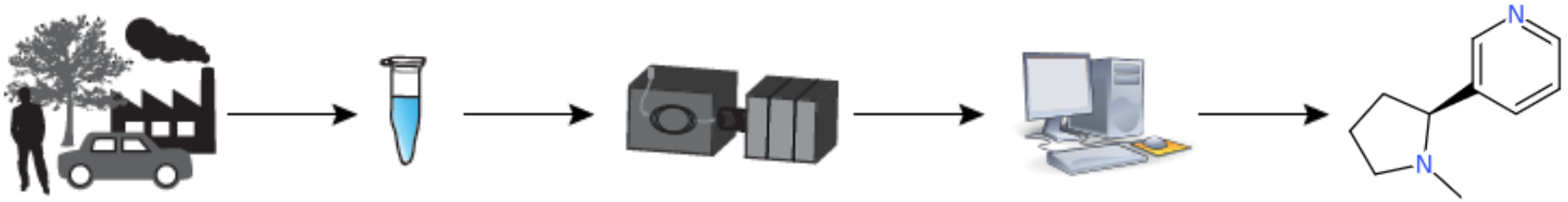
Luxembourg National Research Fund

Data Science and Environmental Cheminformatics



environment | environmental sample | high resolution mass spectrometry | cheminformatics | identify chemicals and toxic effects

Assoc. Prof. Dr. Emma L. Schymanski
FNR ATTRACT Fellow and PI in Environmental Cheminformatics
Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg
Email: emma.schymanski@uni.lu and @ESchymanski

Plus ECI-LSCB, NORMAN, PubChem, IPB, Eawag, UFZ and many other colleagues who contributed to our science over the years!

Talk available under DOI: 10.5281/zenodo.4075013

LCSB

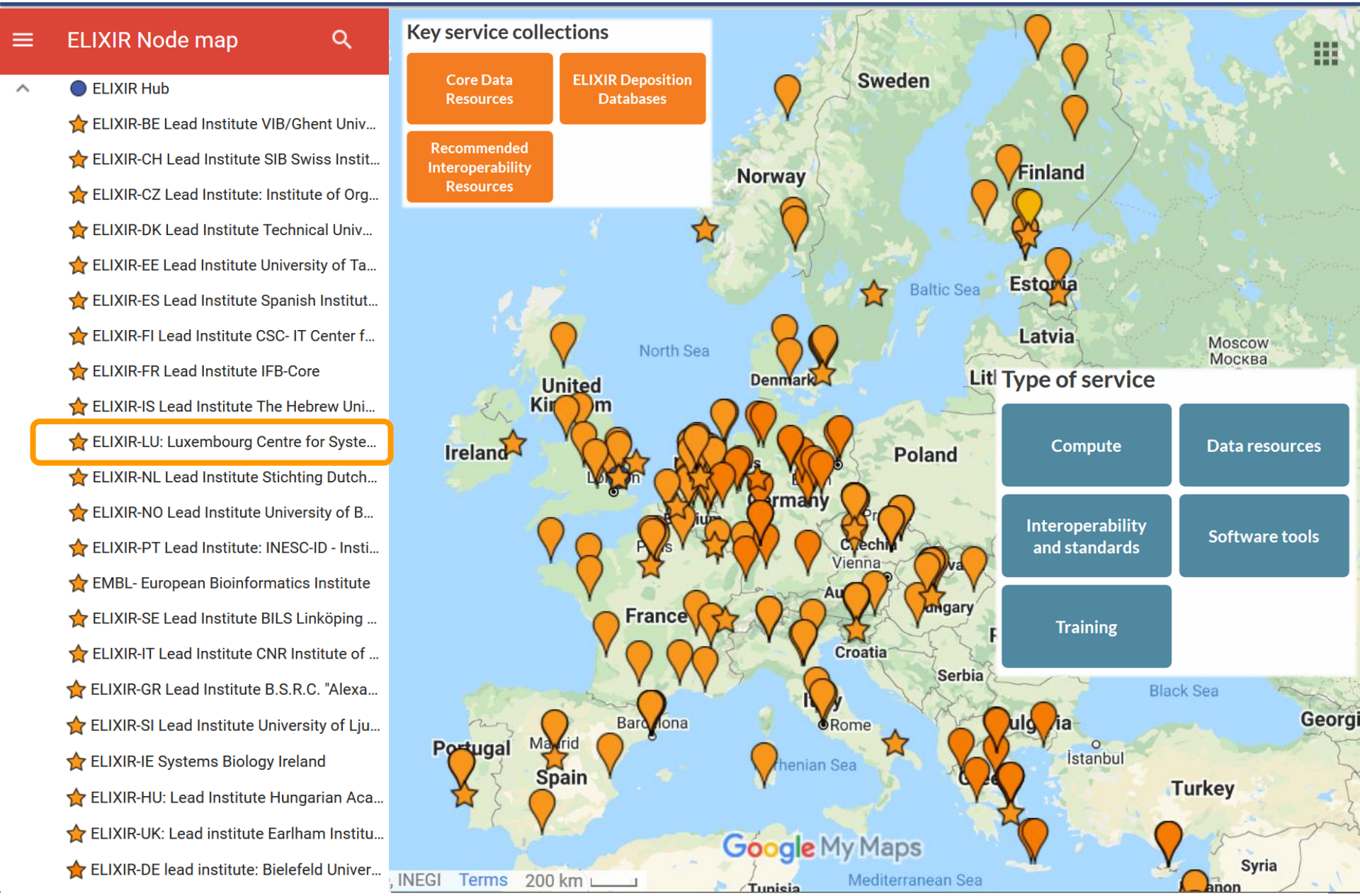
UNIVERSITÉ DU LUXEMBOURG

Source: https://en.wikipedia.org/wiki/File:EU-Luxembourg.svg

Example: NORMAN Collaborative Trial 2015

Schymanski *et al*. 2015, ABC, DOI: 10.1007/s00216-015-8681-7

Example: ELIXIR (https://elixir-europe.org/)

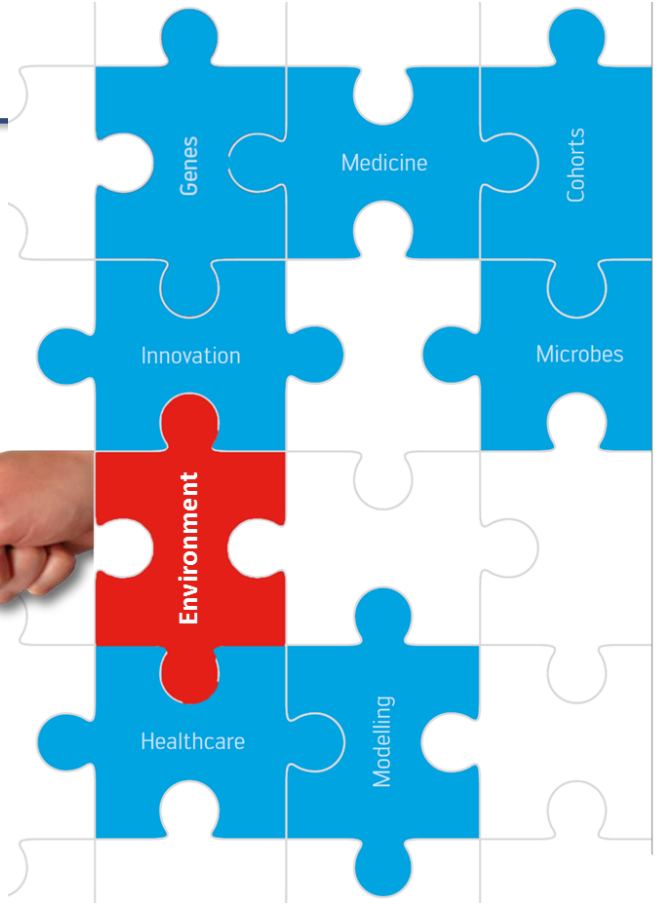


Schymanski *et al*. 2015, ABC, DOI: 10.1007/s00216-015-8681-7

LUXEMBOURG

LET'S MAKE IT HAPPEN

Environmental Cheminformatics @ Luxembourg Centre for Systems Biomedicine



LUXEMBOURG

LET'S MAKE IT HAPPEN

Members with access to **Environmental Cheminformatics**

Adelene Lai @adelene.lai
Given access 2 months ago

Anjana Elapavalore @anjana.elapavalore
Given access 4 weeks ago

Corey Griffith @corey.griffith
Given access 2 months ago

Emma Schymanski @emma.schymanski It's you
Given access 2 months ago

German Andres Preciat Gonzales @german.preciat
Given access 2 months ago

Hiba Hiba @hiba.hiba
Given access 4 weeks ago

Jessy Krier @jessy.krier
Given access 1 week ago

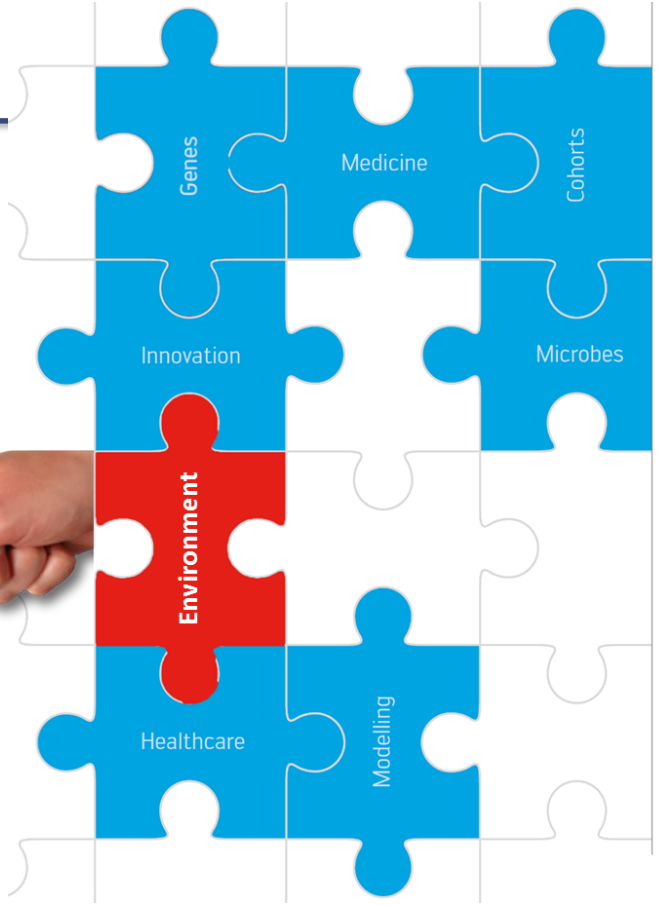
Lorenzo Favilli @lorenzo.favilli
Given access 2 months ago

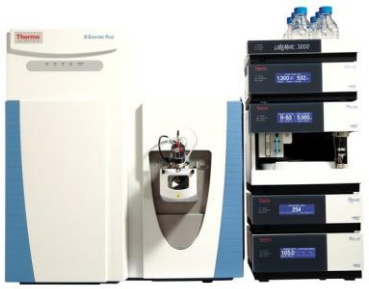
Mira Narayanan @mira.narayanan
Given access 4 weeks ago

Randolph Singh @randolph.singh
Given access 2 months ago

Todor Kondić @todo
Given access 2

R3 LCSB





Luxembourg National Research Fund

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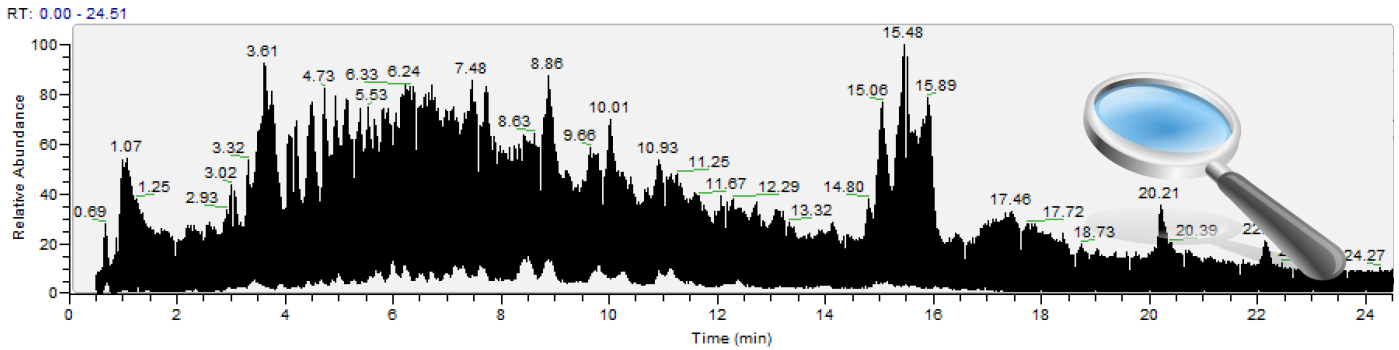
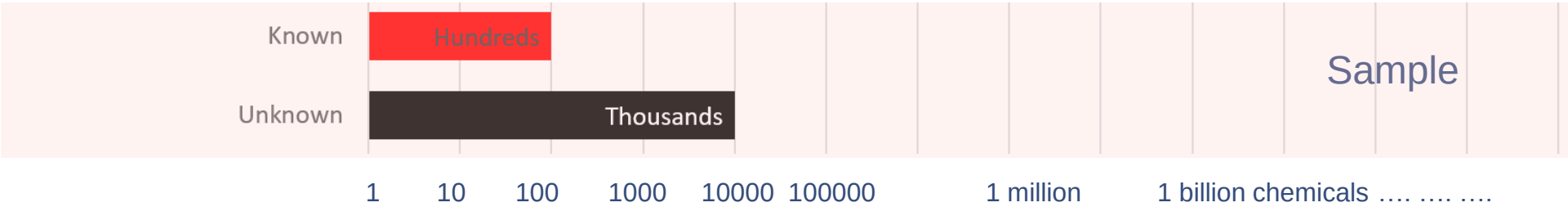
Our (Community) Challenge: Identifying Chemicals

High resolution mass spectrometry



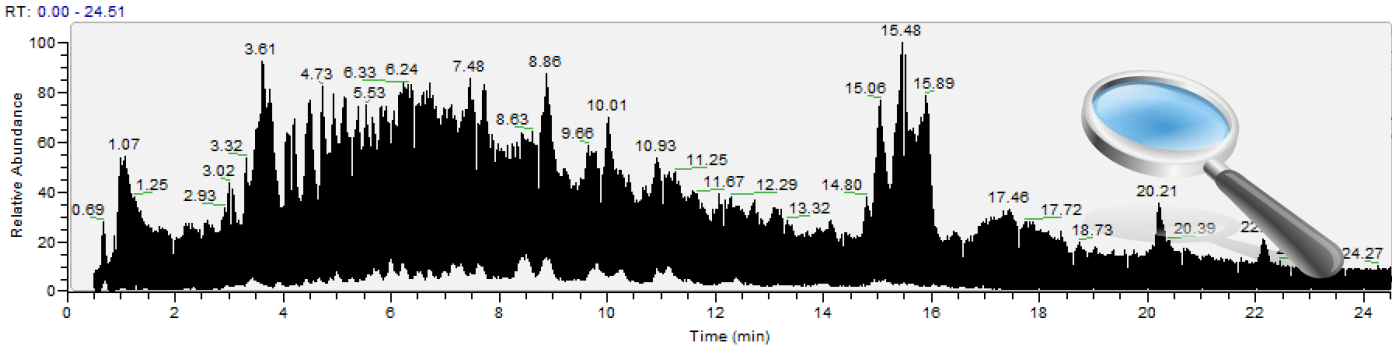


Schymanski *et al*. (2014) DOI: 10.1021/es4044374; Vermeulen *et al.* (2020) DOI: 10.1126/science.aay3164

Our (Community) Challenge: Identifying Chemicals

High resolution mass spectrometry

AND connecting chemical knowledge



Known — Hundreds

Unknown — Thousands

Sample

1 10 100 1000 10000 100000 1 million 1 billion chemicals …. …. ….

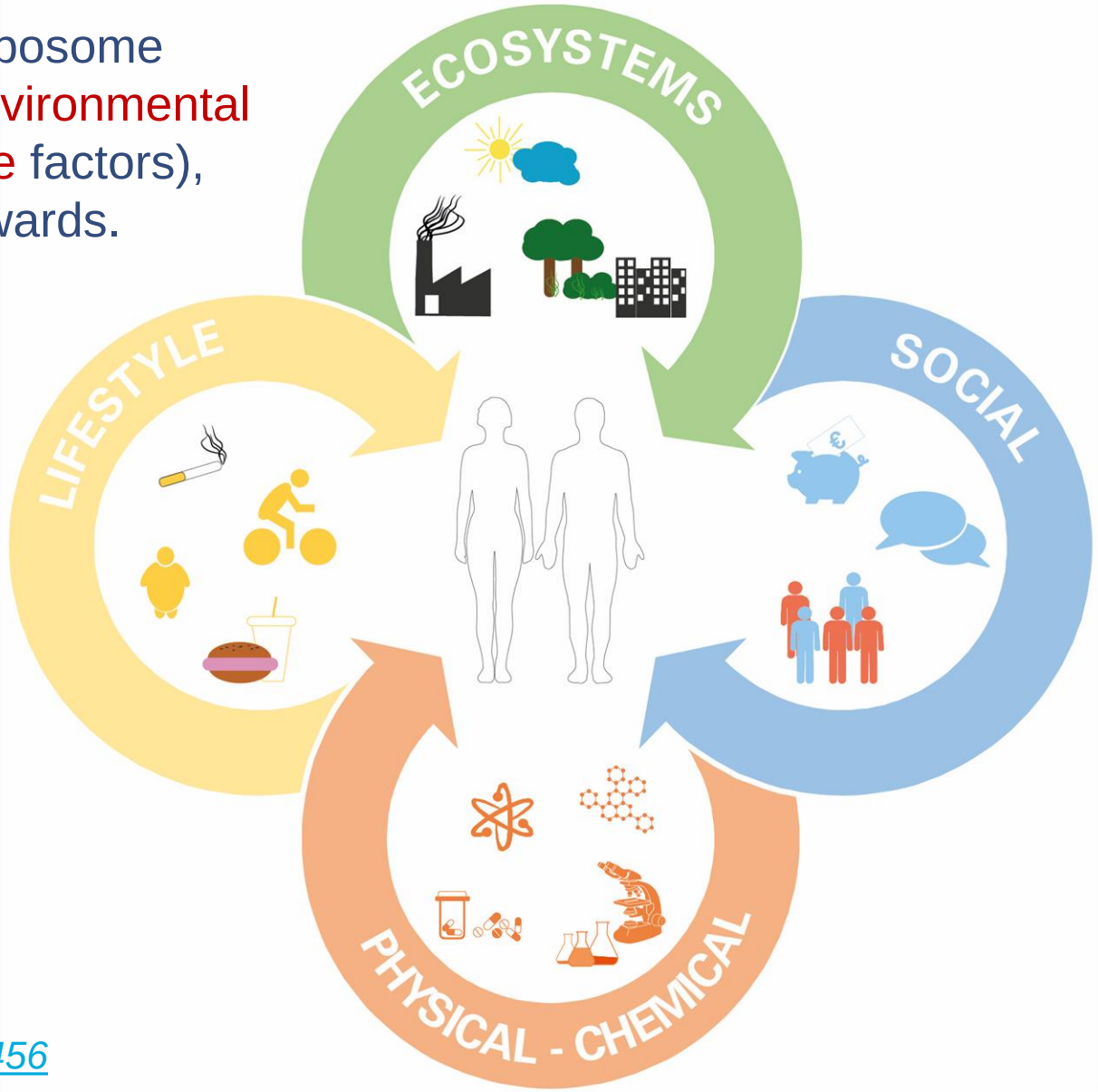
Chemicals

Suspect Chemicals	100s-1000s — norman suspects
Mass Spectral Libraries	~80,000 — MassBank.eu
CompTox Dashboard	882,000 — EPA Chemicals
PubChem Compound	>111 million — PubChem
1st Gen. PubChem Metabolites	>2 billion — PubChem
Generated Structures	Millions of billions

Schymanski *et al*. (2014) DOI: 10.1021/es4044374; Vermeulen *et al.* (2020) DOI: 10.1126/science.aay3164

