MS2Tox & MS2Quant: automated prediction of toxicity and concentration

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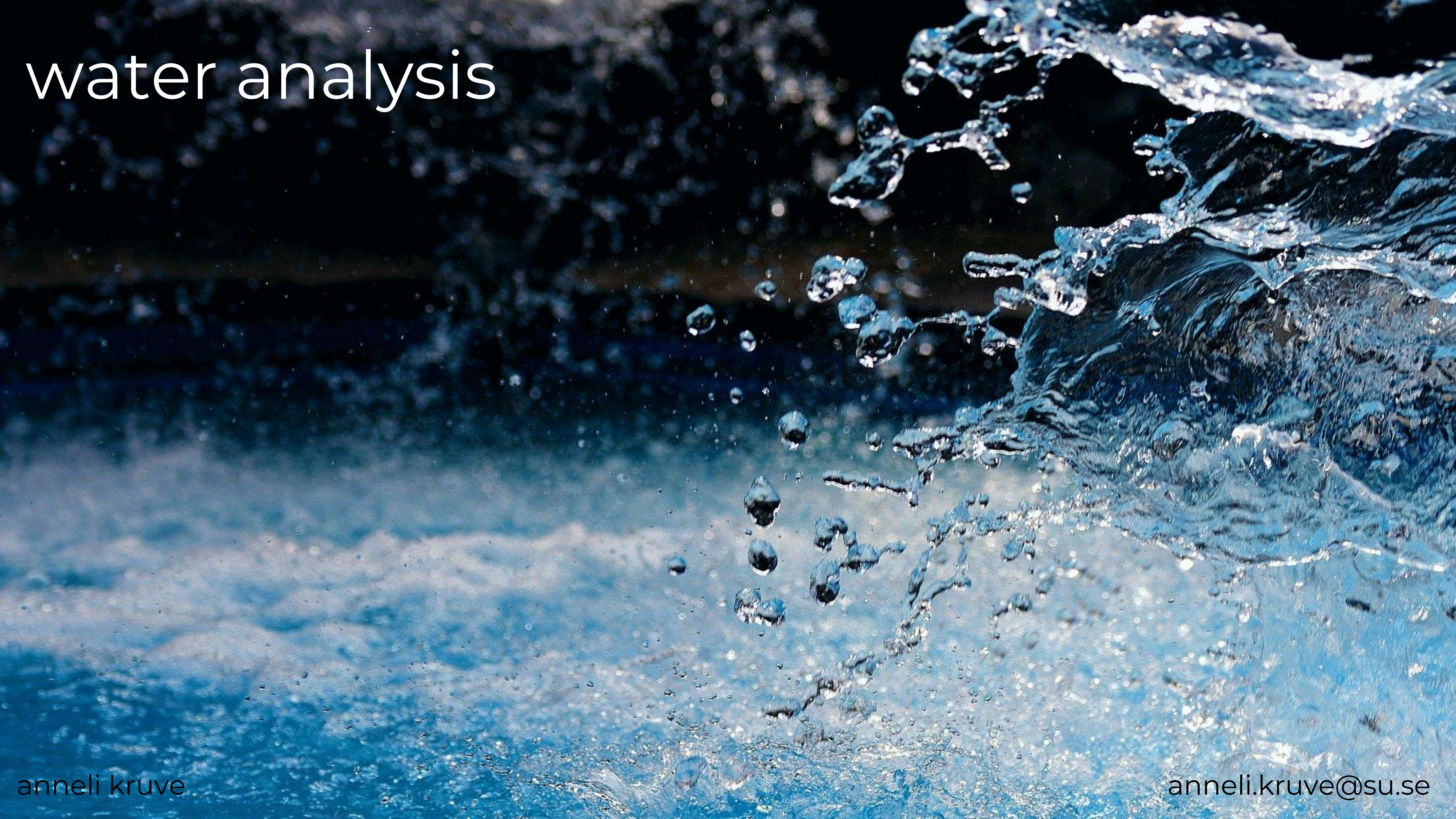
kruvelab.com

water analysis



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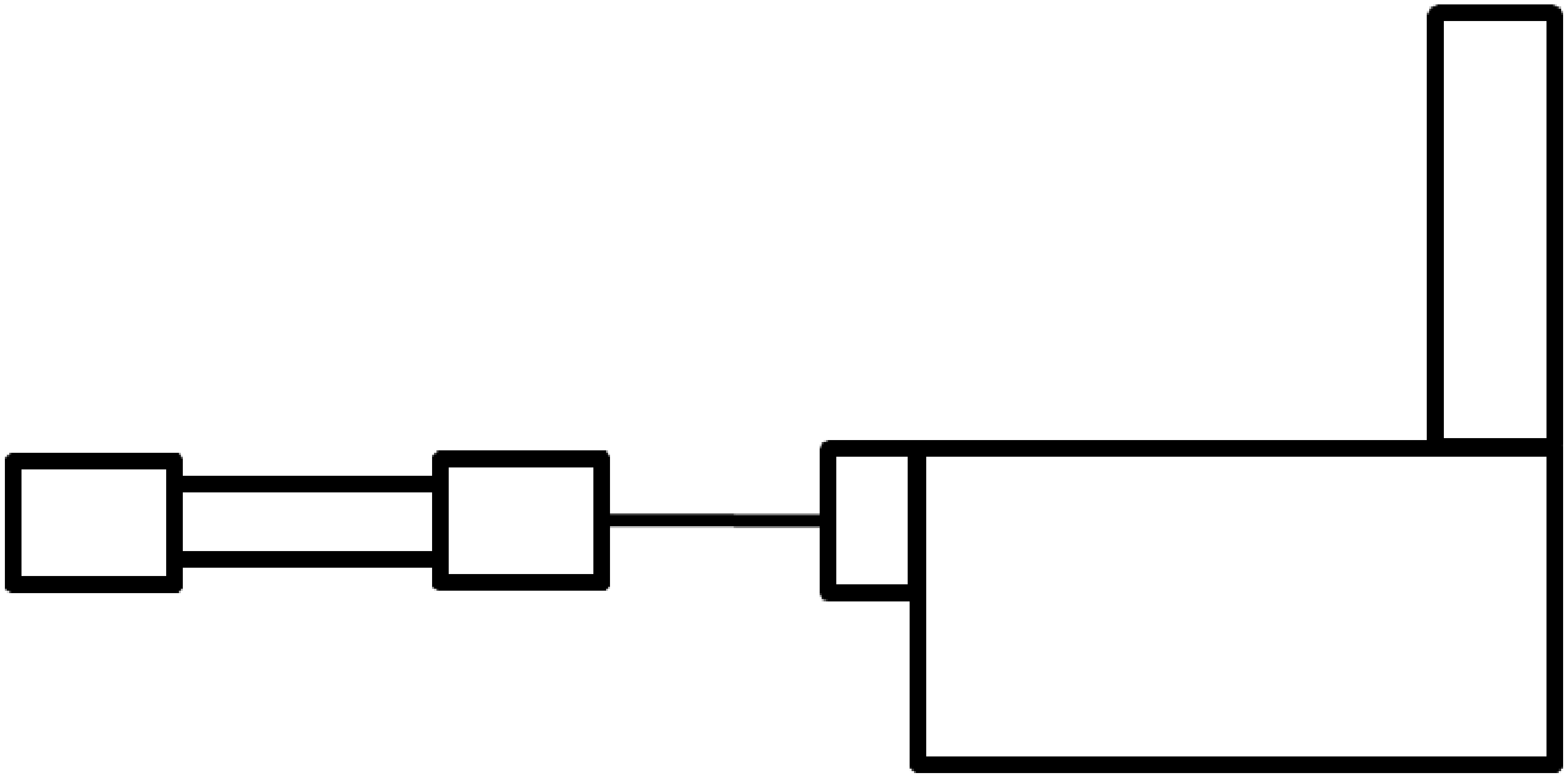
nontarget screening with LC/HRMS



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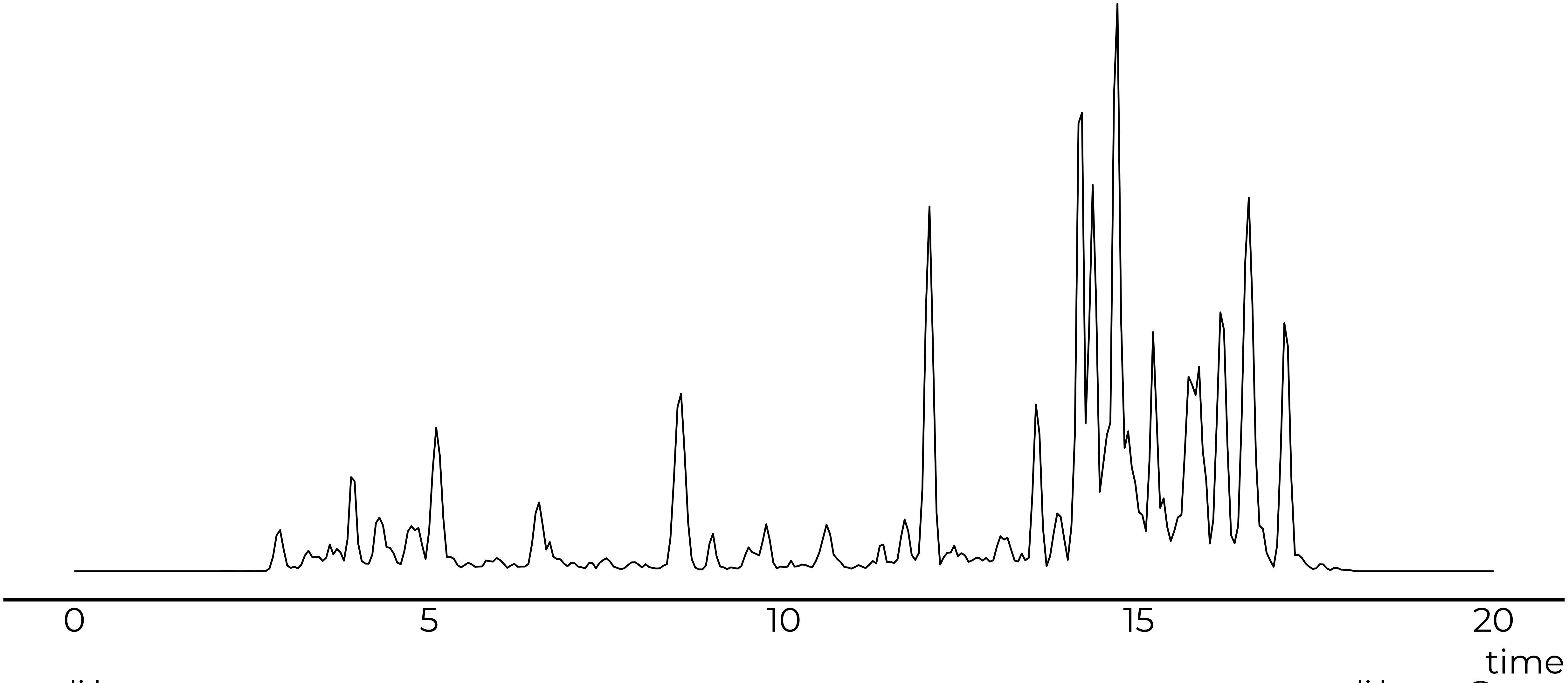
nontarget screening with LC/HRMS



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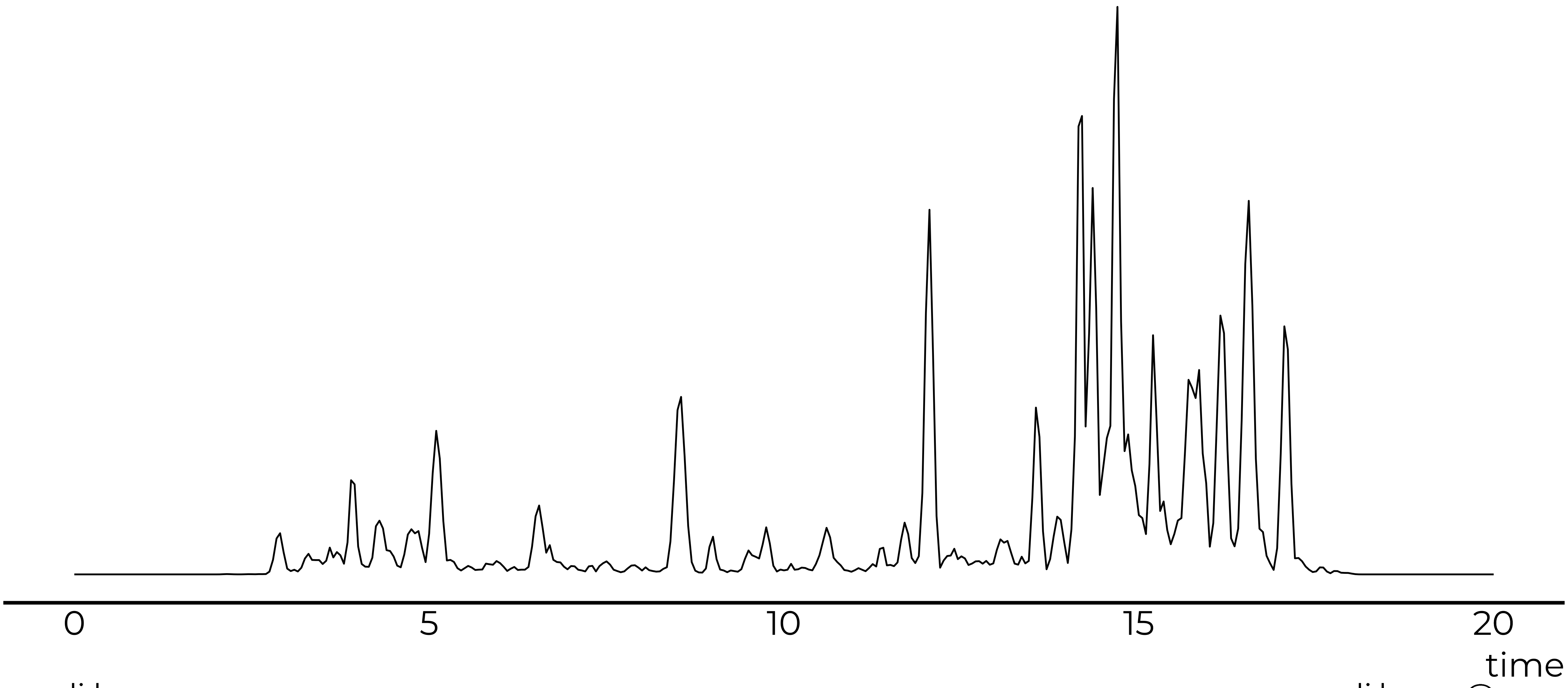
what next?



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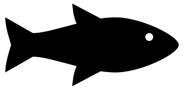
prioritization



toxicity

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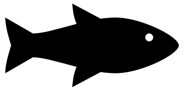
prioritization



toxicity

concentration

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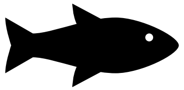
prioritization



toxicity

concentration

risk

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prioritization

toxicity

concentration

risk $$\mathrm{PriorityScore} = \frac{c_{\mathrm{predicted}}}{AC_{50}^{\mathrm{5th\ percentile}}}$$

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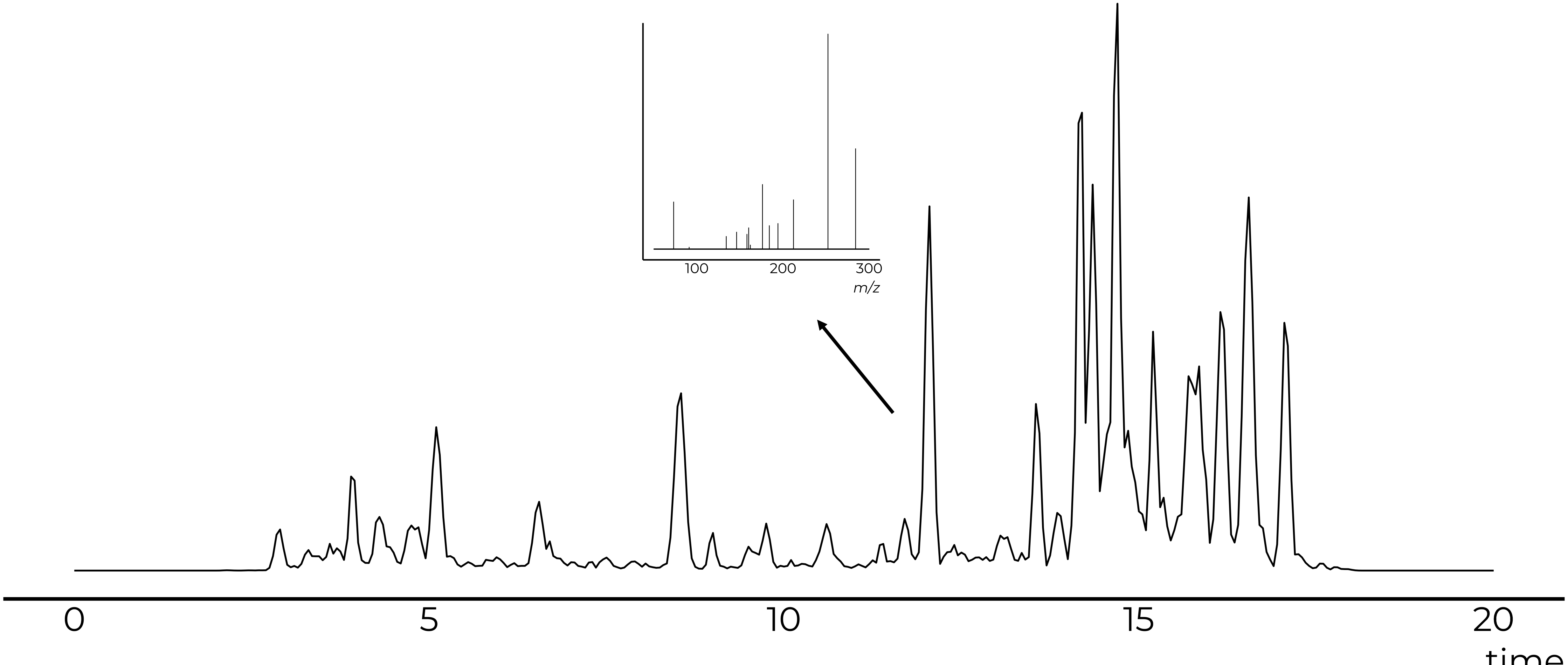
nontarget screening with LC/HRMS



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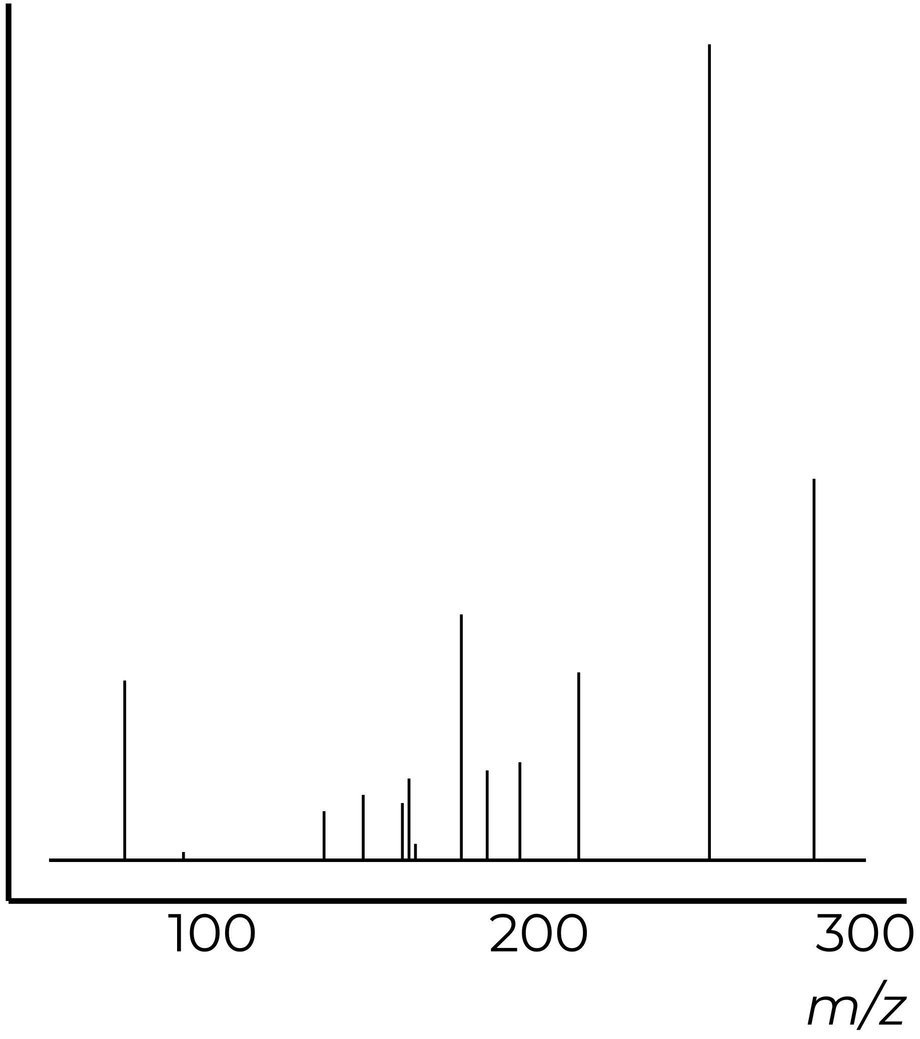
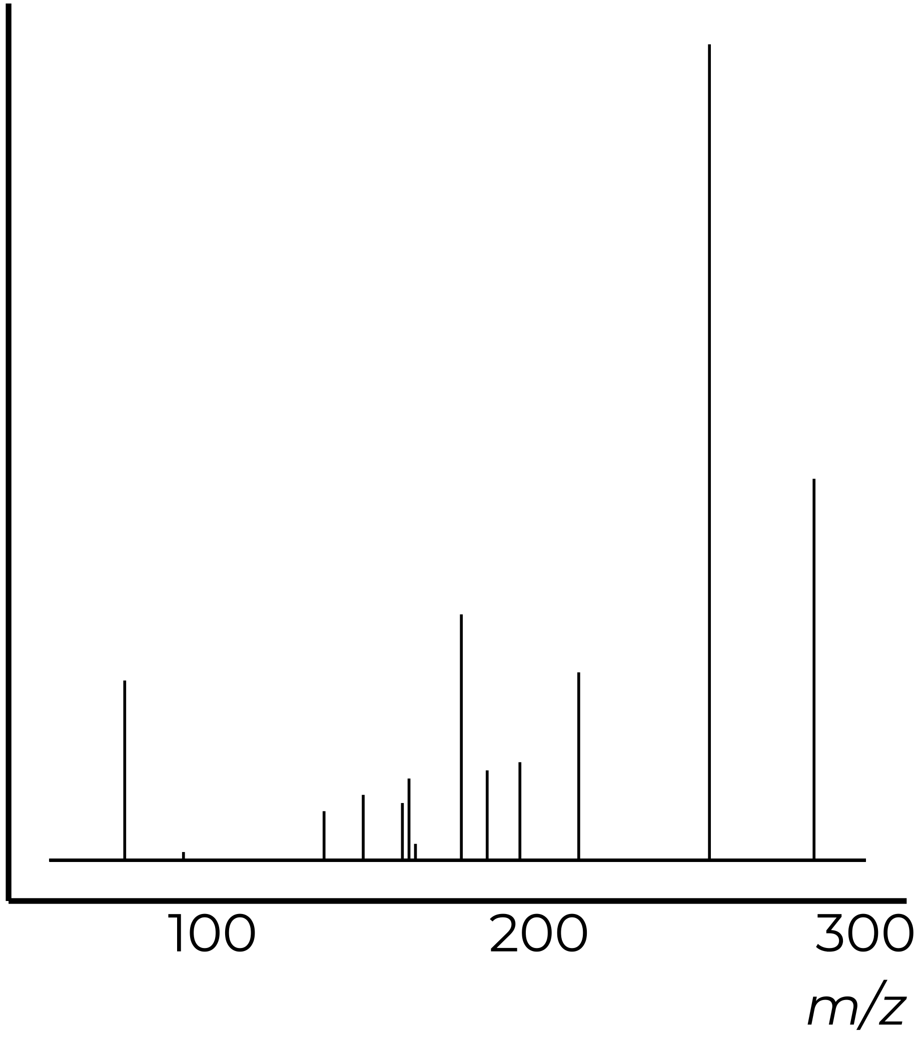
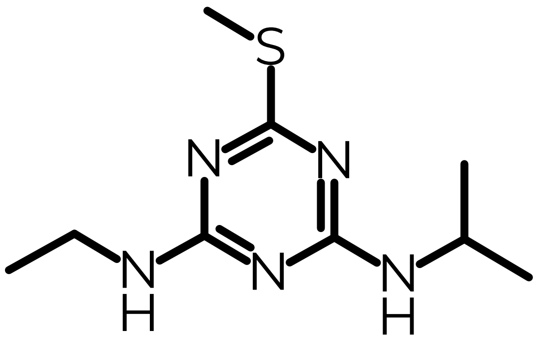
toxicity assessment



toxicity assessment





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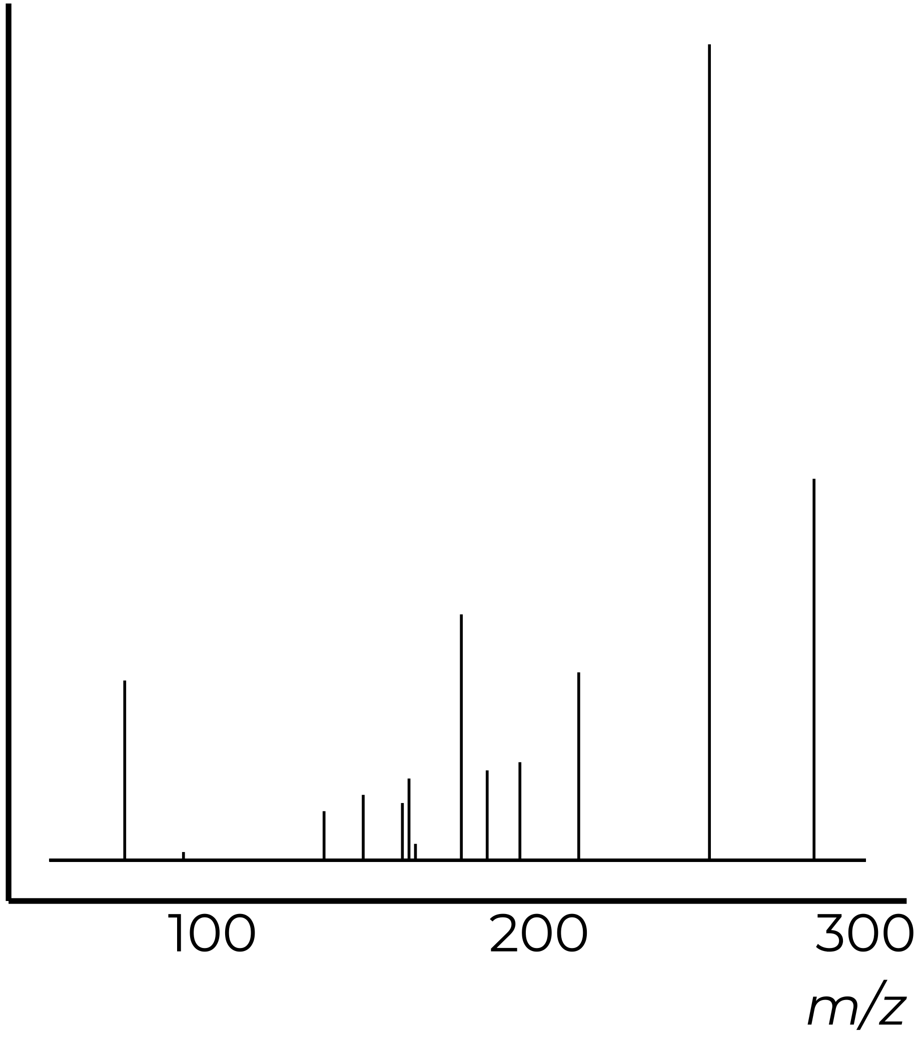
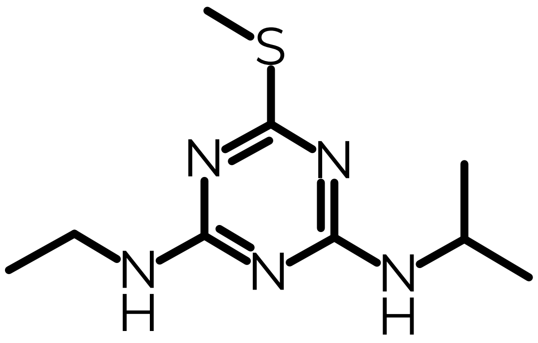
toxicity assessment





LC_{50} = 9.3 mg/L

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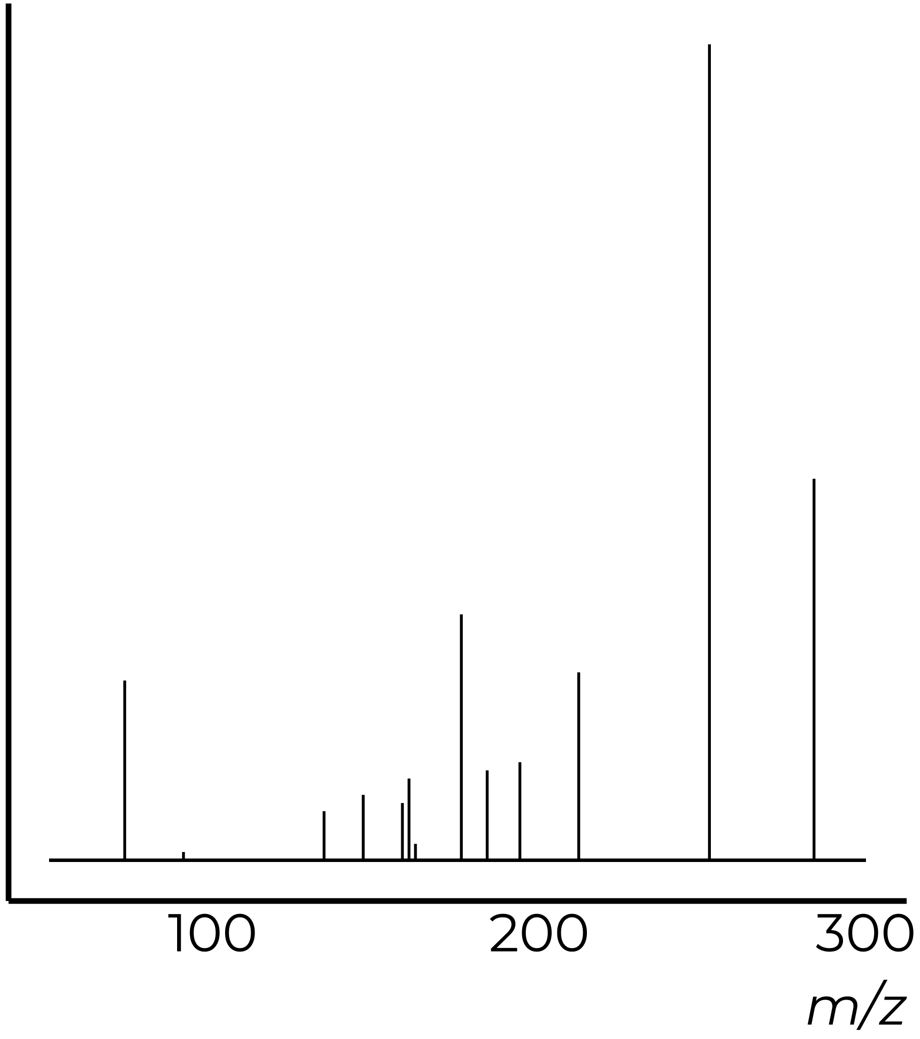
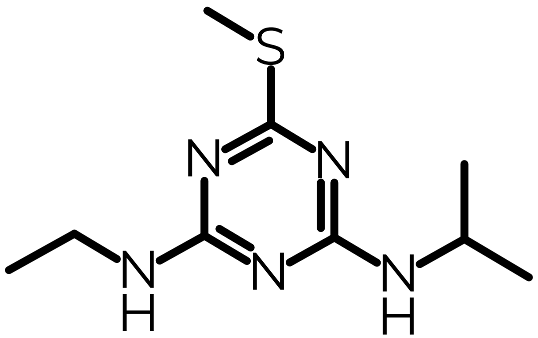
toxicity assessment





