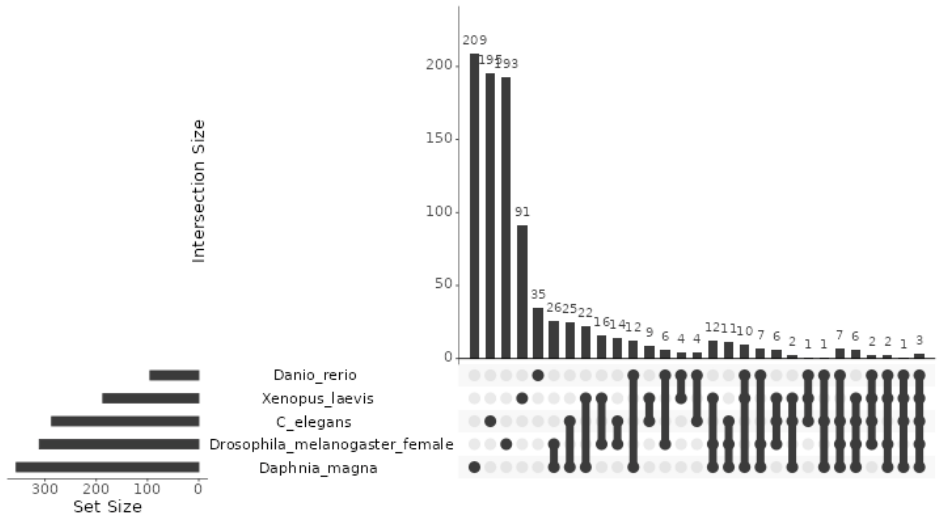
0 10

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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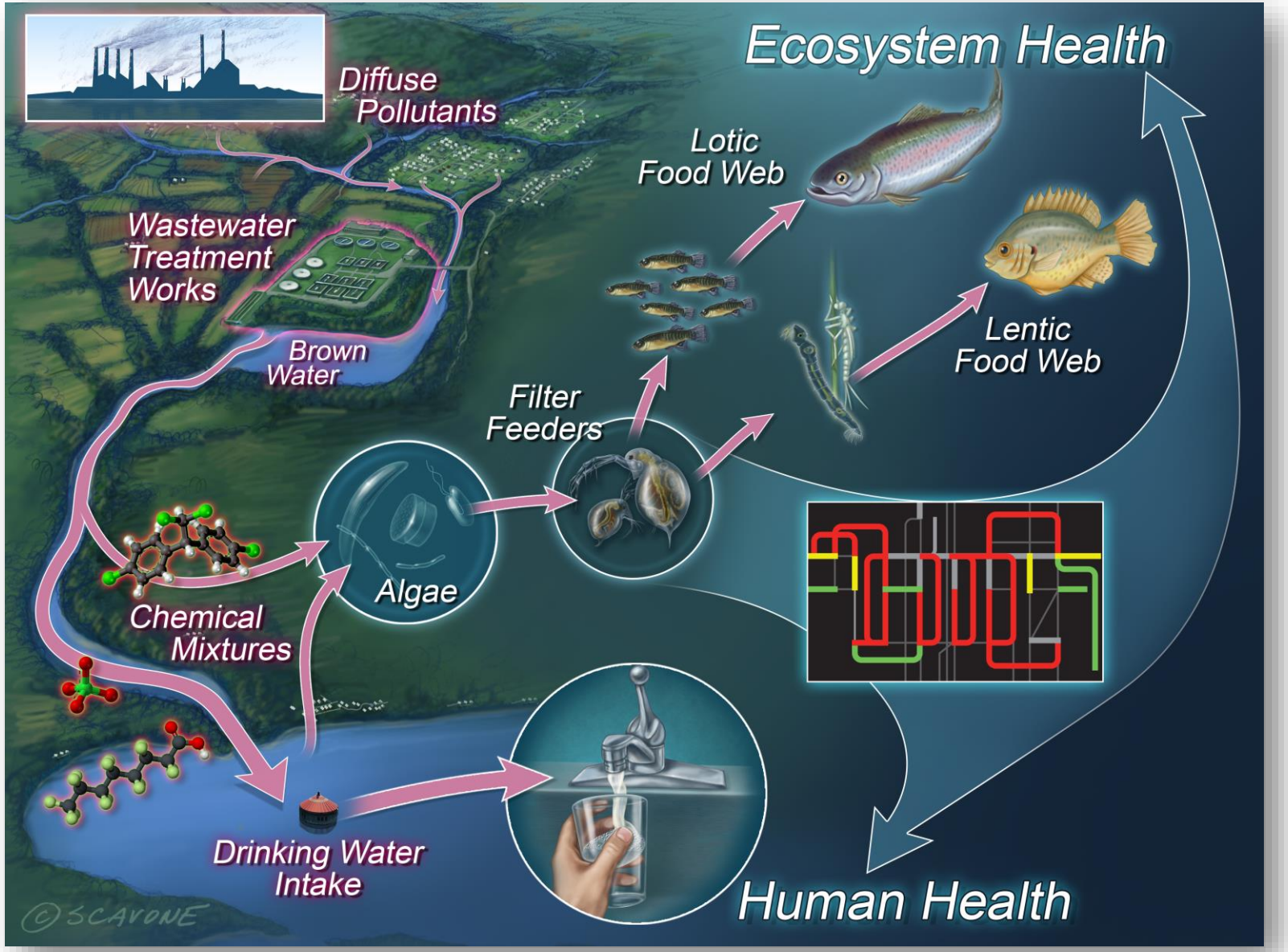
Evolution-informed sentinel species for 1-Health Toxicology



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