Our Context (“worst case”): The Exposome

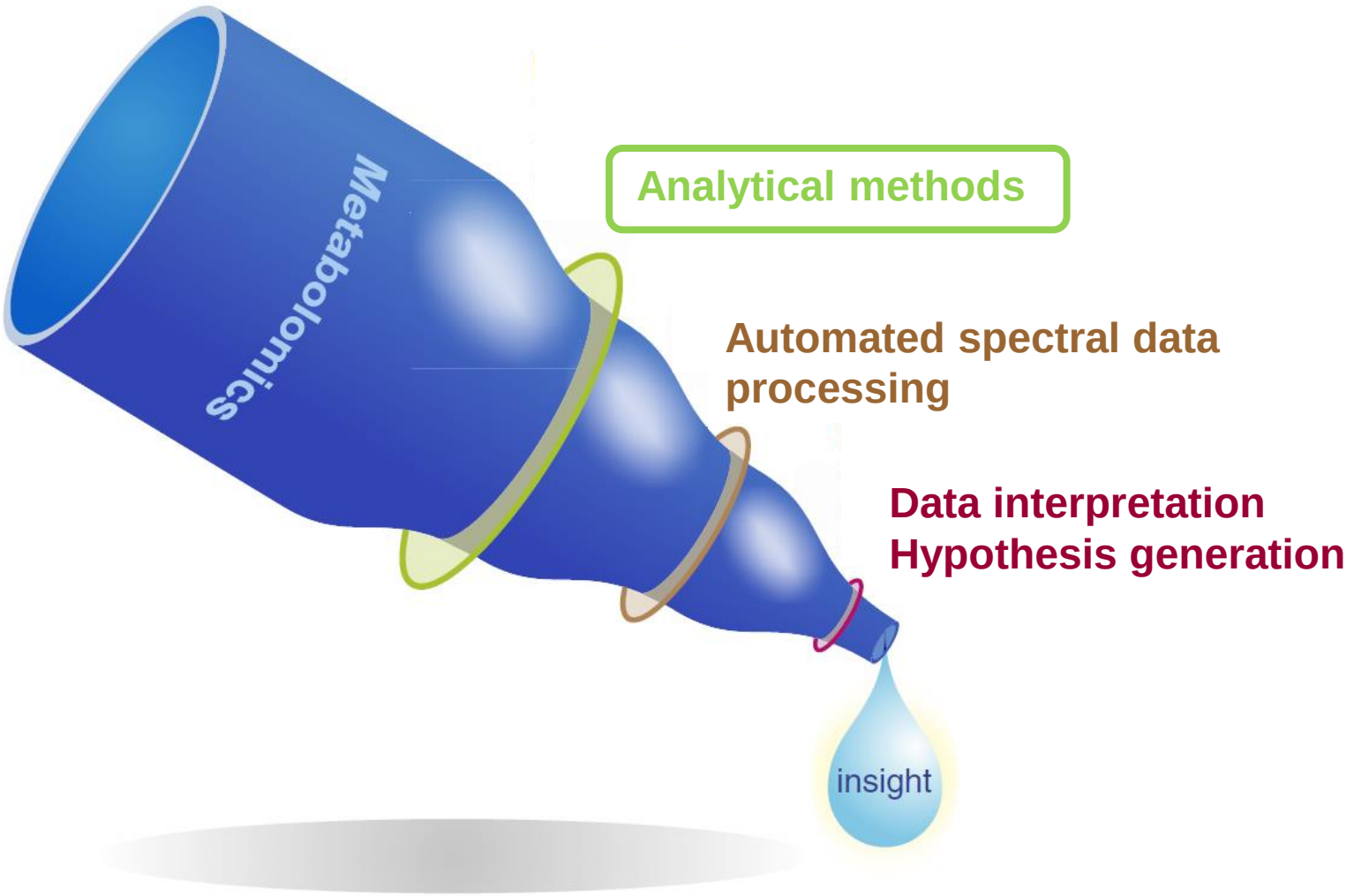
At its most complete, the exposome encompasses life-course environmental exposures (including lifestyle factors), from the prenatal period onwards.



Christopher P. Wild, 2005.
DOI: *10.1158/1055-9965.EPI-05-0456*

Image c/o uni.lu (LCSB); modified from Vermeulen *et al* (2020) Science. DOI: 10.1126/science.aay3164

Our Aim: Generating Insight from Measurements

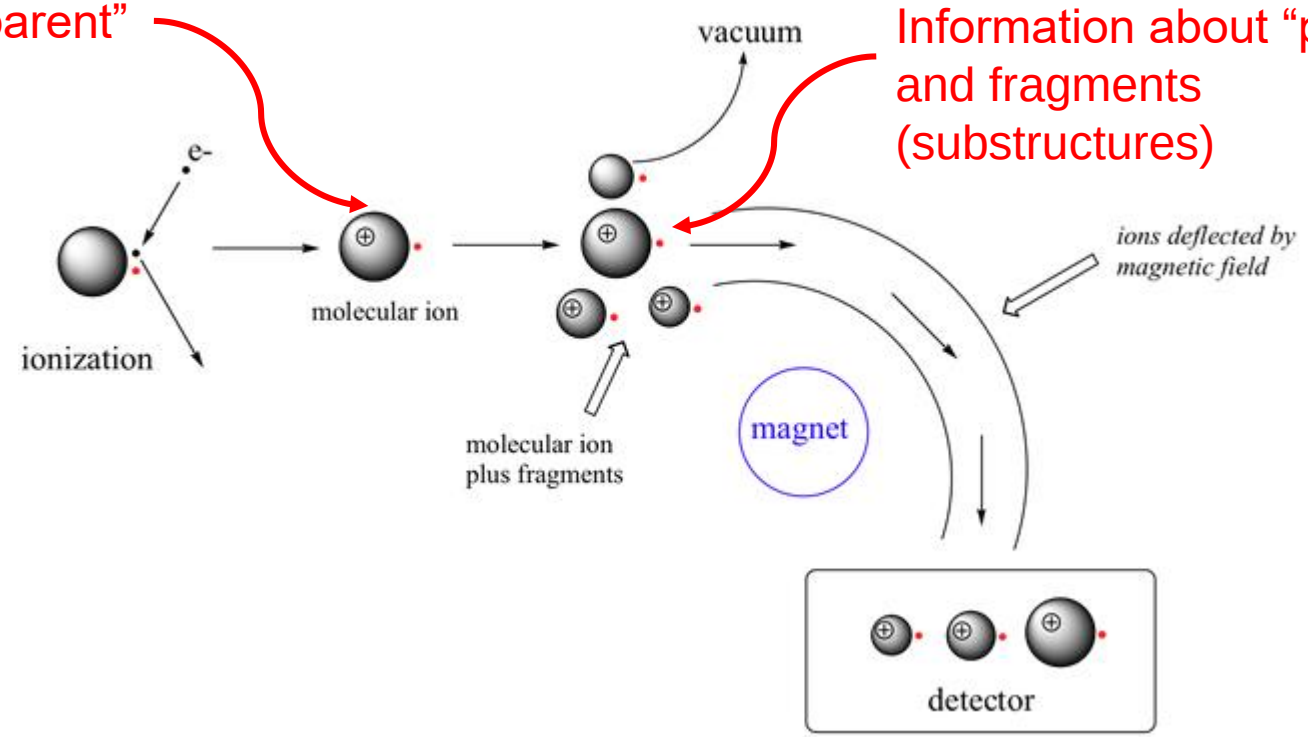


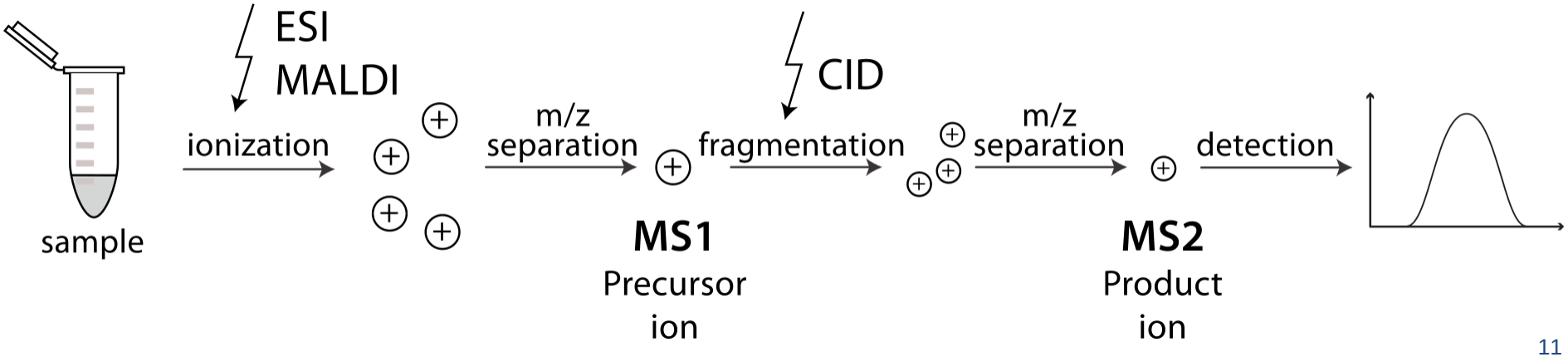
Mod. From Fig. 2, Sevin *et al* 2015, Current Opinion in Biotechnology. DOI: 10.1016/j.copbio.2014.10.001

General Scheme(s) of Mass Spectrometry

Information about "parent"

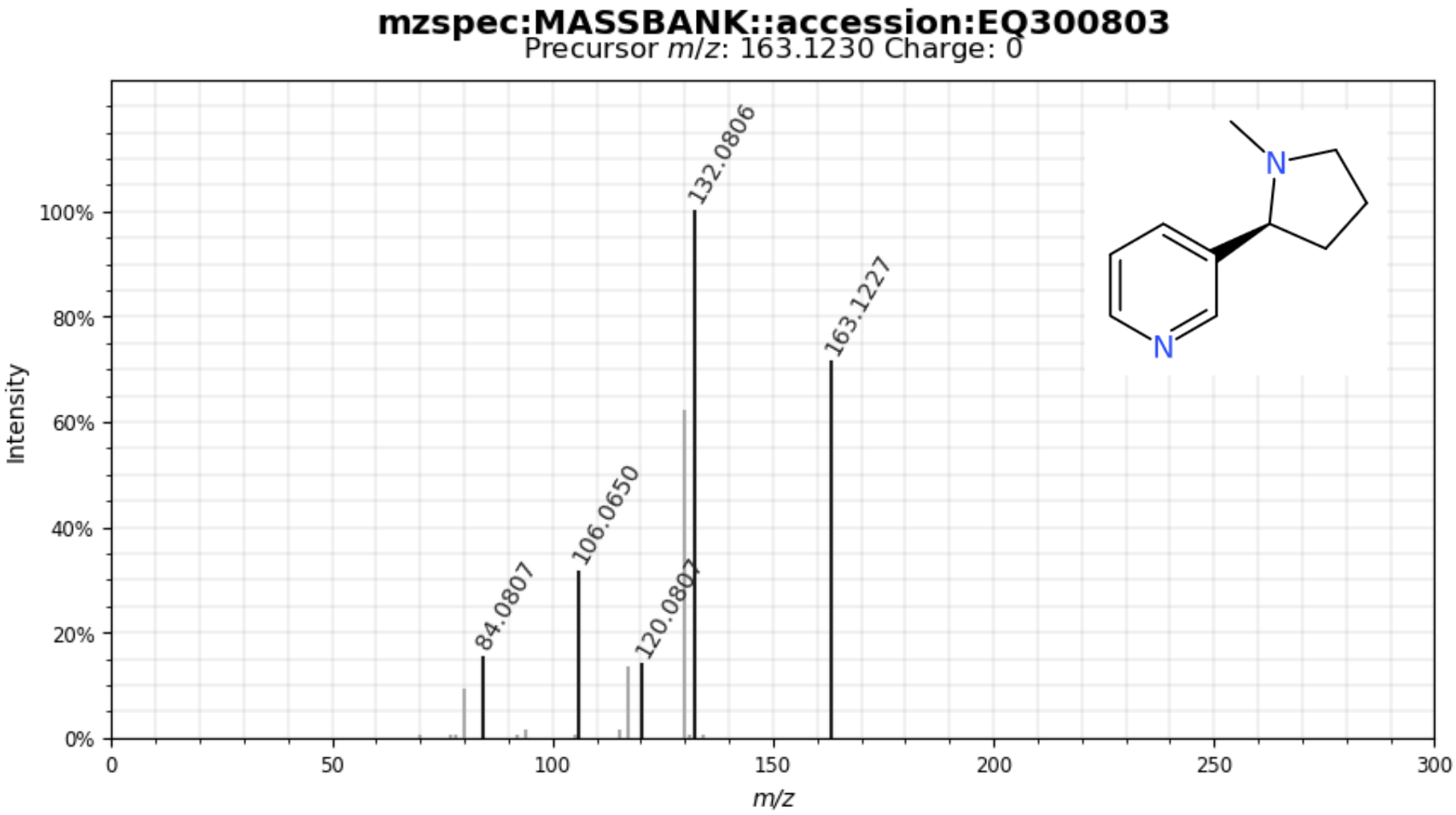
Information about "parent" and fragments (substructures)





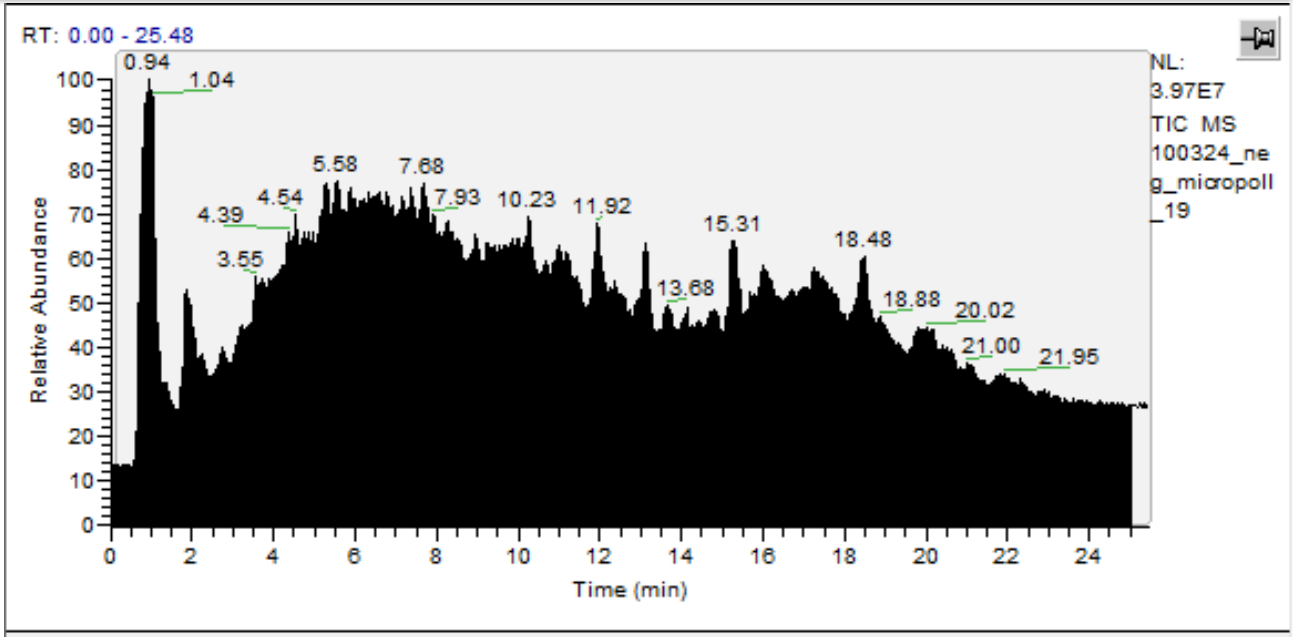
Top: chemwiki.ucdavis.edu. Bottom H. Röst & M. Steiner. Own work. https://commons.wikimedia.org/w/index.php?curid=11640370

Mass Spectra are our “fingerprints”



https://metabolomics-usi.ucsd.edu/spectrum/?usi=mzspec:MASSBANK::accession:EQ300803

But … this is what the output “really” looks like …



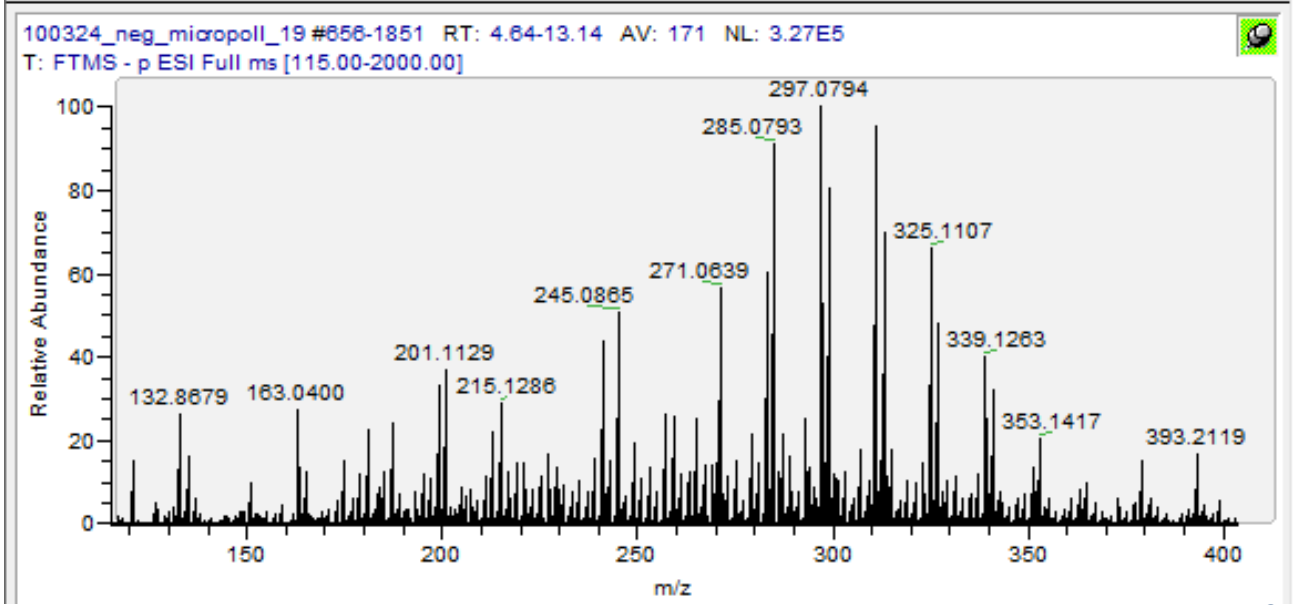
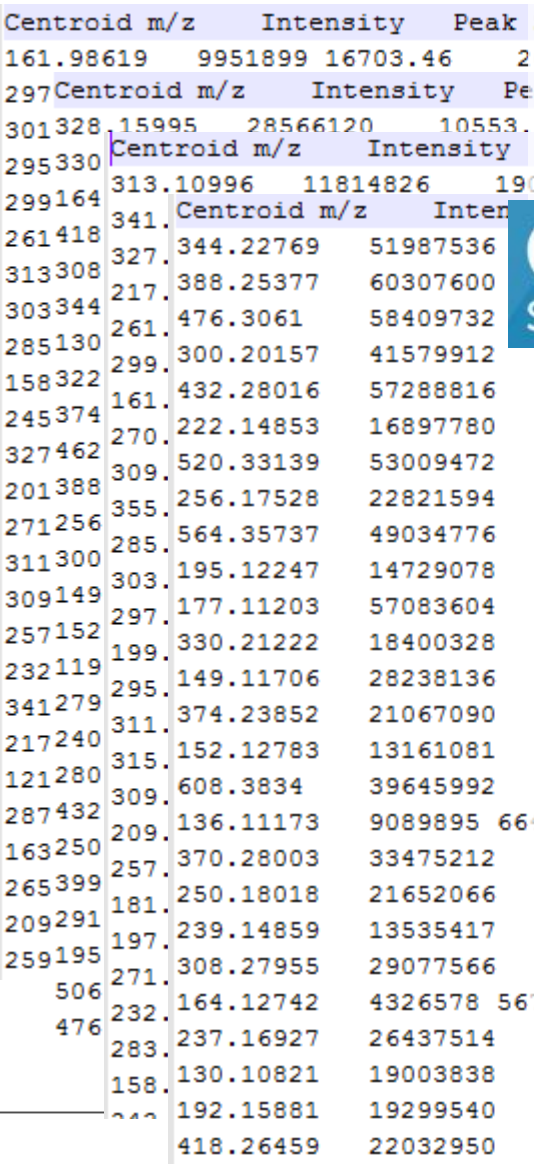
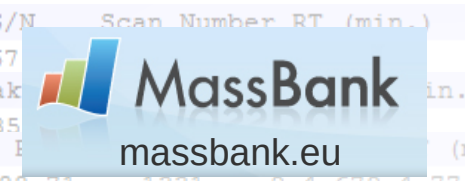


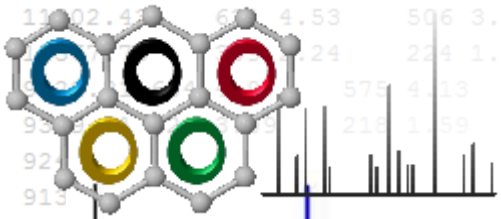
Image © www.planetorbitrap.com/q-exactive