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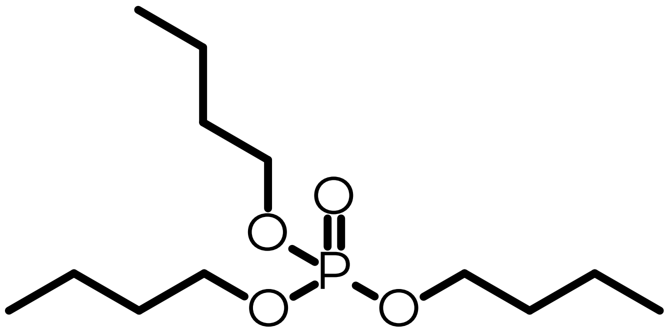

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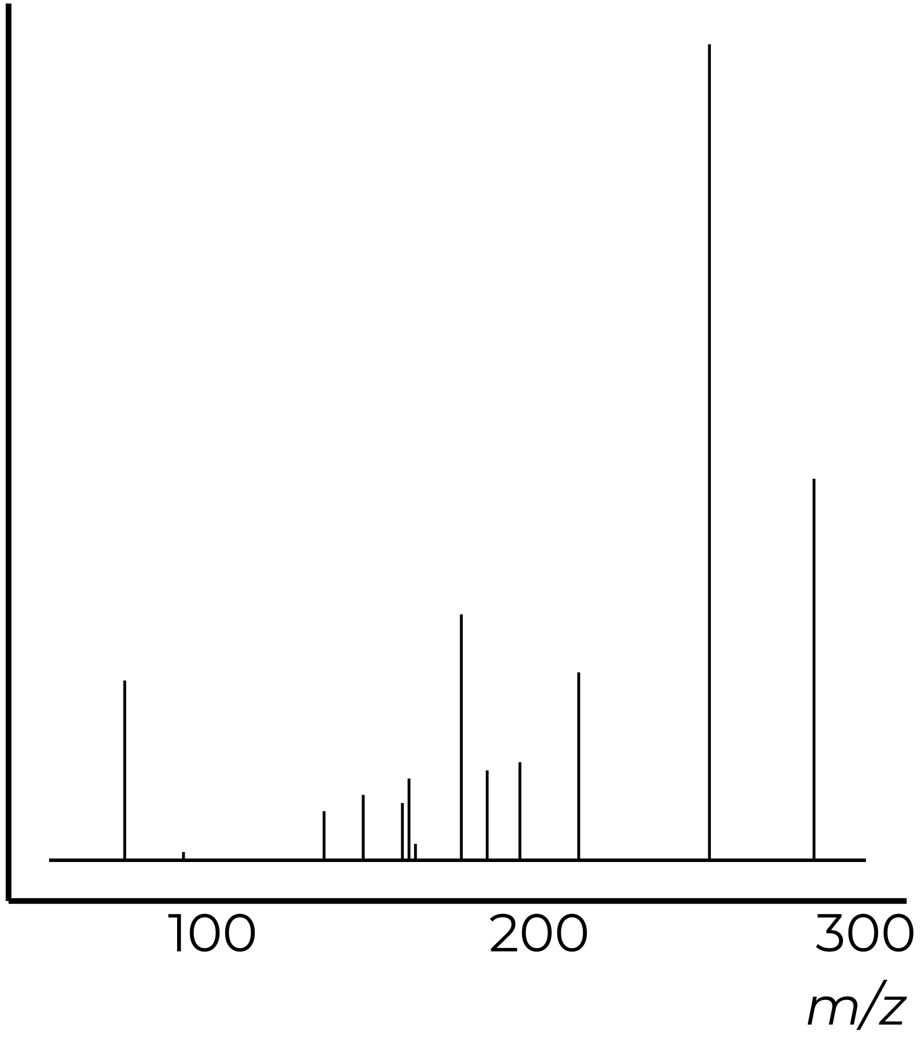
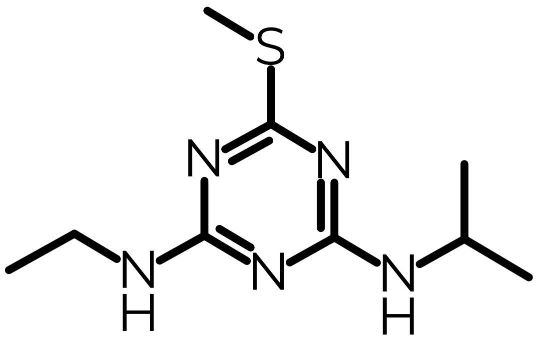
toxicity assessment





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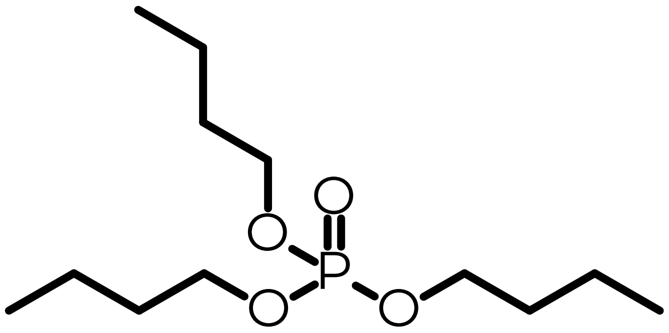

LC_{50} = ? mg/L

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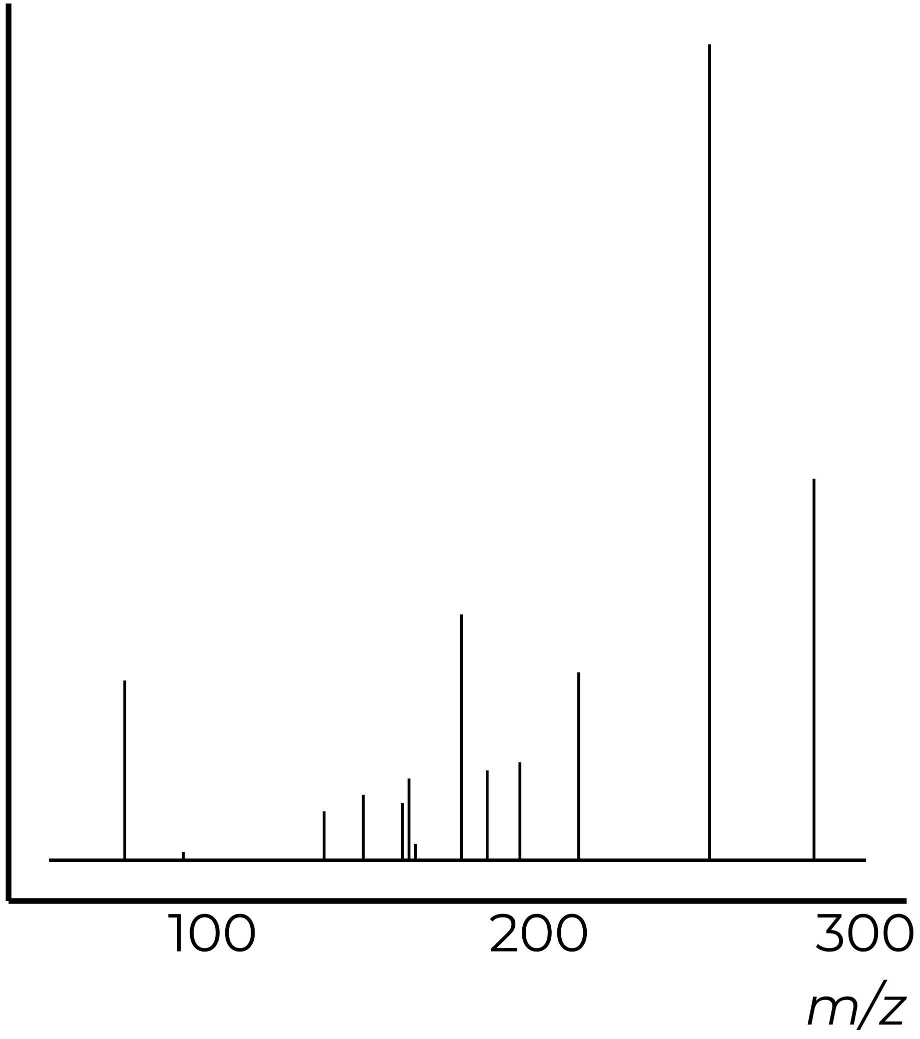
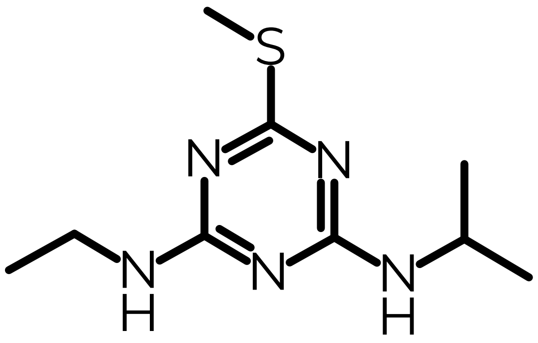
toxicity assessment





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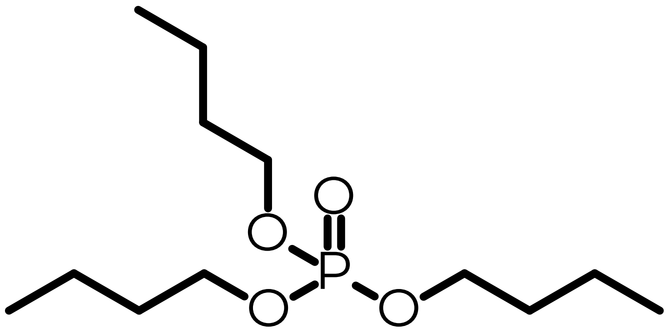

LC_{50} = ? mg/L

?

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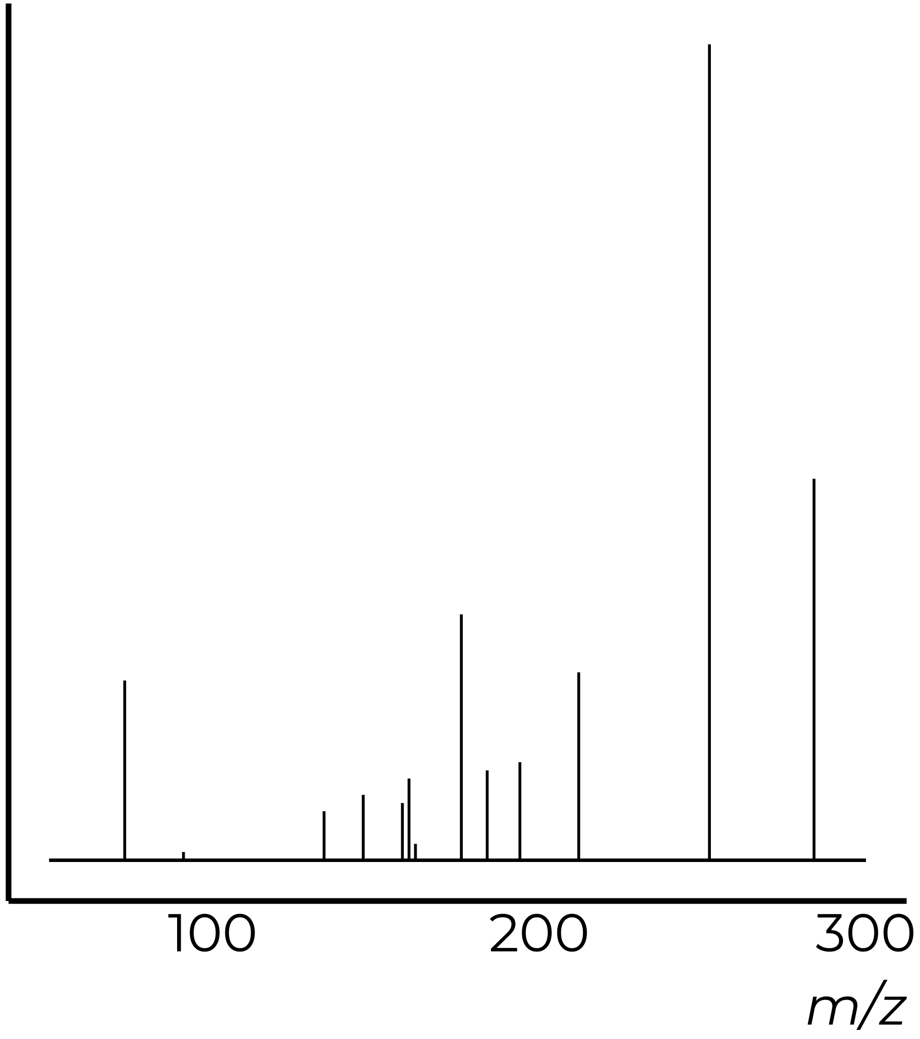
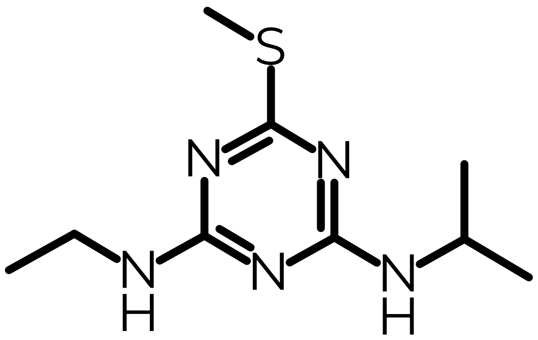
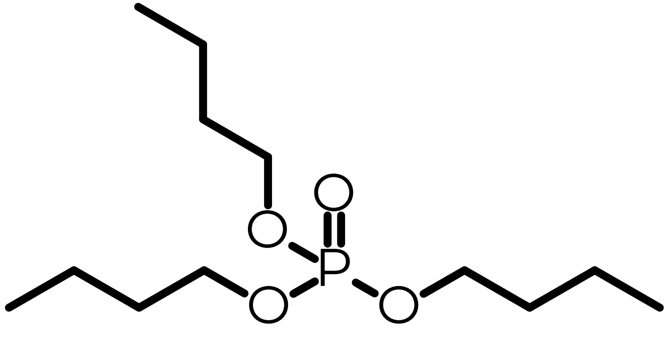
toxicity assessment





LC_{50} = 9.3 mg/L



LC_{50} = ? mg/L

?

LC_{50} = ? mg/L

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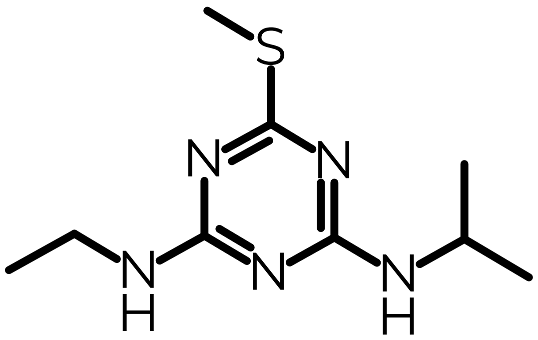
toxicity assessment



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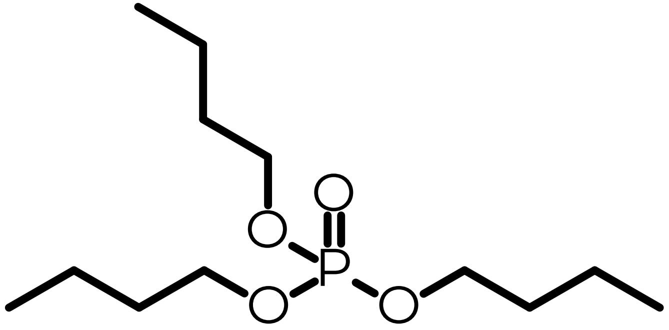

LC_{50} = ? mg/L

?

LC_{50} = ? mg/L

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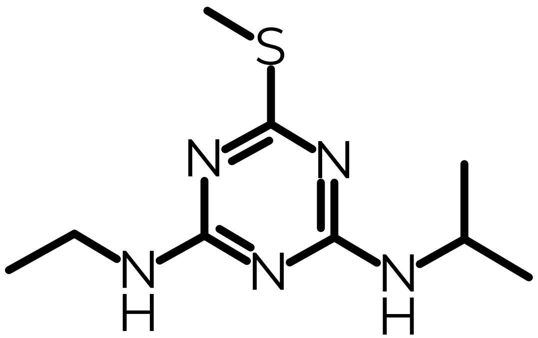
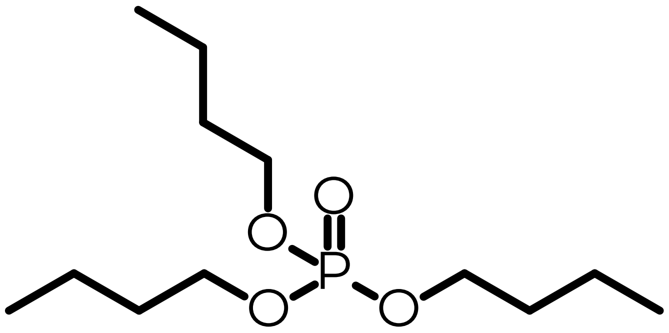
toxicity assessment

<1%



LC_{50} = 9.3 mg/L



LC_{50} = ? mg/L

?

LC_{50} = ? mg/L

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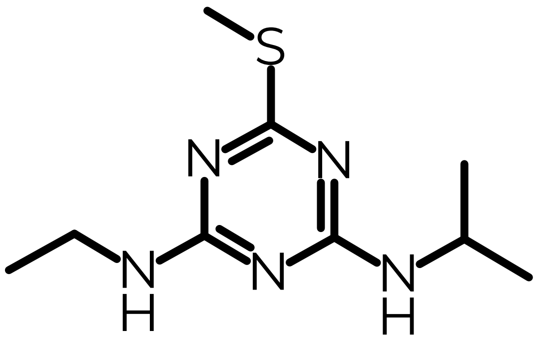
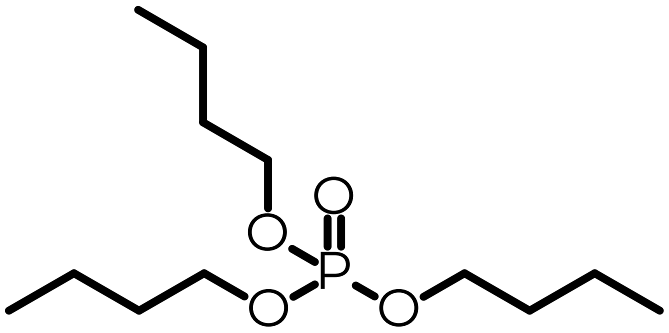
toxicity assessment

<1%



LC$_{50}$ = 9.3 mg/L

<2%



LC$_{50}$ = ? mg/L

?

LC$_{50}$ = ? mg/L

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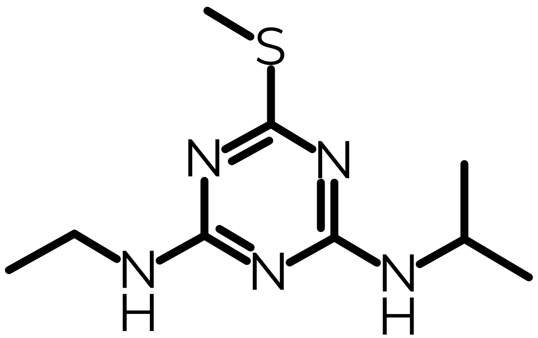
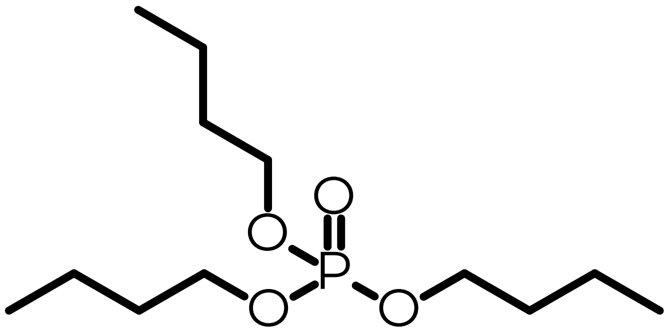
toxicity assessment

<1%



LC_{50} = 9.3 mg/L

<2%



LC_{50} = ? mg/L

~98%

?

LC_{50} = ? mg/L

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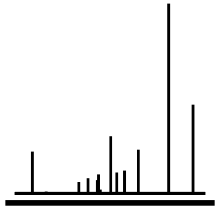
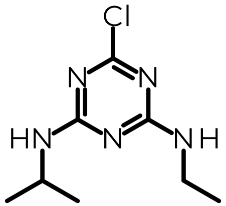
predicting toxicity

for detected chemicals

workflow

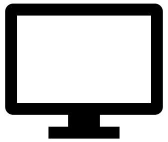


MS^2 spectra



structure as SMILES

molecular descriptors



predict toxicity

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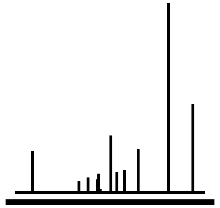
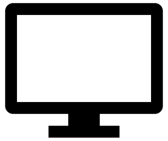
workflow



MS^2 spectra

molecular descriptors



predict toxicity

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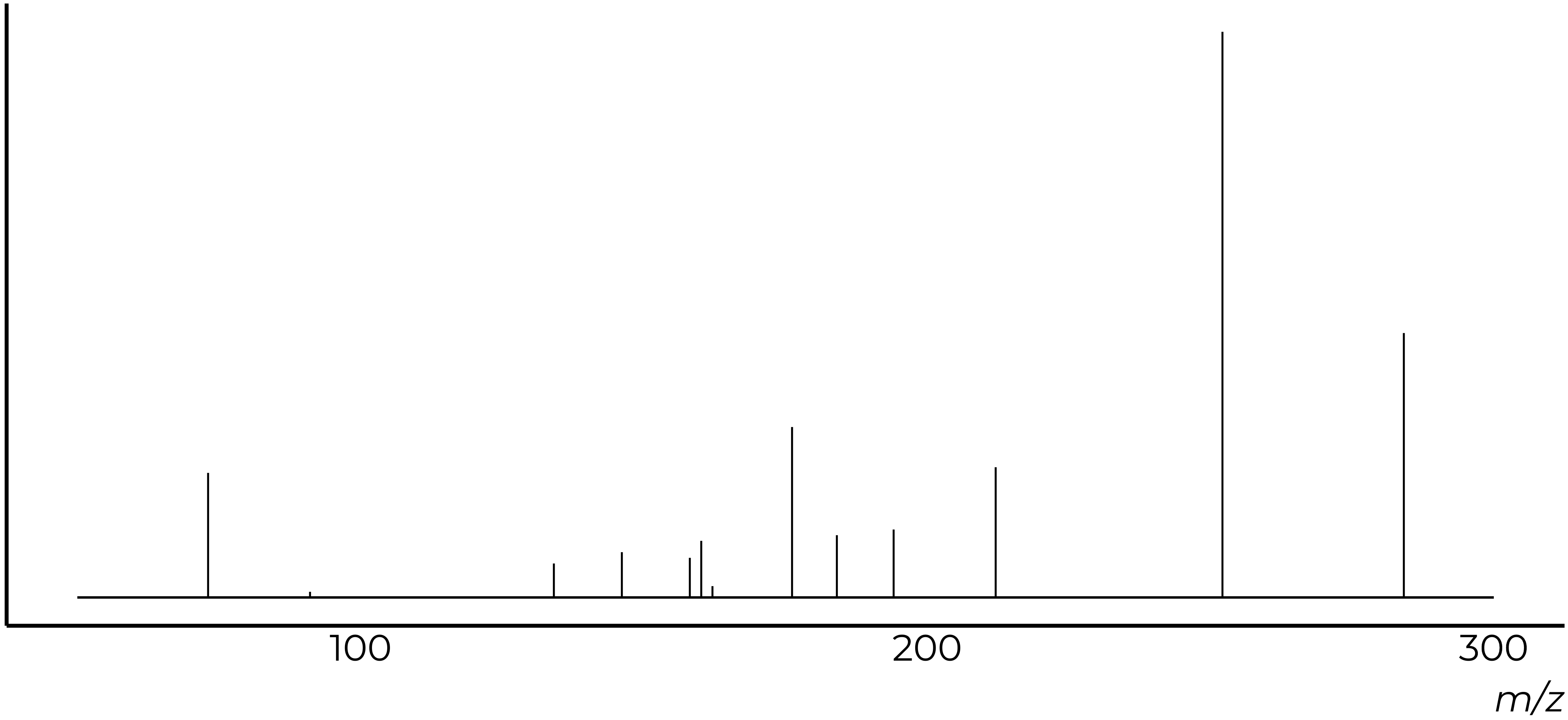
information available

in MS^2 spectra

MS² spectra



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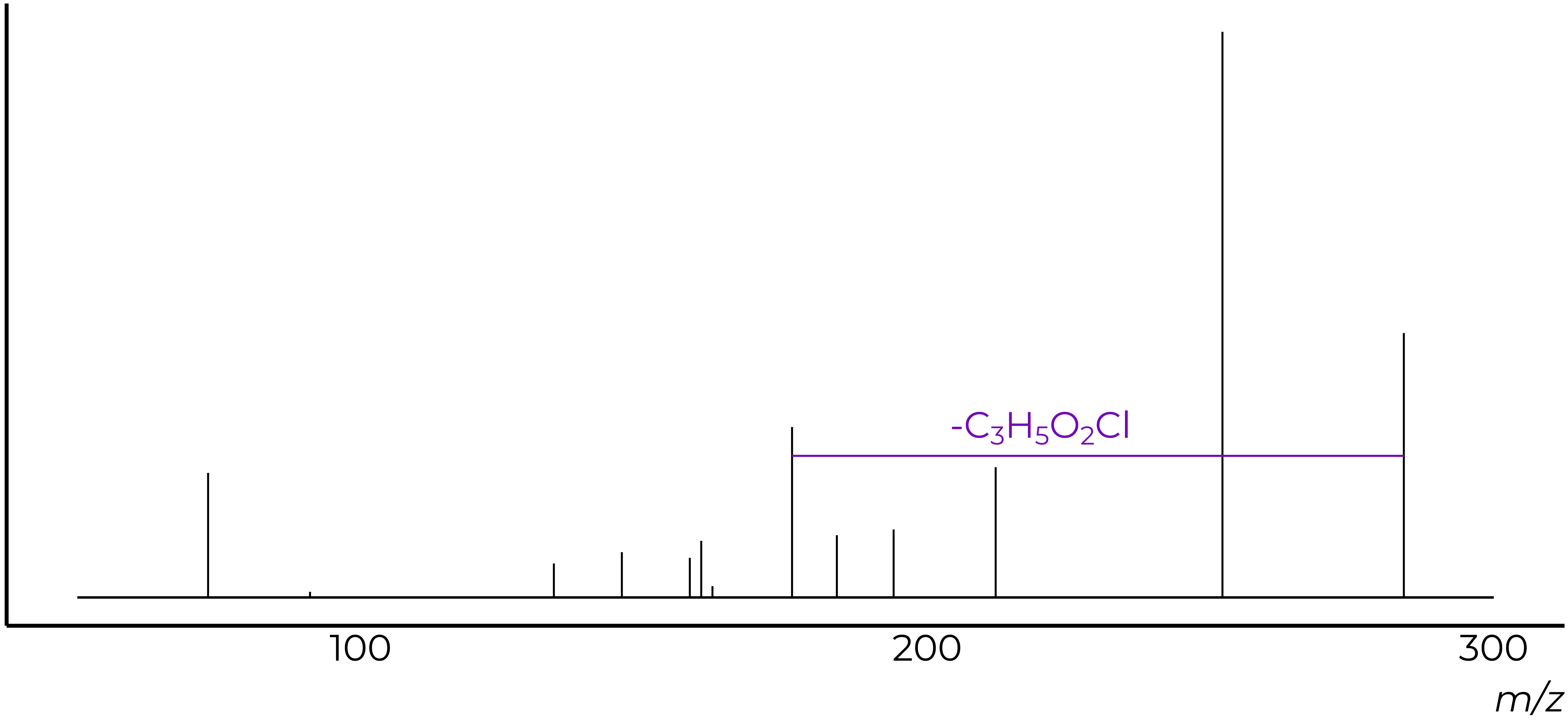
MS^2 spectra



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data for machine learning models

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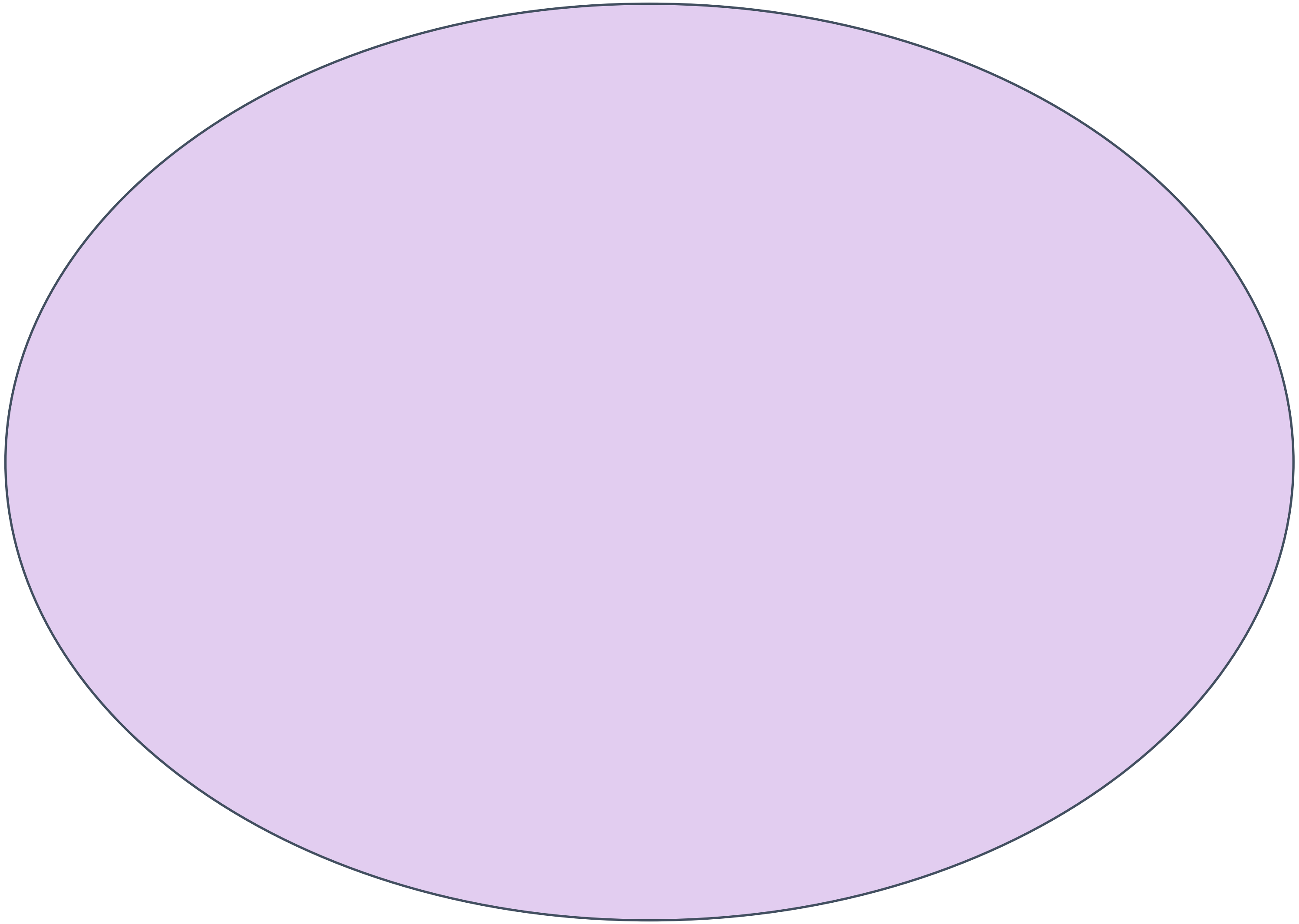
data for machine learning models