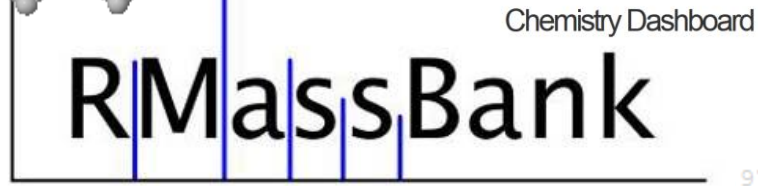
From Sample to Numbers (Masses) to Molecules

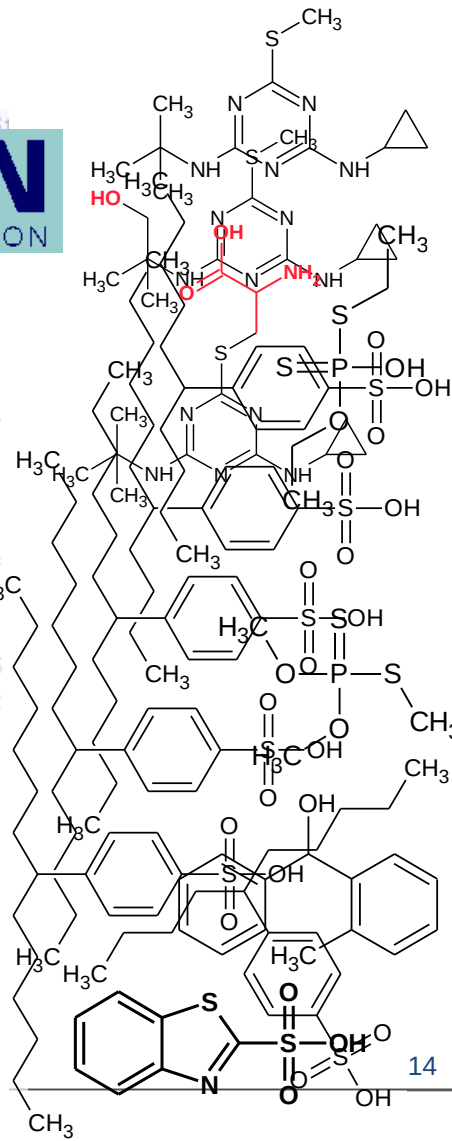
- Identification = turning numbers into structures



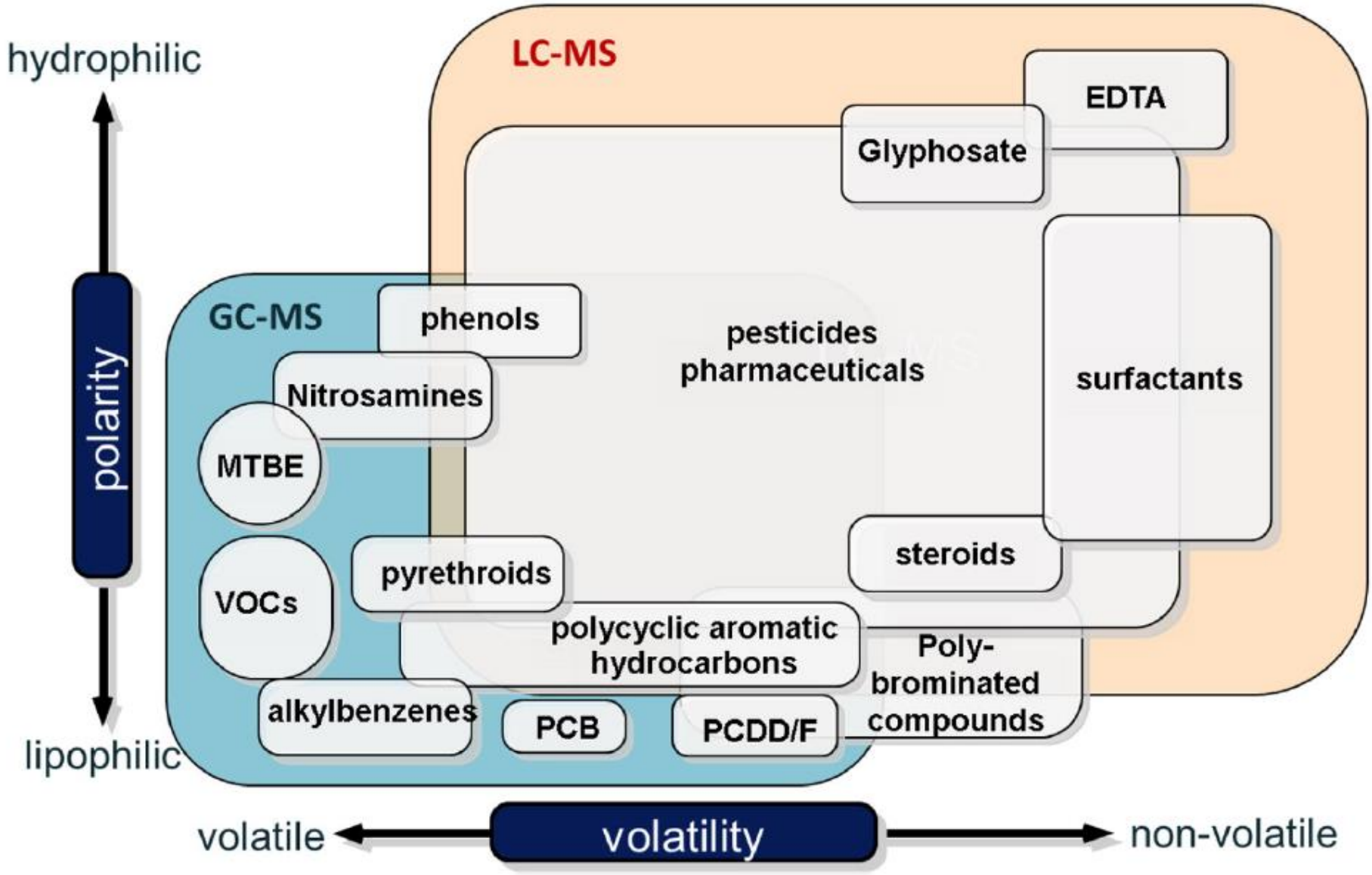






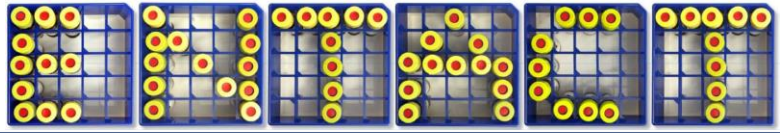


How to measure? LC vs GC?

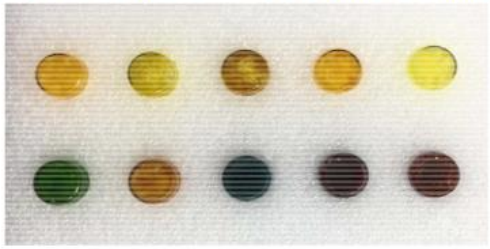


Brack *et al* 2016. DOI: 10.1016/j.scitotenv.2015.11.102

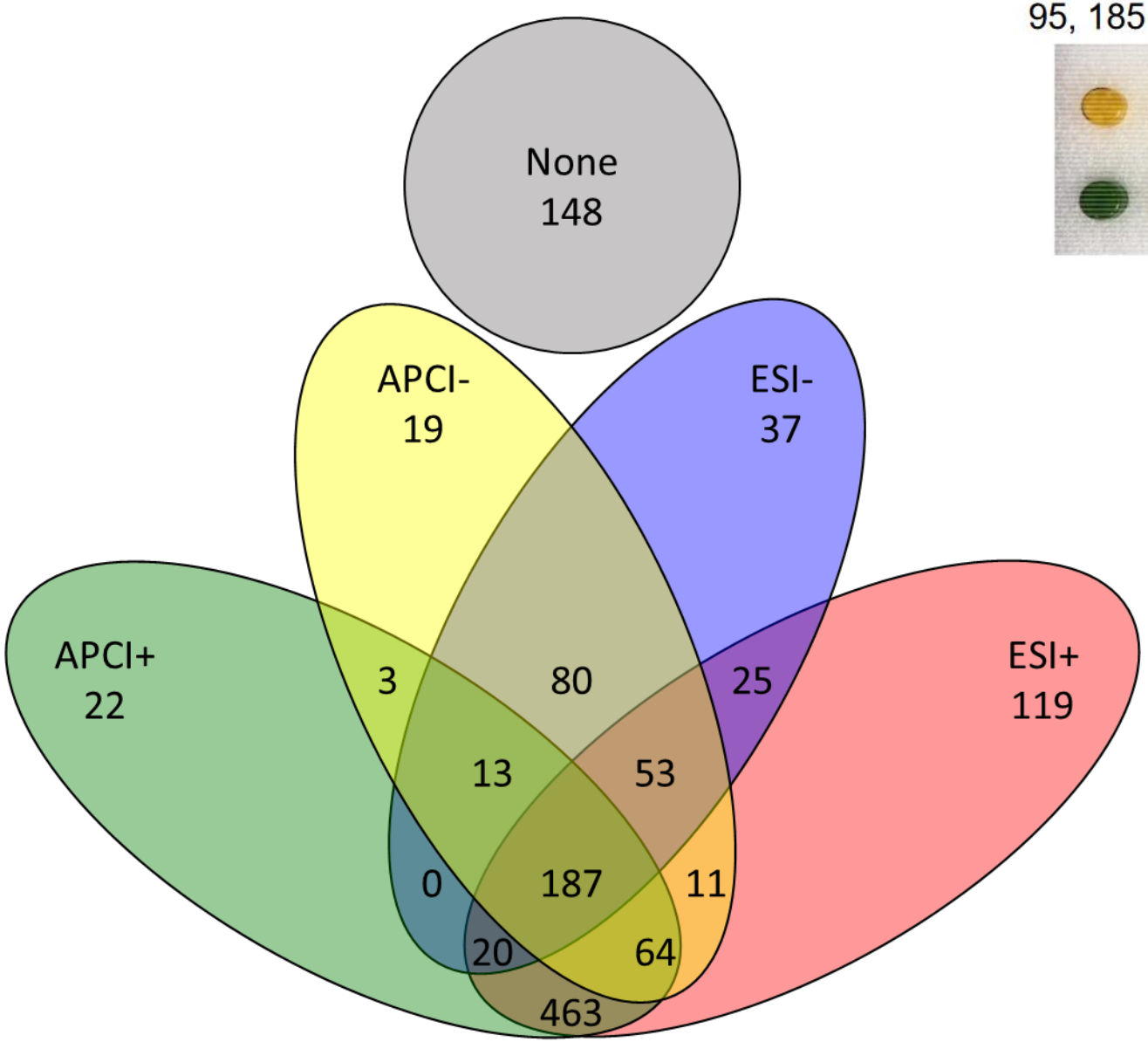
How to measure? Ionisation



95, 185 or 365 substances/mixture

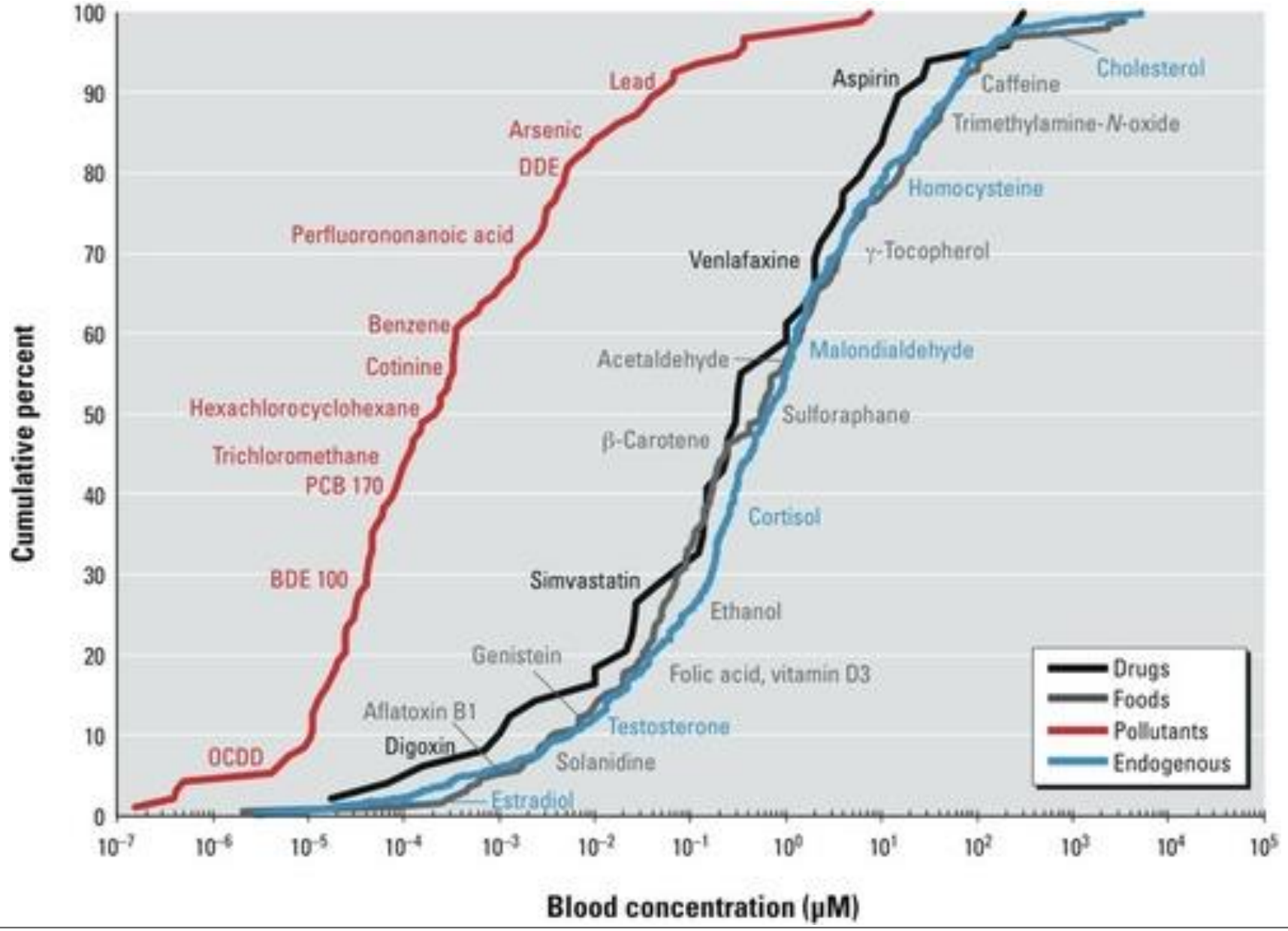


n=1264



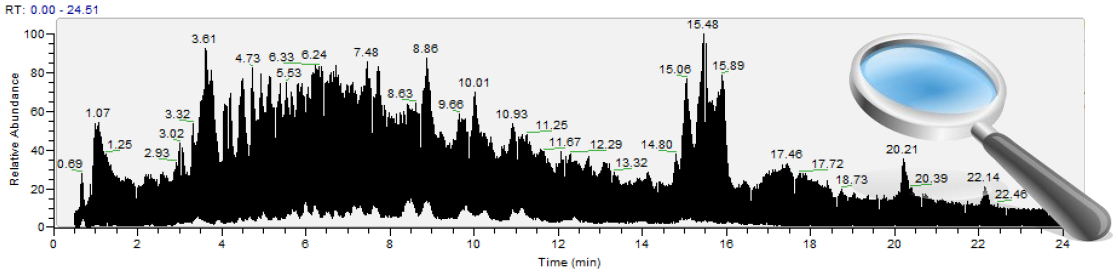
Singh, RR *et al* (2020) DOI: 10.1007/s00216-020-02716-3 ; Ulrich, EM *et al* (2019) DOI: 10.1007/s00216-018-1435-6

How to measure? Widely Varying Concentrations

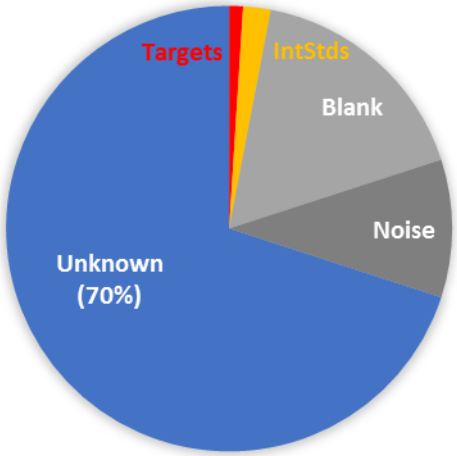


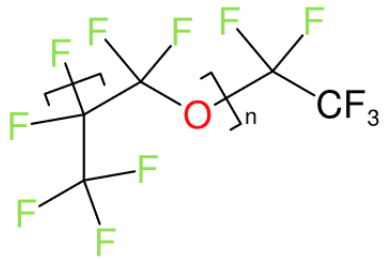
Rappaport *et al* (2014) *Environmental Health Perspectives*. DOI: 10.1289/ehp.1308015

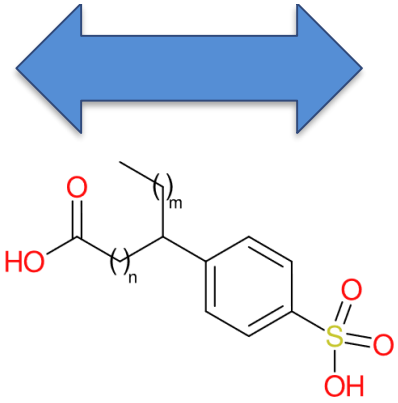
Our challenge? We have many unknowns …



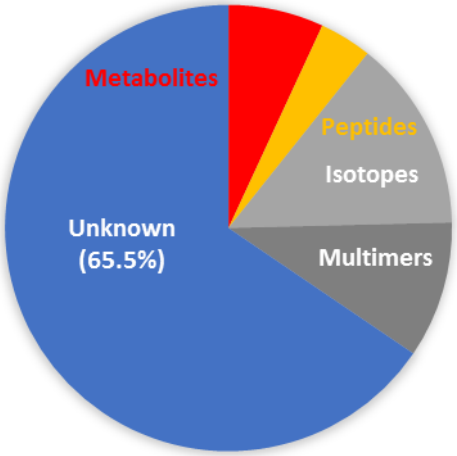
Wastewater







SPACs; n+m>=0



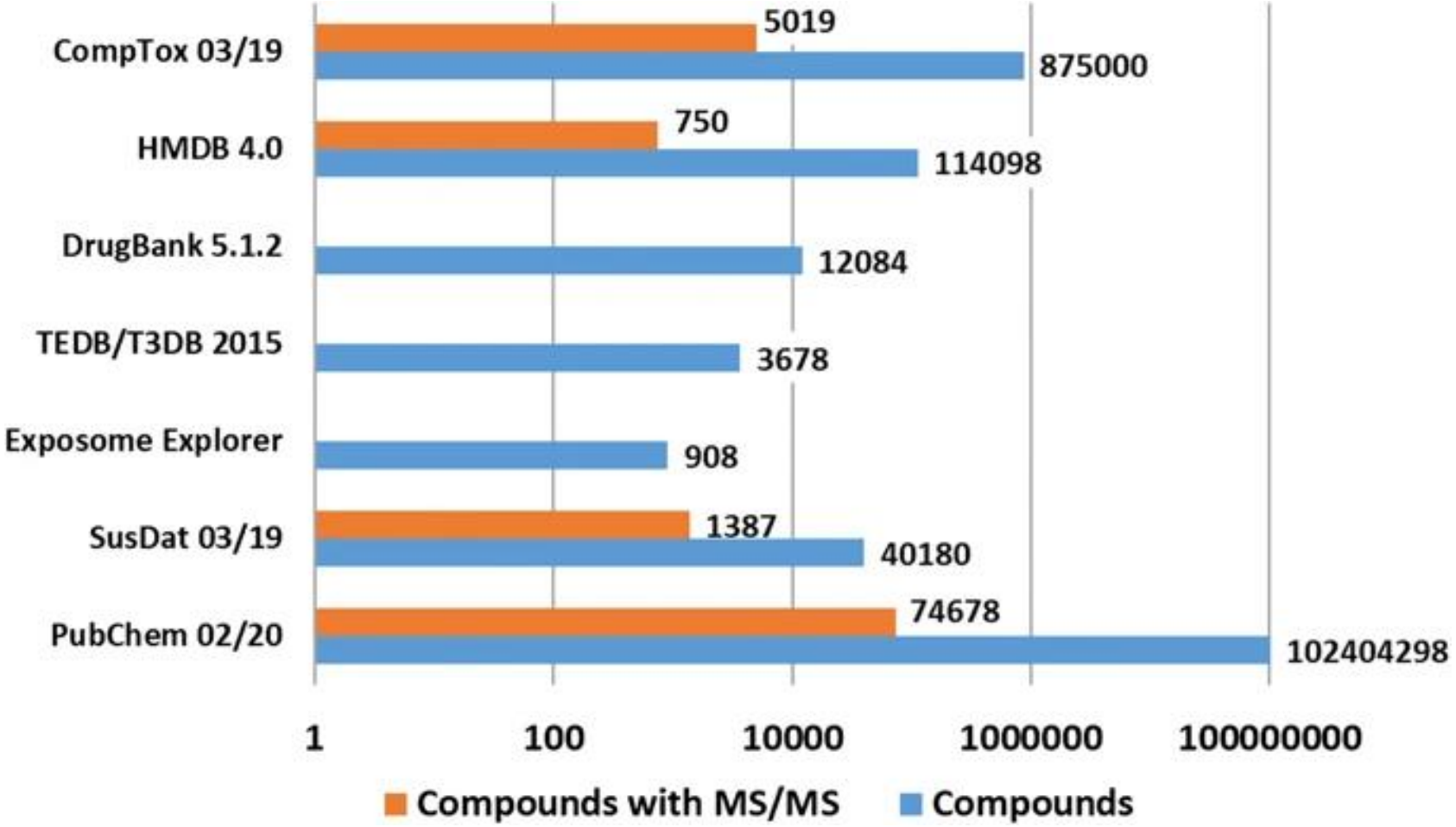
Cells

(l) Data from Schymanski *et al* 2014, ES&T DOI: 10.1021/es4044374. (r) *E. coli* data provided by N. Zamboni, IMSB, ETH Zürich.