CompTox



all toxicity values

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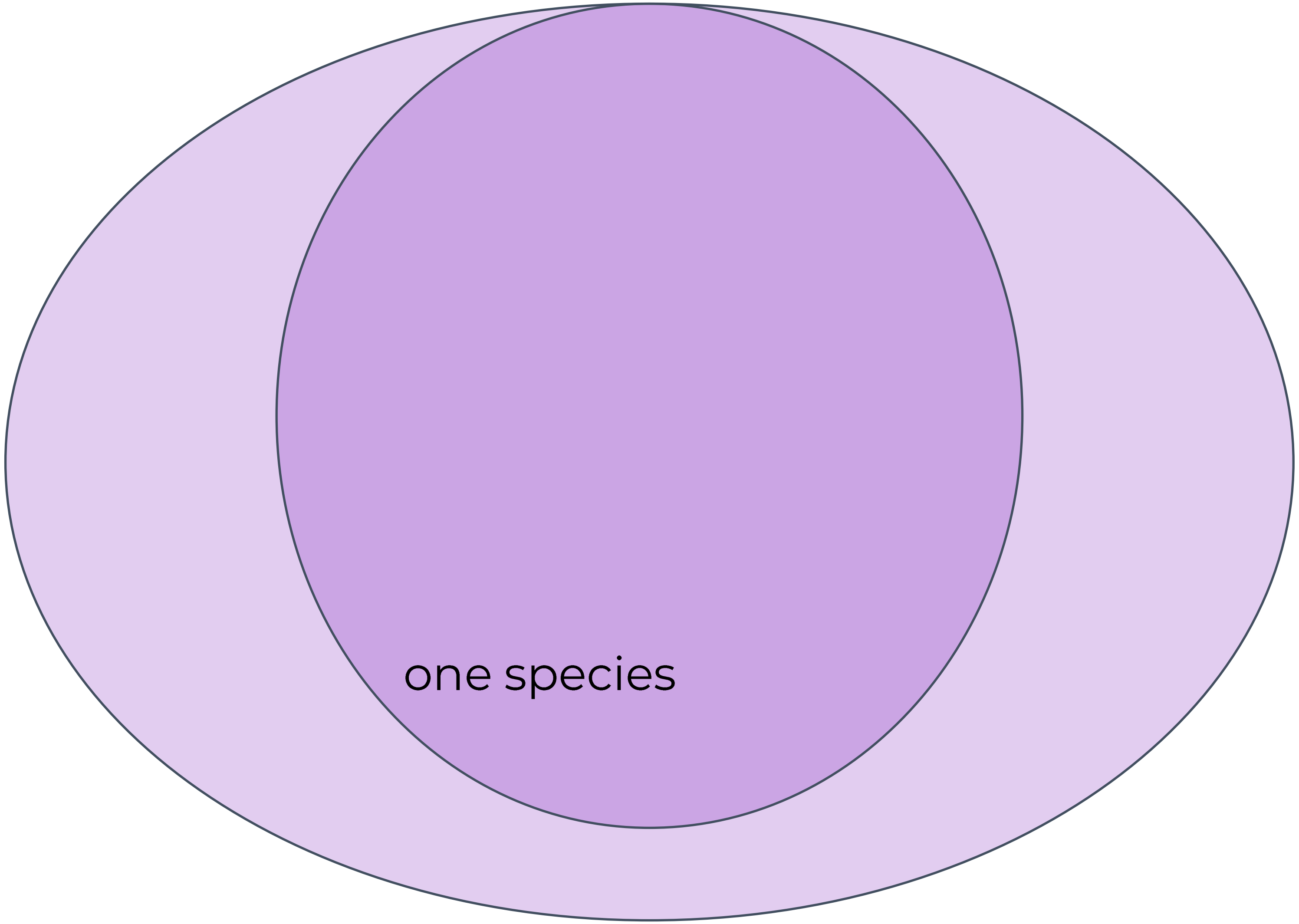
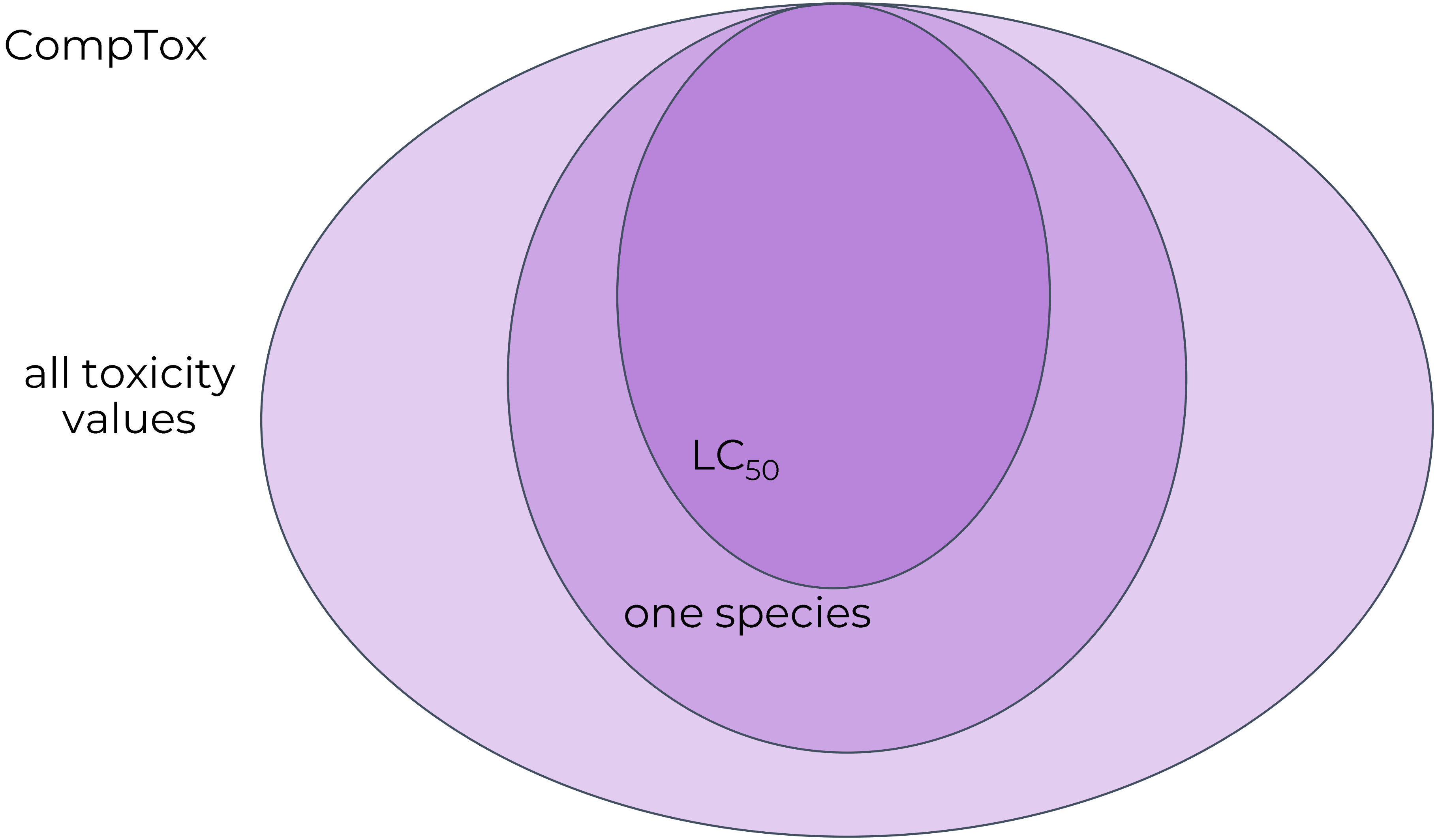
data for machine learning models

CompTox

all toxicity values



data for machine learning models



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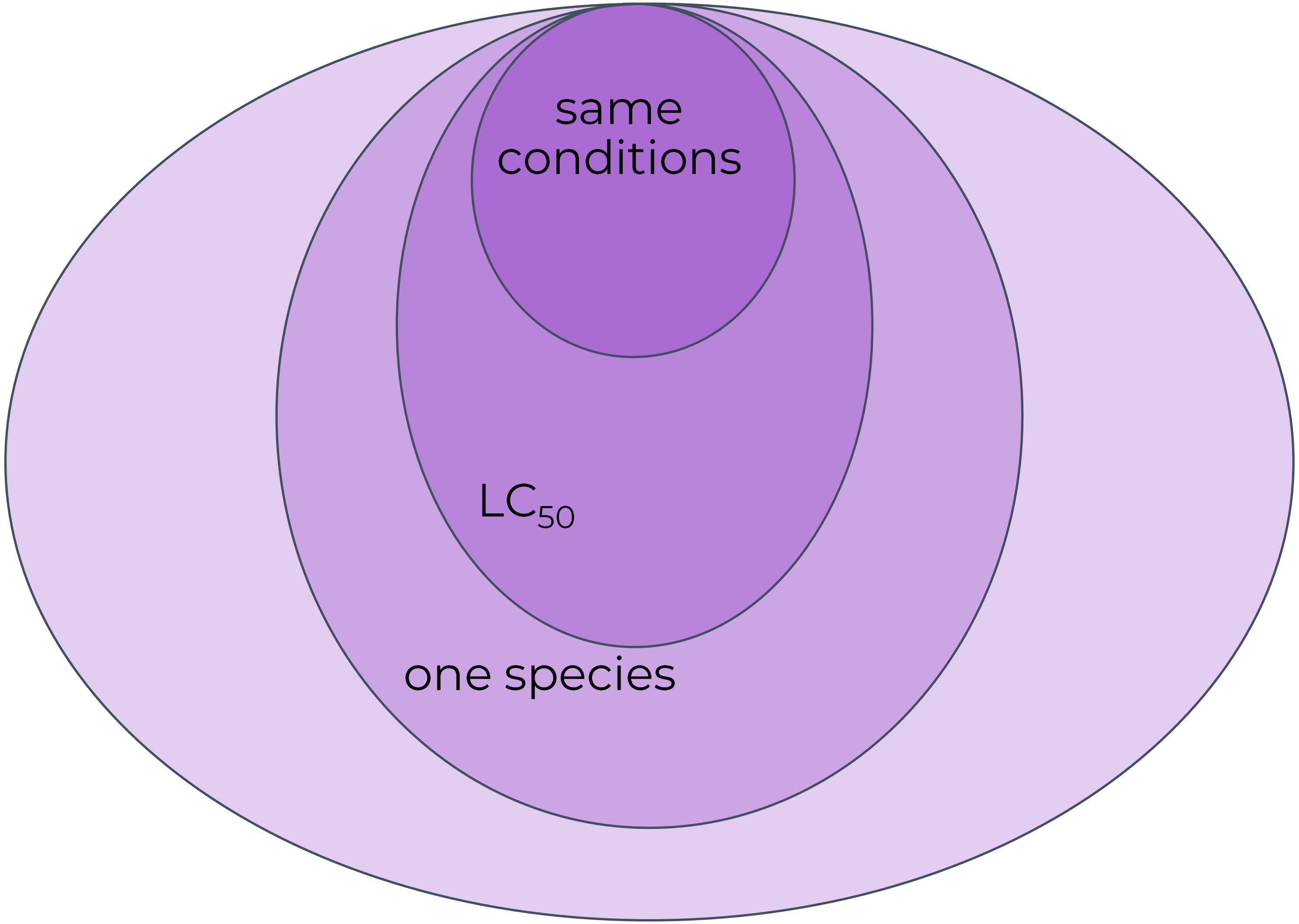
data for machine learning models

CompTox

all toxicity values



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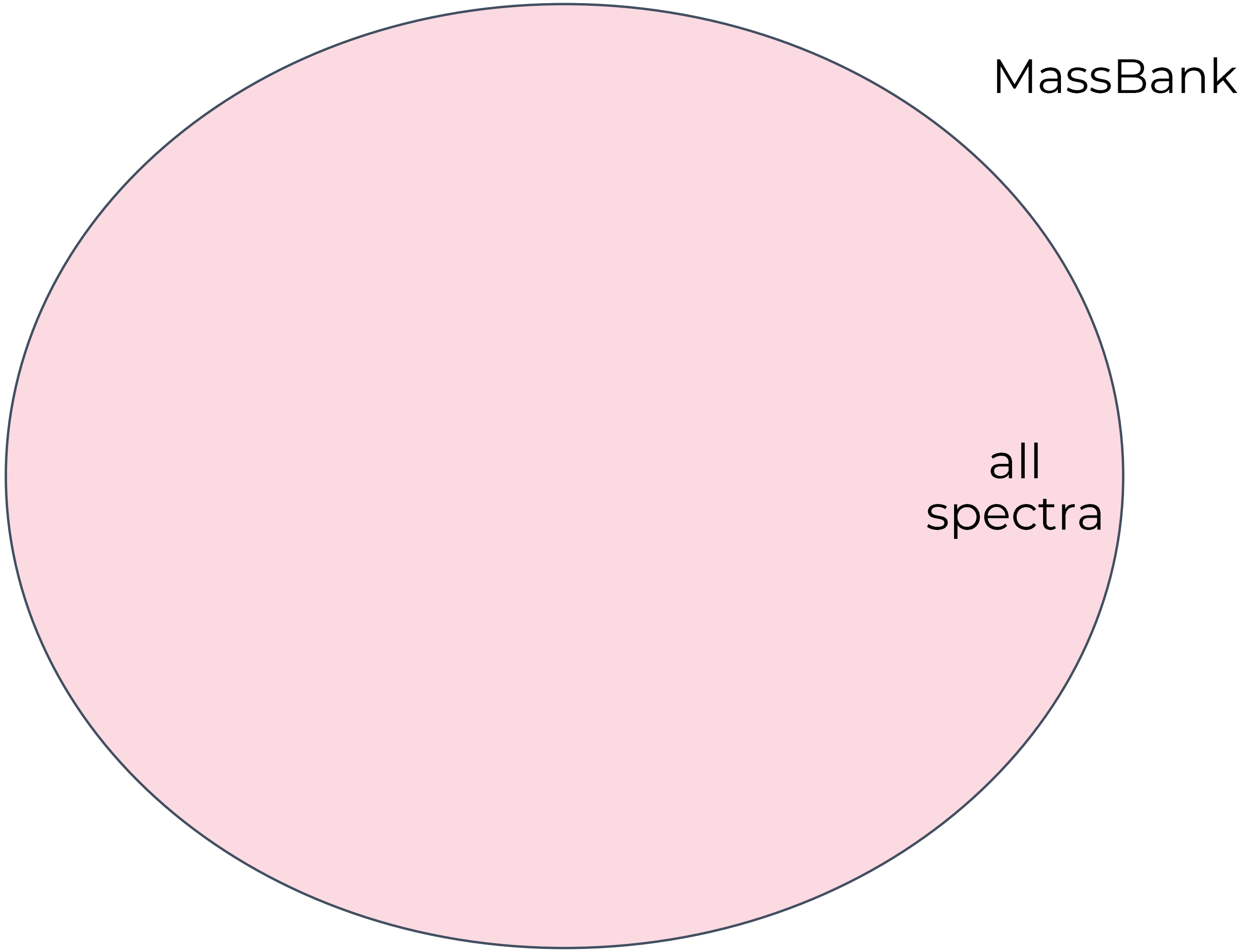
data for machine learning models



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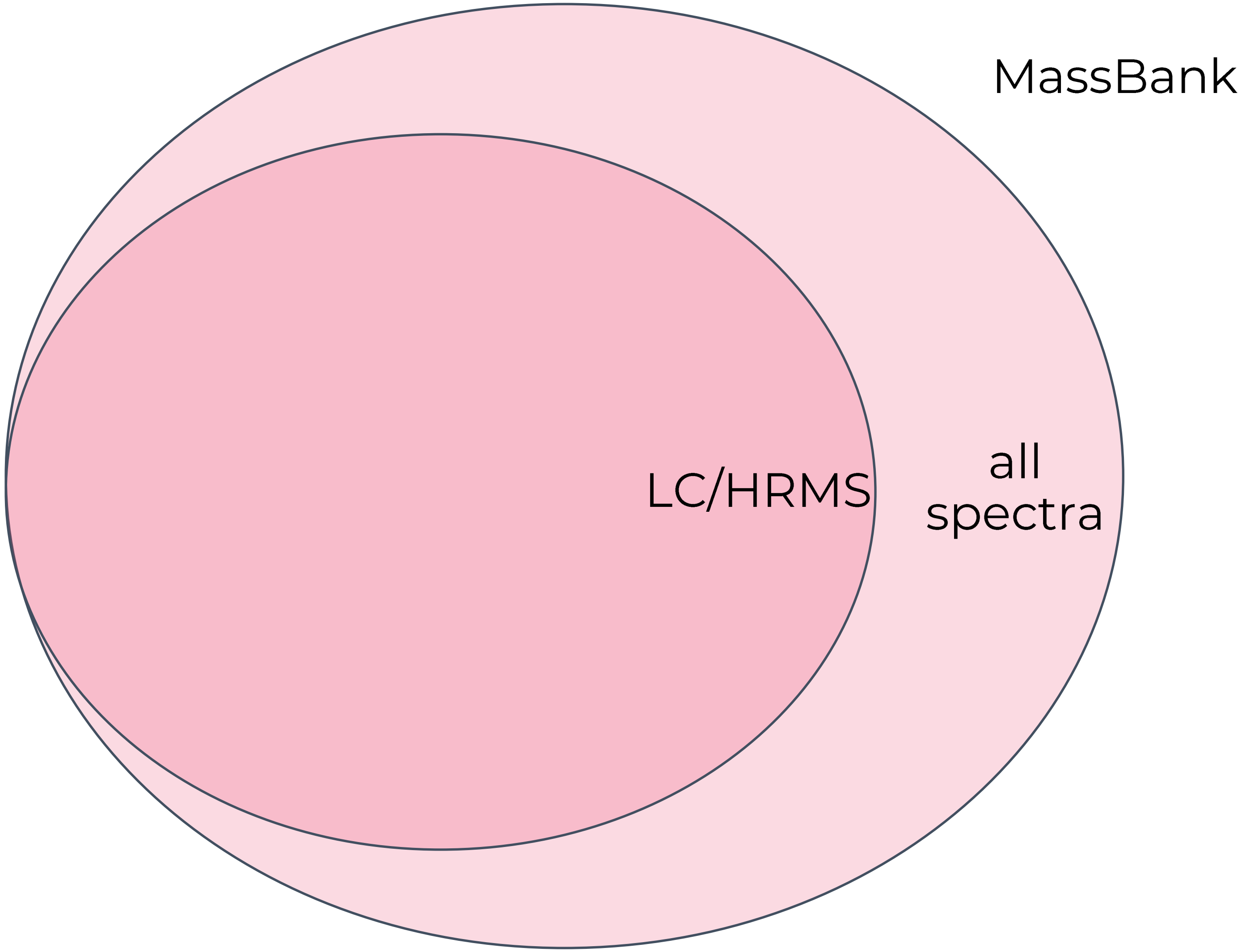
data for machine learning models



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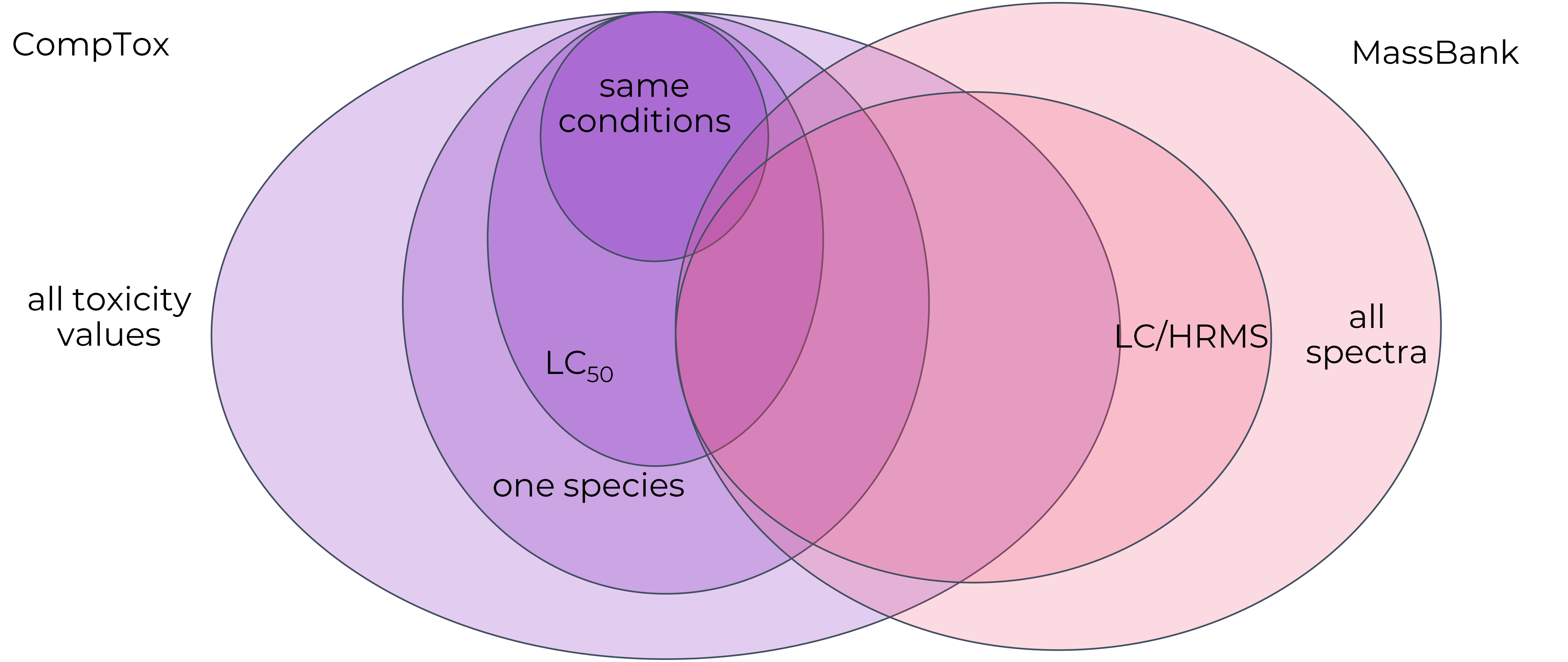

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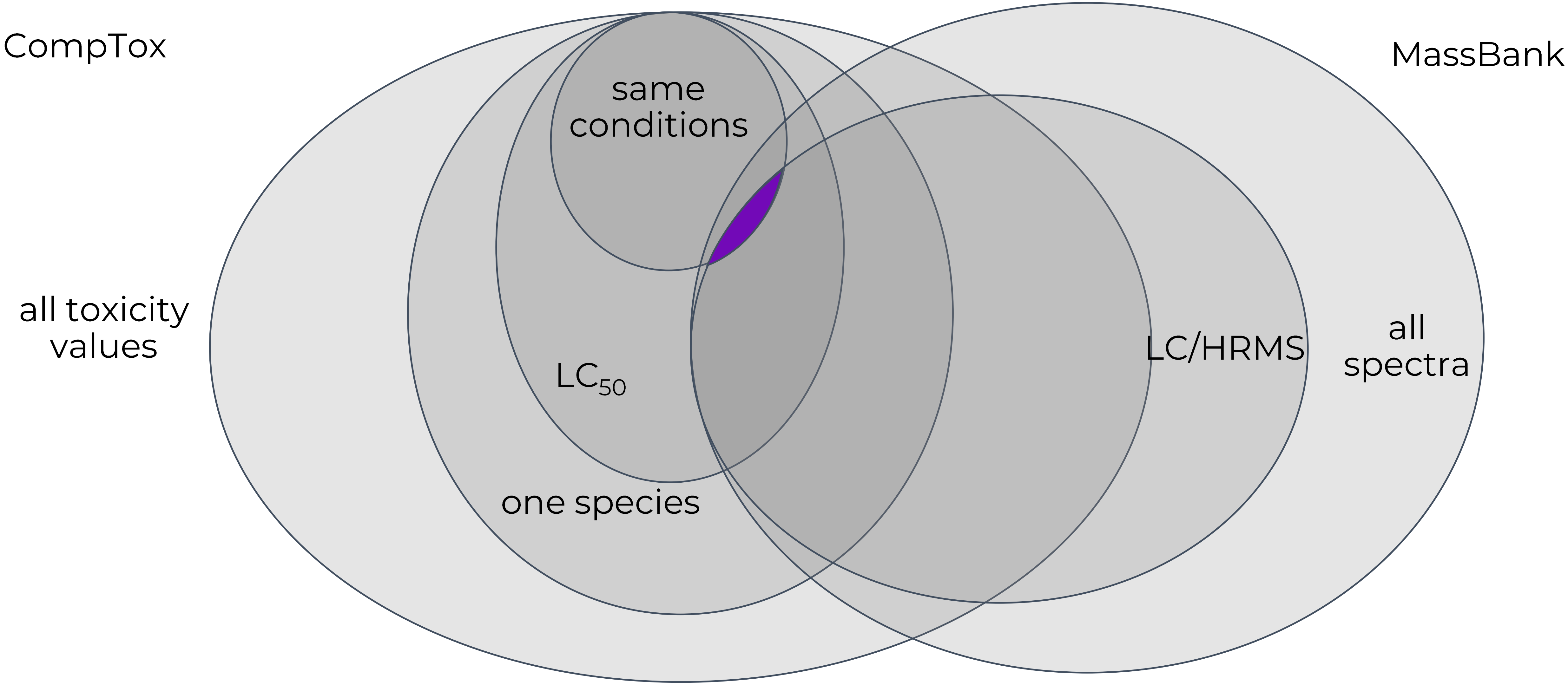
data for machine learning models



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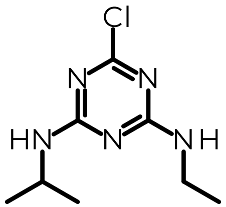
predicting toxicity

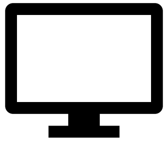
from the structure

workflow



structure as SMILES

molecular fingerprints



machine learning for predicting toxicity

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selected endpoint

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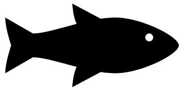
selected endpoint



fathead minnow, bluegill, and rainbow trout

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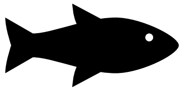
selected endpoint



fathead minnow, bluegill, and rainbow trout

water flea

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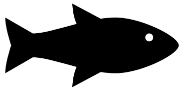
selected endpoint

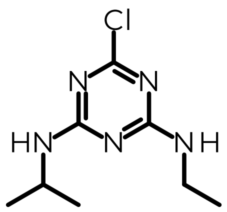


fathead minnow, bluegill, and rainbow trout

water flea

algae

workflow



structure as SMILES

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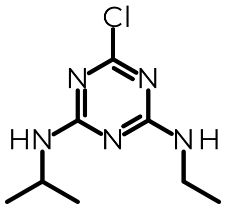
workflow



structure as SMILES

molecular fingerprints

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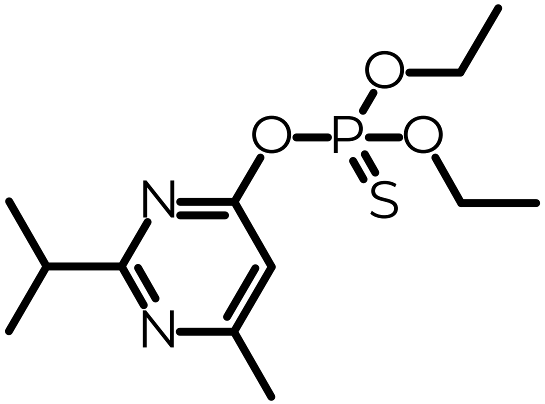
structural fingerprints



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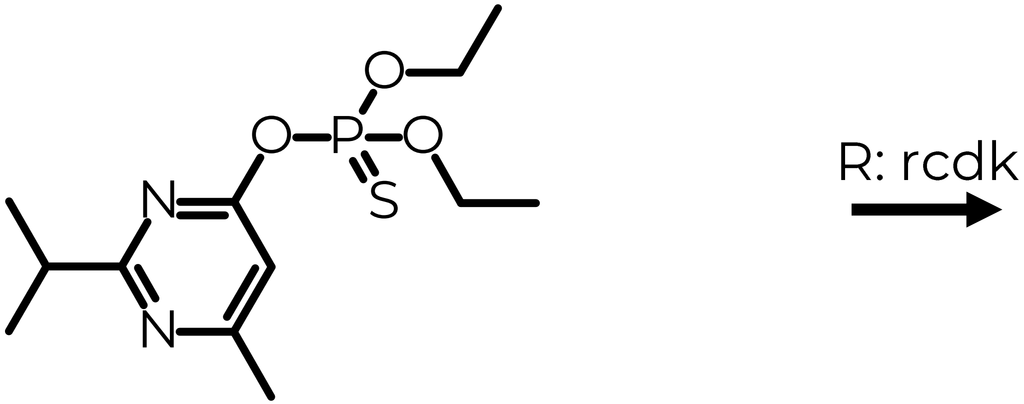
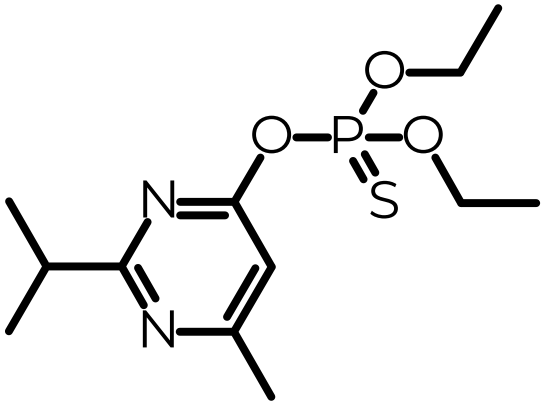
structural fingerprints



structural fingerprints



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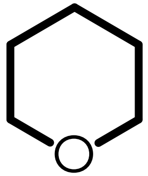
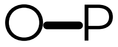
0	
1	
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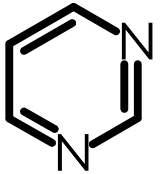
1	