…and insufficient reference data (mass spectra)

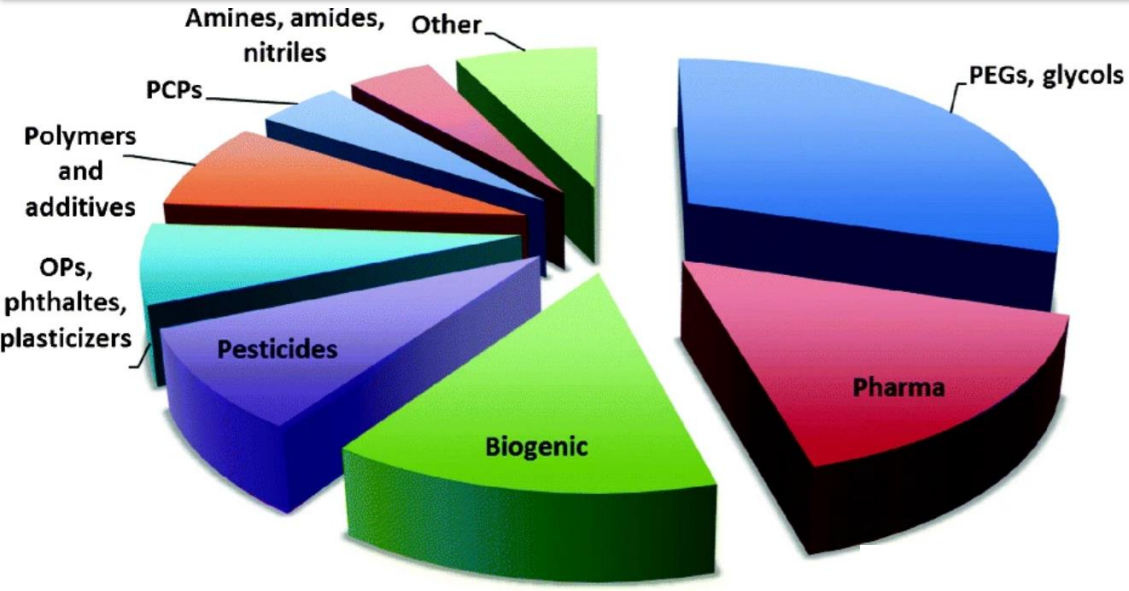
MEDIZINISCHE UNIVERSITÄT INNSBRUCK

- Mass spectra are our “fingerprints” for identification
- Only available for ~0.1-4 % of Exposomics-relevant resources



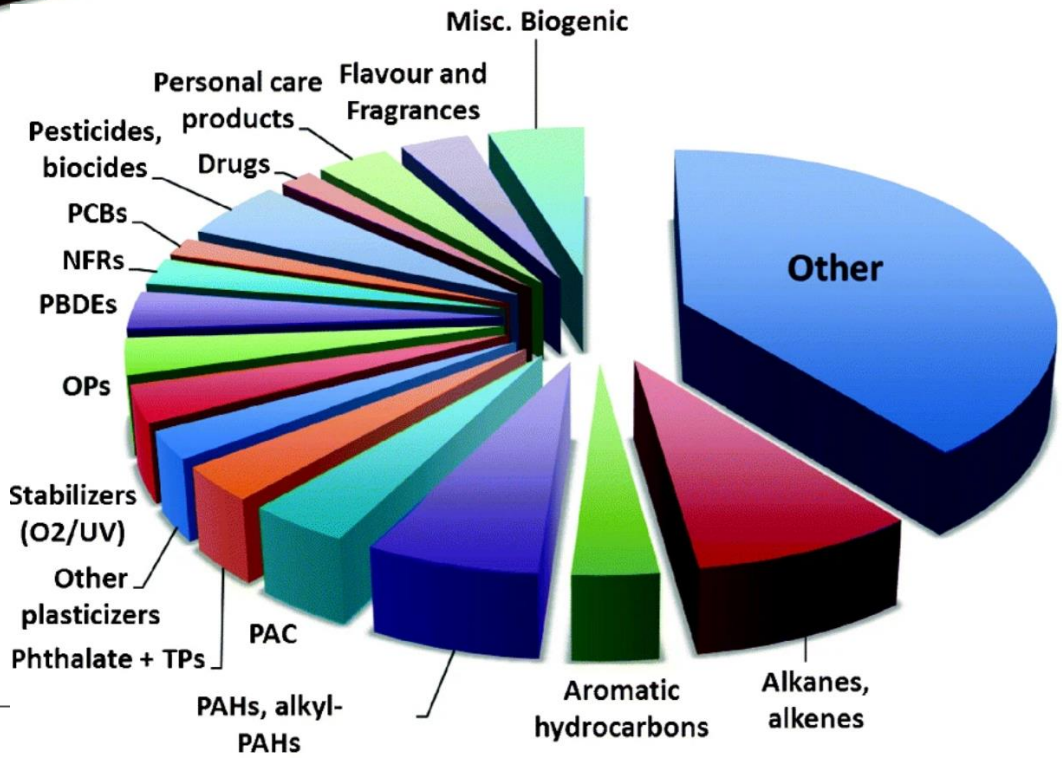
H. Oberacher *et al.* (2020) Environmental Sciences Europe 32: 43. DOI: 10.1186/s12302-020-00314-9

What we measure (in dust): LC vs GC



LC-MS
(n=969)

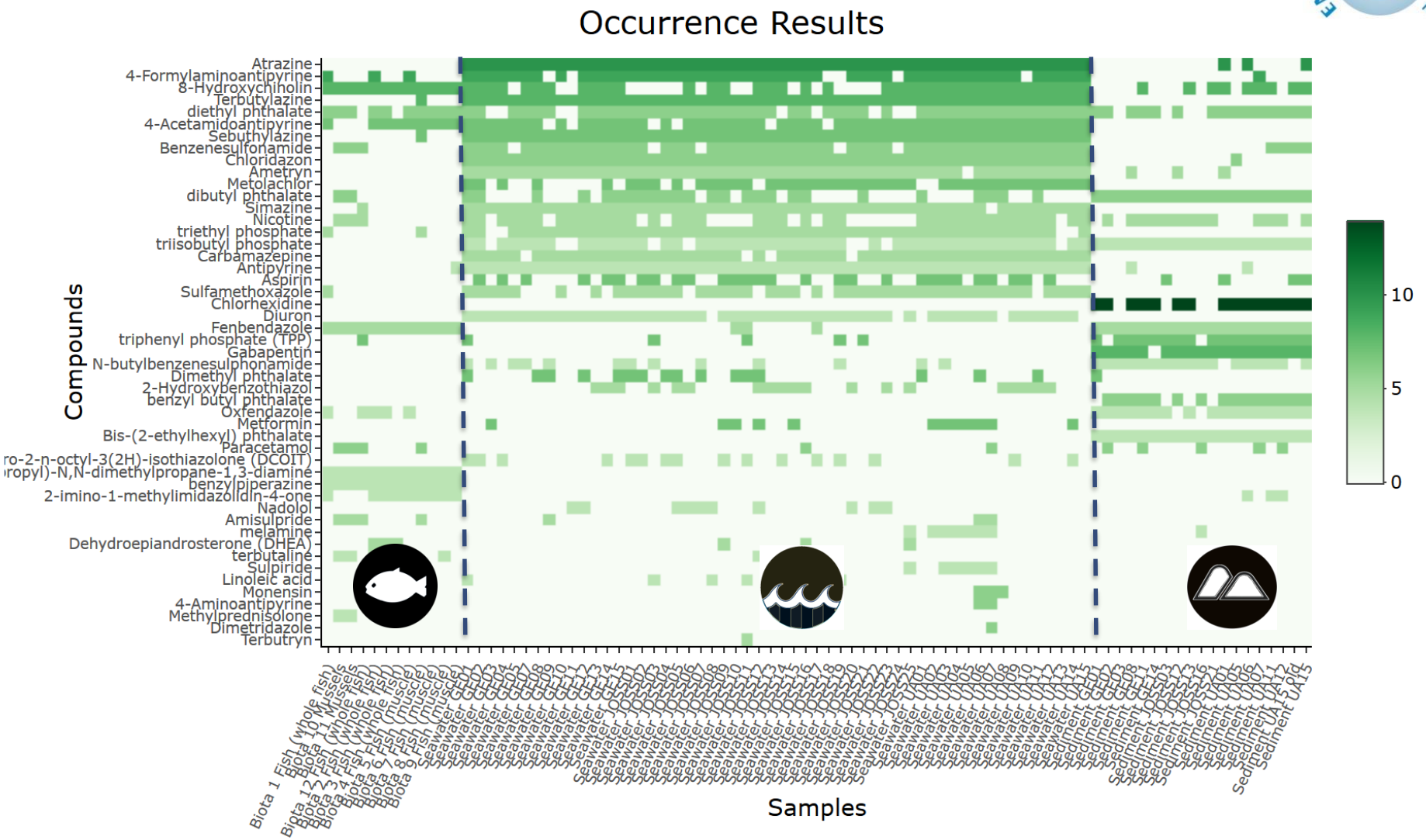
GC-MS
(n=592)



Rostkowski *et al* 2019. DOI: 10.1007/s00216-019-01615-6

What we measure in biota/water/sediment

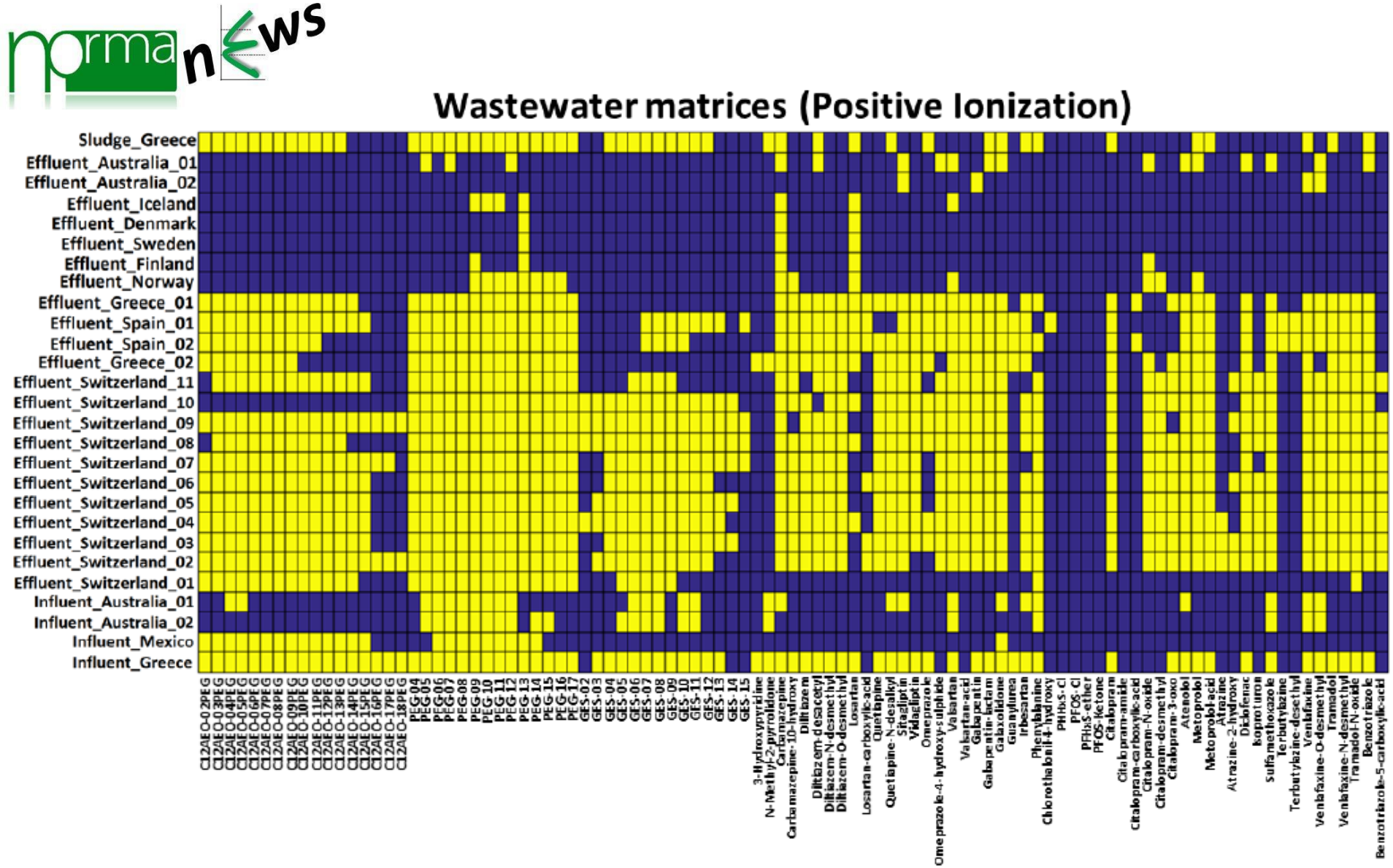
Retrospective screening of REACH chemicals in Black Sea samples (various matrices)



Alygizakis NA *et al* (2019) DOI: 10.1016/j.trac.2019.04.008

Interactive heatmap at http://norman-data.eu/NORMAN-REACH

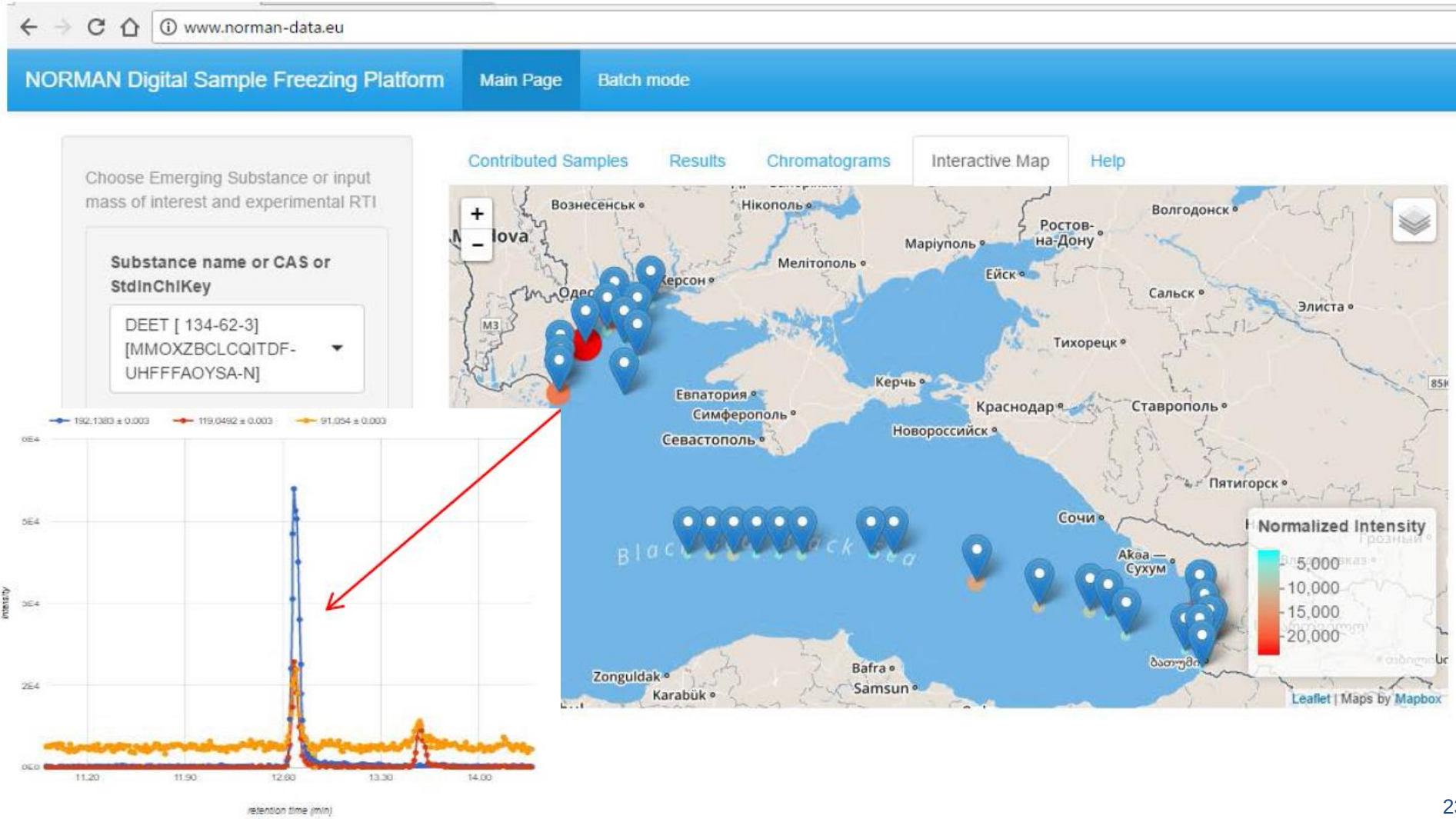
Emerging contaminants in different countries



Alygizakis NA *et al* (2018) DOI: 10.1021/acs.est.8b00365 and DOI: 10.5281/zenodo.2623815

NORMAN Digital Sample Freezing Platform

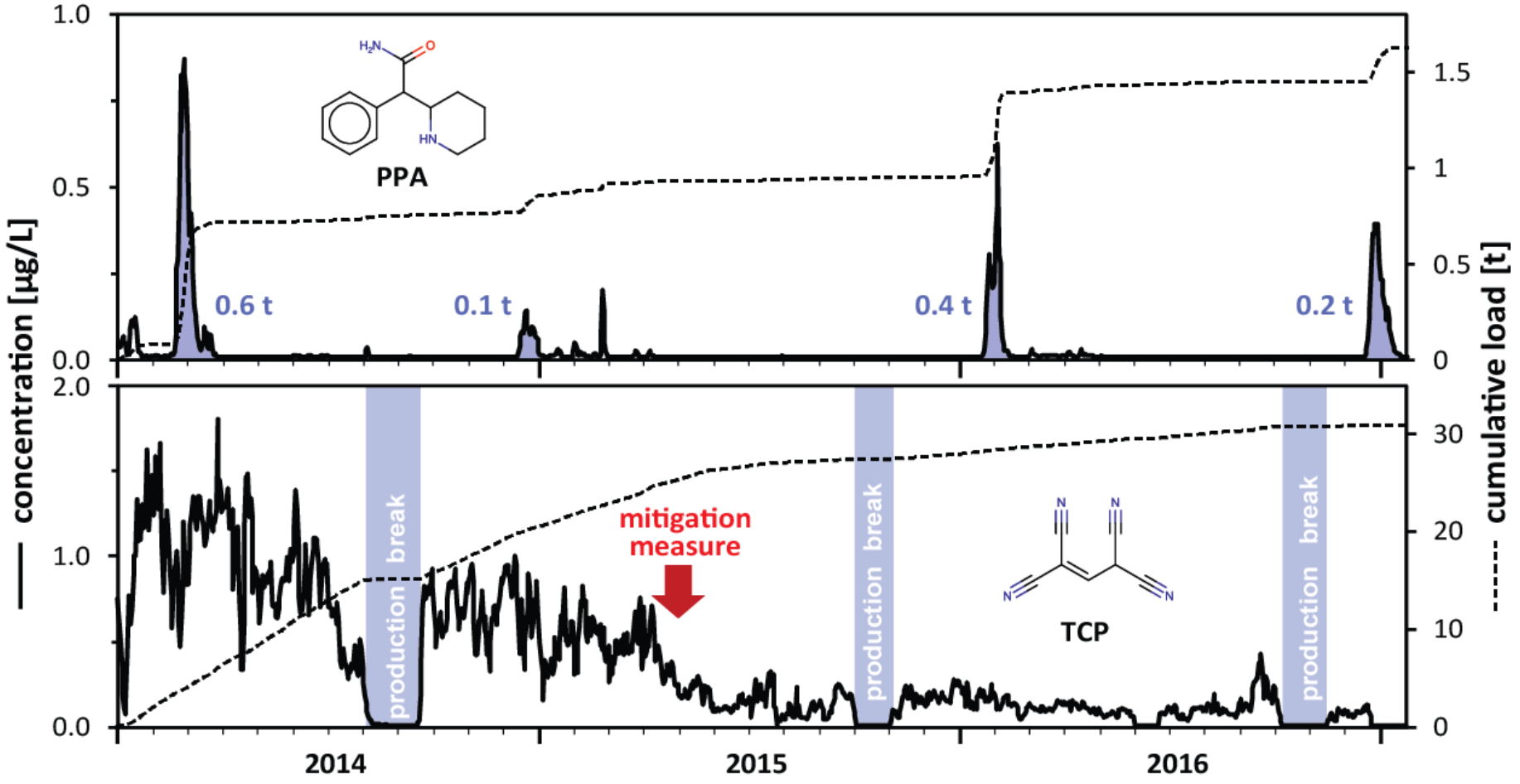
"Live" retrospective screening of known and unknown chemicals in European samples (various matrices)



http://norman-data.eu/ and Alygizakis NA *et al* (2019) DOI: 10.1016/j.trac.2019.04.008.