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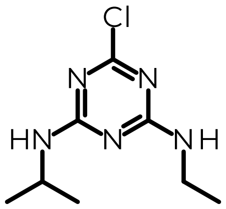
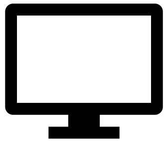
workflow



structure as SMILES

molecular fingerprints



machine learning for predicting LC_{50}

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model training

mass (Da)	fp1	...	fp243
317.32000	0	...	0
208.26100	1	...	0
240.21499	1	...	0
300.57998	0	...	0
201.22500	0	...	0

model training

mass (Da)	fp1	…	fp243
317.32000	0	…	0
208.26100	1	…	0
240.21499	1	…	0
300.57998	0	…	0
201.22500	0	…	0

training set

517
chemicals

test set

130
chemicals

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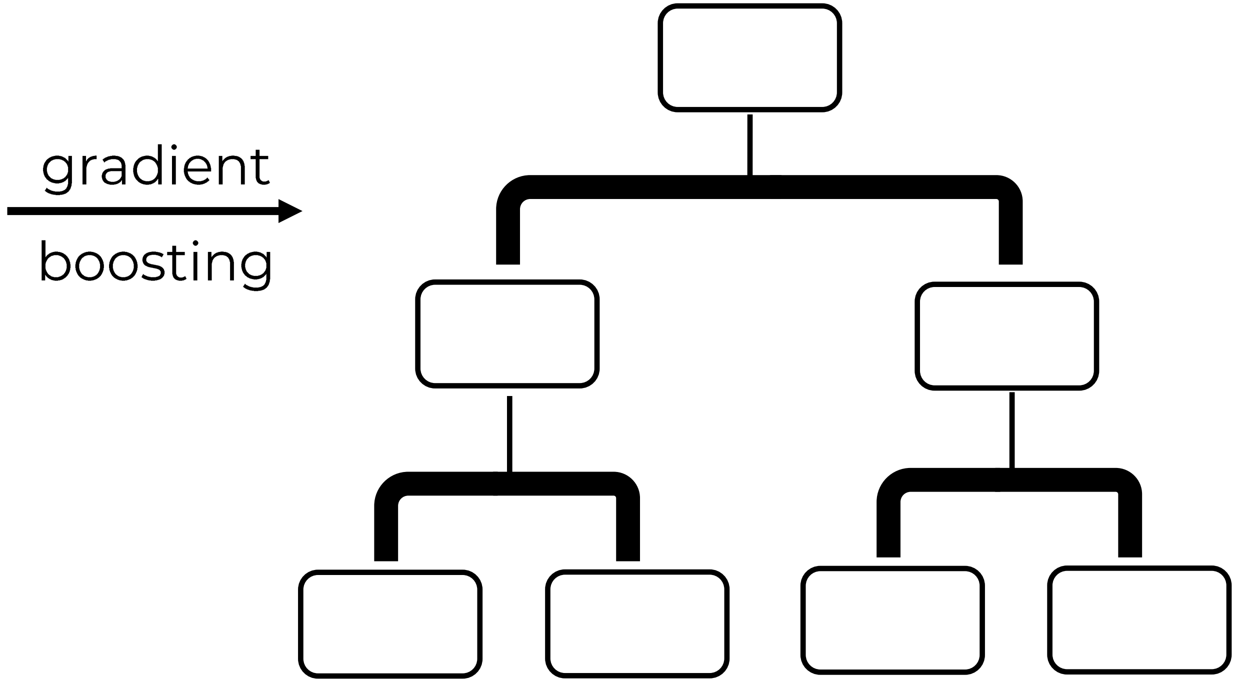
model training

mass (Da)	fp1	...	fp243
317.32000	0	...	0
208.26100	1	...	0
240.21499	1	...	0
300.57998	0	...	0
201.22500	0	...	0

training set
517 chemicals

test set
130 chemicals



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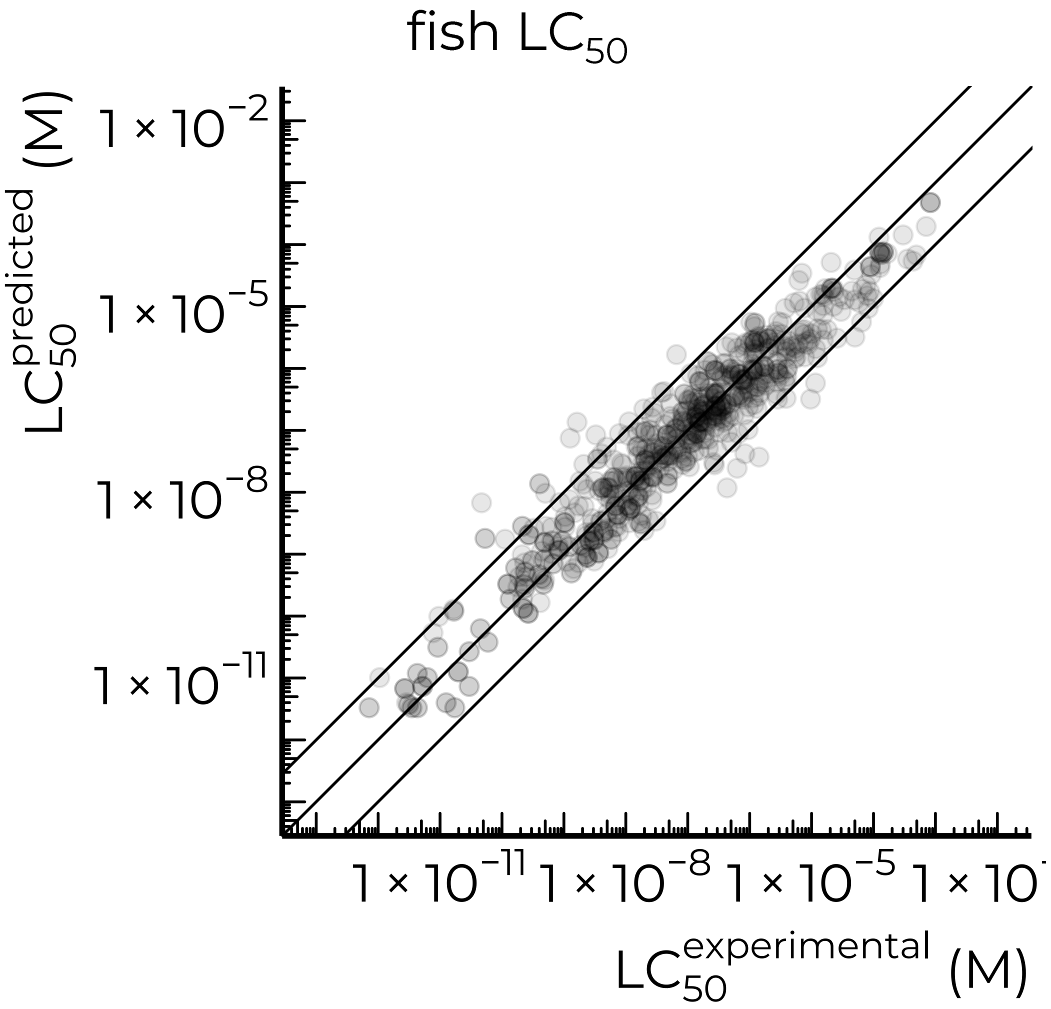
performance

of LC_{50} predictions with molecular fingerprints

LC_{50} predictions

Peets et al. ES&T 2022



training set

RMSE 0.52 log(M)

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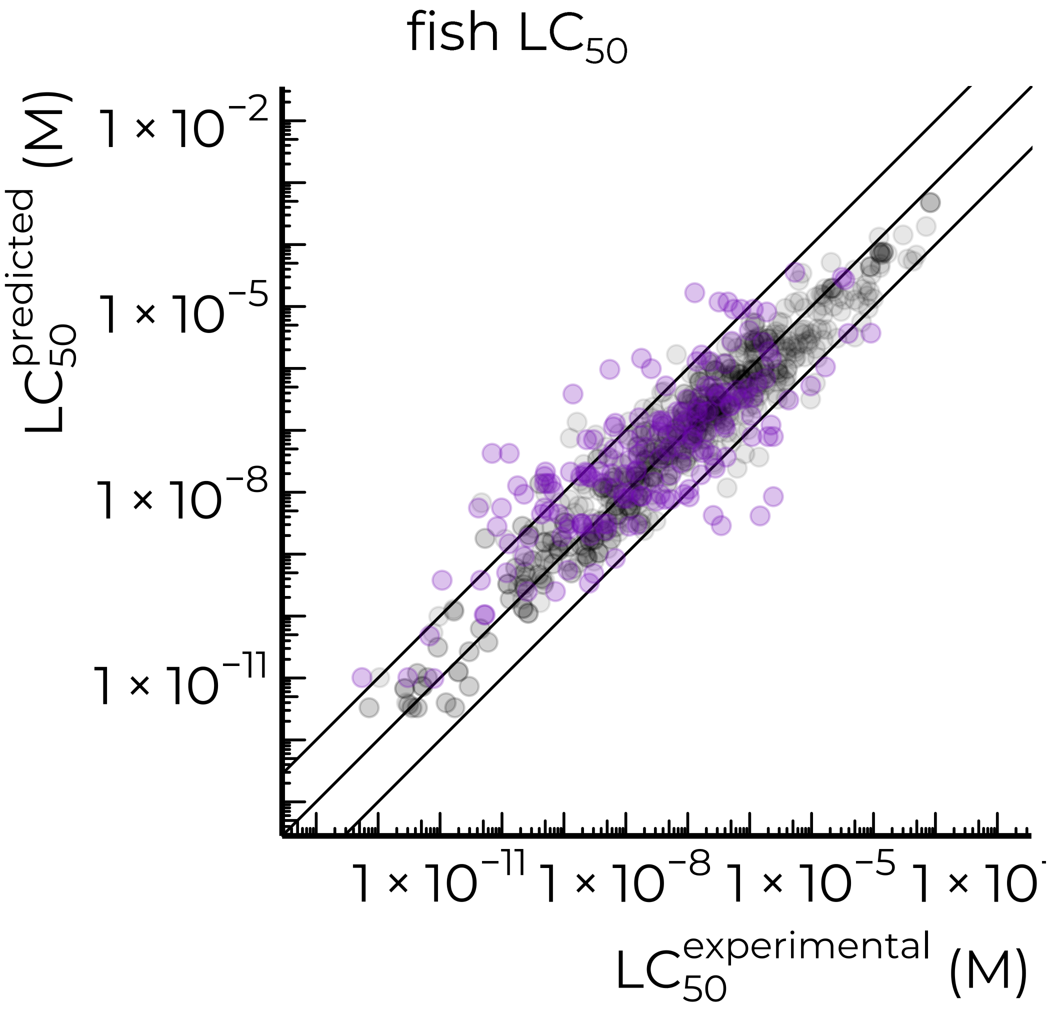
LC_{50} predictions

Peets et al. ES&T 2022



training set

RMSE 0.52 log(M)

test set

RMSE 0.78 log(M)

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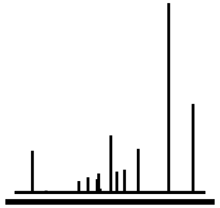
unidentified chemicals

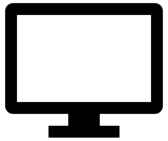
from MS^2 spectra

workflow



MS^2 spectra

molecular fingerprints with SIRIUS+CSI:FingerID



predict LC_{50} with pretrained gradient boosting

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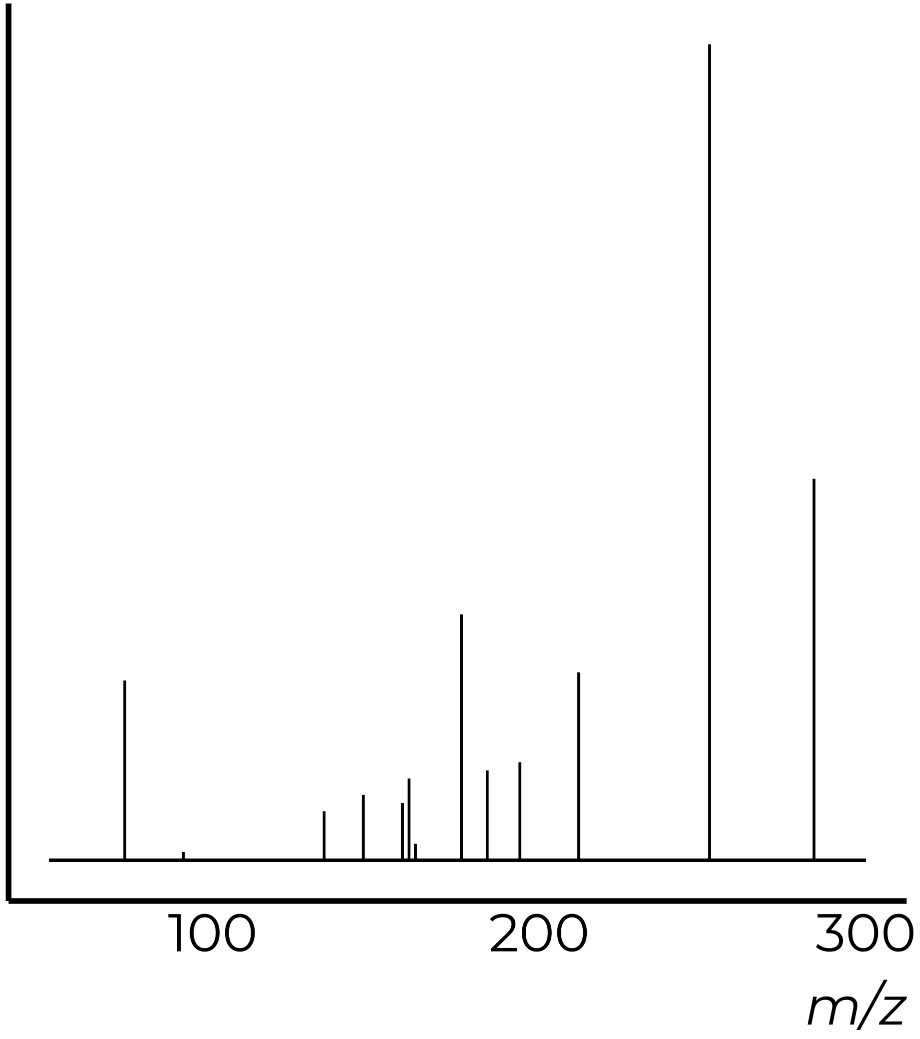
predict for unknown chemicals



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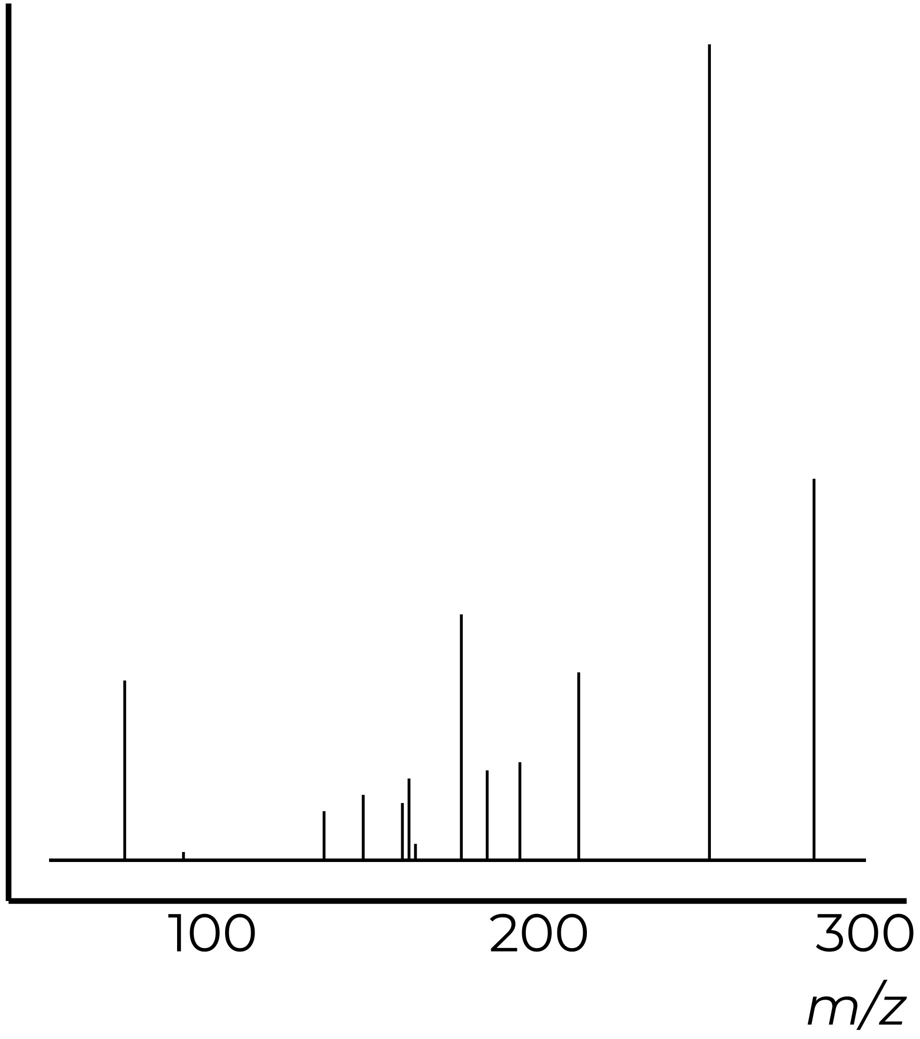
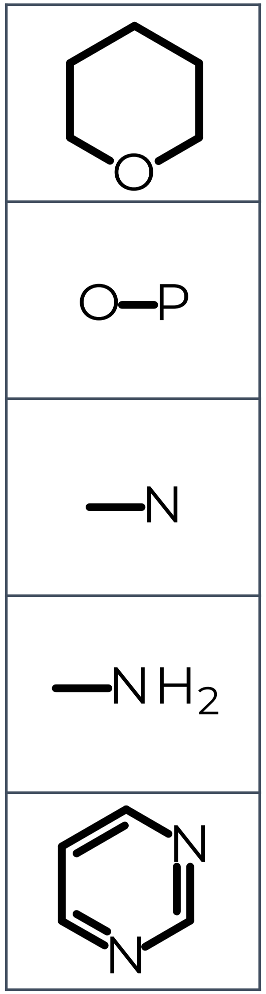
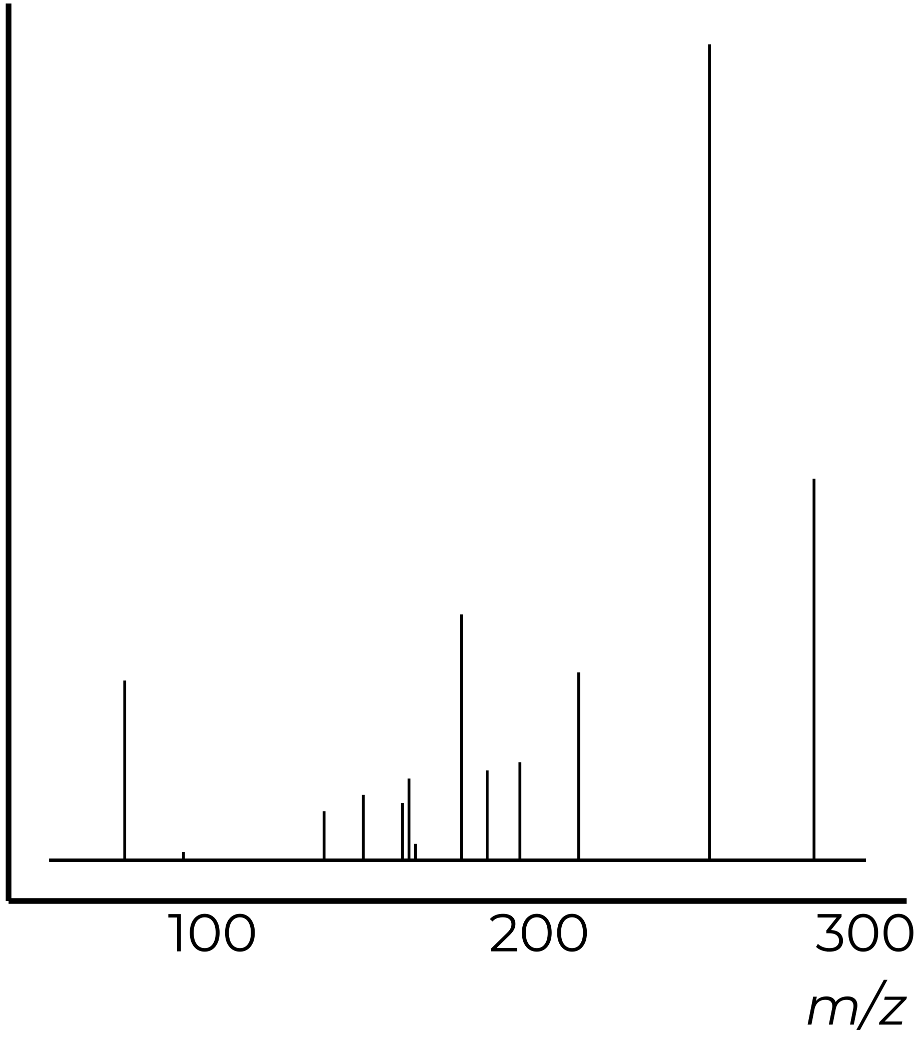
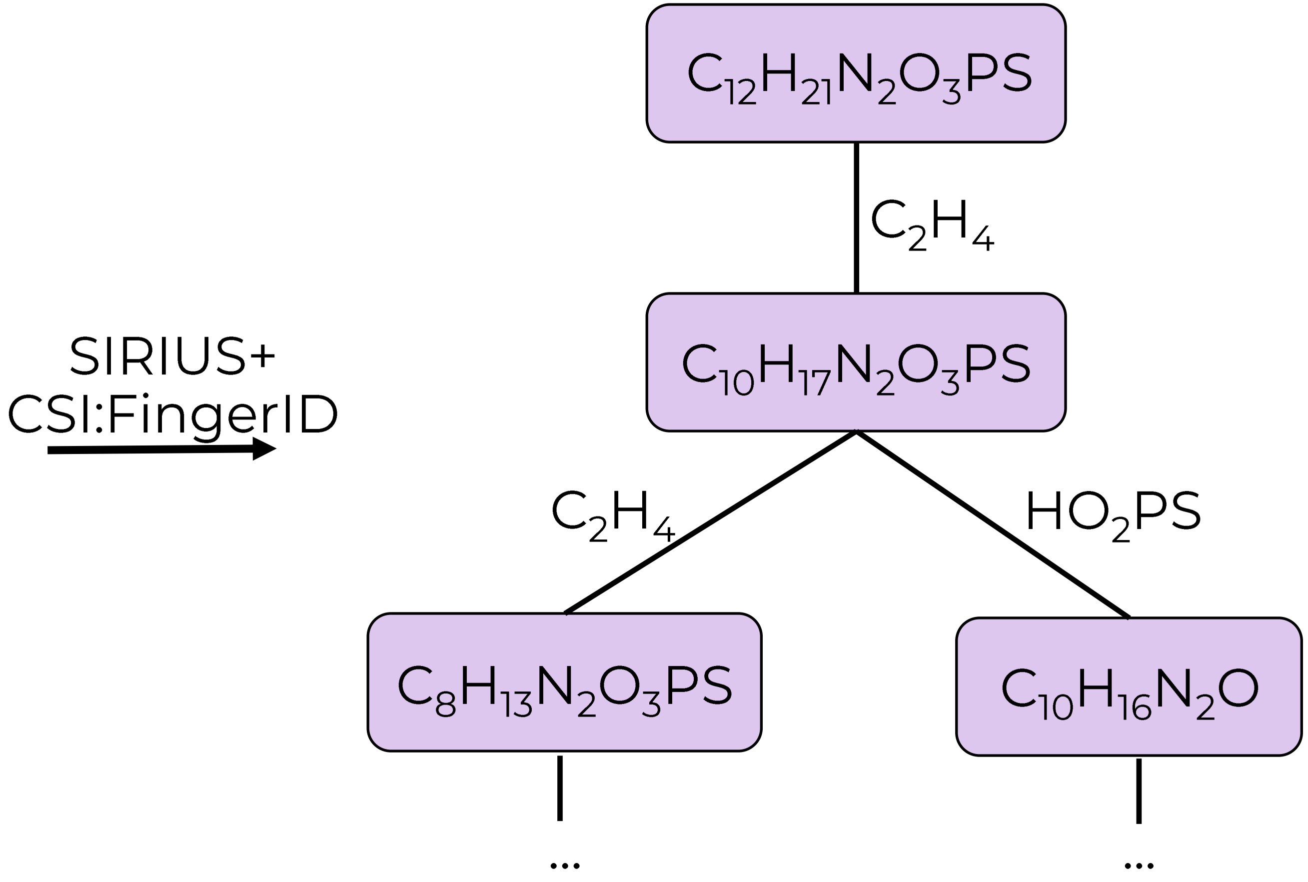
predict for unknown chemicals





predict for unknown chemicals





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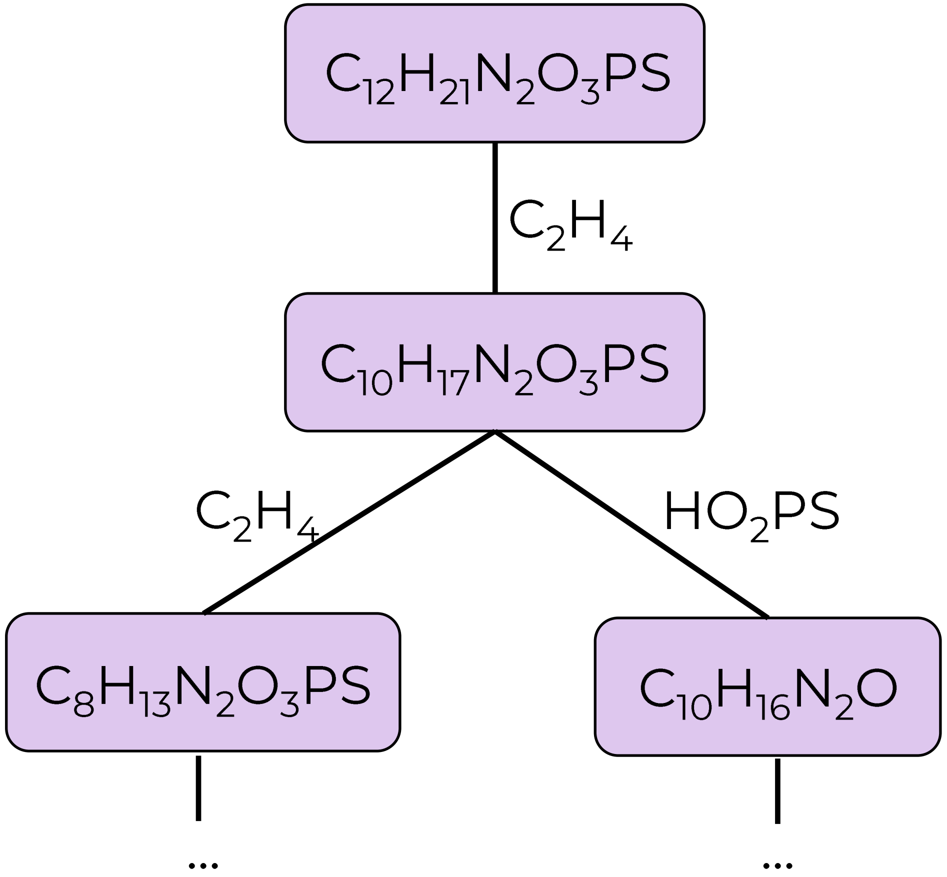
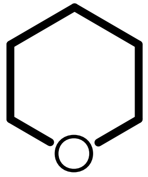
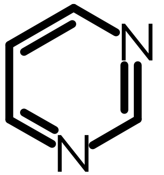
predict for unknown chemicals



SIRIUS+
CSI:FingerID →

0.001	
0.999	O–P
0.999	–N
0.198	–NH_2
0.988	

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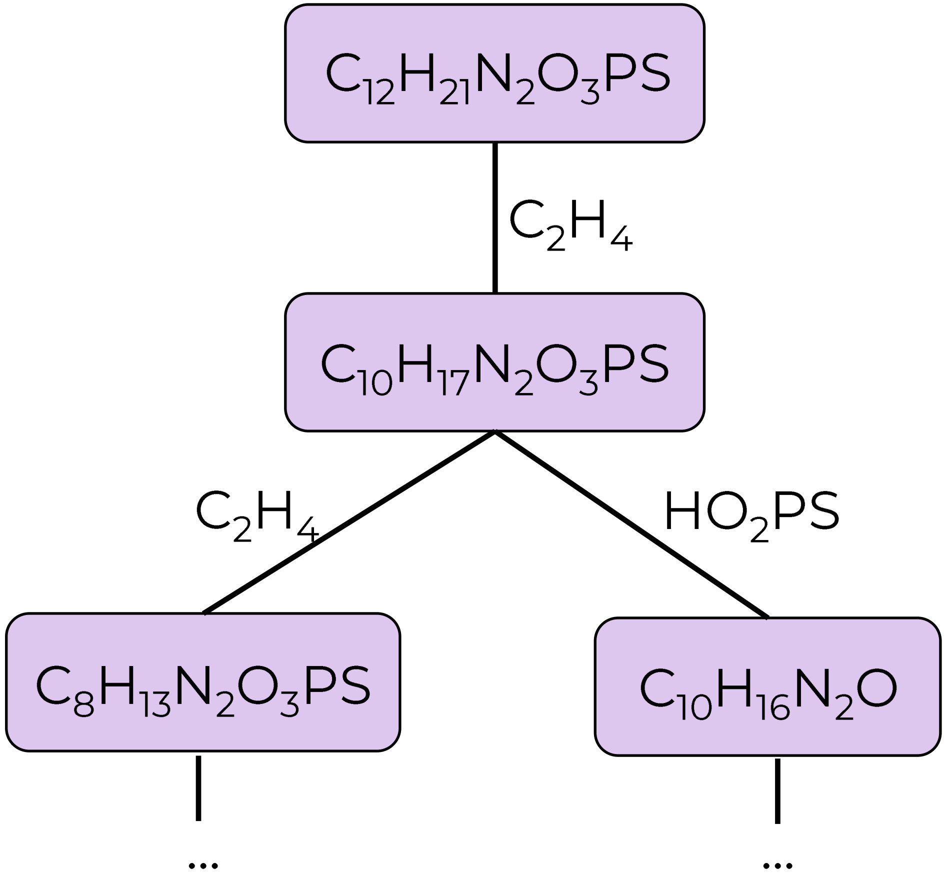
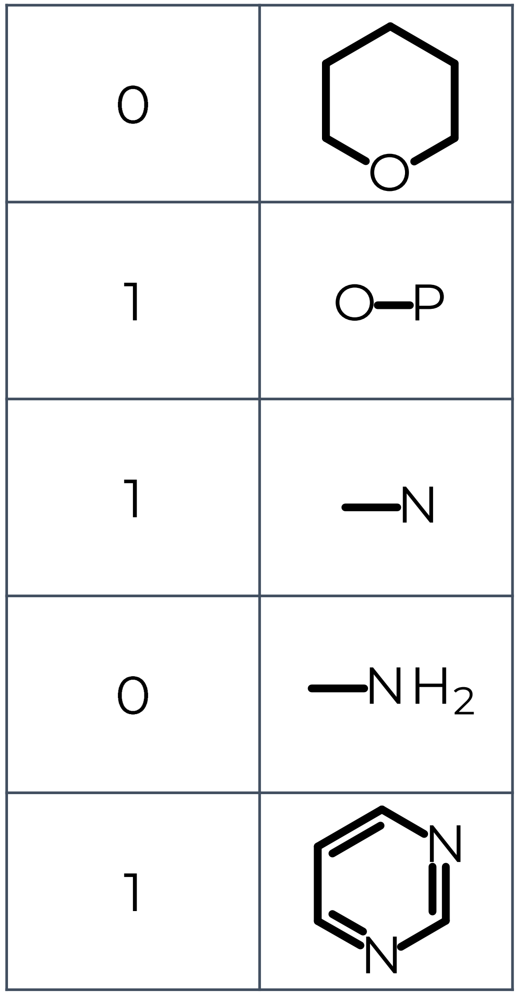
predict for unknown chemicals



SIRIUS+
CSI:FingerID



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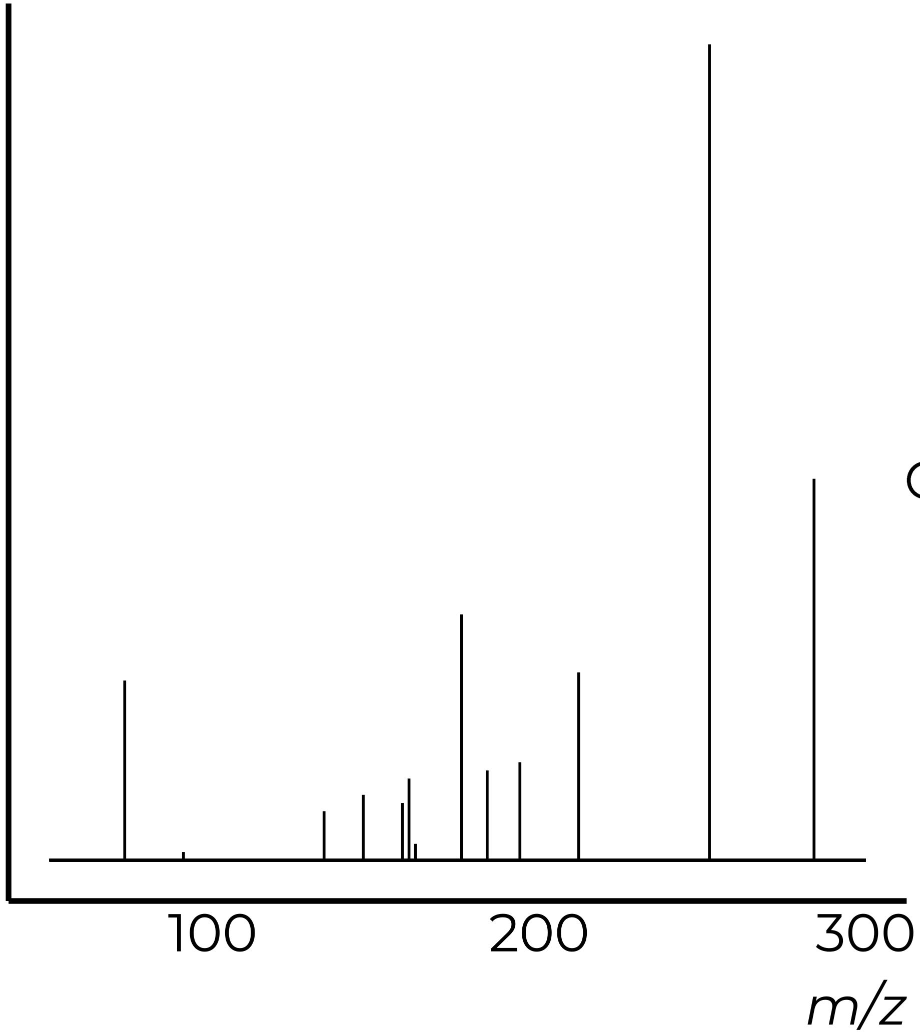
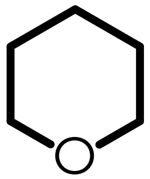
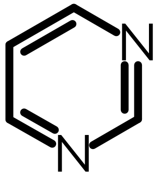
predict for unknown chemicals



SIRIUS+
CSI:FingerID →

0	
1	O—P
1	—N
0	—NH_2
1	

gradient
boosting →

LC_{50} =
-2.2 log(mM)