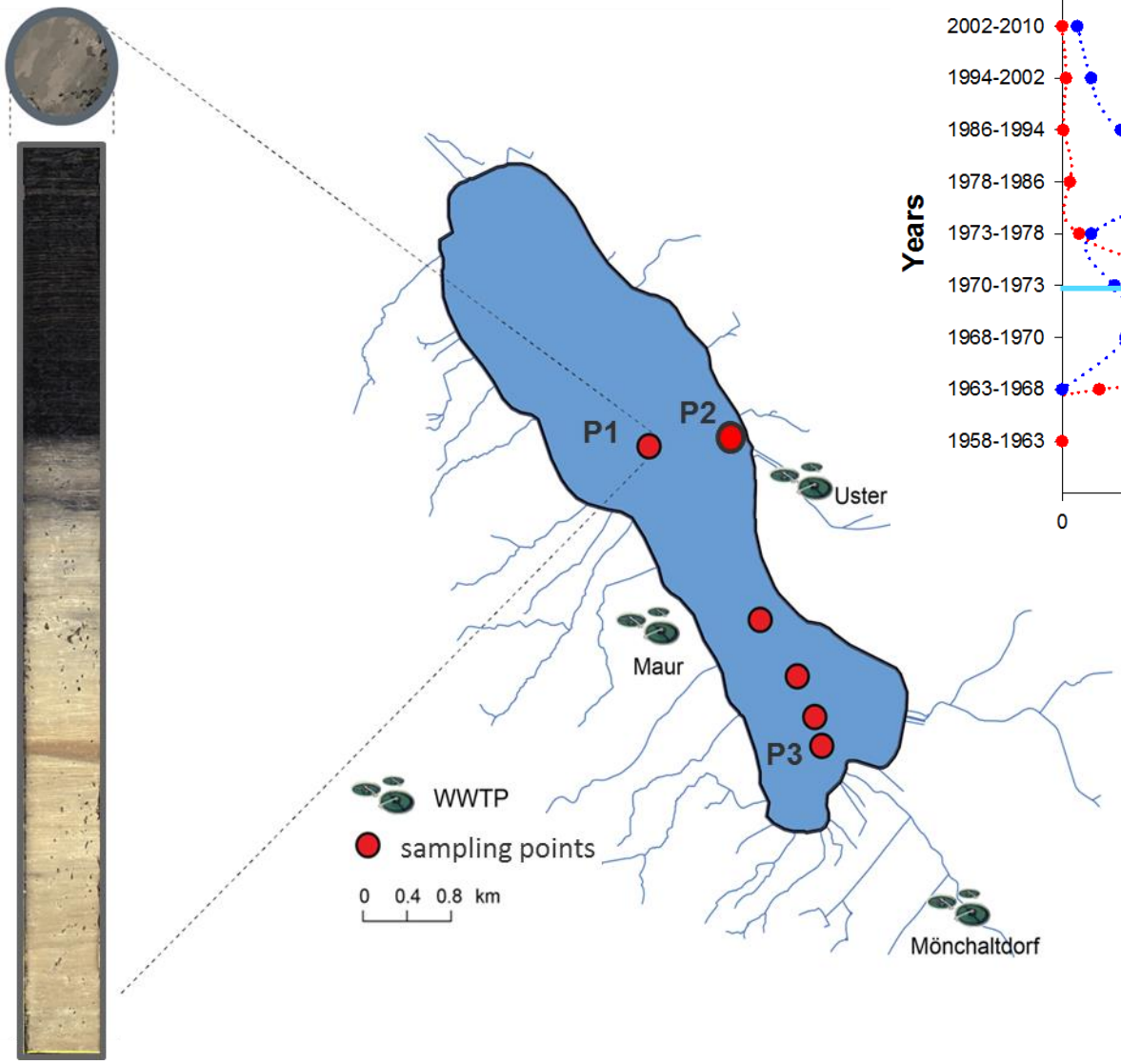
Real-time Monitoring of the Rhine River

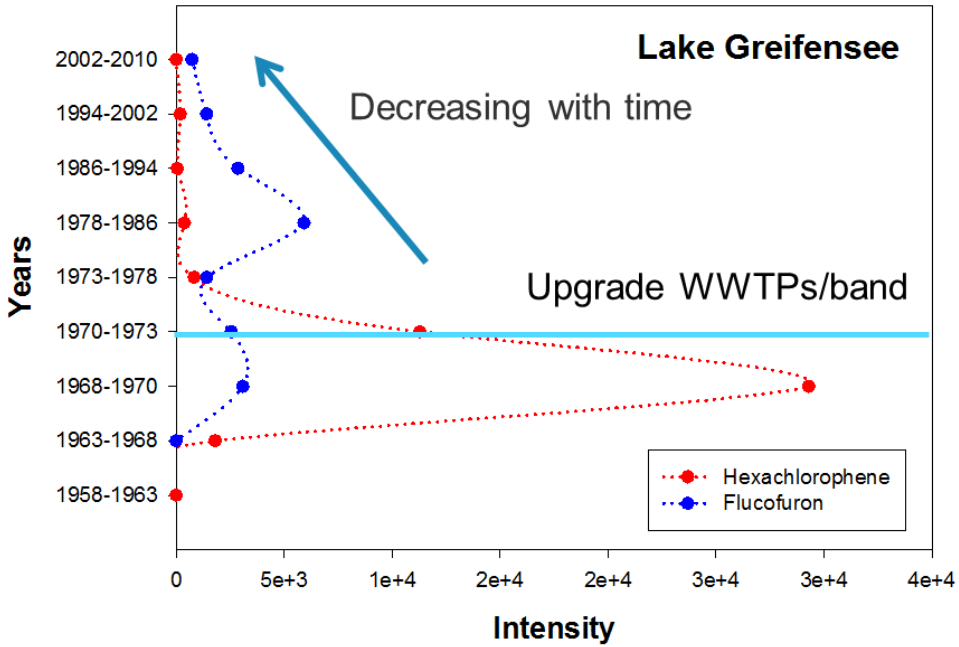
Previously unknown chemicals detected due to “stand-out” patterns



Hollender, Schymanski, Singer & Ferguson, 2018, ES&T Feature, 51:20, 11505-11512. DOI: 10.1021/acs.est.7b02184

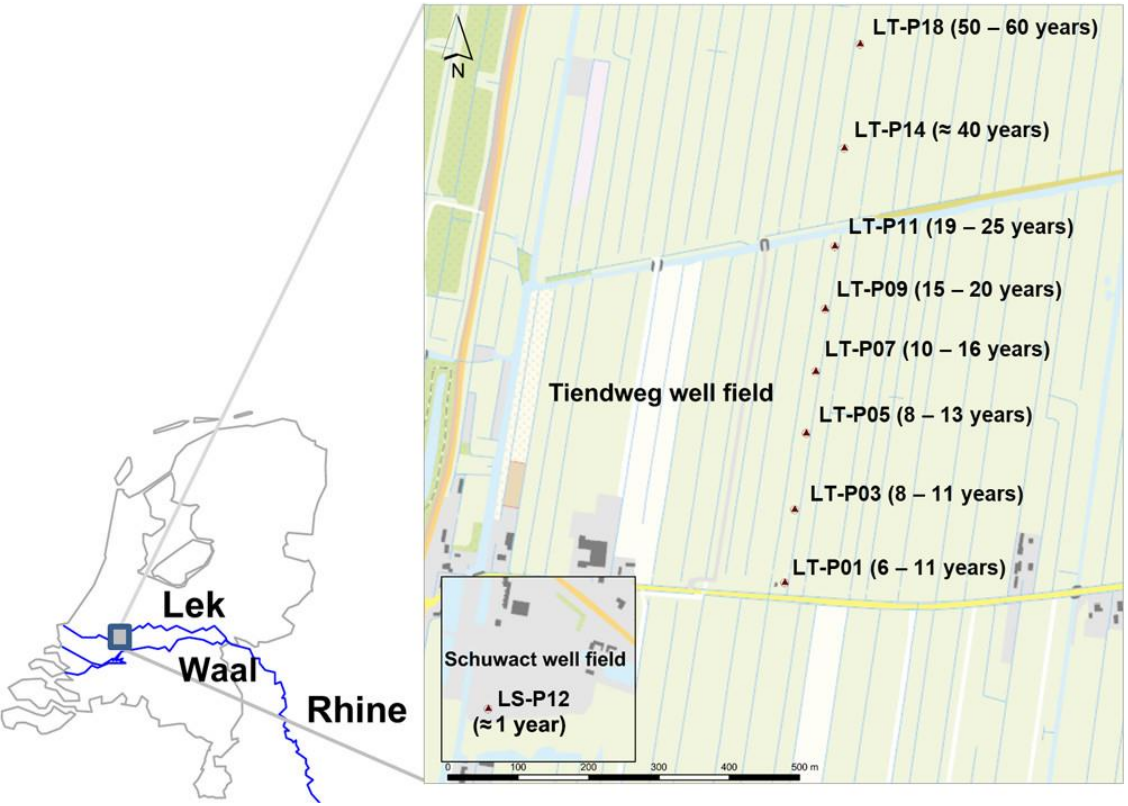
Historical Contamination in Lake Sediments

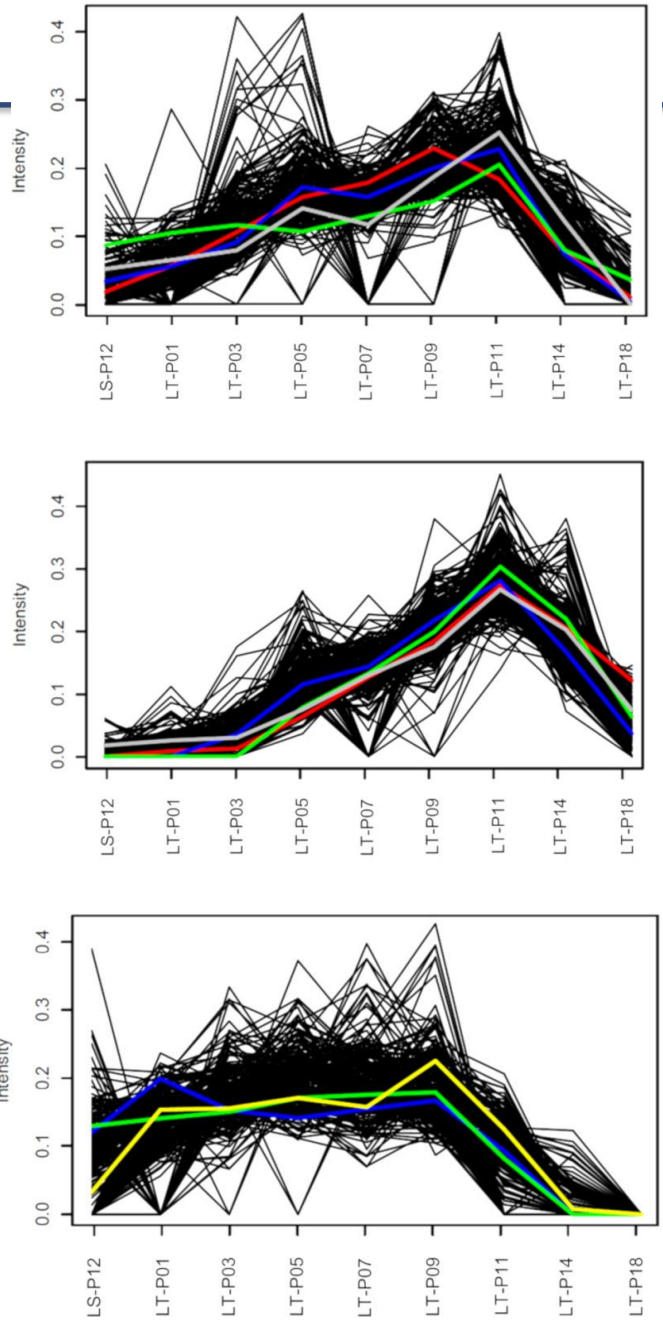




Chiaia-Hernandez *et al.* Anal. Bioanal. Chem. 2014, 406 (28), pp 7323-7335. DOI: 10.1007/s00216-014-8166-0

Micropollutant Time Trends in Riverbank Filtration Systems





Albergamo *et al*. 2019 *Environ. Sci. Technol.* 53 (13), 7584-7594, DOI: 10.1021/acs.est.9b01750

Analytical Methods: Target vs Non-target

KNOWNS → **TARGET ANALYSIS** → Targets found

SUSPECTS → **SPECTRUM SEARCH** → Spectral match

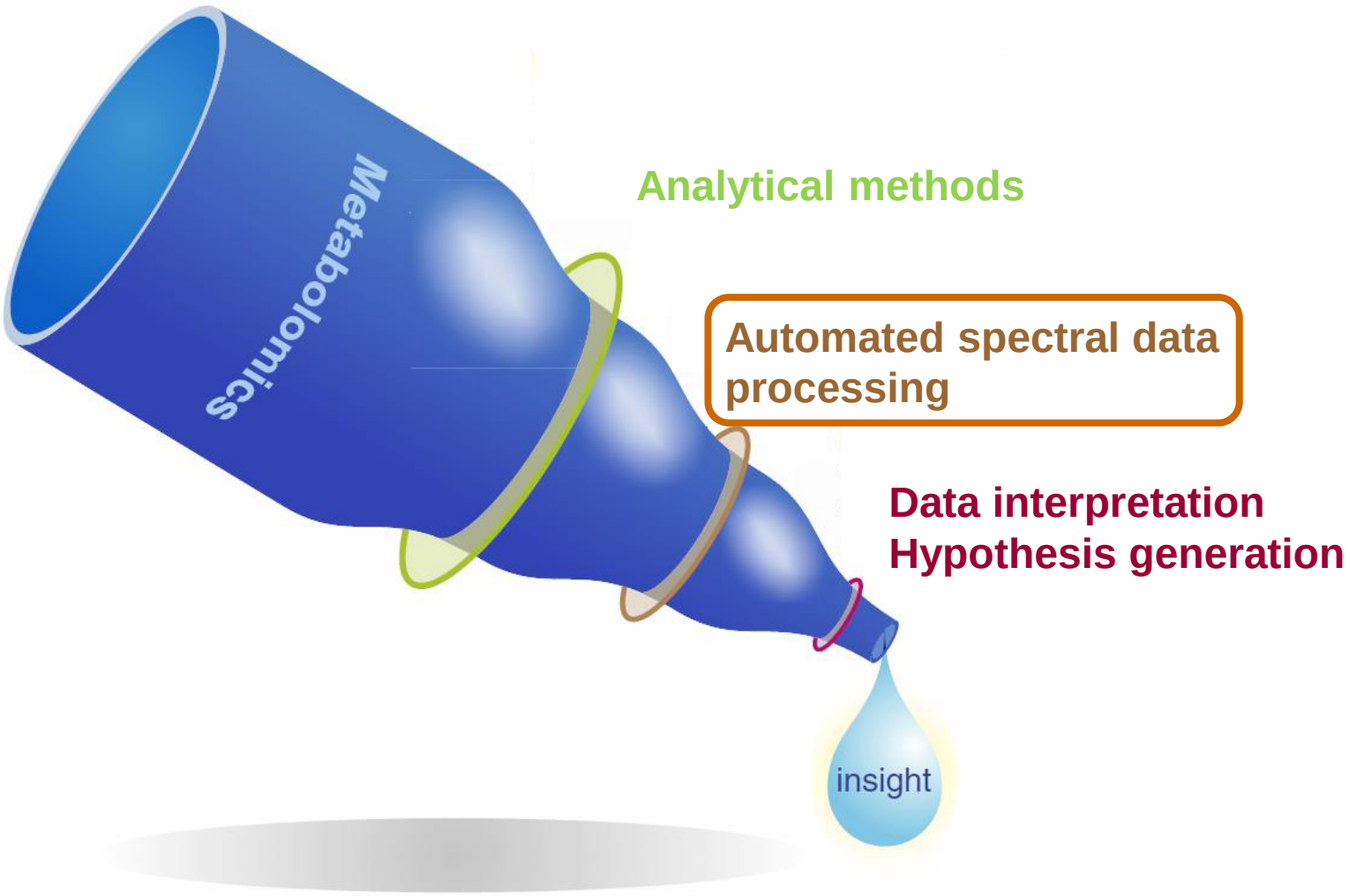
SUSPECTS → **SUSPECT SCREENING** → Suspects found

No Prior Knowledge → **NON-TARGET SCREENING** → Masses of interest → (Molecular formula) → **DATABASE SEARCH** / **STRUCTURE GENERATION**

Candidate selection (retention time, MS/MS, calculated properties)

Time, Effort & Number of Compounds….

Our Aim: Generating Insight from Measurements



Mod. From Fig. 2, Sevin *et al* 2015, Current Opinion in Biotechnology. DOI: 10.1016/j.copbio.2014.10.001

Sampling  extraction (SPE)  HPLC separation  HR-MS/MS 

Conversion (Proteowizard) and Peak Picking (enviPick, xcms, MZmine, …)

Detection of blank/blind/noise/internal standards; time trend analysis (enviMass)

Target List

TARGET ANALYSIS

(enviMass, vendor software)

Suspect List (e.g. NORMAN, LMC, Eawag-PPS, ReSOLUTION)

SUSPECT SCREENING

Gather evidence (nontarget, ReSOLUTION, RMassBank)

NON-TARGET SCREENING

Componentization (nontarget)

Prioritization (enviMass)

Masses of interest

Molecular formula determination (enviPat, GenForm)

MS/MS Extraction (RMassBank)

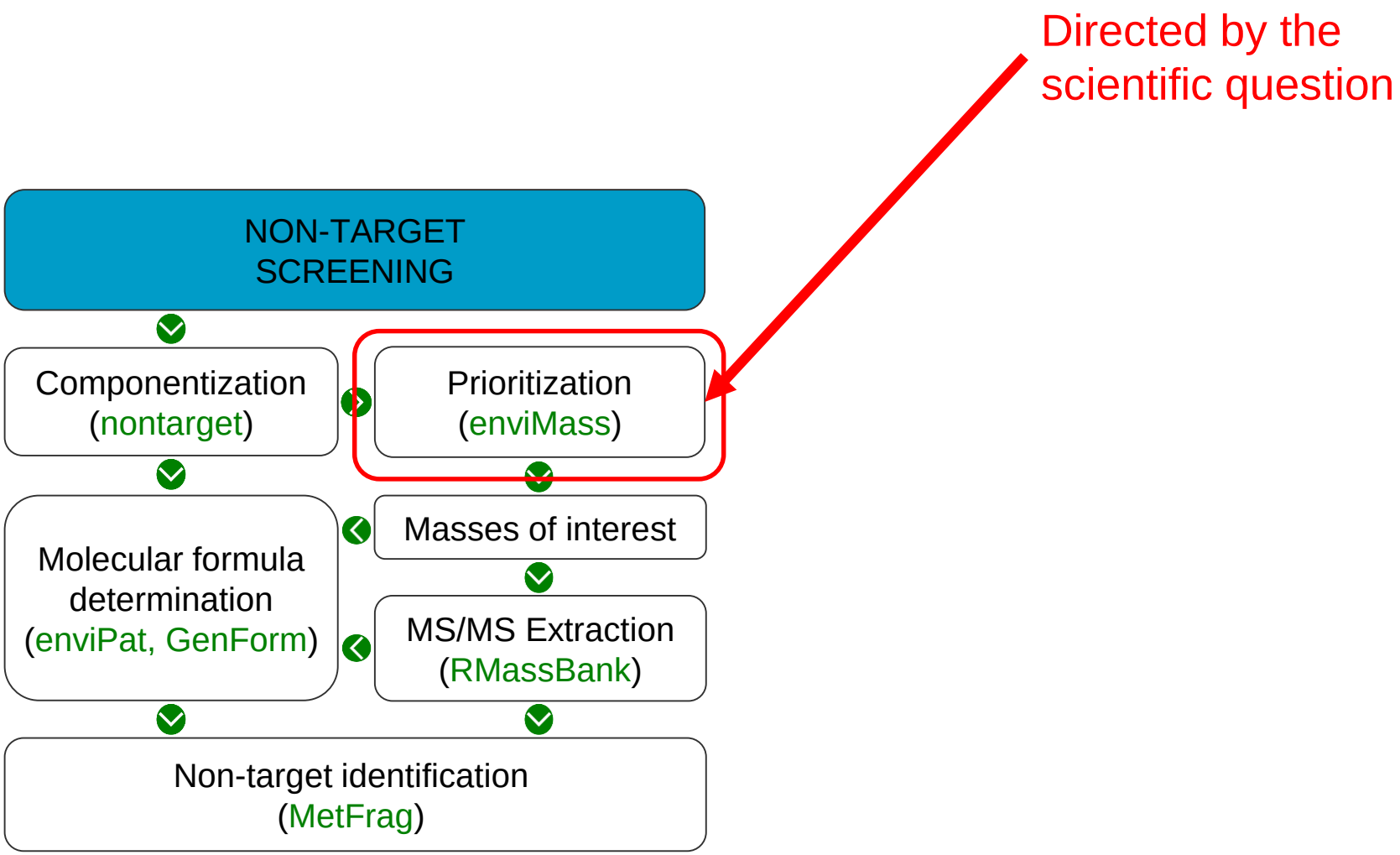
Non-target identification (MetFrag2.3, ReSOLUTION)

Interpretation, confirmation, peak inventory, confidence and reporting

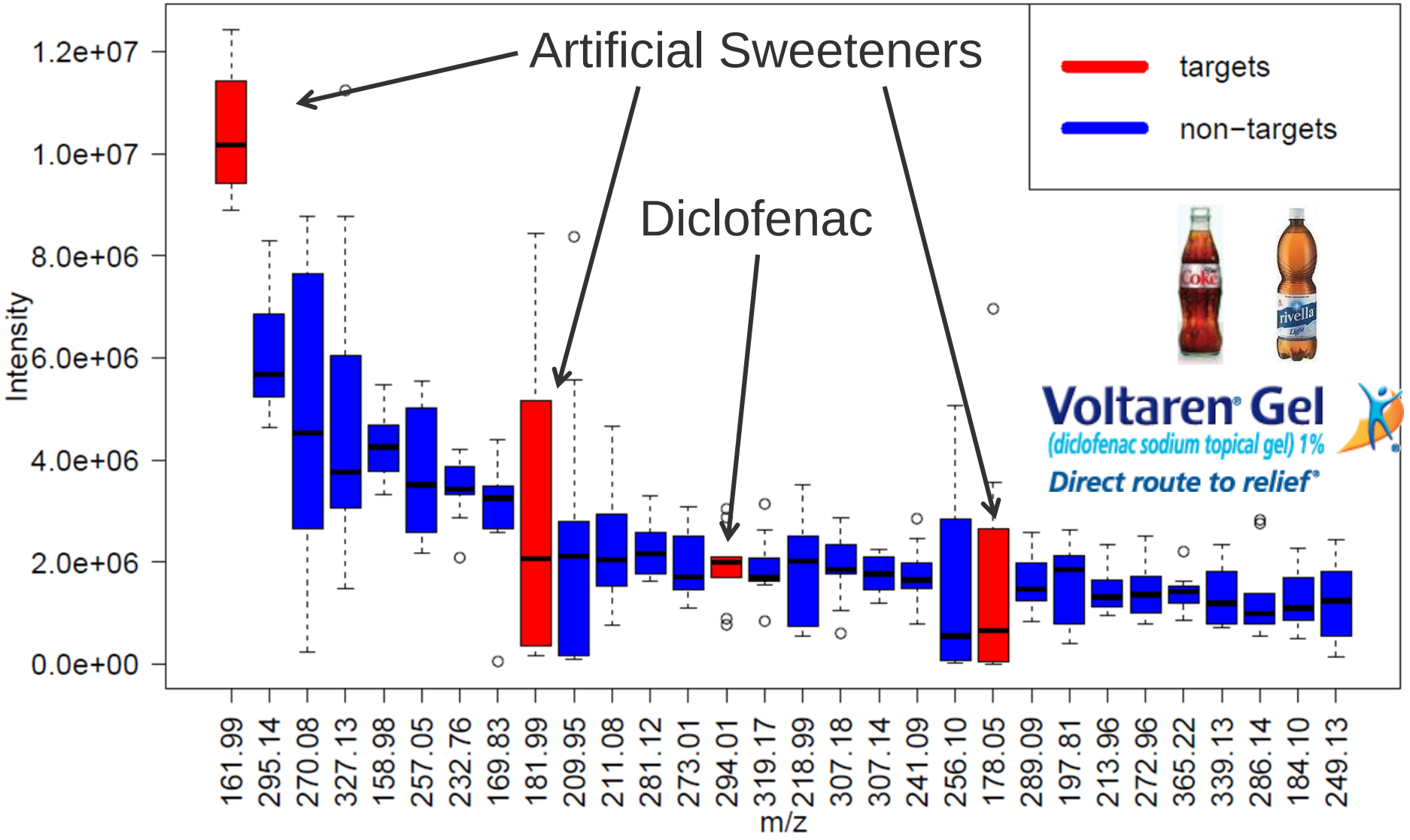
Altenburger *et al*, 2019, Env. Sci. Europe. DOI: 10.1186/s12302-019-0193-1

solutions

Non-target Identification: Where to start?



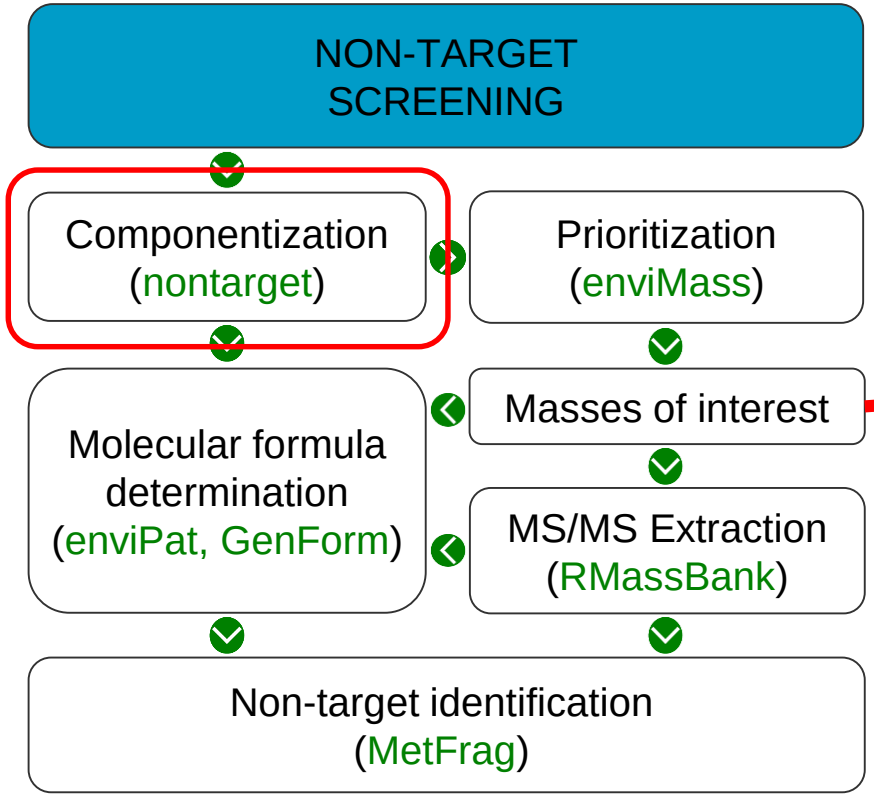
Targets, Non-targets and Isotopes (ESI-) by Intensity



Pictures: www.coca-cola-com; www.rivella.ch; www.voltargengel.com

Schymanski et al. 2014, ES&T, 48: 1811-1818. DOI: 10.1021/es4044374

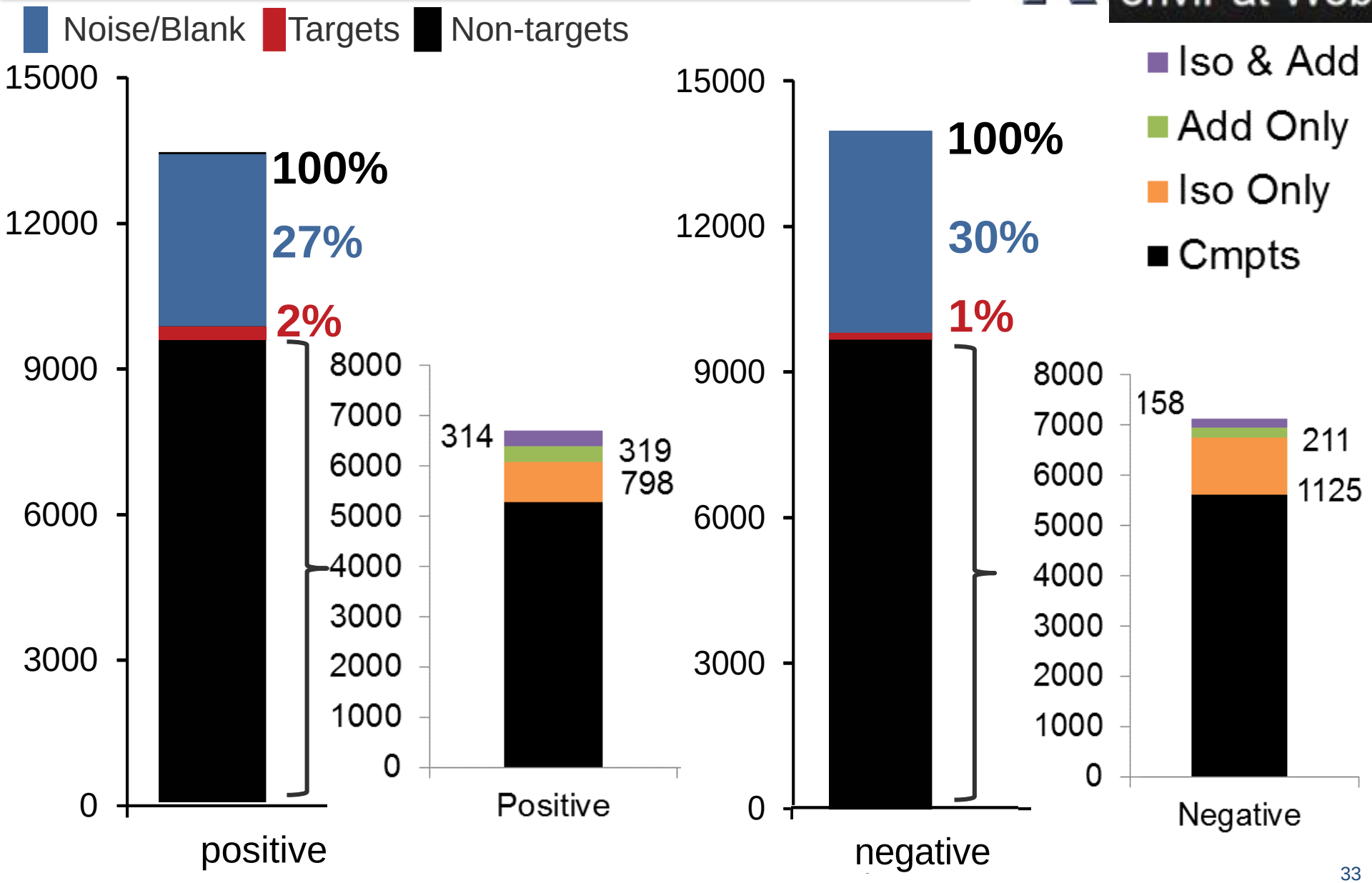
Non-target Identification: Where to start?



Centroid m/z	Intensity	Peak S/N	Scan Number	RT (min.)	Start Scan Number	Start RT (min.)	End Scan Number	End RT (min.)	Chrom. S/N
169.8336	3325231	5329.19	134	0.93	79	0.55	646	4.55	0.991
299.095	3170282	4921.75	1149	8.13	595	4.18	1597	11.31	0.973
365.1626	3203921	4917.57	2094	14.86	2017	14.31	2200	15.61	0.986
163.04	2891540	4754.39	792	5.58	79	0.55	3514	24.95	0.985
132.8678	3211435	4736.29	148	1.03	79	0.55	3514	24.95	0.938
309.1519	2837347	4531.15	2493	17.69	2233	15.84	2857	20.27	0.956
134.8651	3063484	4518.08	148	1.03	79	0.55	3514	24.95	0.951
234.7607	2748982	4266.01	155	1.08	79	0.55	415	2.92	0.994
311.095	2770672	4249.3	1114	7.88	763	5.37	1513	10.7	0.961
293.1747	2720875	4220.98	1688	11.95	1030	7.28	2185	15.5	0.988
257.0483	2577542	4130.58	750	5.28	316	2.21	1366	9.67	0.988
174.9557	2597792	4079.03	155	1.08	79	0.55	3514	24.95	0.864
213.9636	2352410	3890.96	645	4.54	631	4.44	778	5.48	0.995
167.8364	2376150	3808.14	134	0.93	79	0.55	1381	9.78	0.99
297.0798	2561181	3789.71	1170	8.27	679	4.78	1288	9.12	0.964
201.113	2299642	3706.57	1128	7.98	442	3.11	1696	12.01	0.984
310.1024	2335010	3645.29	1310	9.27	1288	9.12	1624	11.5	0.983
241.0716	2141622	3536.71	2514	17.84	1813	12.84	3514	24.95	0.855
374.1311	2580159	3382.28	771	5.43	709	5	898	6.34	0.991

Gather Experimental Evidence

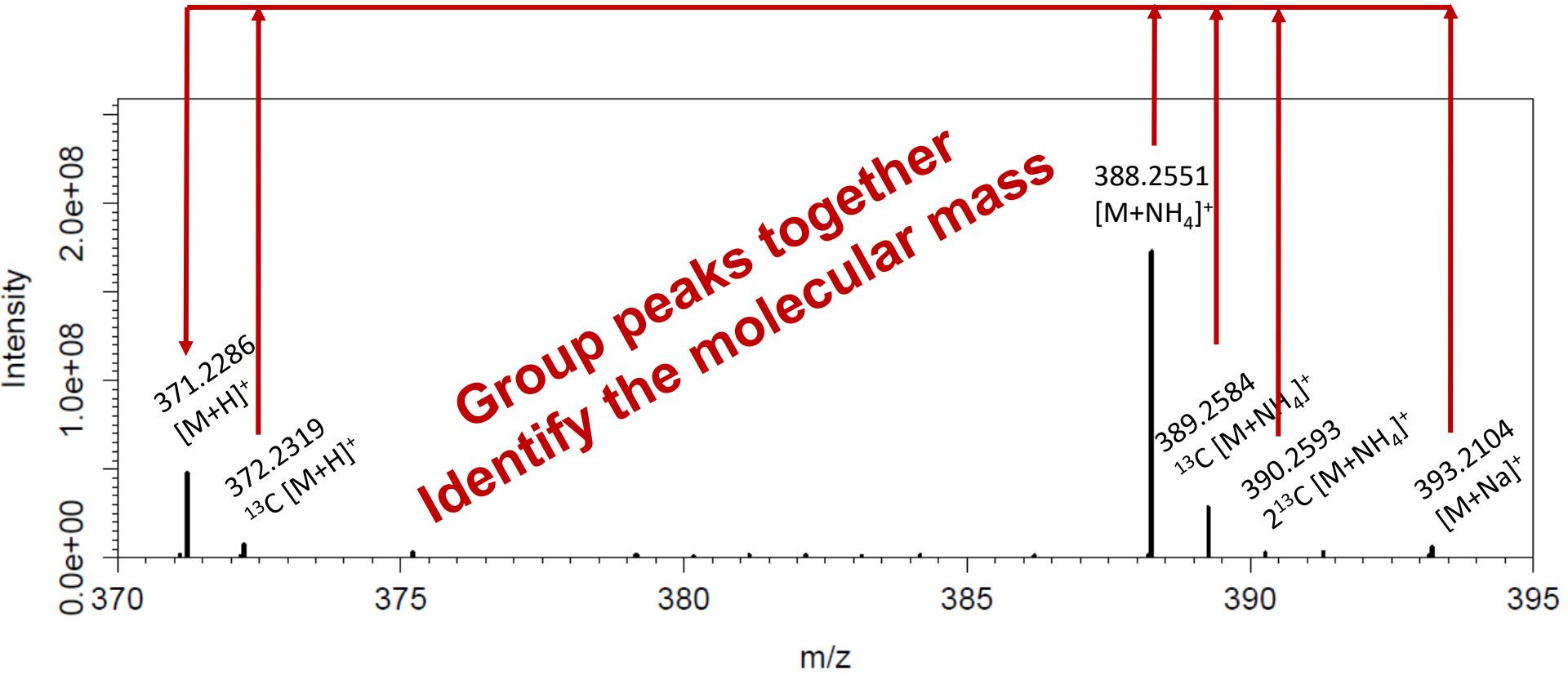
Grouping Adducts and Isotopes



Schymanski et al. 2014, ES&T, 48: 1811-1818. DOI: 10.1021/es4044374

Gathering Evidence for Identification I

Determining the molecular mass and elements, adducts present nontarget



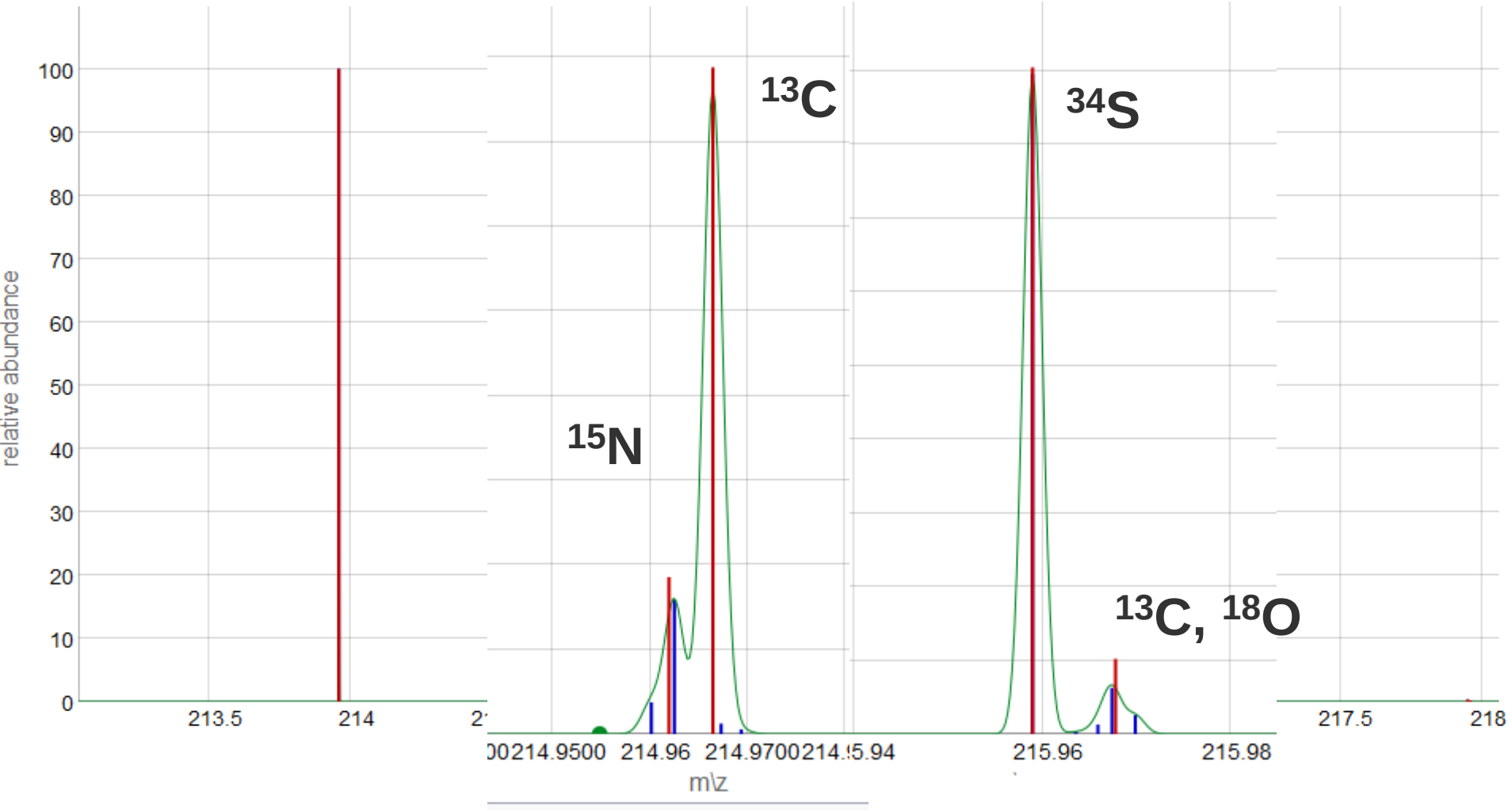
Schymanski *et al*. 2015, ABC, DOI: 10.1007/s00216-015-8681-7
M. Loos, *et al*. 2015, DOI: 10.1021/acs.analchem.5b00941

http://www.eawag.ch/forschung/uchem/software/
http://cran.r-project.org/web/packages/nontarget/
http://cran.r-project.org/web/packages/enviPat/