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LC_{50} predictions

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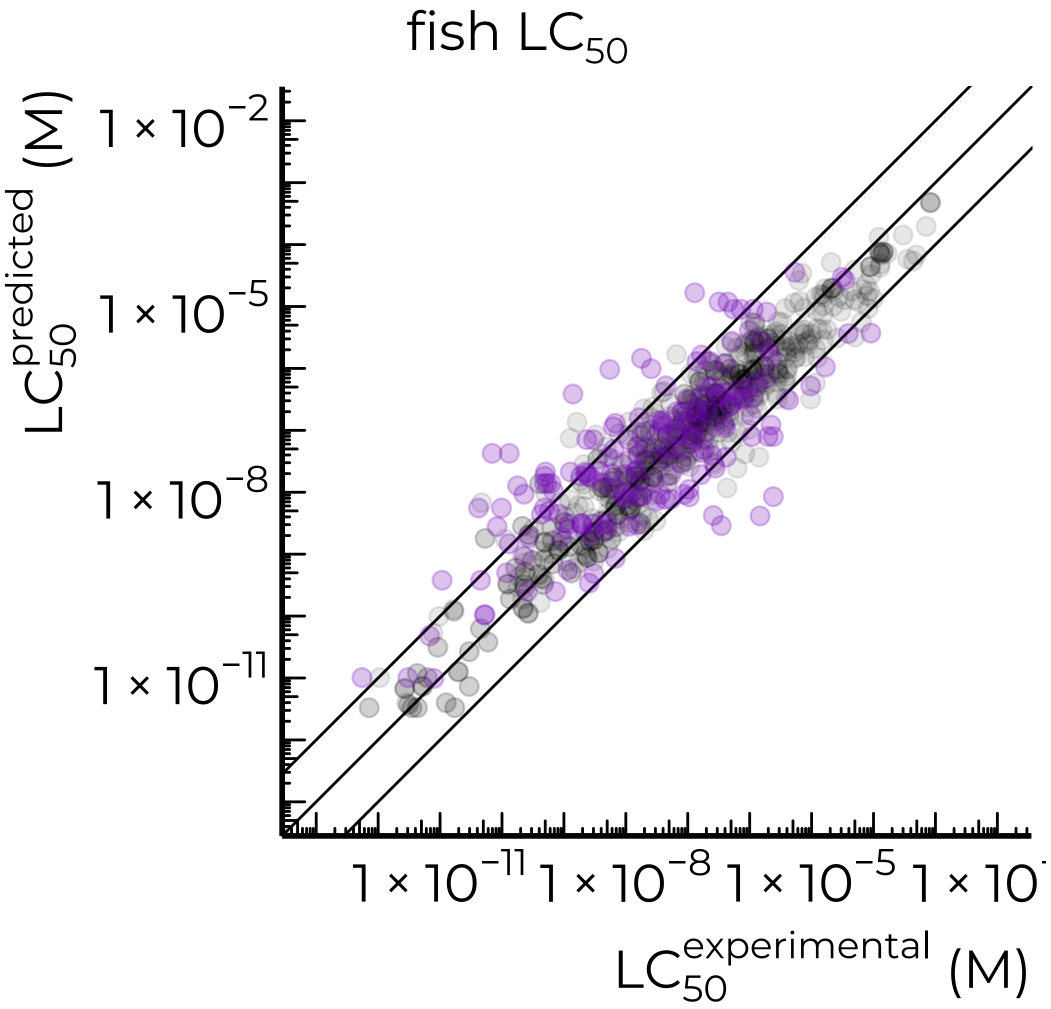
LC_{50} predictions

Peets et al. ES&T 2022



test set on structures

RMSE 0.78 log(M)

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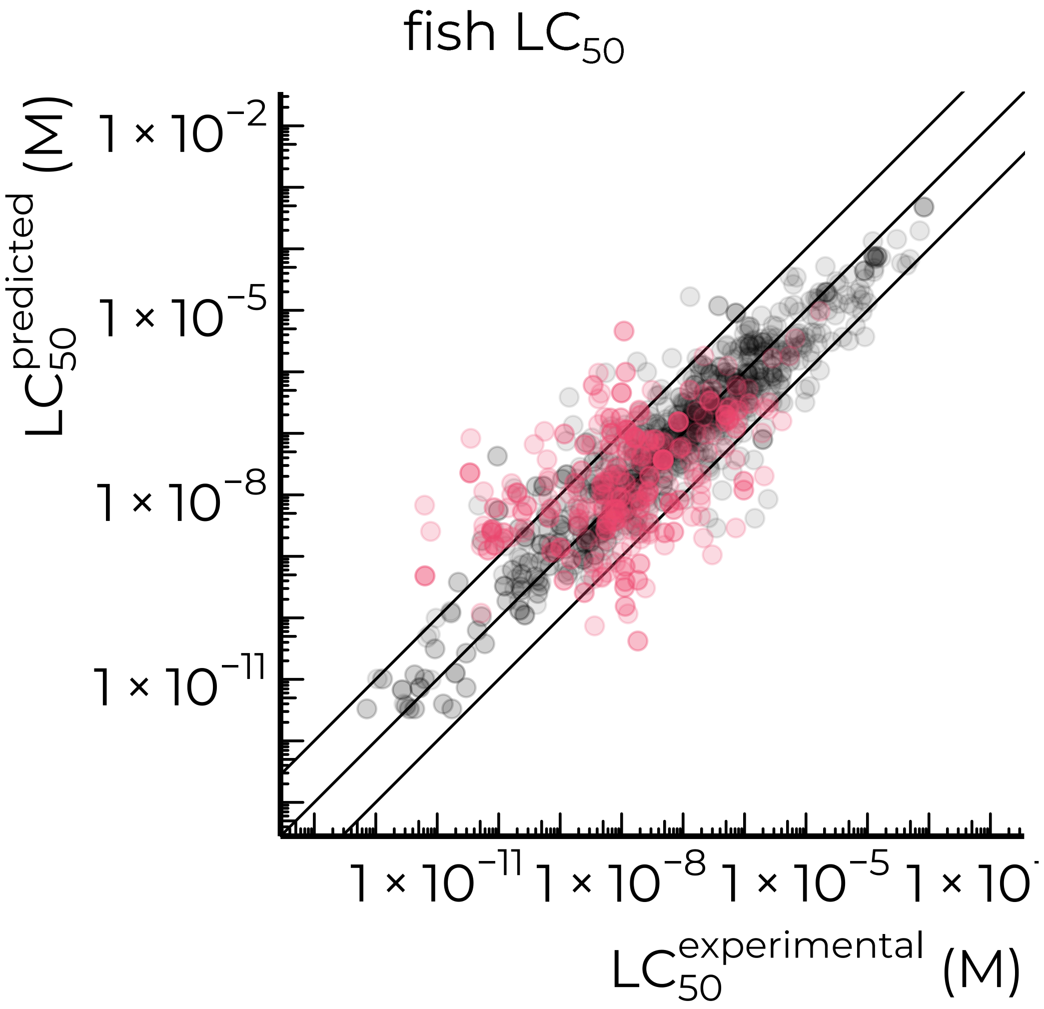
LC_{50} predictions

Peets et al. ES&T 2022



test set on structures

RMSE 0.78 log(M)

validation on MassBank

$RMSE_{model}$ 0.88 log(M)

$SD_{experimental}$ 0.44 log(mM)

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model interpretation

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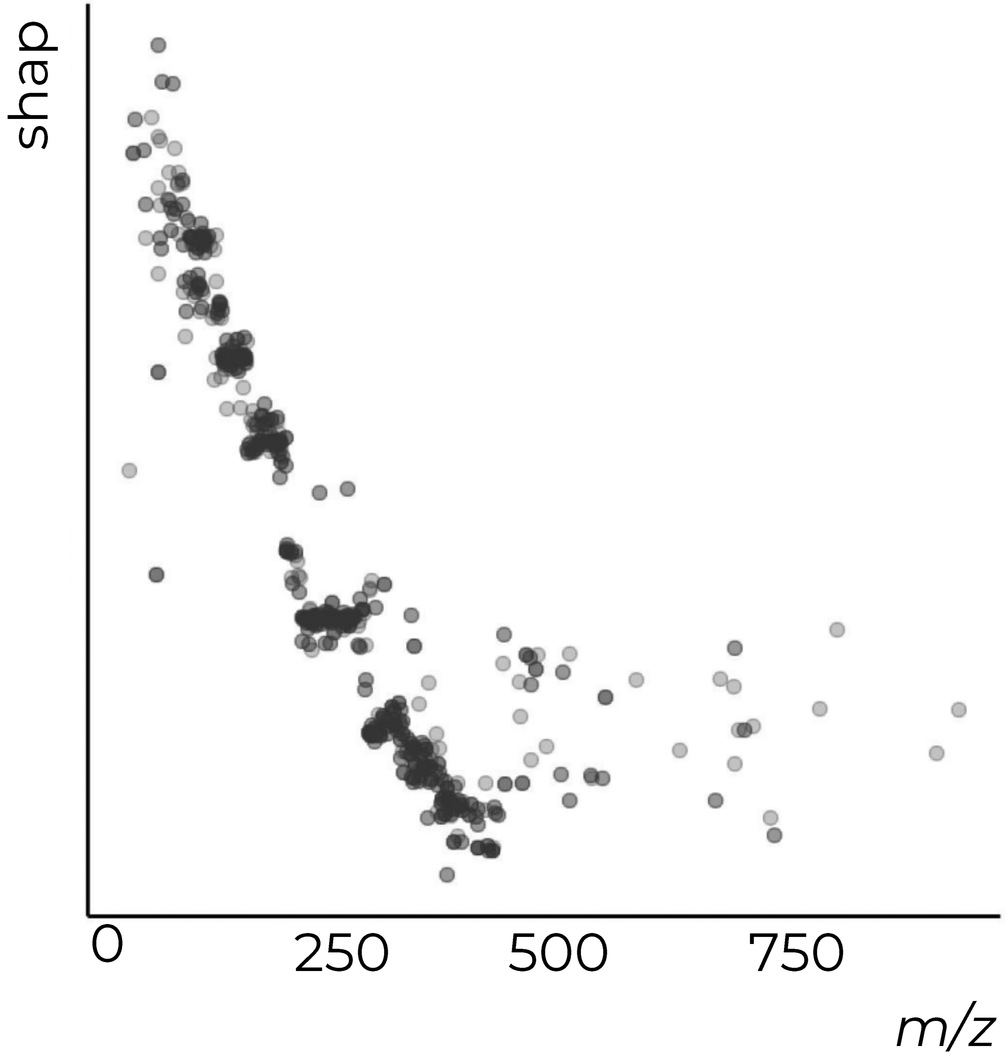
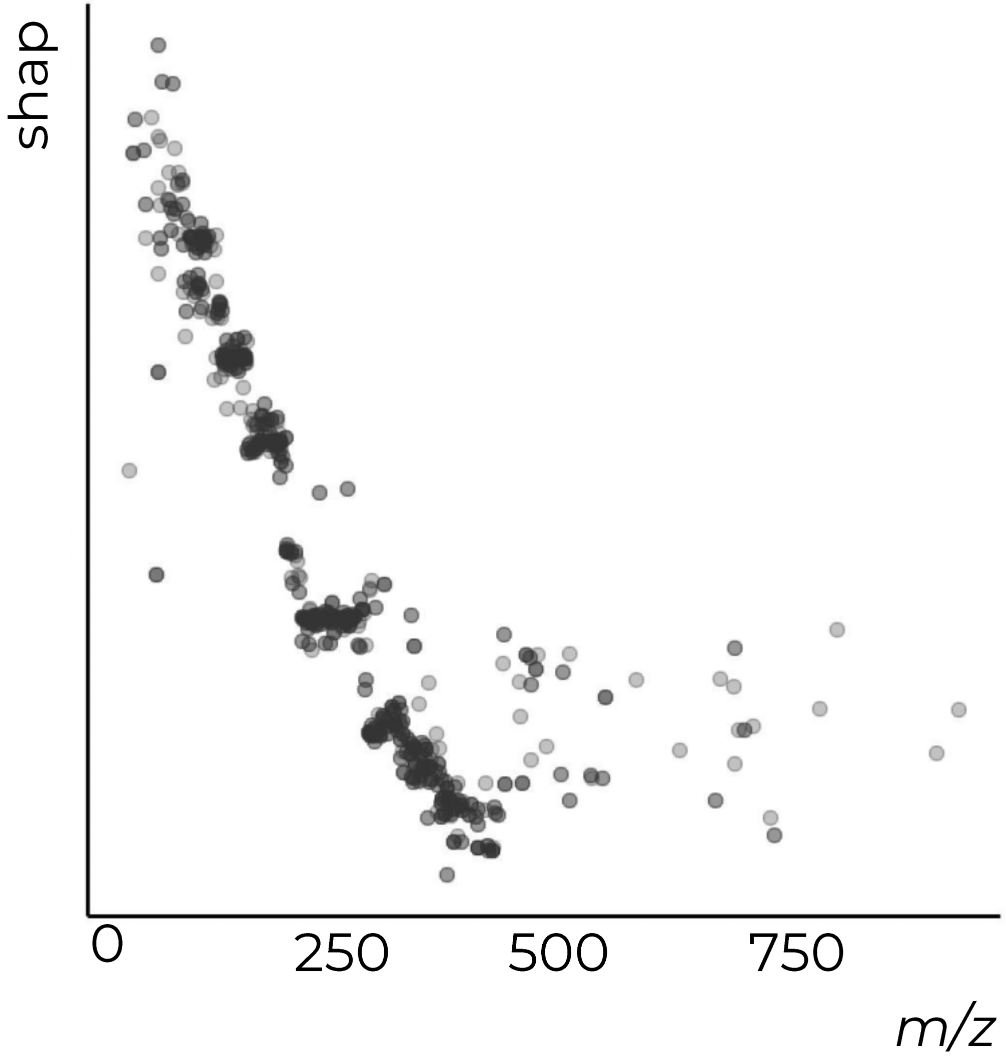
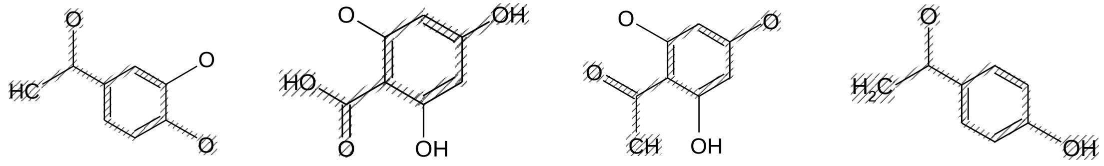
model interpretation



model interpretation





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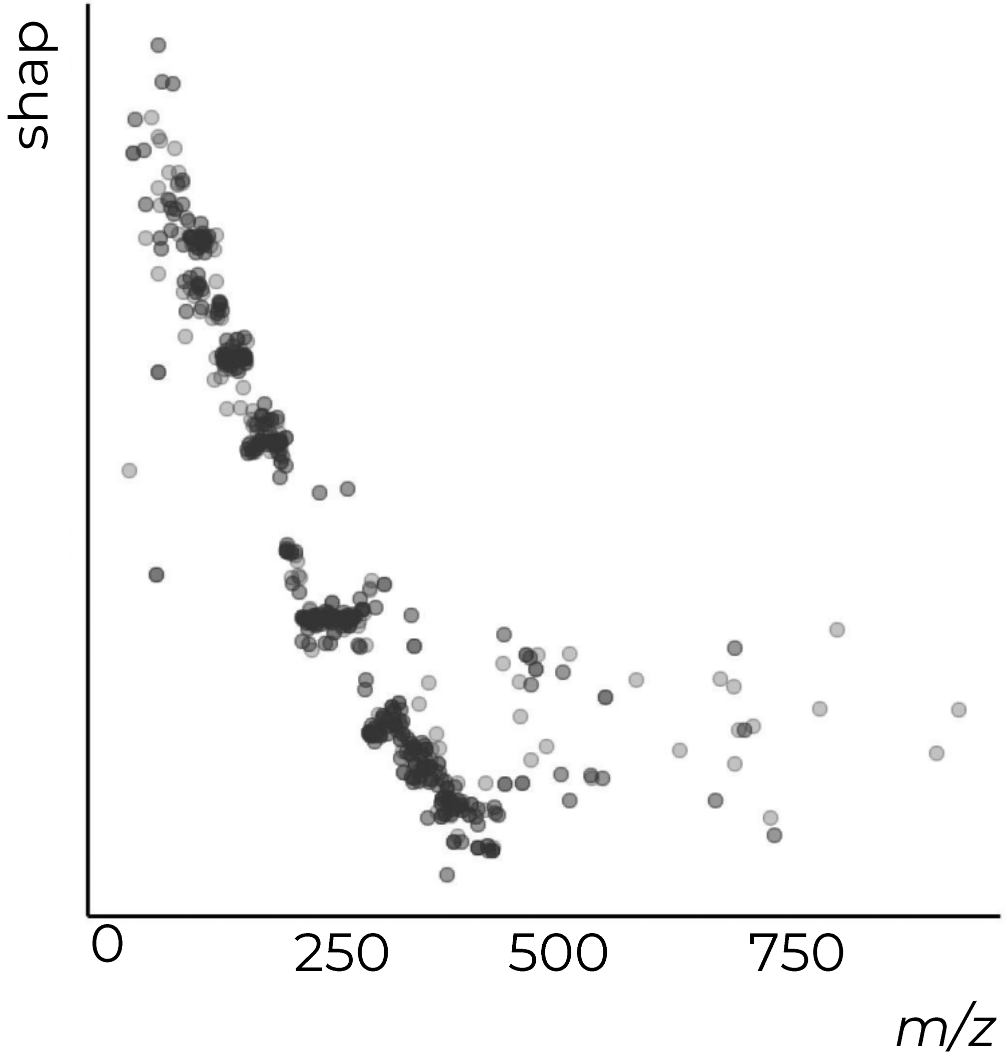
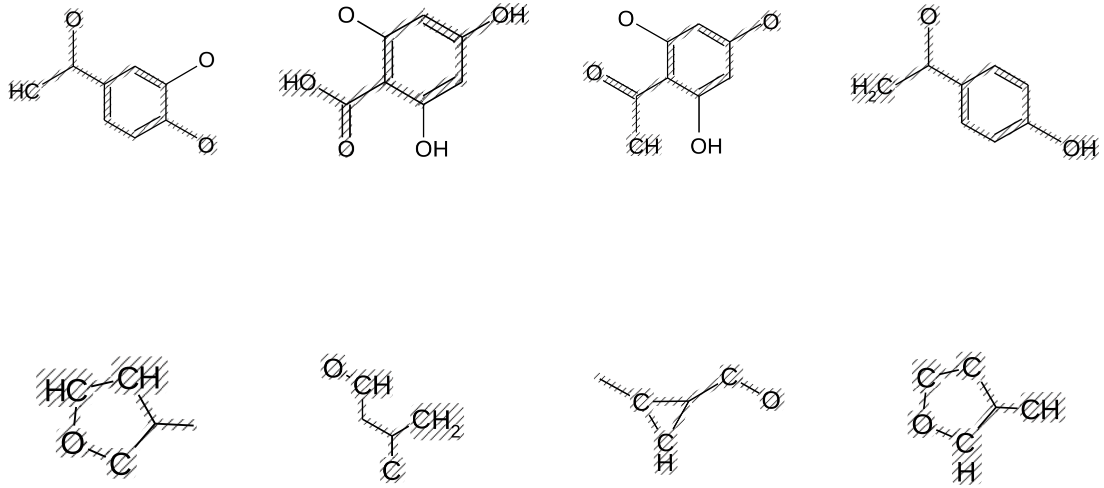
model interpretation





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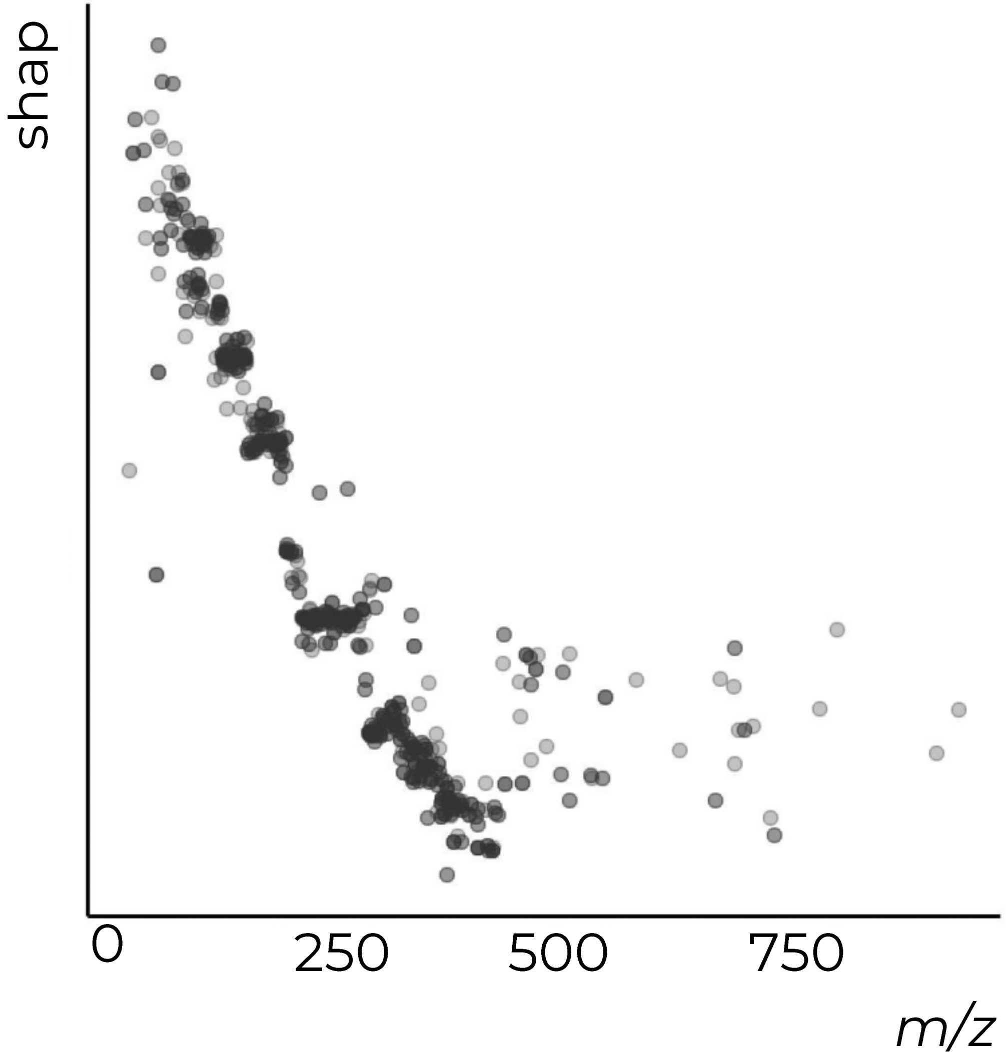
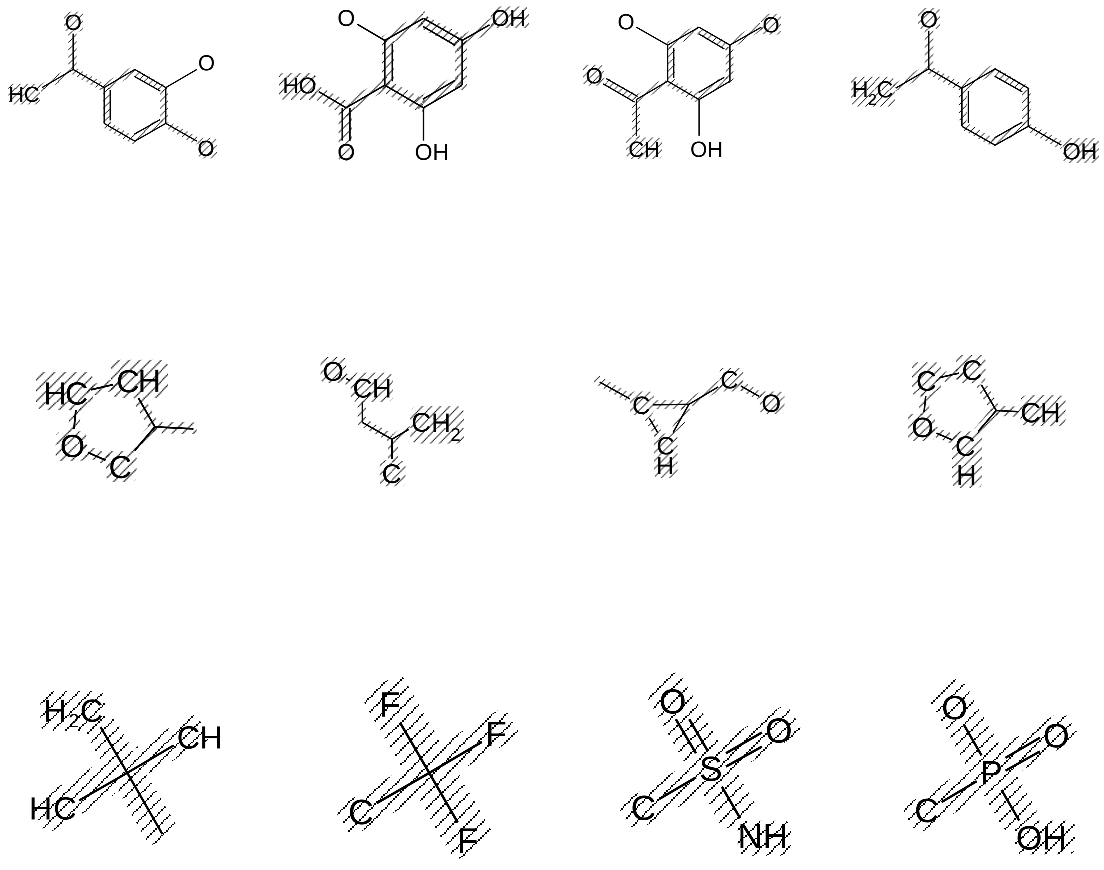
model interpretation





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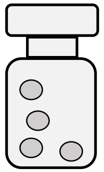
toxic chemicals

in wastewater

case study on wastewater



wastewater samples

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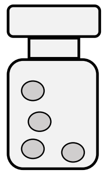
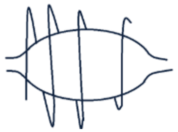
case study on wastewater



wastewater samples



LC/HRMS analysis

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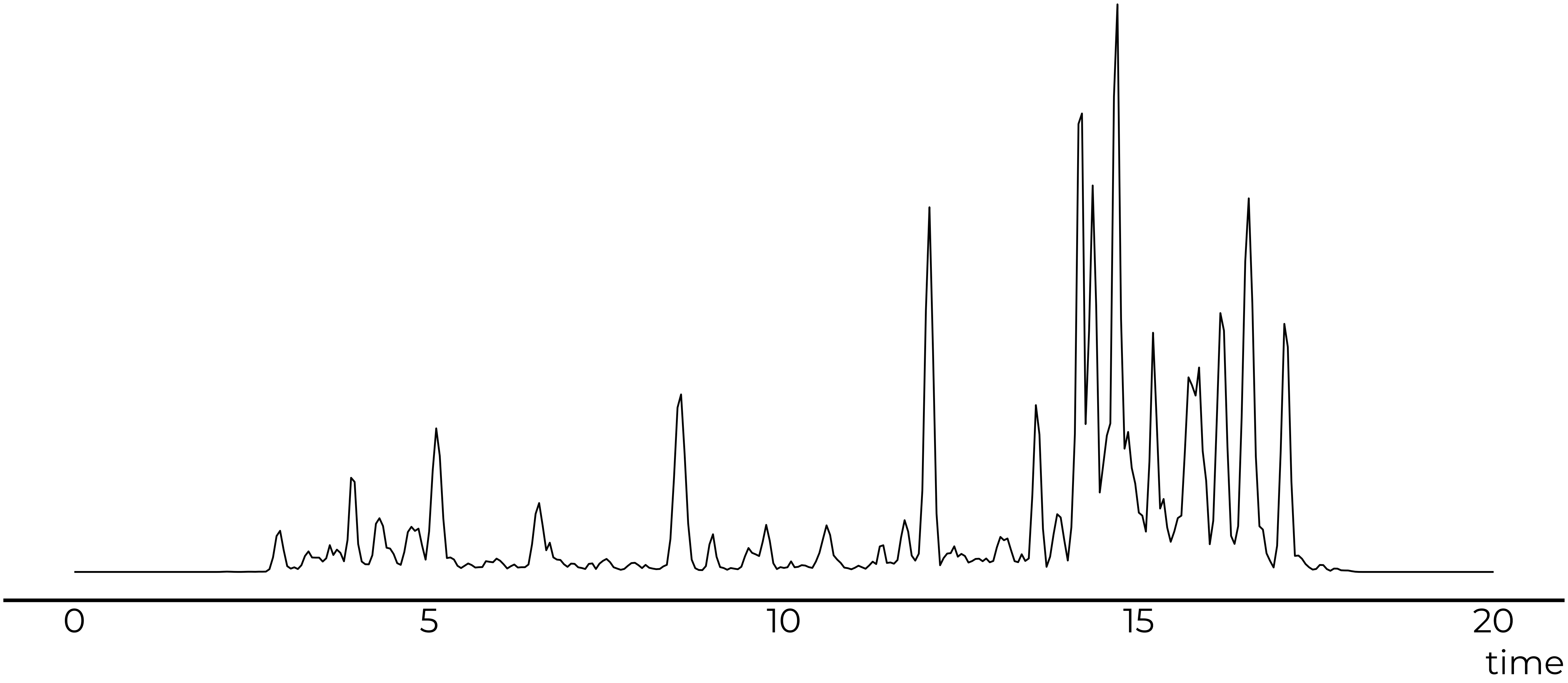
case study on wastewater



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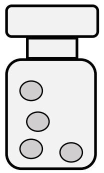
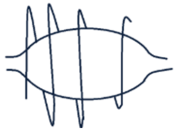
case study on wastewater



wastewater samples



LC/HRMS analysis

molecular fingerprints with SIRIUS+CSI:FingerID

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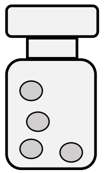
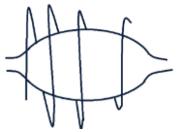
case study on wastewater

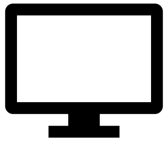


wastewater samples



LC/HRMS analysis

molecular fingerprints with SIRIUS+CSI:FingerID



predict LC_{50} with pretrained gradient boosting

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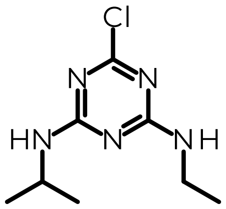
quality control

quality control



216 analytical standard

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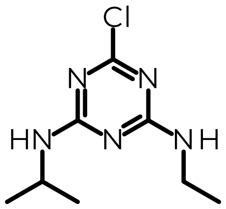
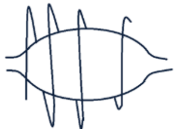
quality control

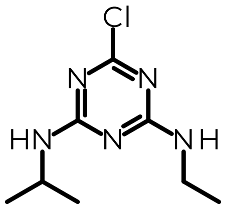


216 analytical standard

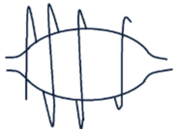


DIA and DDA MS^2 data

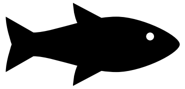
quality control



216 analytical standard



DIA and DDA MS^2 data



comparison with experimental LC_{50}

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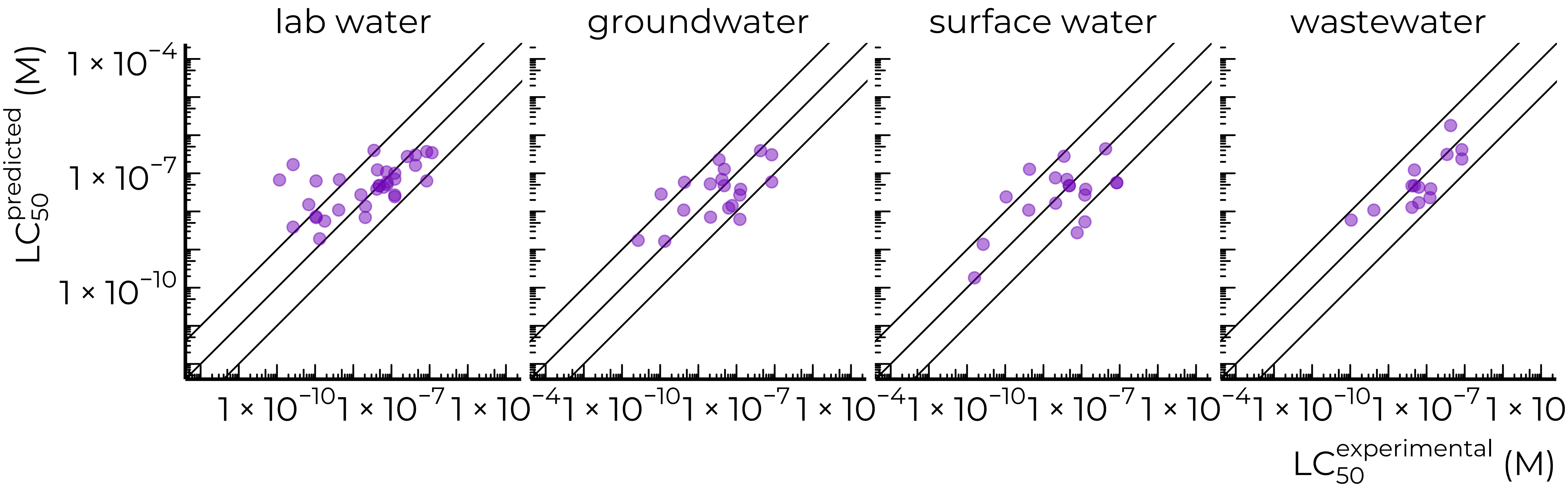
DDA