Gathering Evidence for Identification II

enviPat Web

Detecting the presence of elements with enviPat and nontarget



M. Loos, *et al*. 2015, DOI: 10.1021/acs.analchem.5b00941

Image © www.seanoakley.com/

http://www.envipat.eawag.ch/ http://cran.r-project.org/web/packages/enviPat/

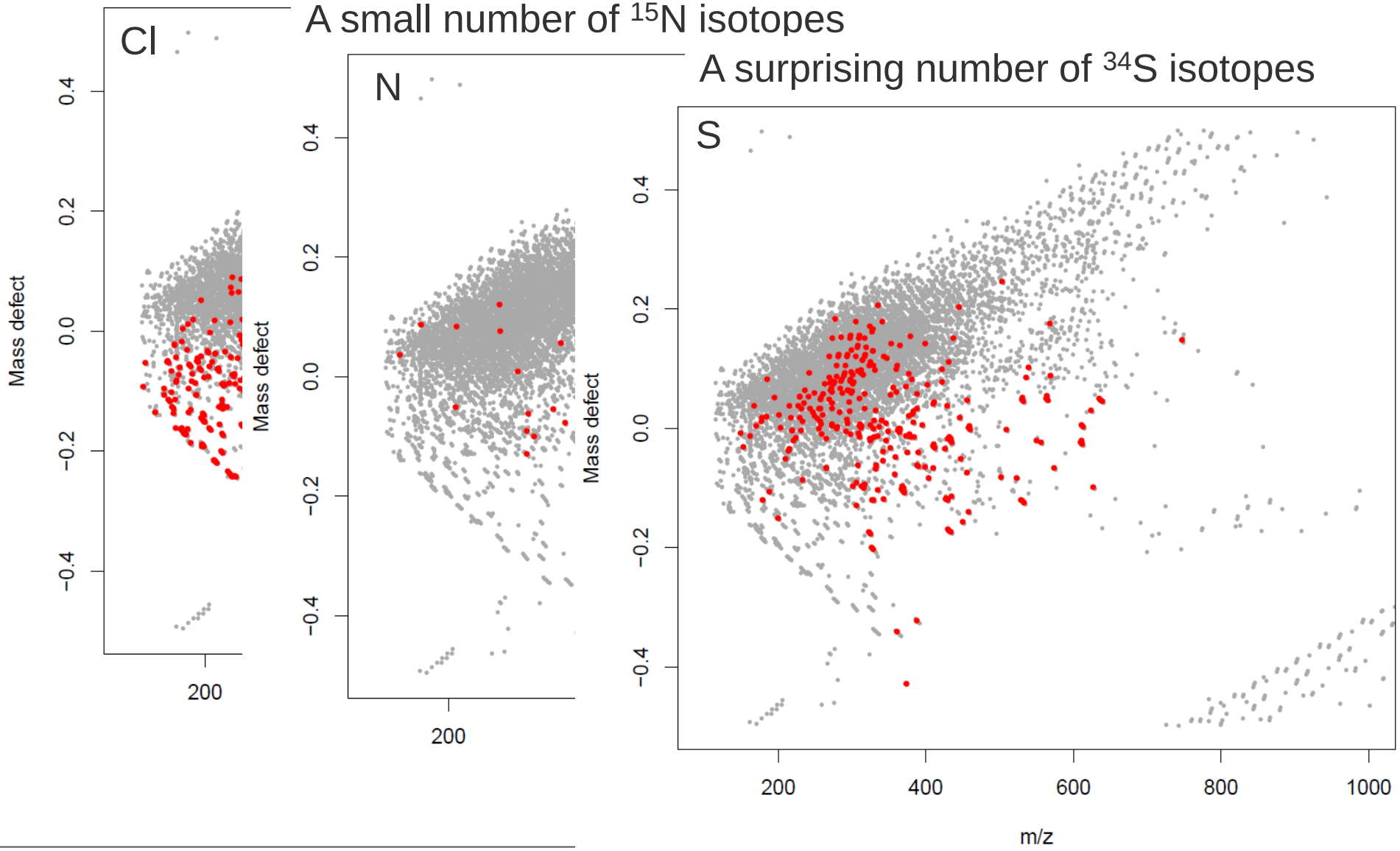
Detecting Isotope Signals in Samples

"Classic" environmental strategy: Cl isotopes

nontarget

A small number of ^{15}N isotopes

A surprising number of ^{34}S isotopes



Schymanski et al. 2014, ES&T, 48: 1811-1818. DOI: 10.1021/es4044374

Peak Grouping in Workflows

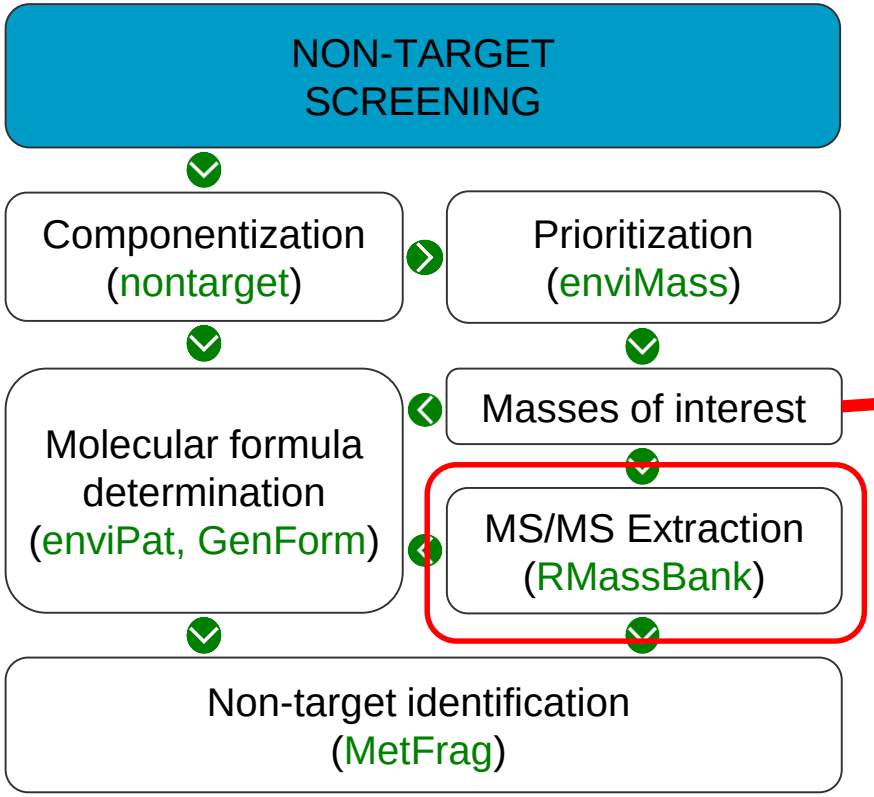
This can be done automatically with nontarget / enviMass (and others)

m.z	max_int	RT	peak ID	group ID	isotope(s)
589.3655	47715916	1281.84	40	304	13C
329.2335	46938304	1232.32	41	0	none
209.0853	44881960	1204.91	42	29	13C/34S

m/z	int	ret	peak ID	adduct(s)
315.1726	1.73E+08	1035.33	74	none
295.2268	1.71E+08	1399.63	75	M+H<->M+Na
288.2532	1.69E+08	1359.84	76	M+H<->M+Na
119.019	1.66E+08	570.906	77	none
315.1057	1.63E+08	965.48	78	M+H<->M+Na
212.1493	1.63E+08	608.964	79	M+NH4<->M+H//M+NH4<->M+Na//M+NH4<->M+K
327.0081	1.6E+08	1244.89	80	M+H<->M+Na//M+H<->M+NH4
155.1591	1.6E+08	689.237	81	none
375.2109	1.58E+08	684.805	82	none
329.0052	1.58E+08	1[illegible]	83	M+H<->M+Na//M+H<->M+NH4
356.1768	1.57E+08	1000.85	84	none
240.1523	1.54E+08	682.152	85	M+H<->M+Na//M+H<->M+NH4//M+H<->M+K
300.2016	1.52E+08	686.578	86	none
404.2068	1.51E+08	1224.56	87	M+K<->M+H//M+NH4<->M+H//M+NH4<->M+Na//M+NH4<->M+K
219.1167	1.5E+08	1167.08	88	M+H<->M+Na
158.154	1.45E+08	1211.29	89	M+H<->M+Na

This information can be used as input later…

Non-target Identification: Where to start?



Centroid m/z	Intensity	Peak S/N	Scan Number	RT (min.)	Start Scan Number	Start RT (min.)	End Scan Number	End RT (min.)	Chrom. S/N
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365.1626	3203921	4917.57	2094	14.86	2017	14.31	2200	15.61	0.986
163.04	2891540	4754.39	792	5.58	79	0.55	3514	24.95	0.985
132.8678	3211435	4736.29	148	1.03	79	0.55	3514	24.95	0.938
309.1519	2837347	4531.15	2493	17.69	2233	15.84	2857	20.27	0.956
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311.095	2770672	4249.3	1114	7.88	763	5.37	1513	10.7	0.961
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297.0798	2561181	3789.71	1170	8.27	679	4.78	1288	9.12	0.964
201.113	2299642	3706.57	1128	7.98	442	3.11	1696	12.01	0.984
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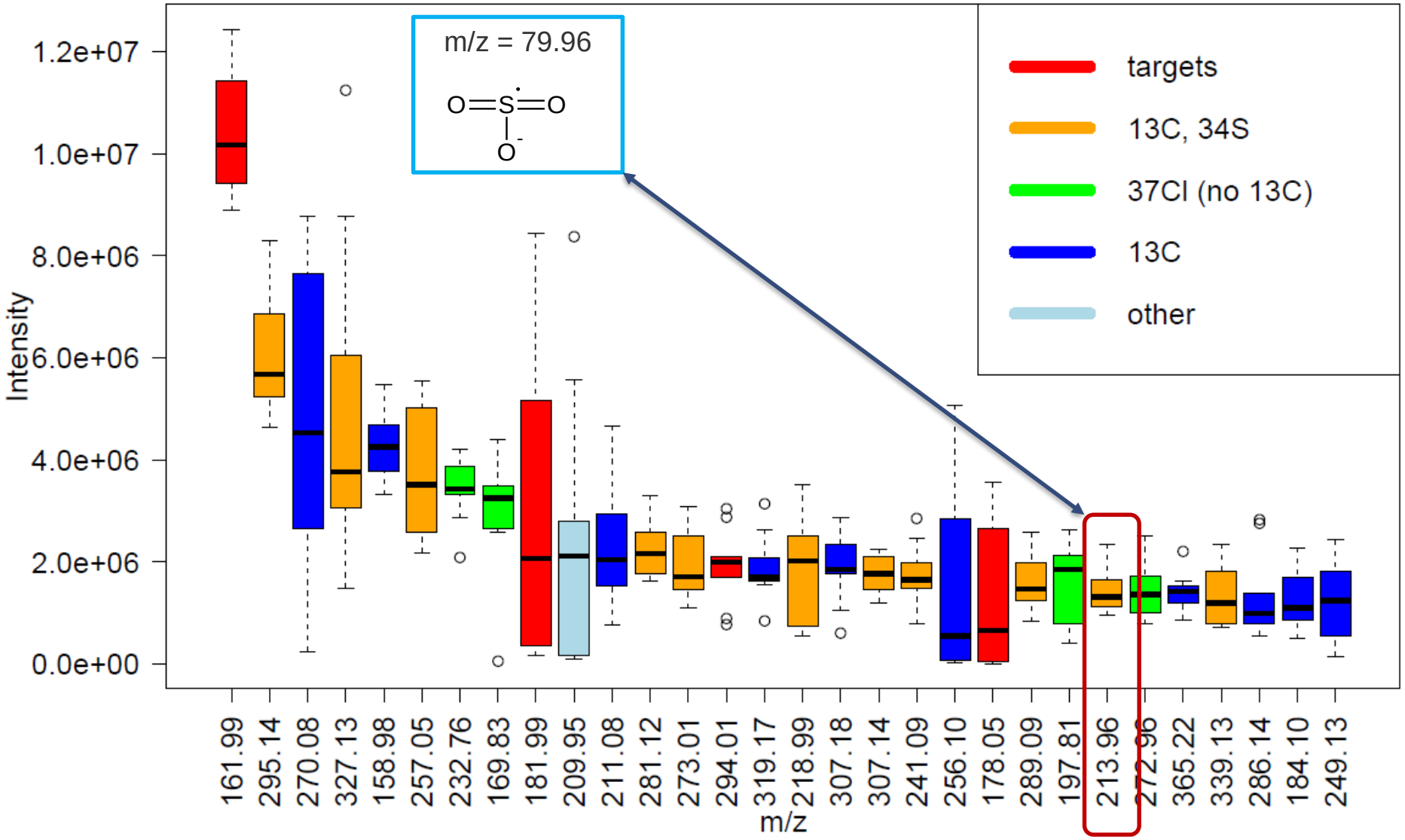
241.0716	2141622	3536.71	2514	17.84	1813	12.84	3514	24.95	0.855
374.1311	2580159	3382.28	771	5.43	709	5	898	6.34	0.991

Gather Evidence

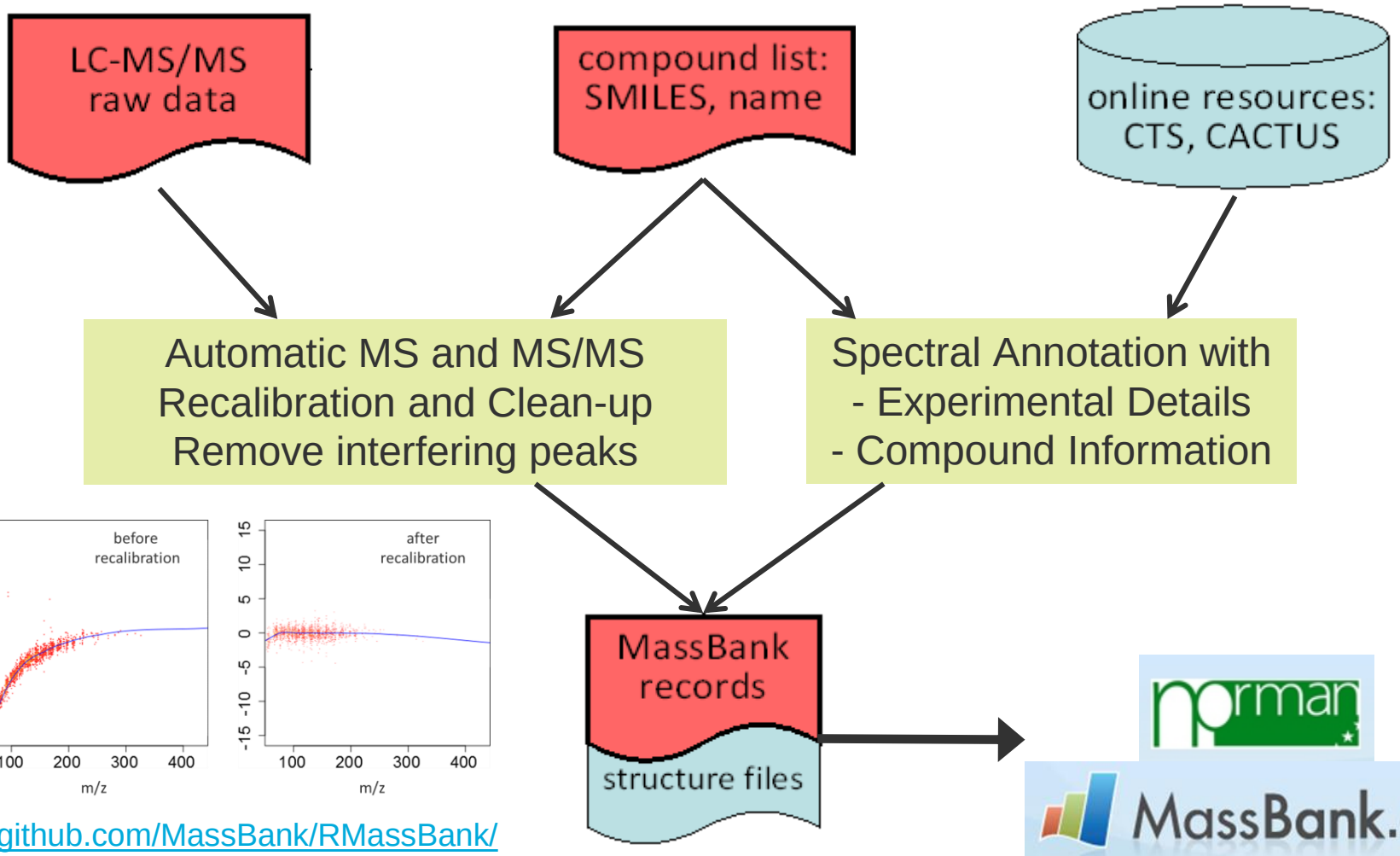
Targets, Non-targets and Isotopes (ESI-)



Schymanski et al. 2014, ES&T, 48: 1811-1818. DOI: 10.1021/es4044374

MS2: Extracting Mass Spectra I

RMassBank

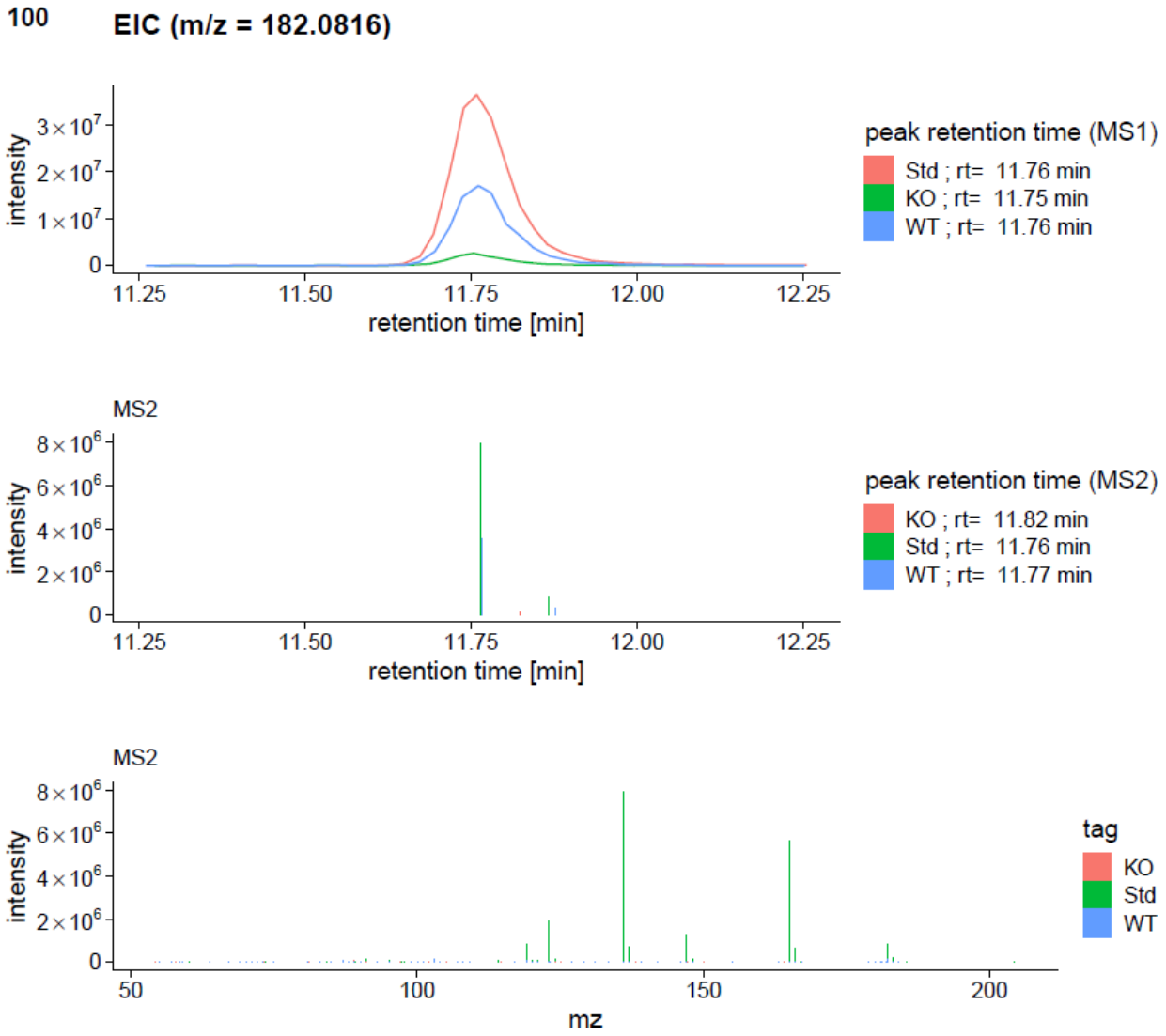


https://github.com/MassBank/RMassBank/
http://bioconductor.org/packages/RMassBank/