RMSE = 0.95 log-mM 0.74 log-mM 0.86 log-mM 0.47 log-mM

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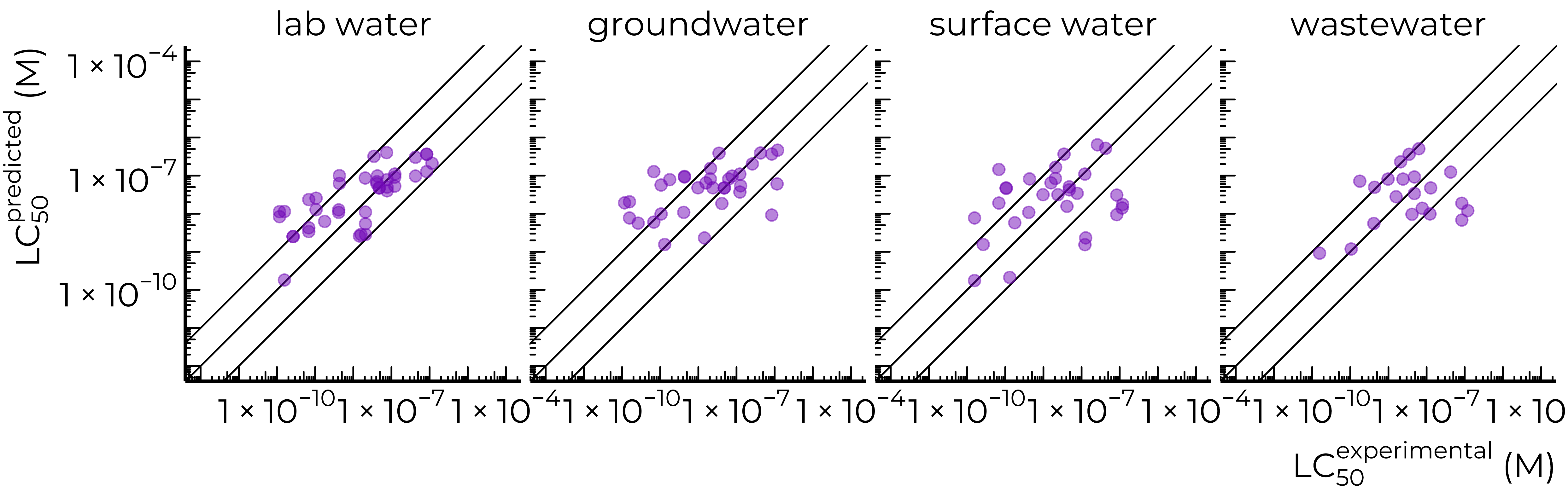
DIA



RMSE = 0.85 log-mM 1.09 log-mM 1.18 log-mM 1.03 log-mM

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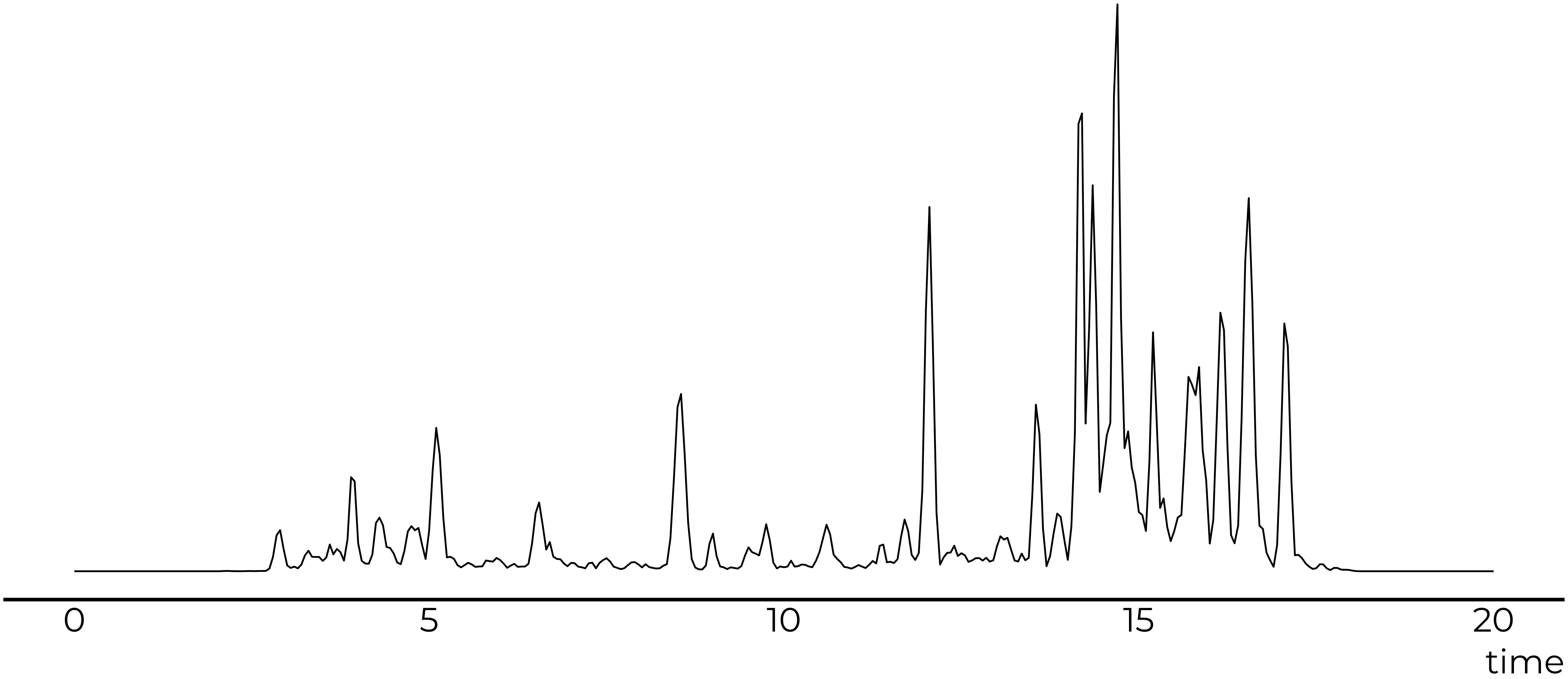
pinpointing toxic chemicals

case study on wastewater



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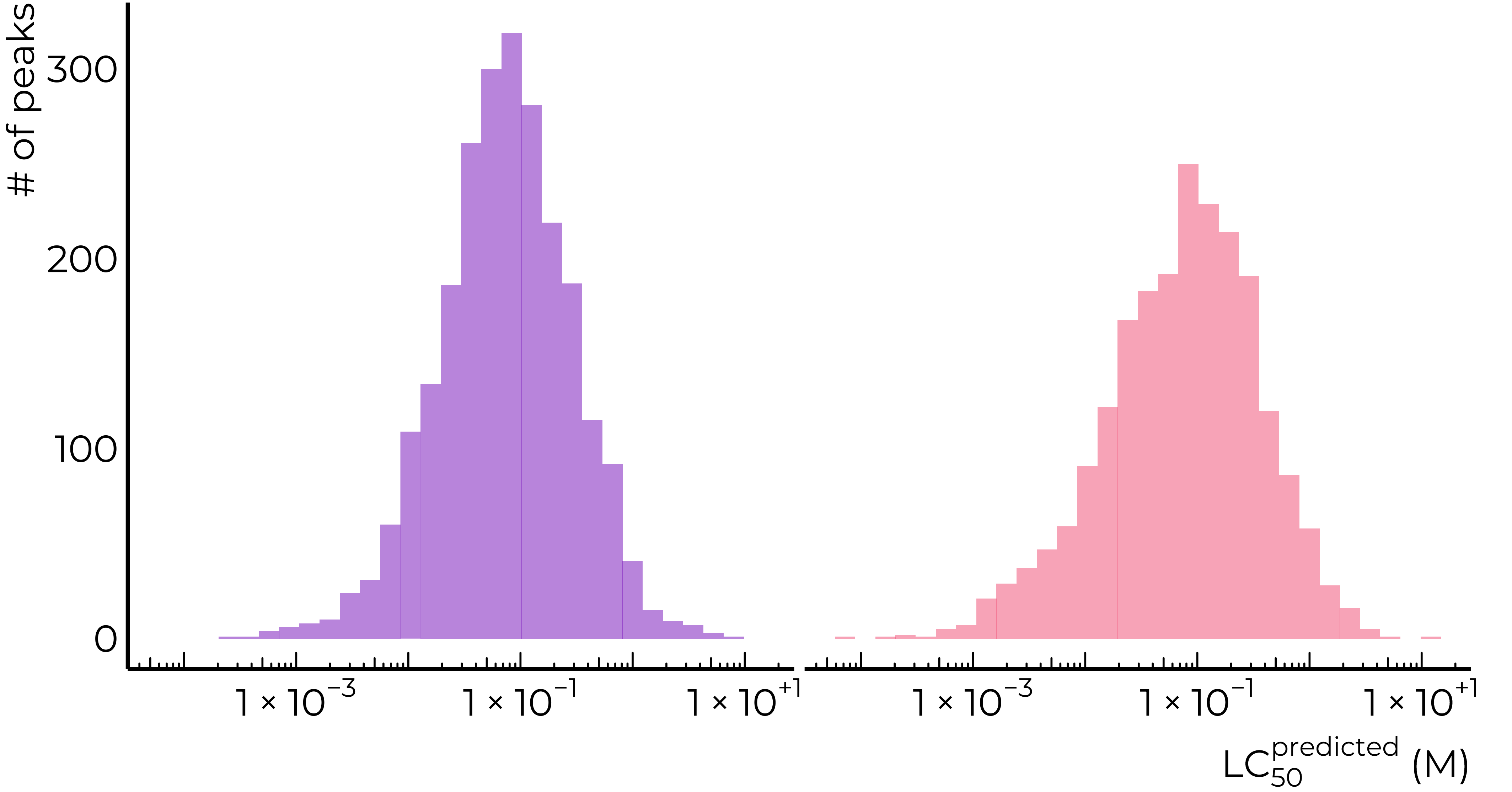
LC_{50} distribution



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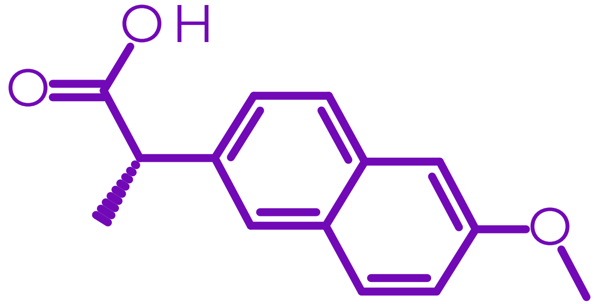
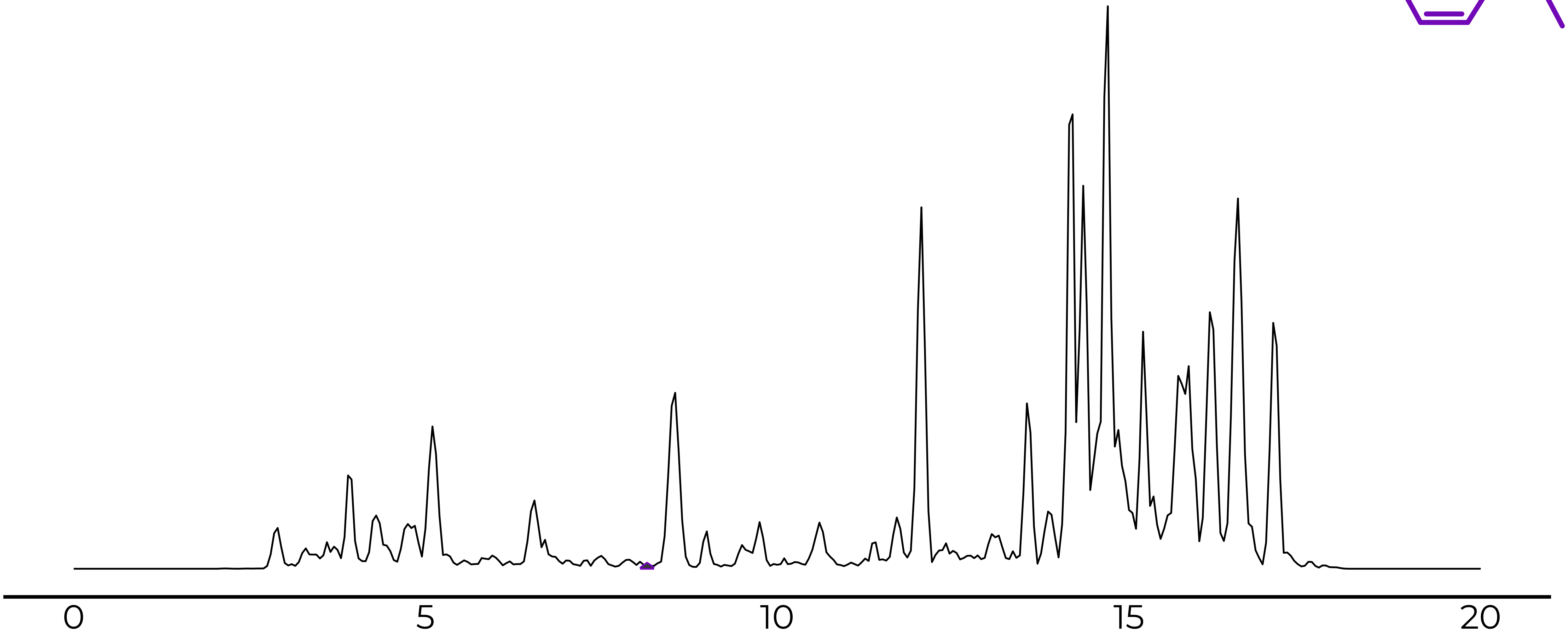
naproxen





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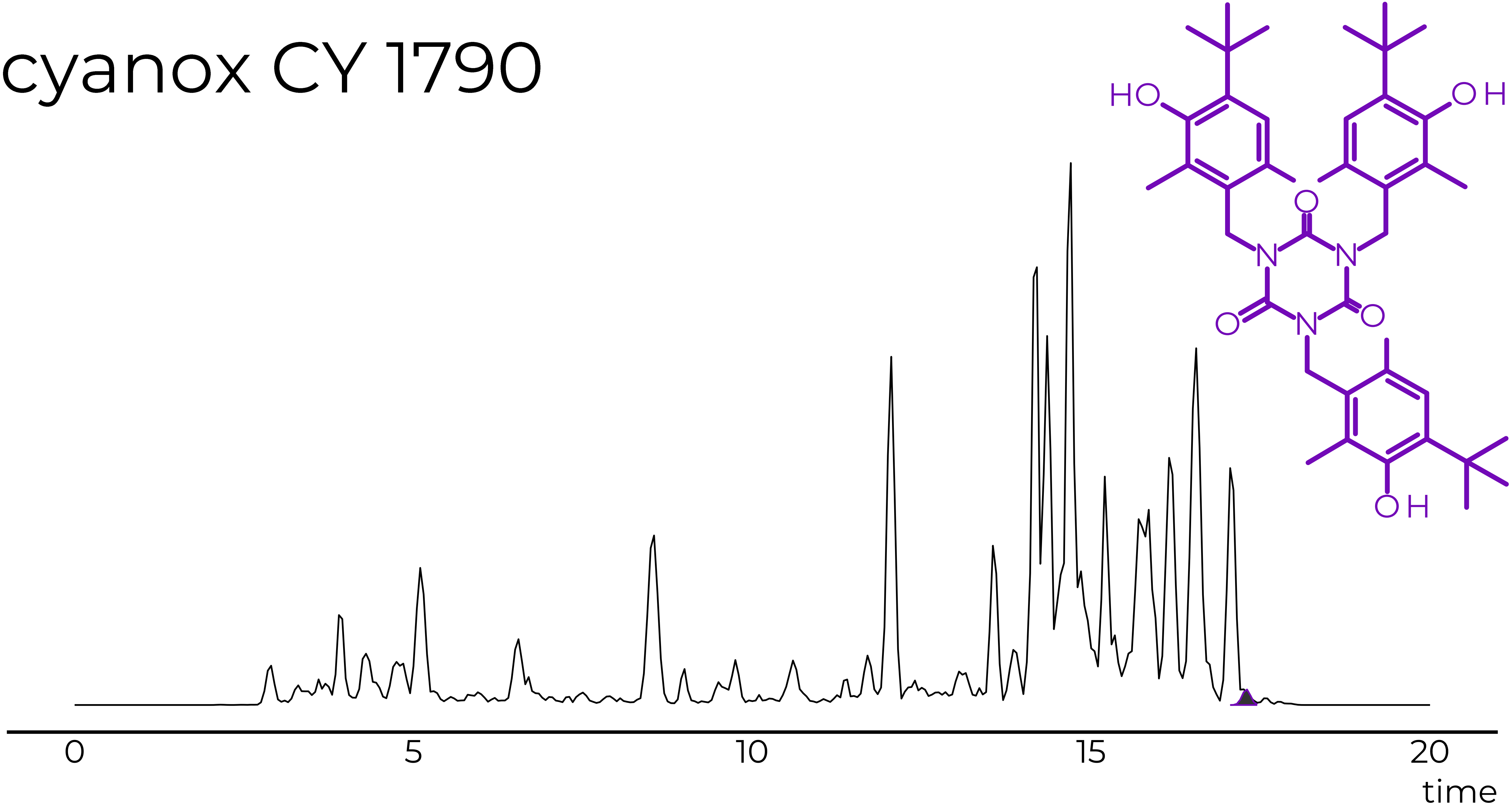
cyanox CY 1790



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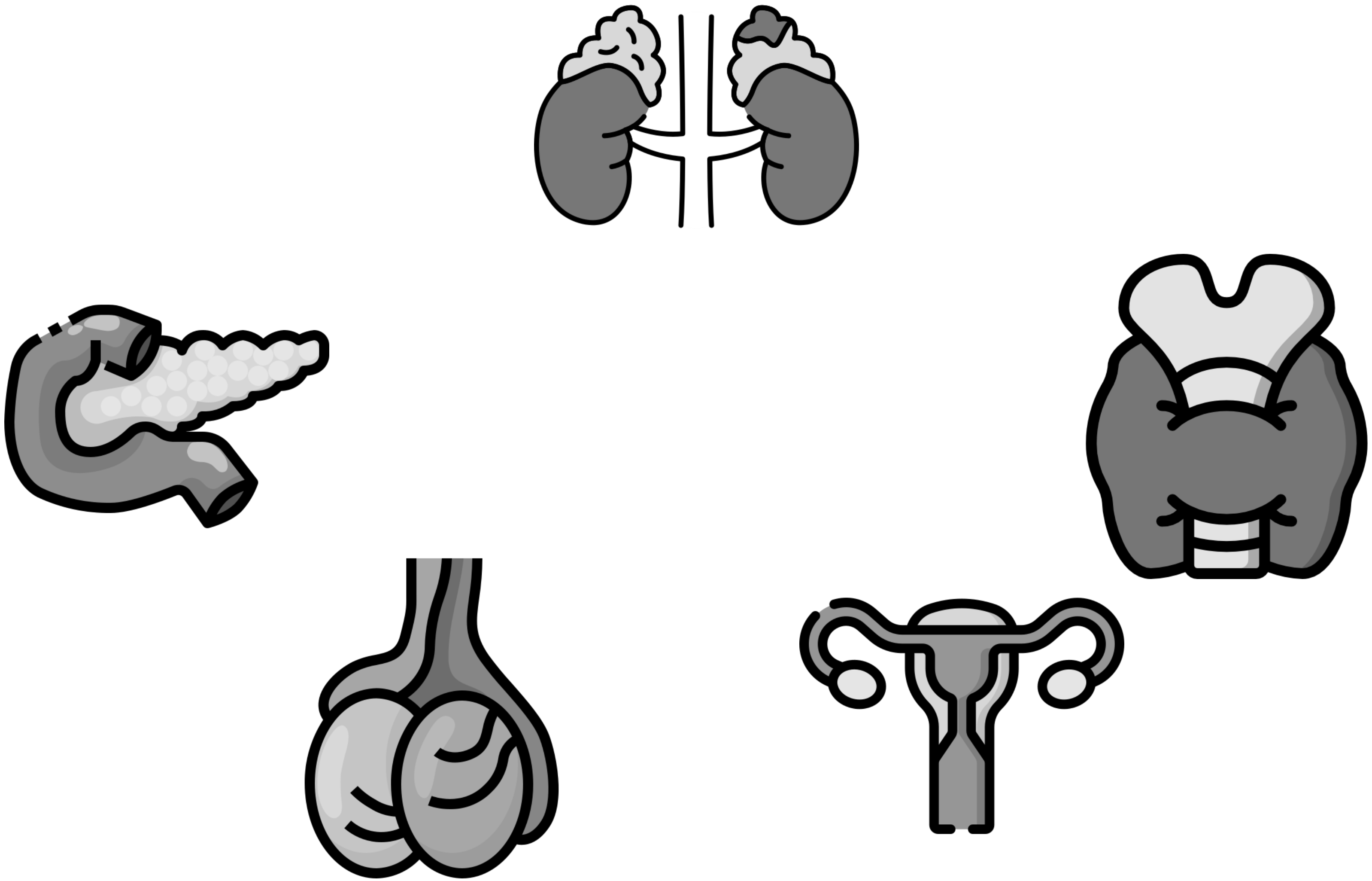
endocrine disrupting chemicals

endocrine disruption



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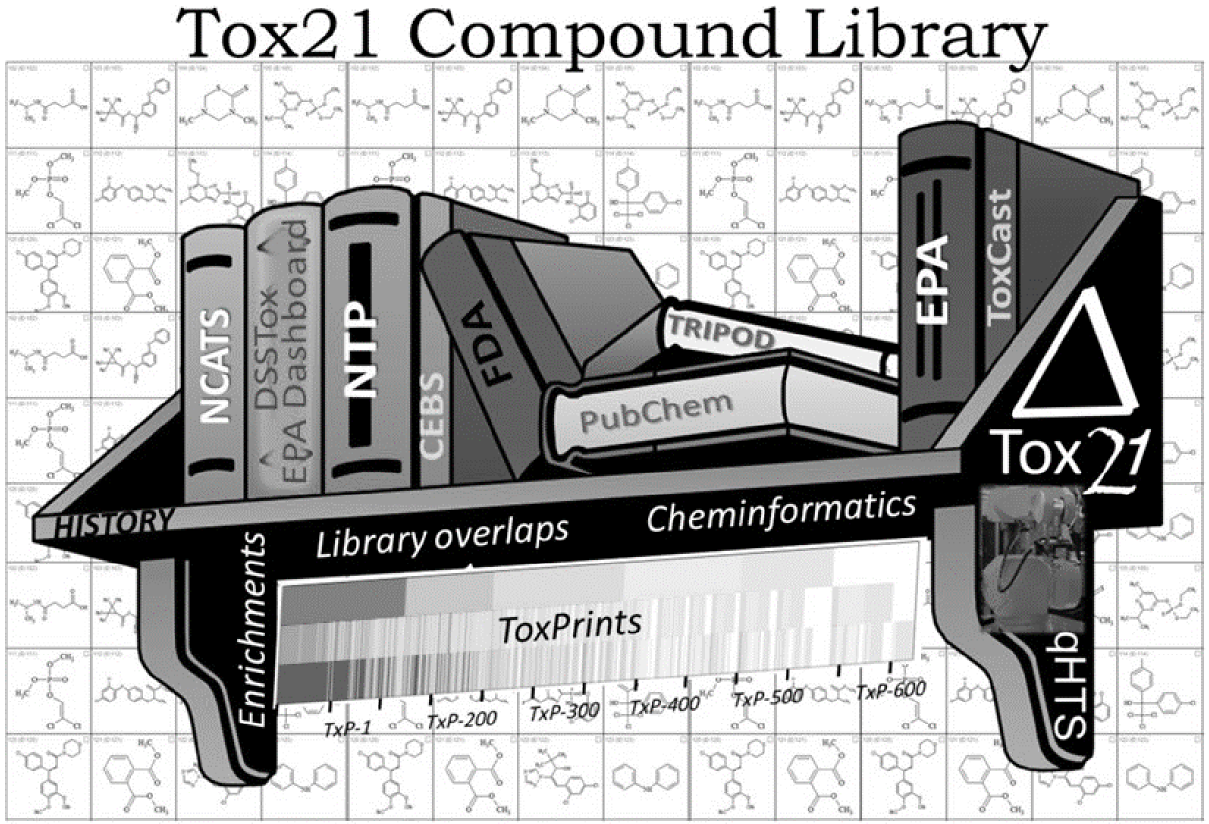
data



nuclear receptor panel

- nr.ahr
- nr.ar.lbd
- nr.ar
- nr.aromatase
- nr.er.lbd
- nr.er
- nr.ppar.gamma

stress response panel

- sr.are
- sr.atad5
- sr.hse
- sr.mmp
- sr.p53

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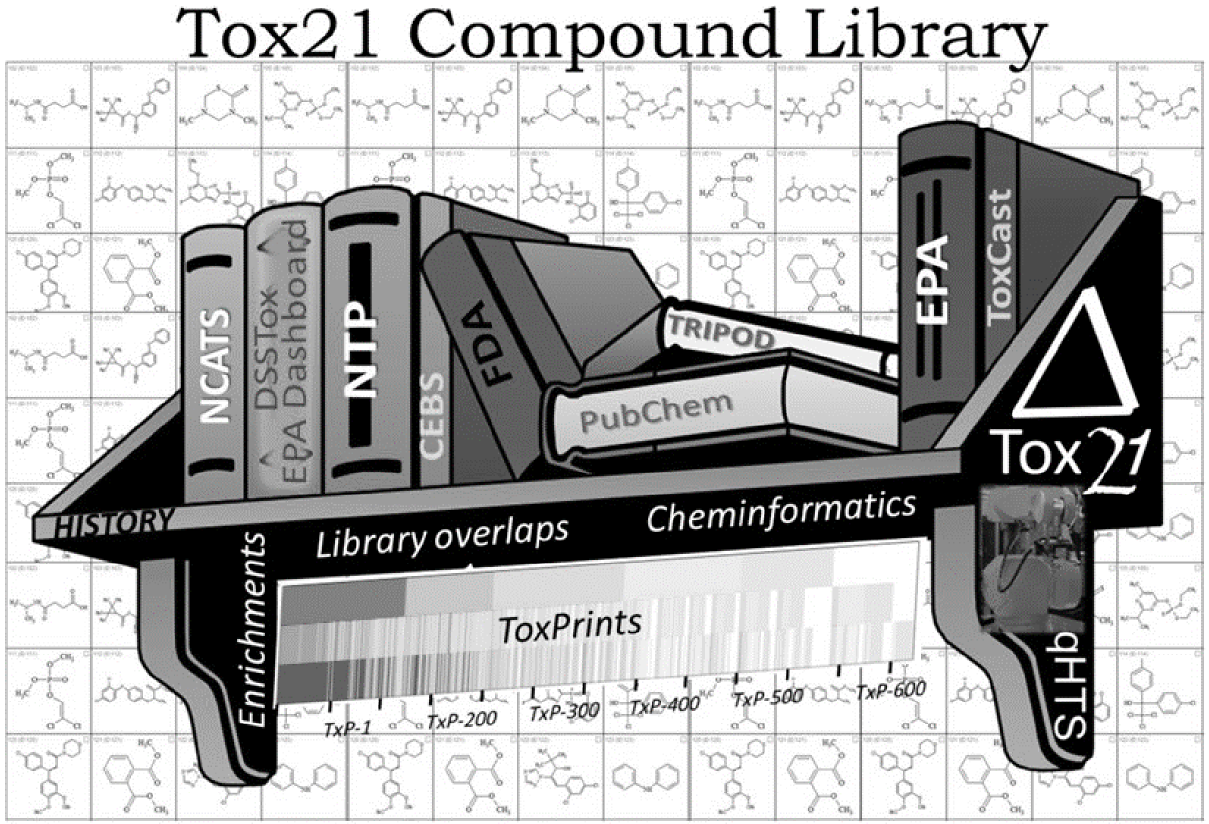
data



8,043 chemicals

5090 no replica

2953 with replica

replica often inconsistent

precautionary principle

active chemicals

4% to 16%

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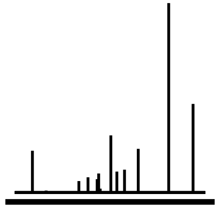
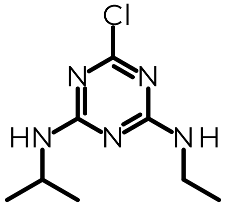
workflow: training

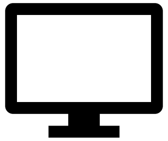


MS^2 spectra



structure as SMILES

molecular descriptors



predict toxicity

anneli kruve

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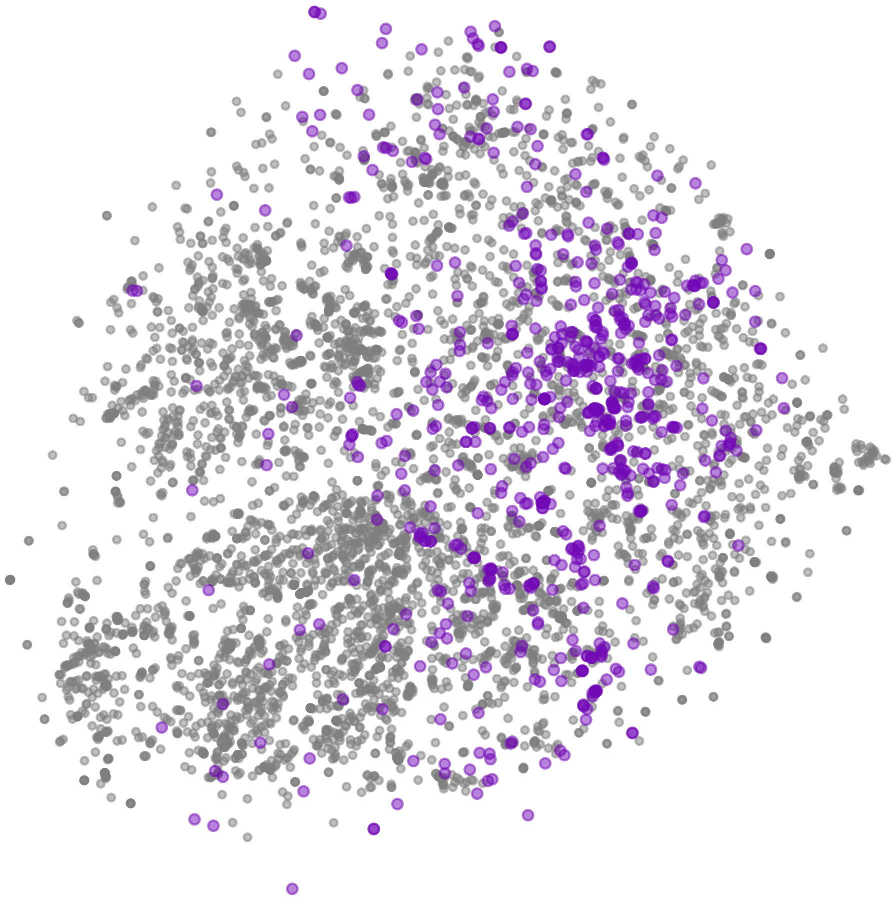
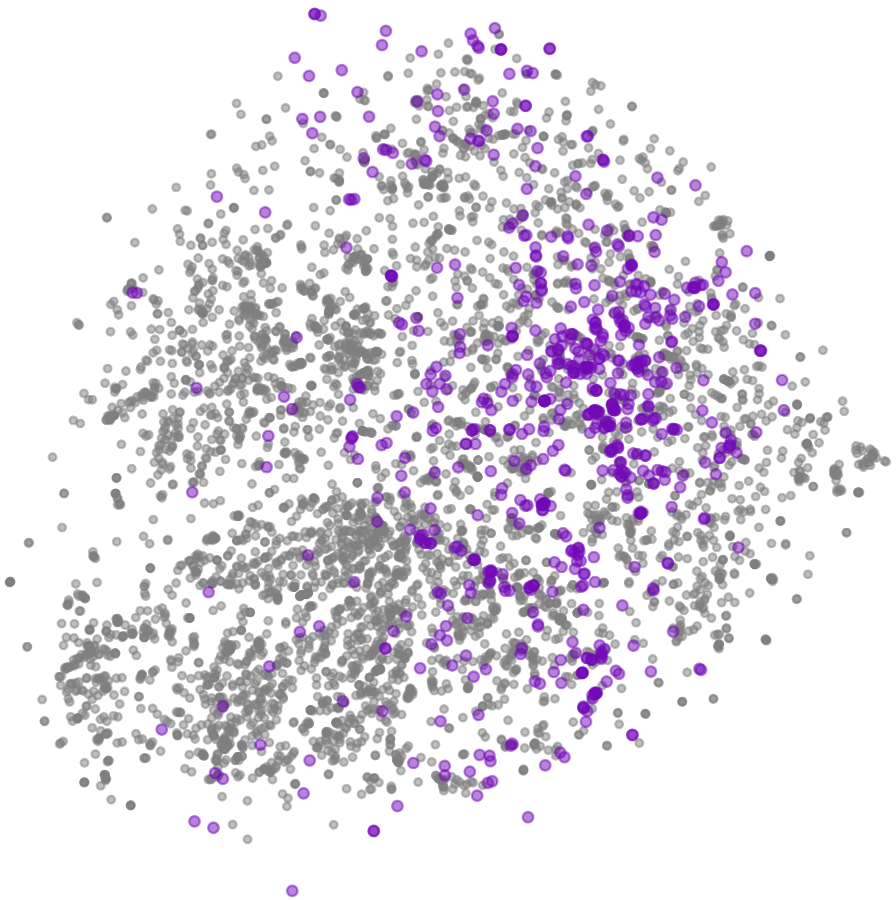
results: t-SNE

aryl hydrocarbon receptor

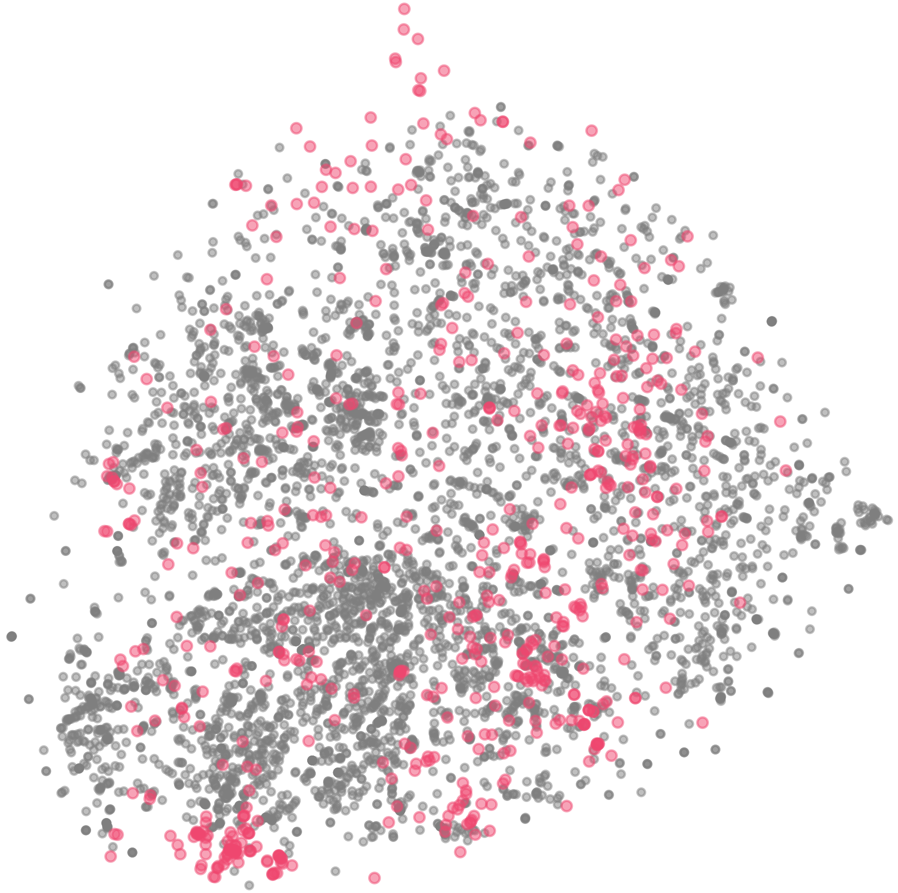


results: t-SNE

aryl hydrocarbon receptor activation



estrogen receptor activation



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metrics

		true label	
		active	non-active
prediction	active	TP	FP
	non-active	FN	TN

which is more dramatic:

type I error

OR

type II error?

FPR @ TPR = 0.9

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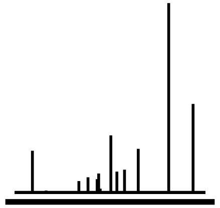
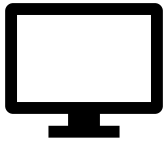
workflow: validation



MS^2 spectra

molecular fingerprints with SIRIUS+CSI:FingerID



predict LC_{50} with pretrained gradient boosting

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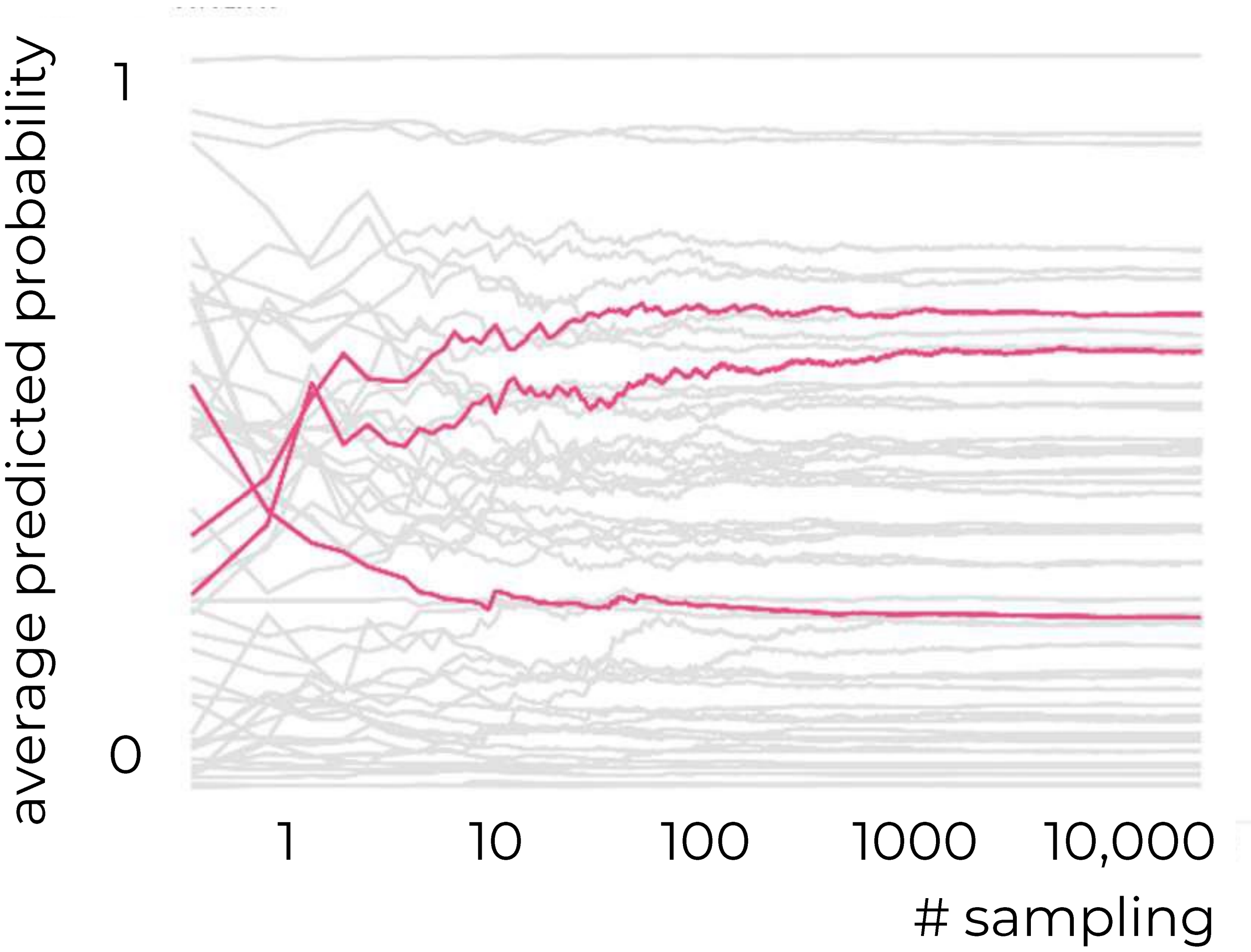
prediction accuracy

bioassay	FPR
sr.mmp	25.1%
sr.p53	25.4%
nr.ahr	41.8%
...	...
nr.ar	82.4%
nr.er	85.0%

MassBank & MoNA

748 compounds with MS^2 & tox

handling probabilistic fingerprints



Monte Carlo sampling

- sampling each fingerprint

prediction changed with # of samples

- 2%...25%
- more prone for multi-output

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MS2Quant

quantification in ESI/HRMS

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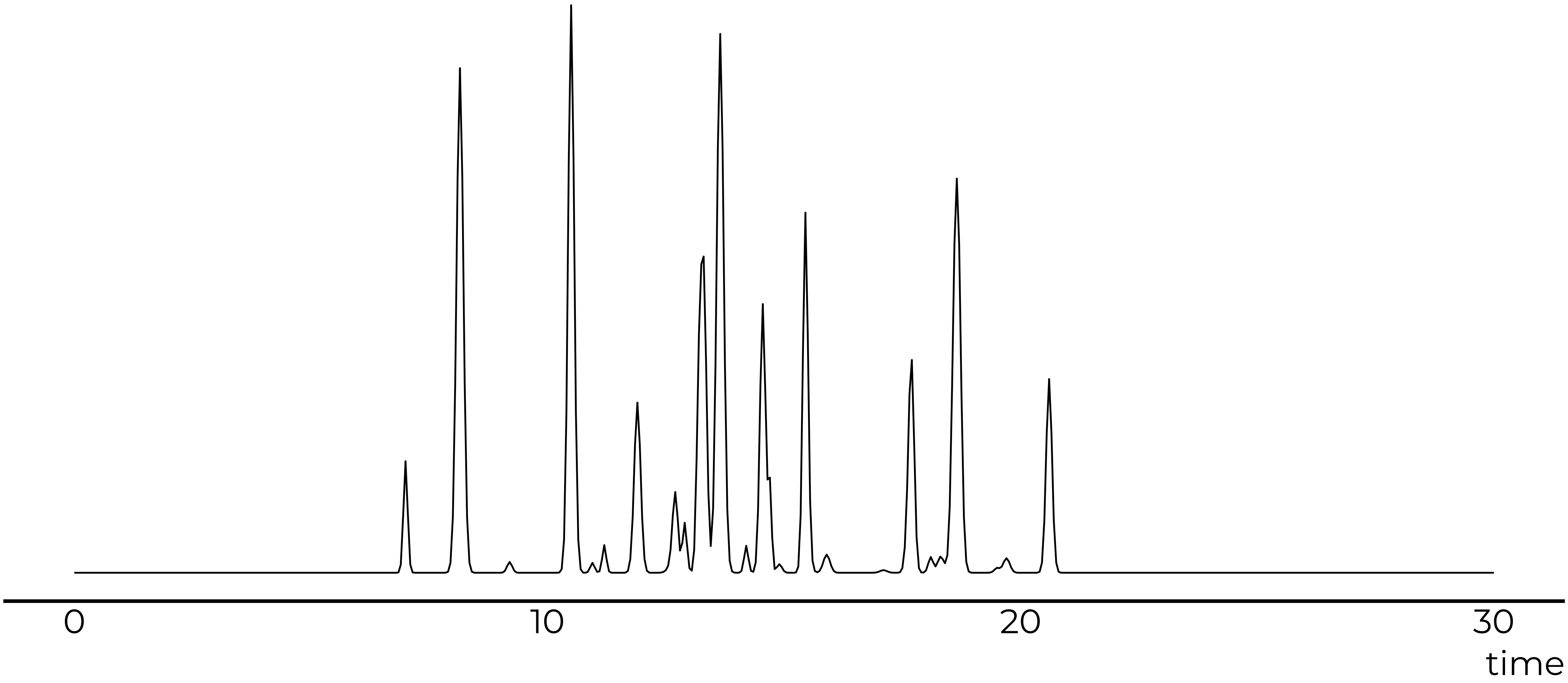
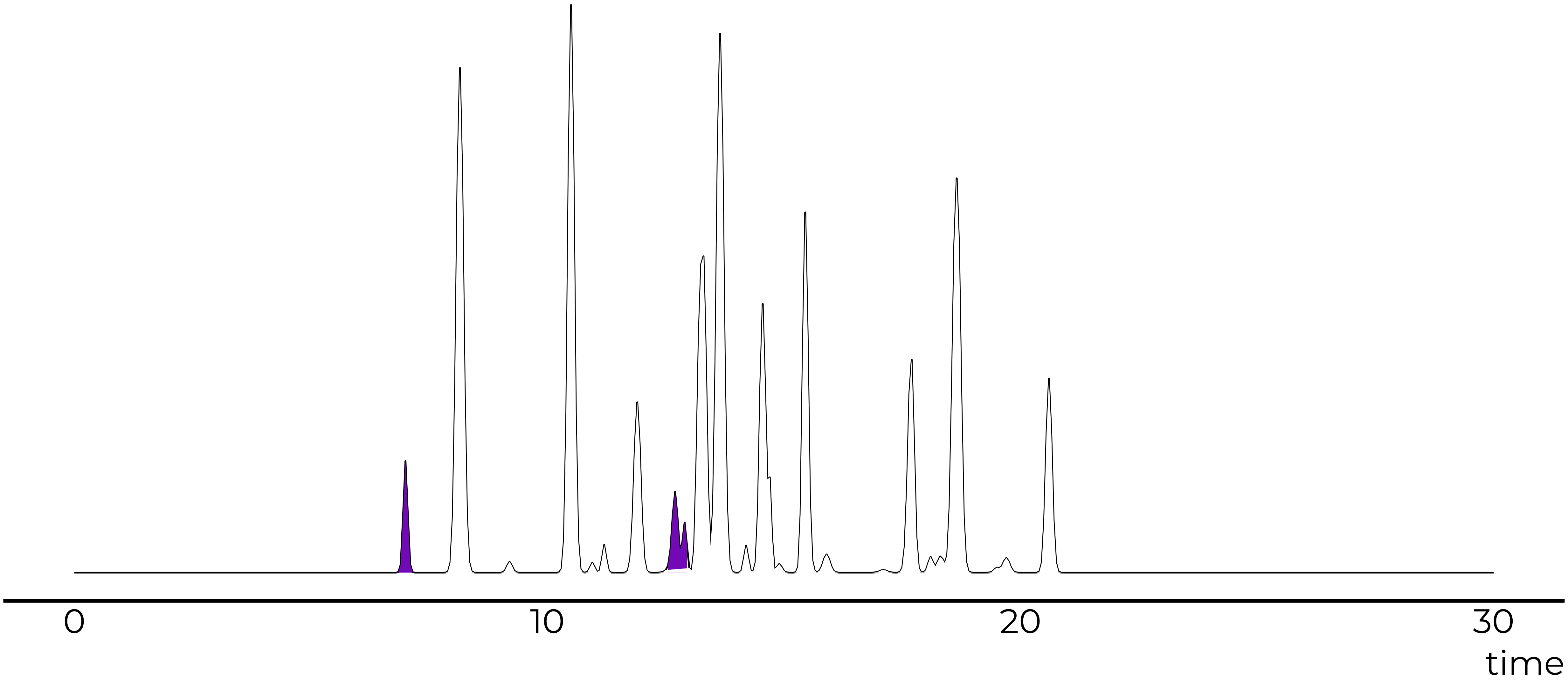
quantification in ESI/HRMS

Malm et al. Molecules 2021



quantification in ESI/HRMS

Malm et al. Molecules 2021



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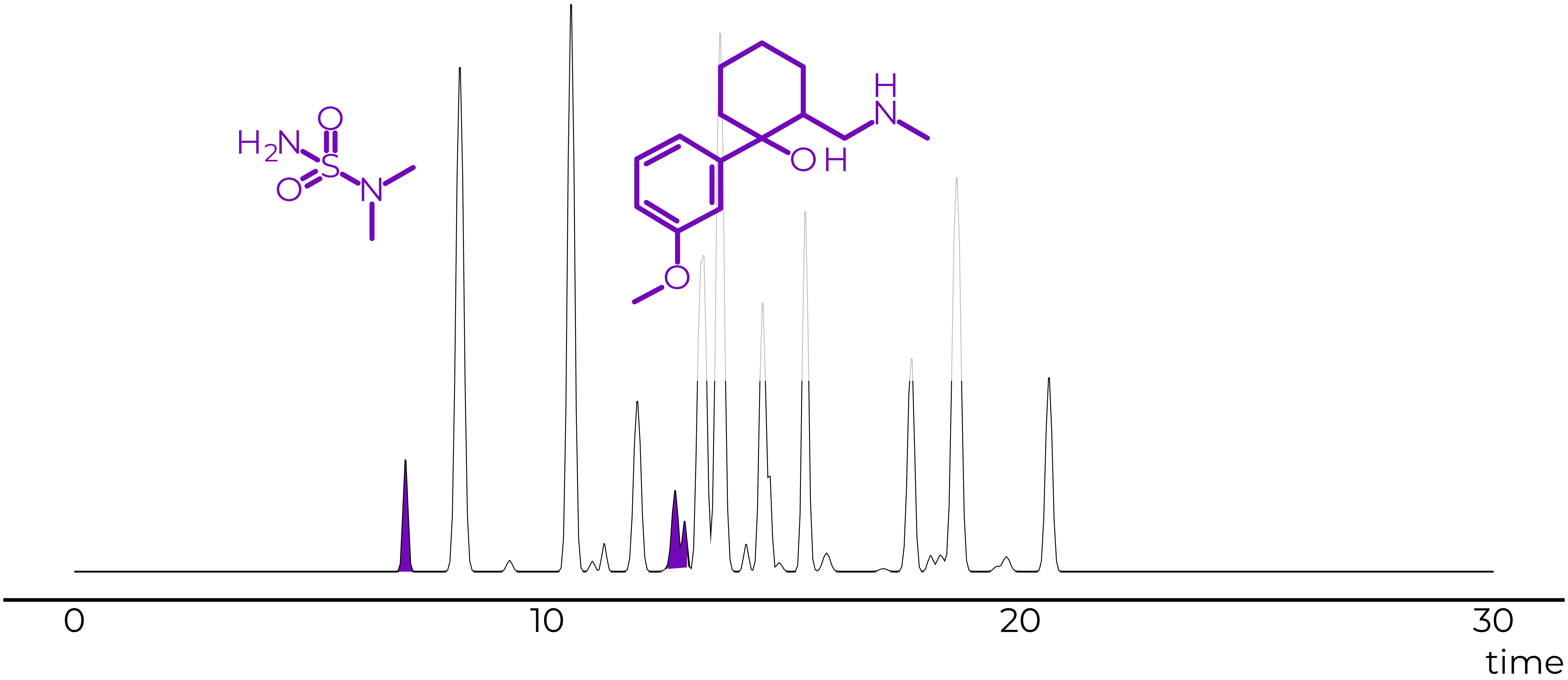
quantification in ESI/HRMS

Malm et al. Molecules 2021



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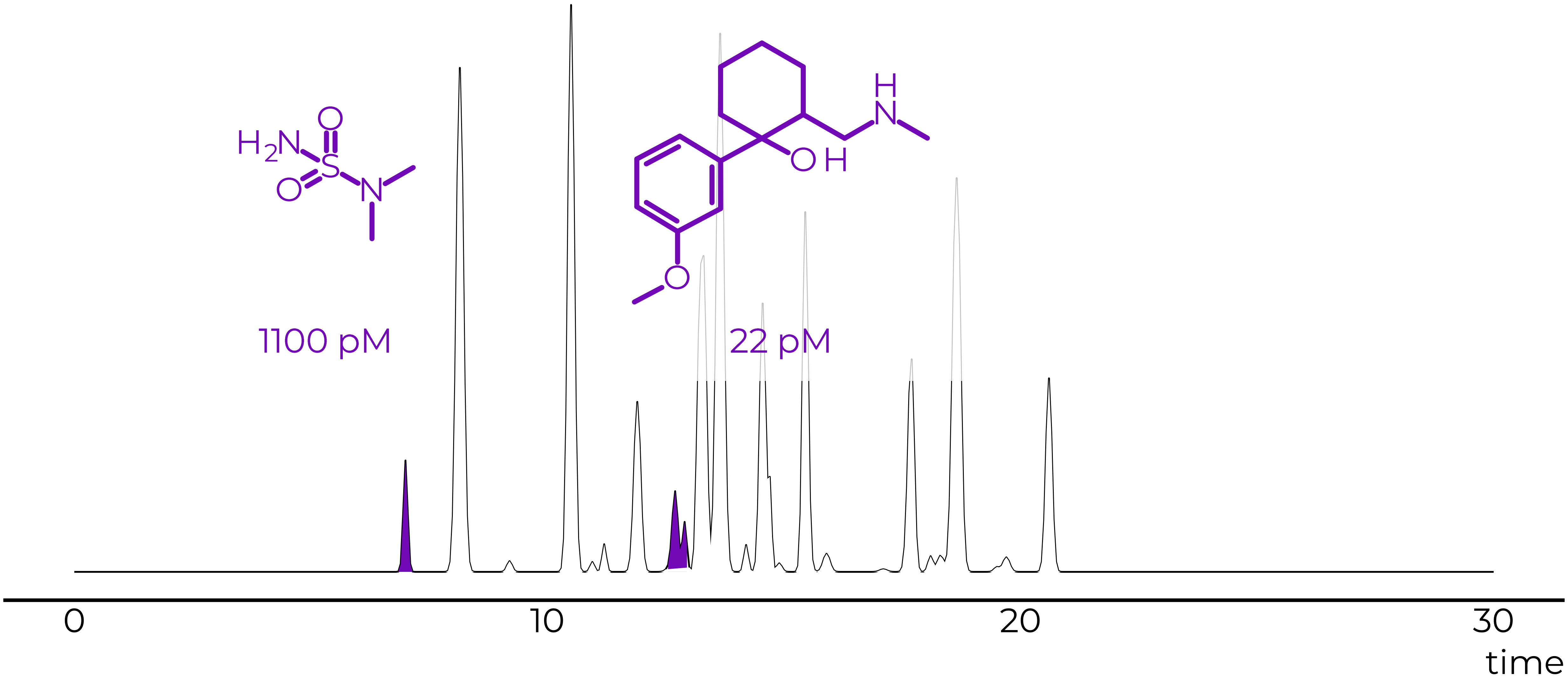
quantification in ESI/HRMS

Malm et al. Molecules 2021



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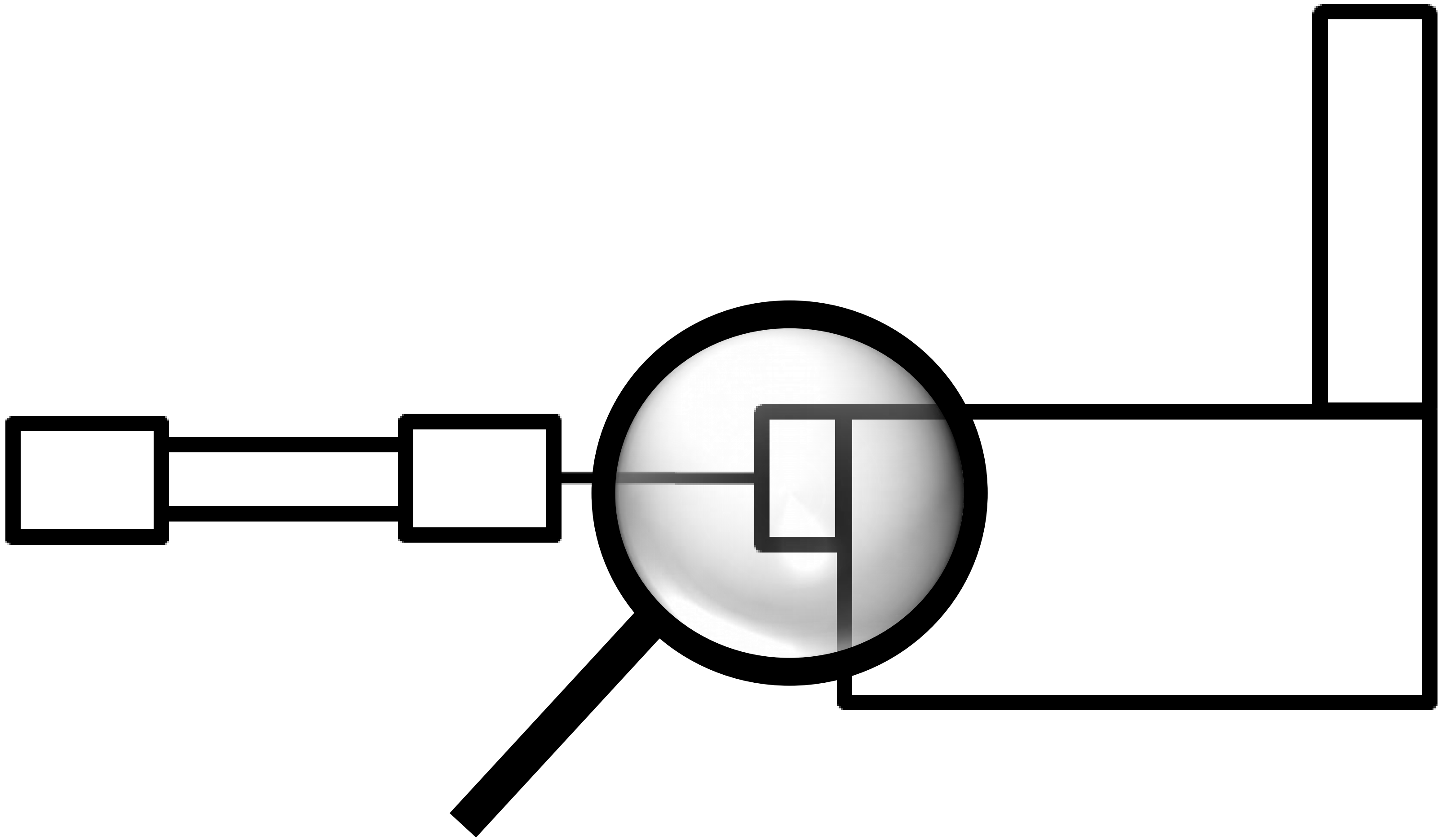
electrospray



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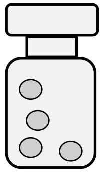
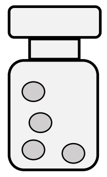
workflow

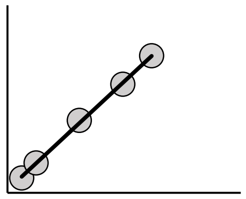


flow injections

workflow

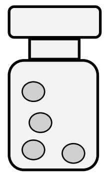


flow injections

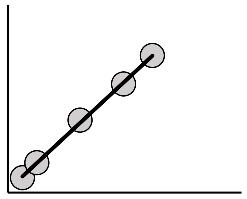


calibration graph

workflow



flow injections



calibration graph

$$\frac{slope_1}{slope_2} \rightarrow IE$$

relative measurements

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structure

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structure

one solvent, purely analyte properties

377 chemicals

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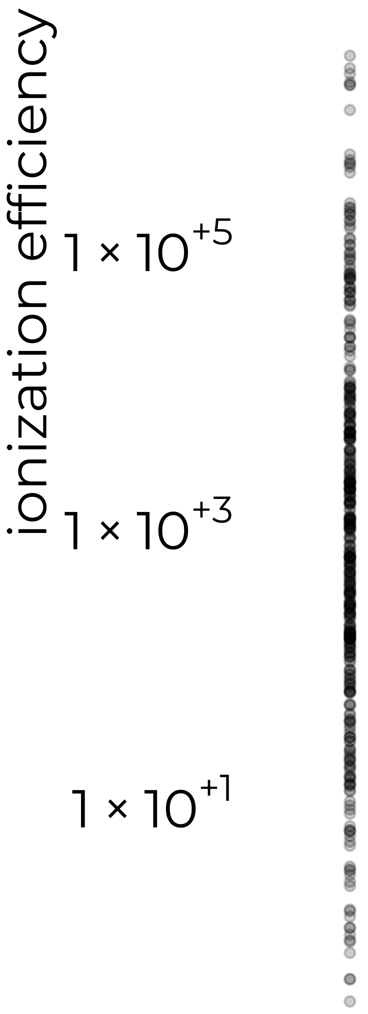
structure



one solvent, purely analyte properties

377 chemicals

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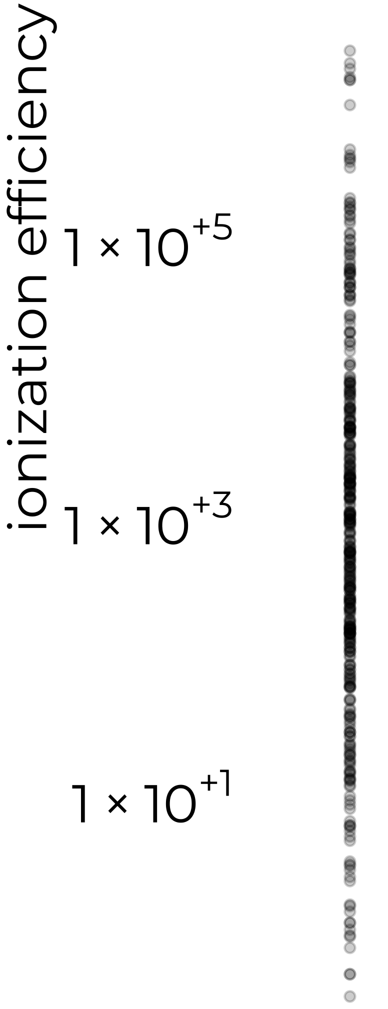
structure



one solvent, purely analyte properties

377 chemicals

10,000,000x difference in ionization efficiency

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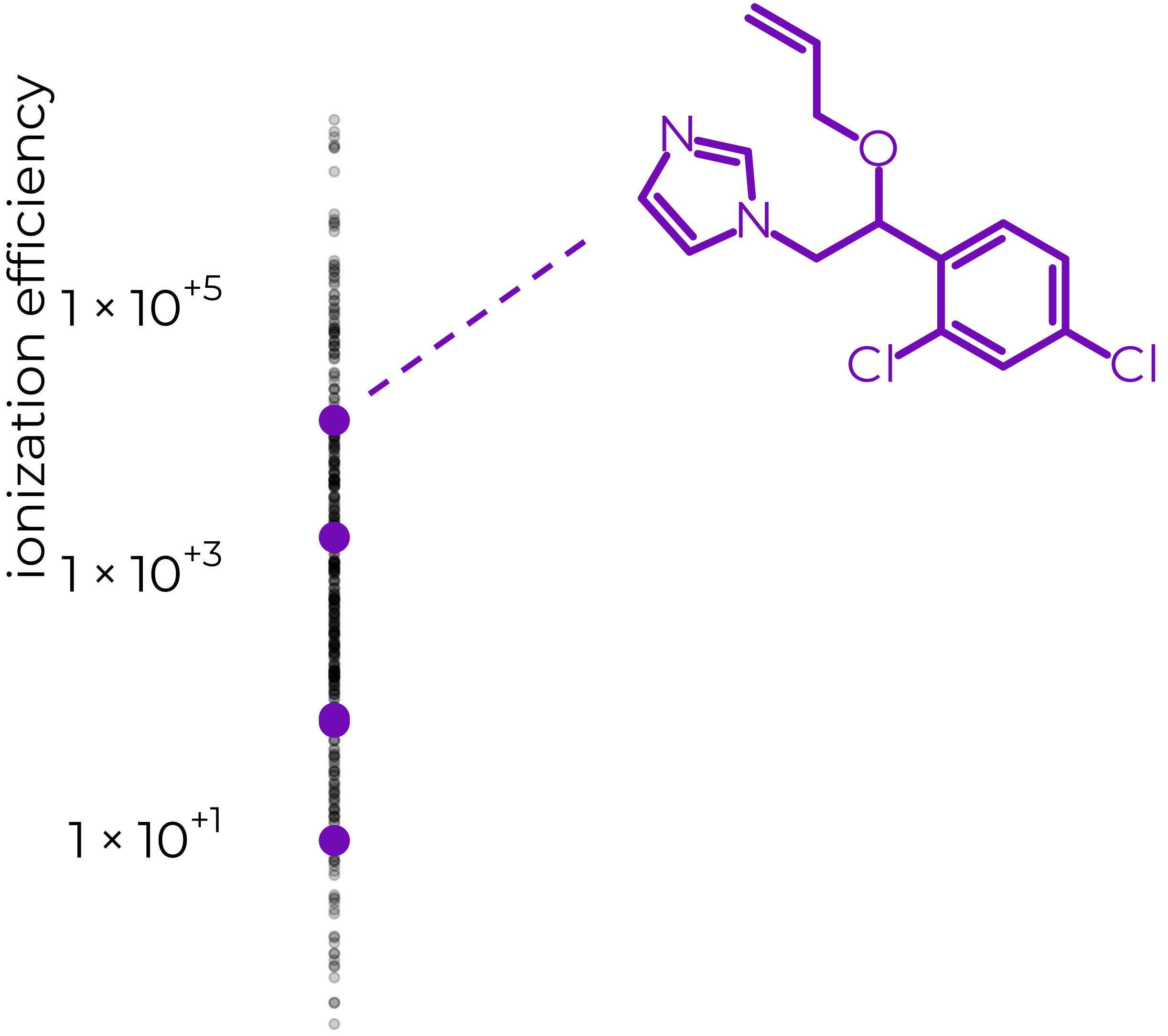
structure



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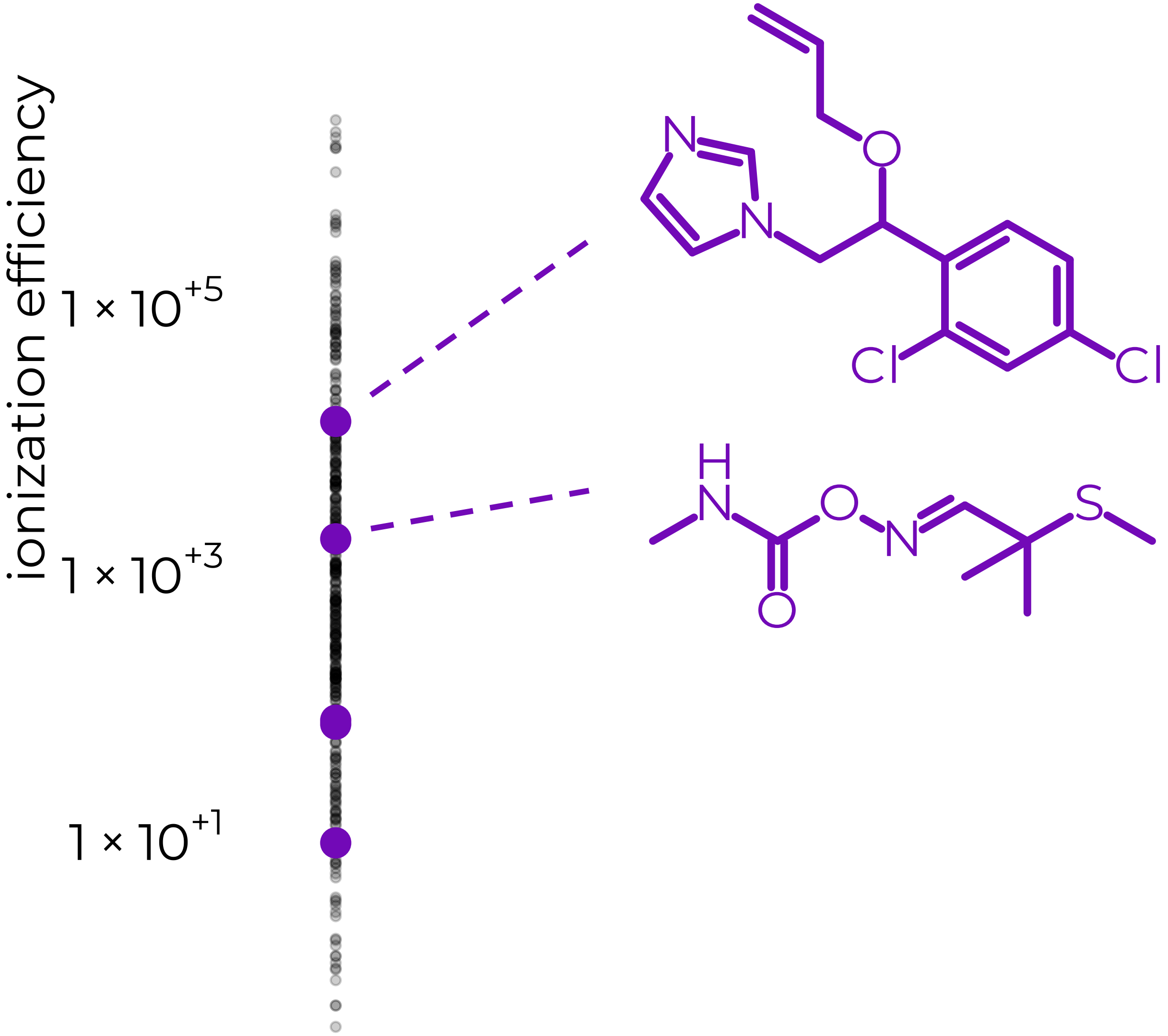
structure



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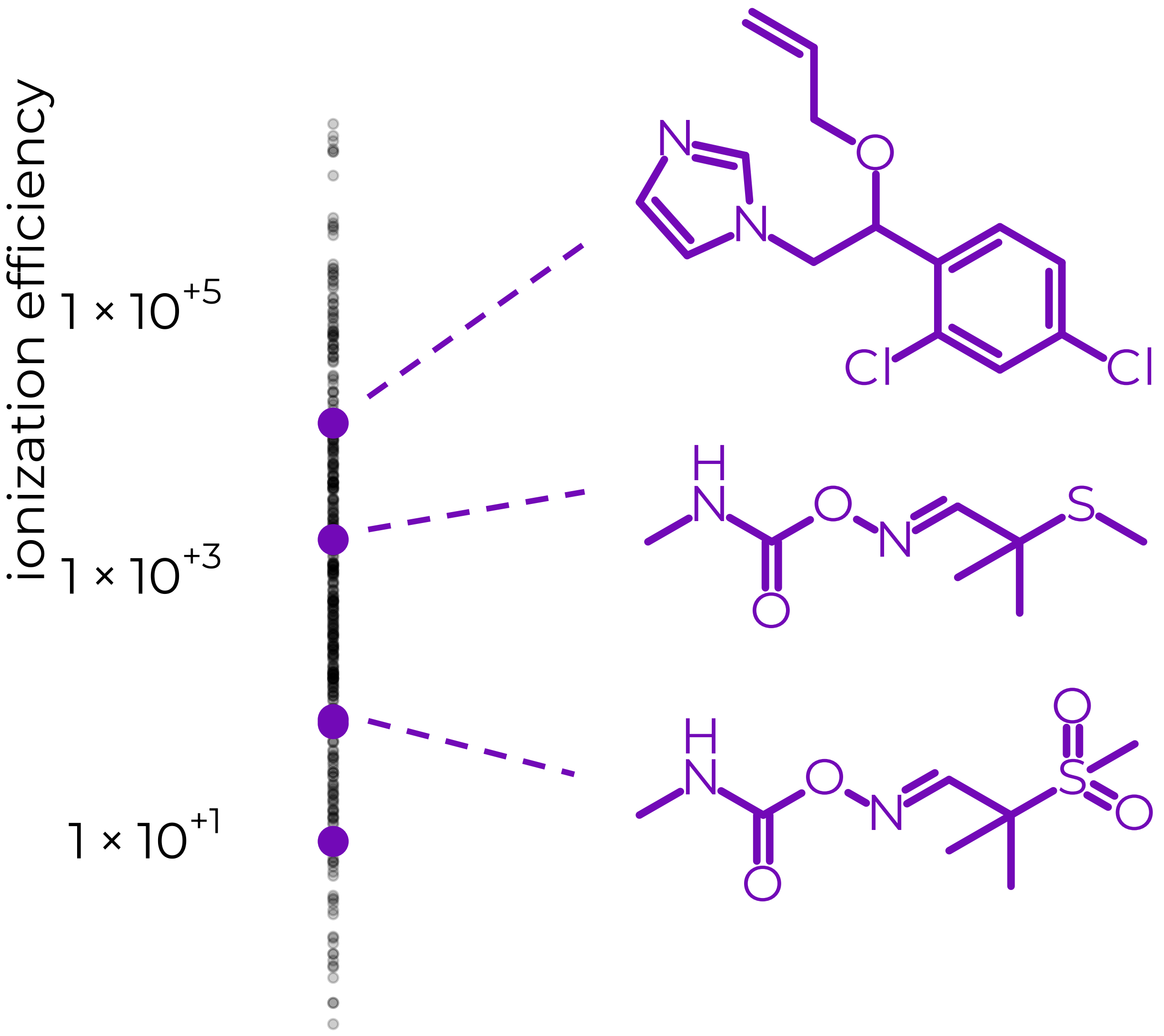
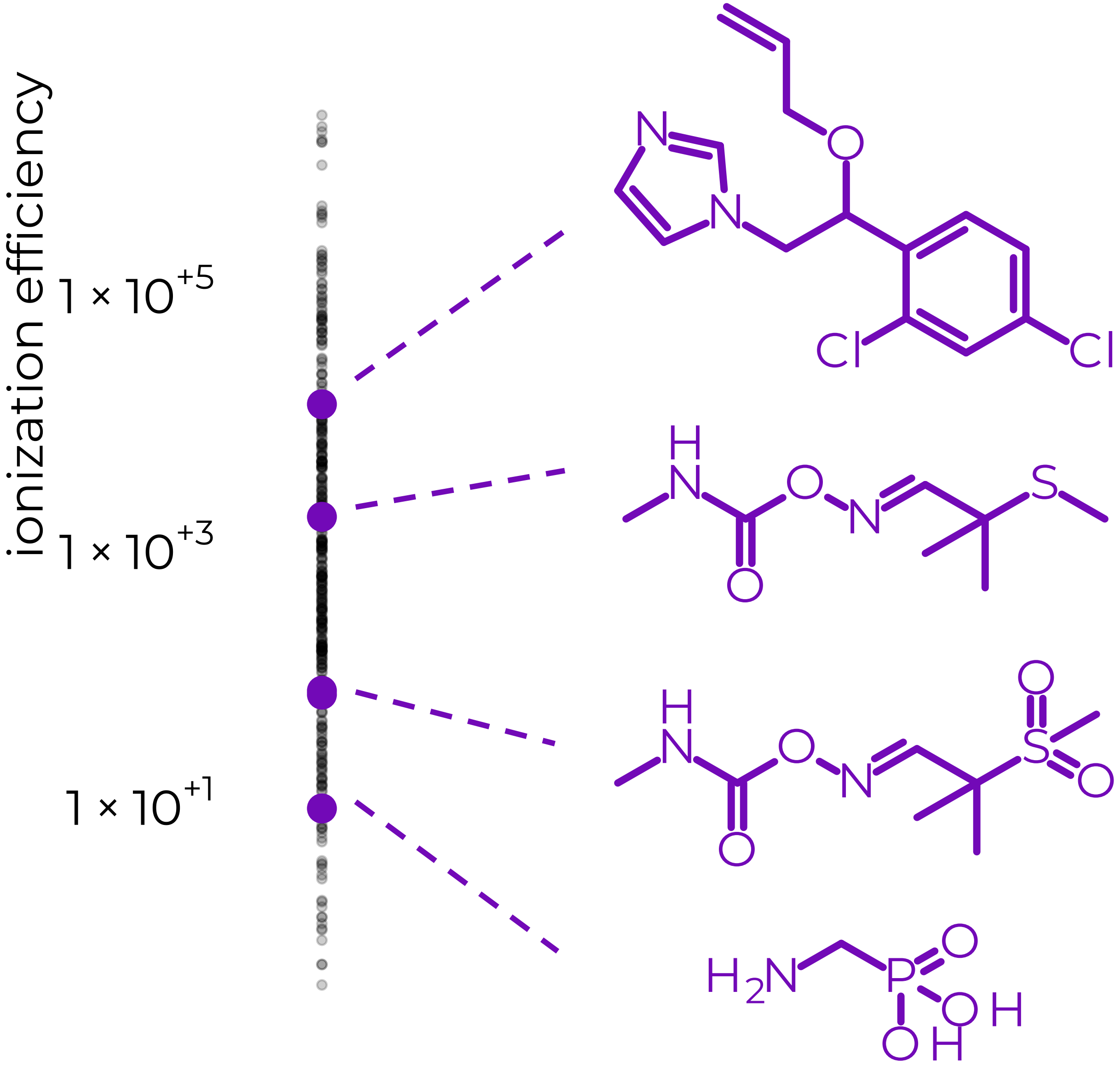
structure


ionization efficiency
1 × 10+5
1 × 10+3
1 × 10+1
N
N
O
Cl
Cl
H
N
O
N
S
O
H
N
O
N
O
S
O
O

structure



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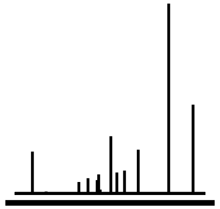
quantification

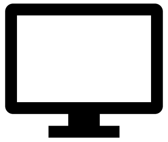
with machine learning

workflow



MS^2 spectra

molecular fingerprints with SIRIUS



predict toxicity and ionization efficiency

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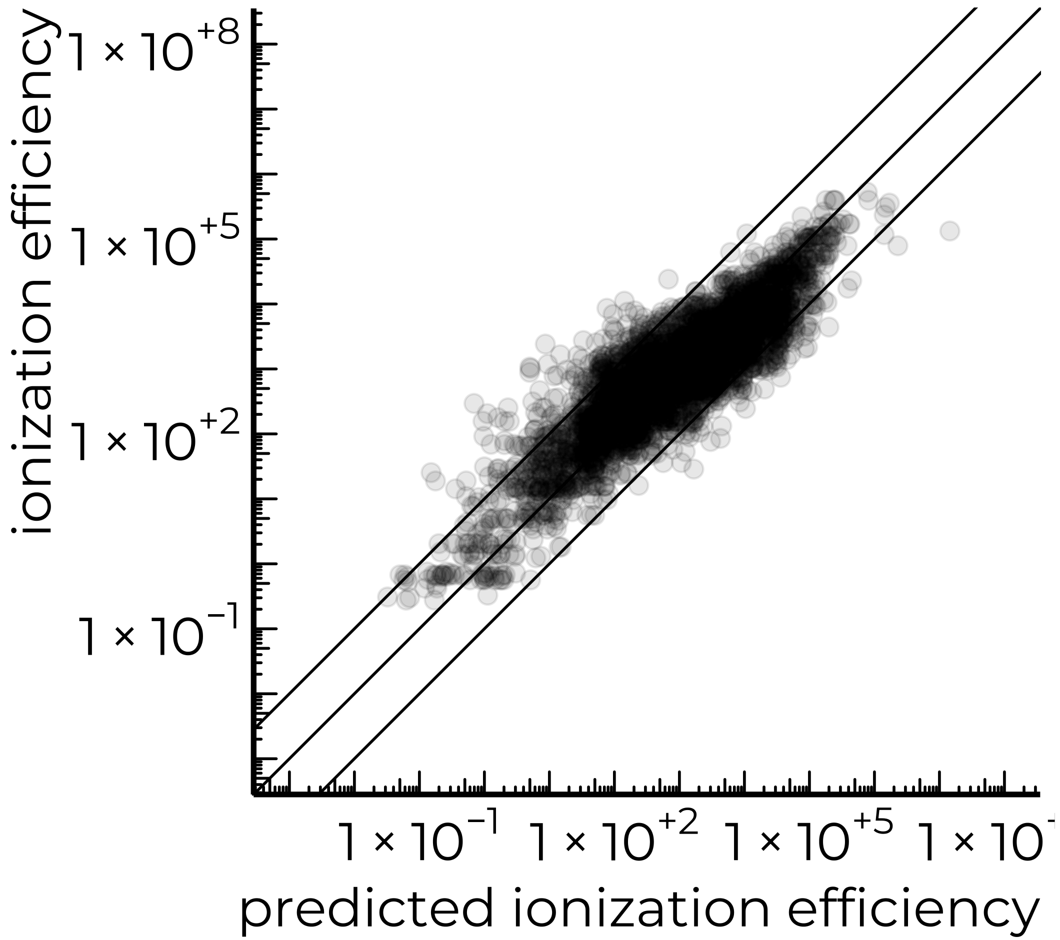
performance

Sepman et al. Anal Chem 2023



IE range

100,000,000

training set

RMSE 3.6x

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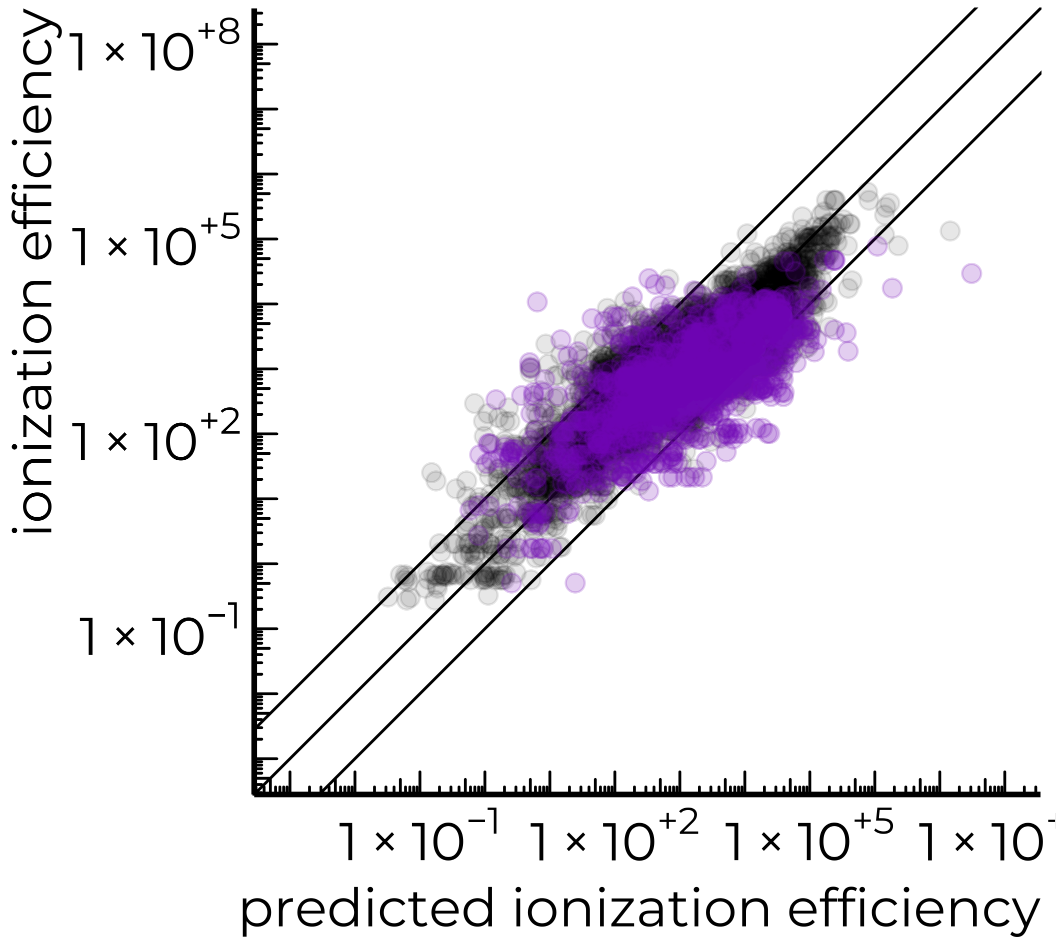
performance

Sepman et al. Anal Chem 2023



IE range

100,000,000

training set

RMSE 3.6x

test set

RMSE 5.6x

application

compound	peak area
methiocarb sulfoxide	5,300
pyridaben	5,400
aldicarb-sulfone	70,800

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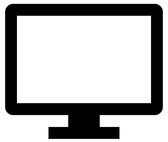
application



predict ionization efficiency

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application

compound	peak area	log*IE*$_{pred}$
methiocarb sulfoxide	5,300	2.57
pyridaben	5,400	3.78
aldicarb-sulfone	70,800	1.99

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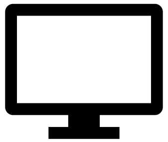
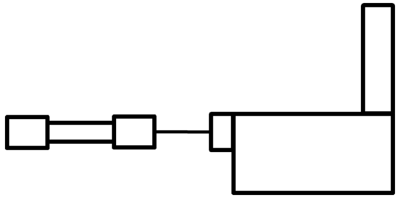
application



predict ionization efficiency



convert to instrument specific values

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application

compound	**peak area**	**log*IE*$_{pred}$**	**c (nM)**
methiocarb sulfoxide	5,300	2.57	
pyridaben	5,400	3.78	
aldicarb-sulfone	70,800	1.99	
atrazine-D5			4.5
gabapentin-lactam			0.35
sitagliptin			0.23
5-methyl-1H-benzotriazole			0.94
neburon			3.4
caffeine			0.50

application

compound	peak area	log*IE*$_{pred}$	c (nM)
methiocarb sulfoxide	5,300	2.57	
pyridaben	5,400	3.78	
aldicarb-sulfone	70,800	1.99	
atrazine-D5	450,000		4.5
gabapentin-lactam	10,400		0.35
sitagliptin	8,100		0.23
5-methyl-1H-benzotriazole	27,000		0.94
neburon	243,000		3.4
caffeine	5,600		0.50

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application

$RF_{measured}$ = peak area $/c$

compound	**peak area**	**log*IE*$_{pred}$**	**c (nM)**	***RF*$_{meas}$·10^{16}**
methiocarb sulfoxide	5,300	2.57		
pyridaben	5,400	3.78		
aldicarb-sulfone	70,800	1.99		
atrazine-D5	450,000		4.5	9.8
gabapentin-lactam	10,400		0.35	3.0
sitagliptin	8,100		0.23	3.5
5-methyl-1H-benzotriazole	27,000		0.94	2.9
neburon	243,000		3.4	7.2
caffeine	5,600		0.50	1.1

application

compound	peak area	$\log IE_{pred}$	c (nM)	$RF_{meas} \cdot 10^{16}$
methiocarb sulfoxide	5,300	2.57		
pyridaben	5,400	3.78		
aldicarb-sulfone	70,800	1.99		
atrazine-D5	450,000	3.46	4.5	9.8
gabapentin-lactam	10,400	2.66	0.35	3.0
sitagliptin	8,100	2.89	0.23	3.5
5-methyl-1H-benzotriazole	27,000	2.46	0.94	2.9
neburon	243,000	3.23	3.4	7.2
caffeine	5,600	2.30	0.50	1.1

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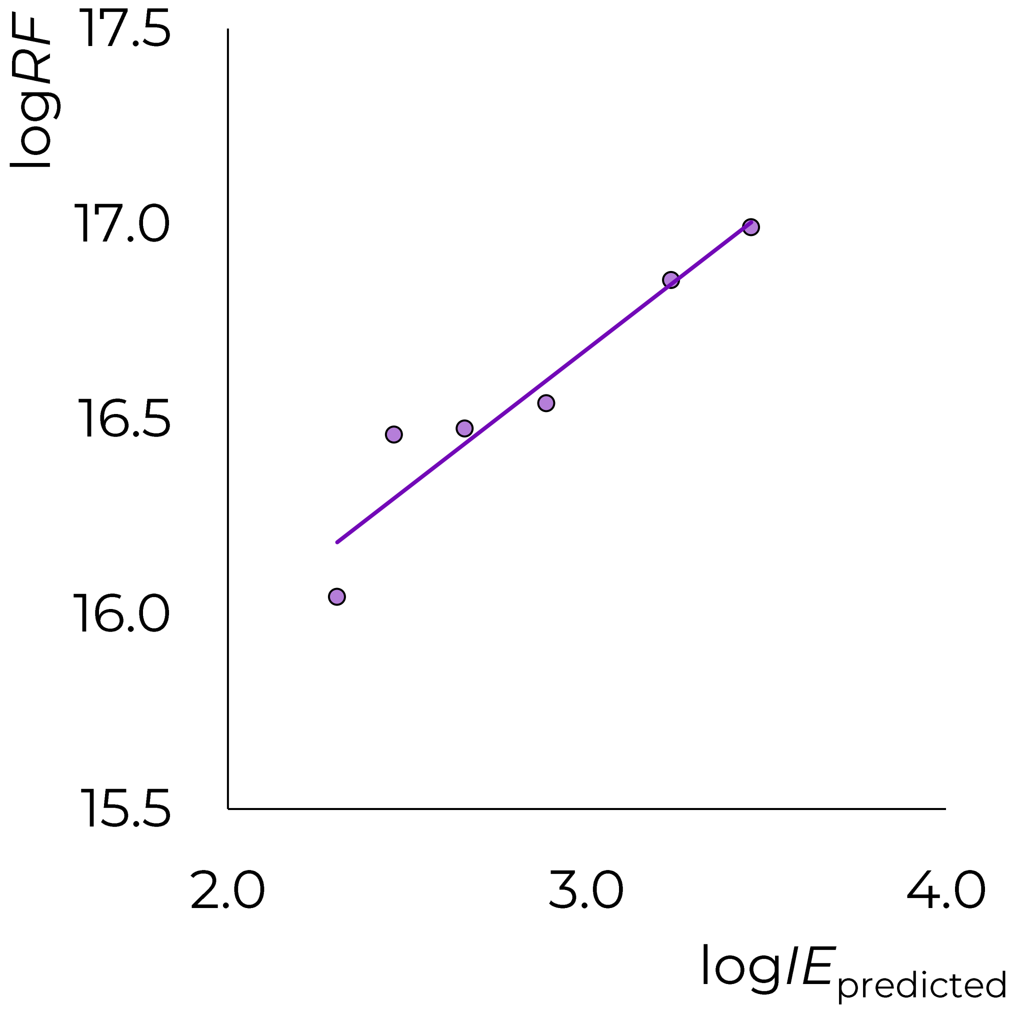
application

compound	peak area	$\log IE_{pred}$
methiocarb sulfoxide	5,300	2.57
pyridaben	5,400	3.78
aldicarb-sulfone	70,800	1.99
atrazine-D5	450,000	3.46
gabapentin-lactam	10,400	2.66
sitagliptin	8,100	2.89
5-methyl-1H-benzotriazole	27,000	2.46
neburon	243,000	3.23
caffeine	5,600	2.30

$$\log RF = \text{slope} \cdot \log IE + \text{intercept}$$



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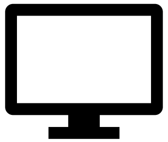
application

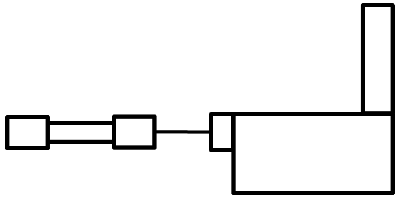
$\log RF_{\text{predicted}} = \text{slope} \cdot \log IE_{\text{predicted}} + \text{intercept}$

compound	**peak area**	**log*IE*$_{pred}$**	**c (nM)**	***RF*$_{meas}$$\cdot 10^{16}$**	***RF*$_{pred}$$\cdot 10^{16}$**
methiocarb sulfoxide	5,300	2.57			2.6
pyridaben	5,400	3.78			15.5
aldicarb-sulfone	70,800	1.99			1.1
atrazine-D5	450,000	3.46	4.5	9.8	
gabapentin-lactam	10,400	2.66	0.35	3.0	
sitagliptin	8,100	2.89	0.23	3.5	
5-methyl-1H-benzotriazole	27,000	2.46	0.94	2.9	
neburon	243,000	3.23	3.4	7.2	
caffeine	5,600	2.30	0.50	1.1	

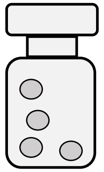
application



predict ionization efficiency



convert to instrument specific values



estimate concentration

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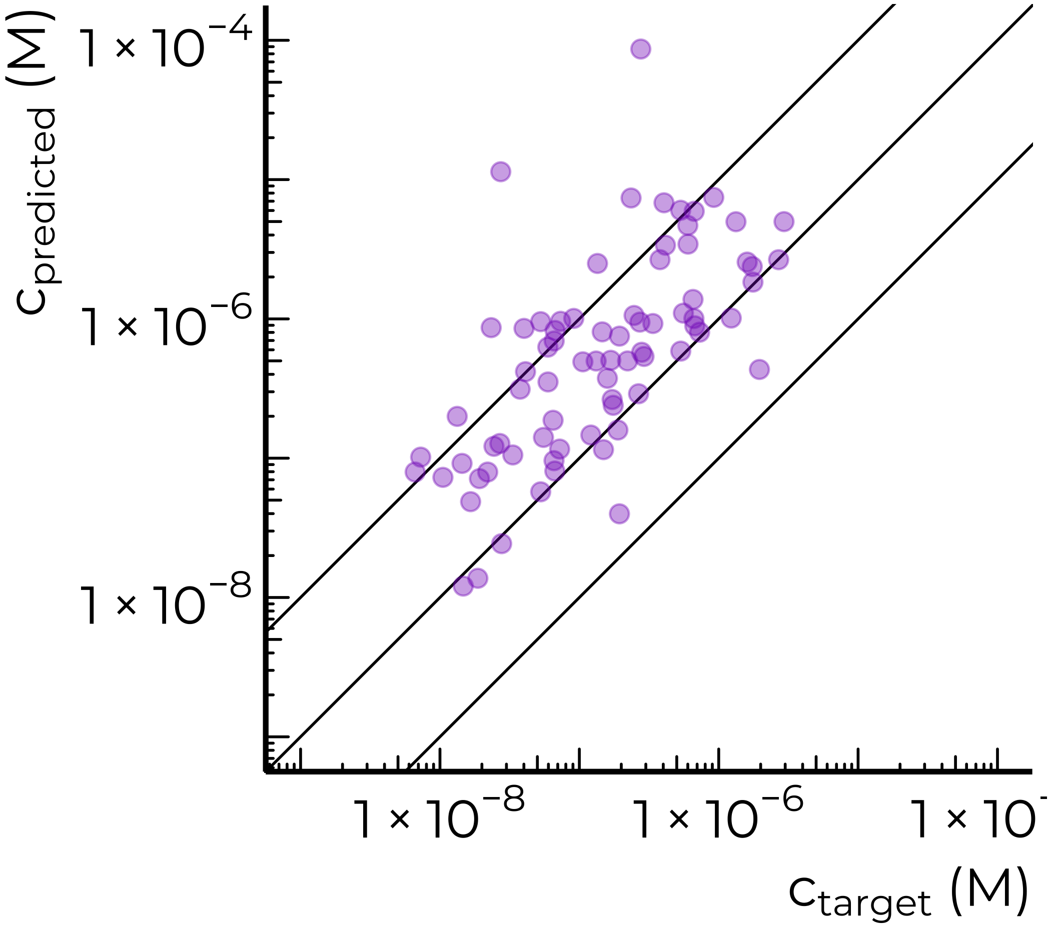
application

c = peak area / $RF_{predicted}$

compound	peak area	$\log IE_{pred}$	c (nM)	$RF_{meas} \cdot 10^{16}$	$RF_{pred} \cdot 10^{16}$	c_{pred} (nM)
methiocarb sulfoxide	5,300	2.57			2.6	0.20
pyridaben	5,400	3.78			15.5	0.035
aldicarb-sulfone	70,800	1.99			1.1	6.3
atrazine-D5	450,000	3.46	4.5	9.8		
gabapentin-lactam	10,400	2.66	0.35	3.0		
sitagliptin	8,100	2.89	0.23	3.5		
5-methyl-1H-benzotriazole	27,000	2.46	0.94	2.9		
neburon	243,000	3.23	3.4	7.2		
caffeine	5,600	2.30	0.50	1.1		

ionization efficiency

Sepman et al. Anal Chem 2023



mean prediction error

7.4x

geometric mean prediction error

4.5x

median prediction error

4.0x

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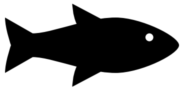
summary

prioritization in NTS

toxicity



concentration

risk

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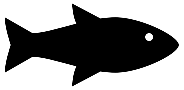
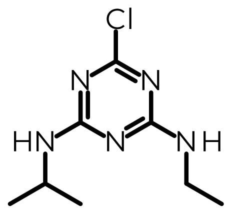
prioritization in NTS

toxicity

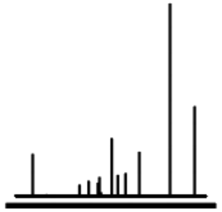


concentration

risk



structure



MS^2 spectrum

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