Stravs, Schymanski, Singer and Hollender, 2013,
Journal of Mass Spectrometry, 48, 89–99. DOI: 10.1002/jms.3131

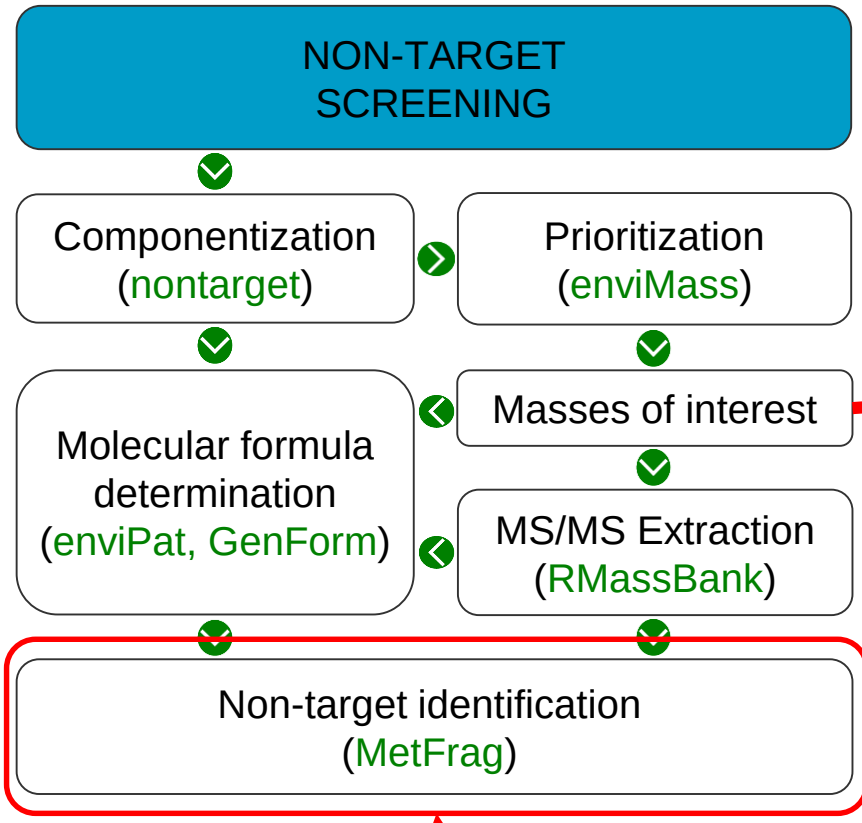
MS2: Extracting Mass Spectra II

https://git-r3lab.uni.lu/eci/shinyscreen



Anjana Elapavalore, Mira Narayanan, Todor Kondic, Jessy Krier, Hiba Mohammed Taha.

Non-target Identification: Next Step: Candidates!



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134.8651	3063484	4518.08	148	1.03	79	0.55	3514	24.95	0.951
234.7607	2748982	4266.01	155	1.08	79	0.55	415	2.92	0.994
311.095	2770672	4249.3	1114	7.88	763	5.37	1513	10.7	0.961
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257.0483	2577542	4130.58	750	5.28	316	2.21	1366	9.67	0.988
174.9557	2597792	4079.03	155	1.08	79	0.55	3514	24.95	0.864
213.9636	2352410	3890.96	645	4.54	631	4.44	778	5.48	0.995
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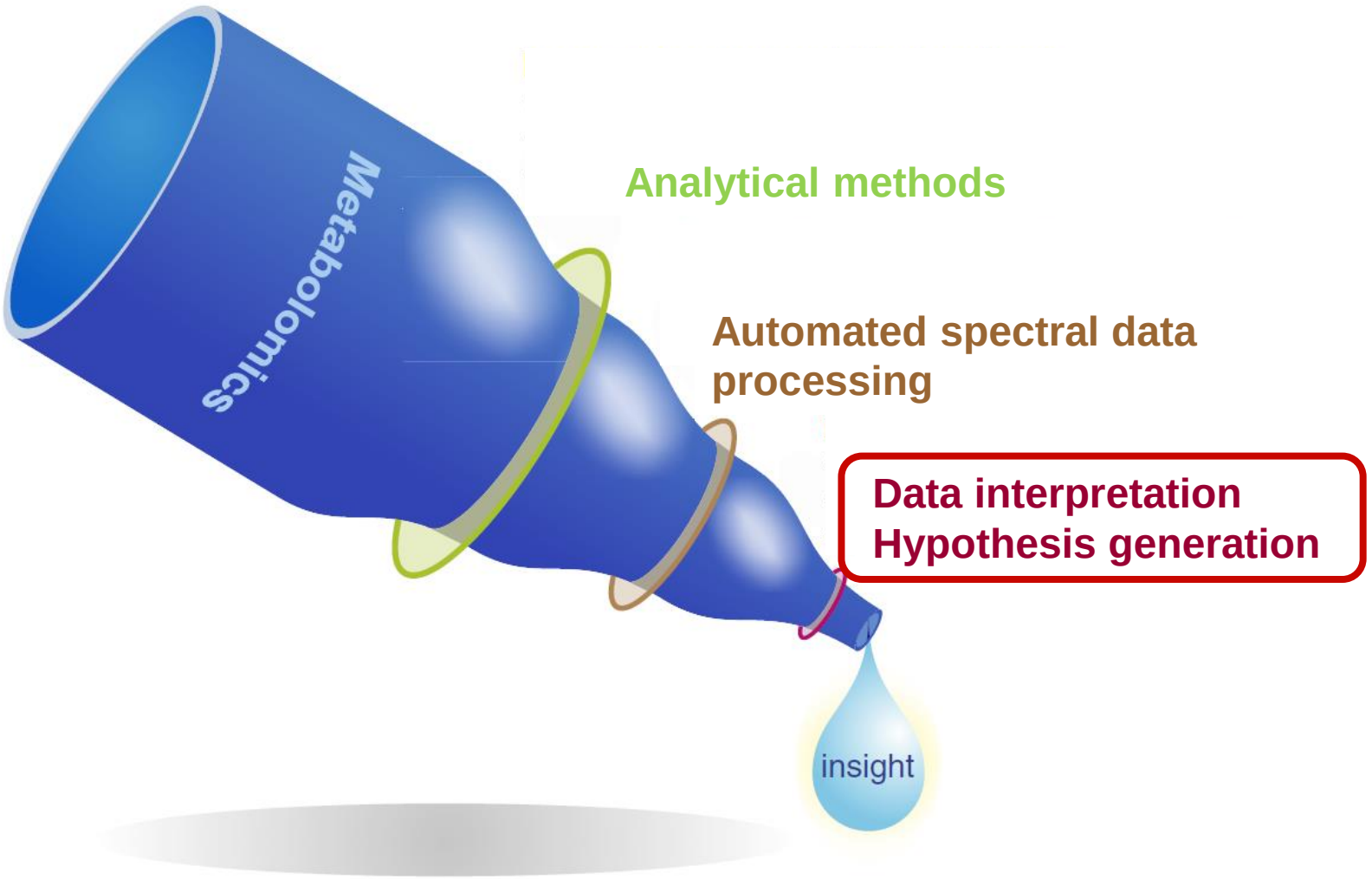
297.0798	2561181	3789.71	1170	8.27	679	4.78	1288	9.12	0.964
201.113	2299642	3706.57	1128	7.98	442	3.11	1696	12.01	0.984
310.1024	2335010	3645.29	1310	9.27	1288	9.12	1624	11.5	0.983
241.0716	2141622	3536.71	2514	17.84	1813	12.84	3514	24.95	0.855
374.1311	2580159	3382.28	771	5.43	709	5	898	6.34	0.991

```
MS1:
213.9637   1168637.0   [M-H]⁻
214.9630     14790.0   M+1/15N
214.9670     94077.2   M+1/13C
215.9595    104643.6   M+2/34S
215.9679      7060.2   M+2/13C
```

```
MS/MS:
134.0054   339689.4
150.0001    77271.2
213.9607   632466.8
```

Our Aim: Generating Insight from Measurements

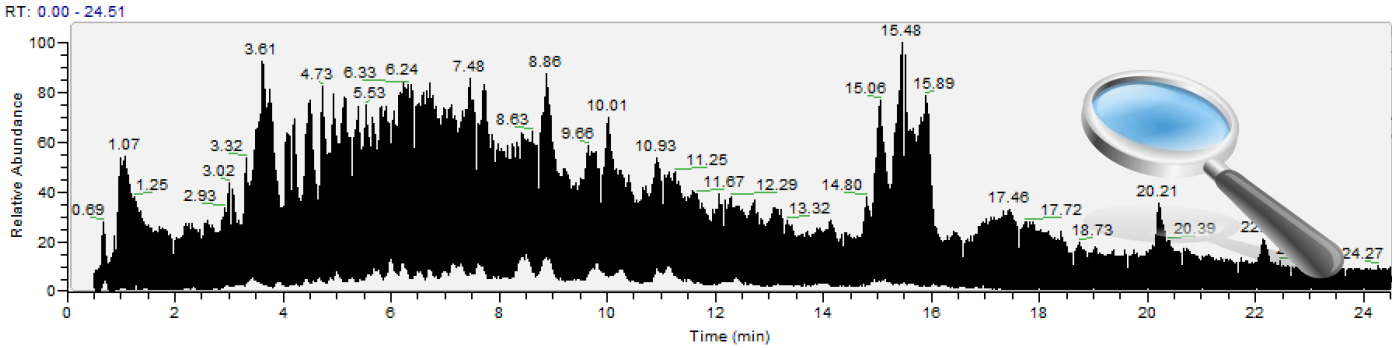


Mod. From Fig. 2, Sevin *et al* 2015, Current Opinion in Biotechnology. DOI: 10.1016/j.copbio.2014.10.001

Our (Community) Challenge: Identifying Chemicals

High resolution mass spectrometry

AND connecting chemical knowledge



Known — Hundreds

Unknown — Thousands

Sample

1 10 100 1000 10000 100000 1 million 1 billion chemicals …. …. ….

Chemicals

Suspect Chemicals	100s-1000s — norman suspects
Mass Spectral Libraries	~80,000 — MassBank.eu
CompTox Dashboard	882,000 — EPA Chemicals
PubChem Compound	>111 million — PubChem
1st Gen. PubChem Metabolites	>2 billion — PubChem
Generated Structures	Millions of billions

Schymanski *et al*. (2014) DOI: 10.1021/es4044374; Vermeulen *et al.* (2020) DOI: 10.1126/science.aay3164

Our Toolkit: NORMAN-SLE: Capturing Expert Knowledge

https://www.norman-network.com/nds/SLE/

NORMAN WEBSITE | NORMAN DATABASE SYSTEM | HOME | LOGIN

NORMAN SUBSTANCE DATABASE

NORMAN Suspect List Exchange – NORMAN SLE

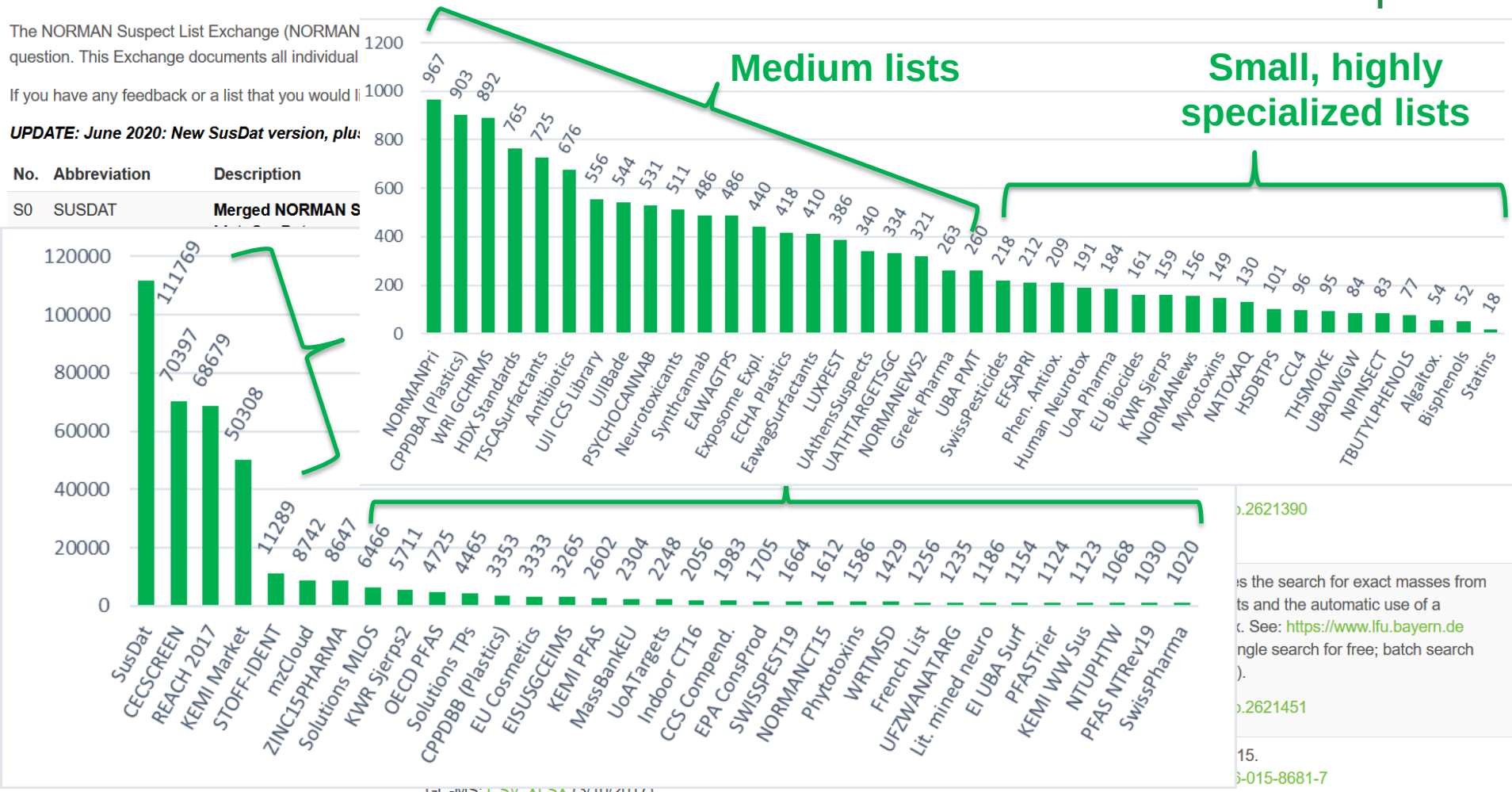
> 73 lists
> 144,980 substances

The NORMAN Suspect List Exchange (NORMAN
question. This Exchange documents all individual

If you have any feedback or a list that you would l

UPDATE: June 2020: New SusDat version, plus

No.	Abbreviation	Description
S0	SUSDAT	**Merged NORMAN S**



.2621390

s the search for exact masses from
ts and the automatic use of a
. See: https://www.lfu.bayern.de
ngle search for free; batch search
).

.2621451

15.
3-015-8681-7

Our Toolkit: NORMAN-SLE: Capturing Expert Knowledge

NORMAN WEBSITE | NORMAN DATABASE SYSTEM | HOME | LOGIN

https://www.norman-network.com/nds/SLE/

NORMAN SUBSTANCE DATABASE

NORMAN Suspect List Exchange – NORMAN SLE

> 73 lists

> 144,980 substances

PFAS

Pesticides

Dust

NPS

Smoke

Water

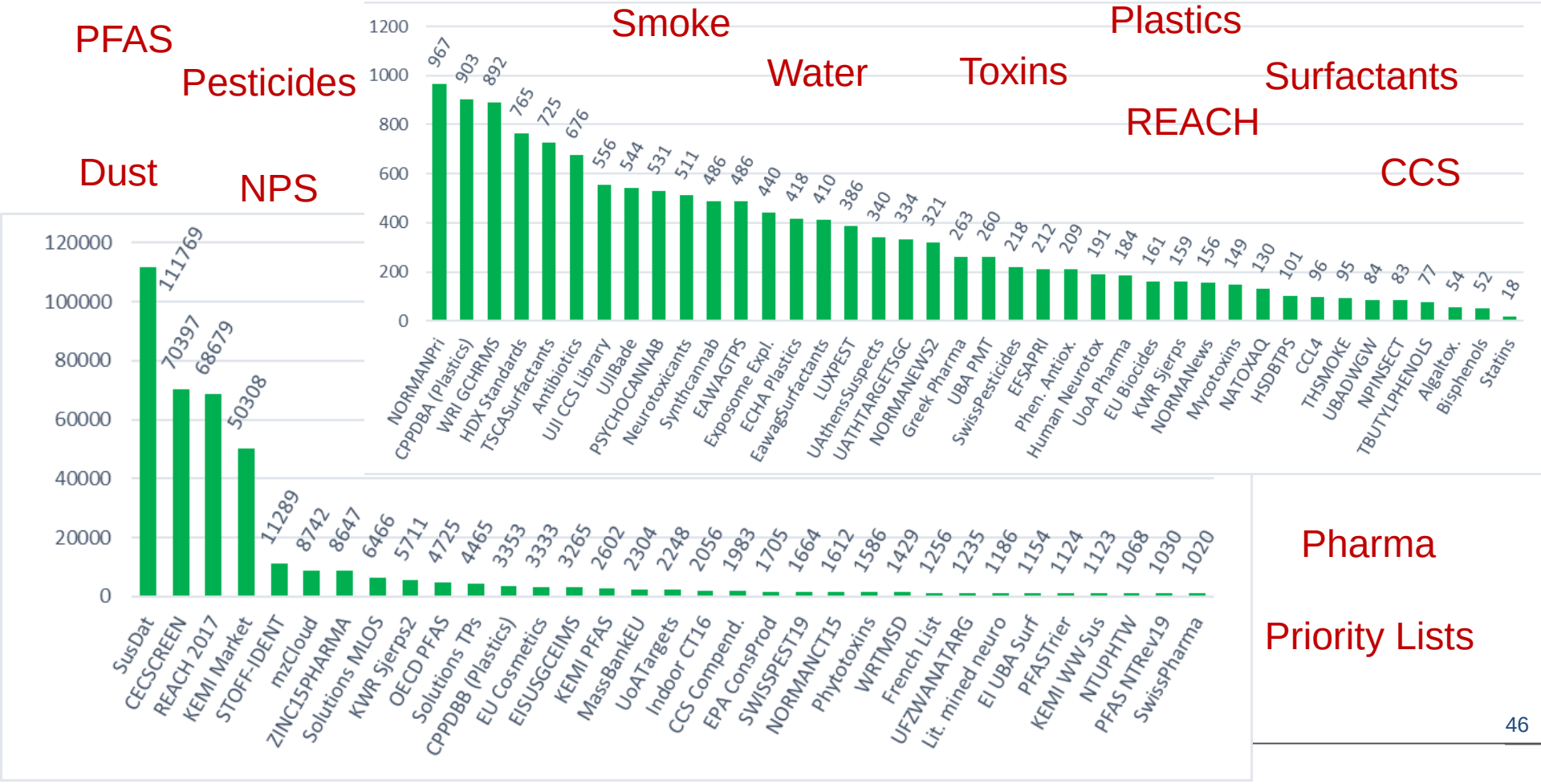
Toxins

Plastics

Surfactants

REACH

CCS

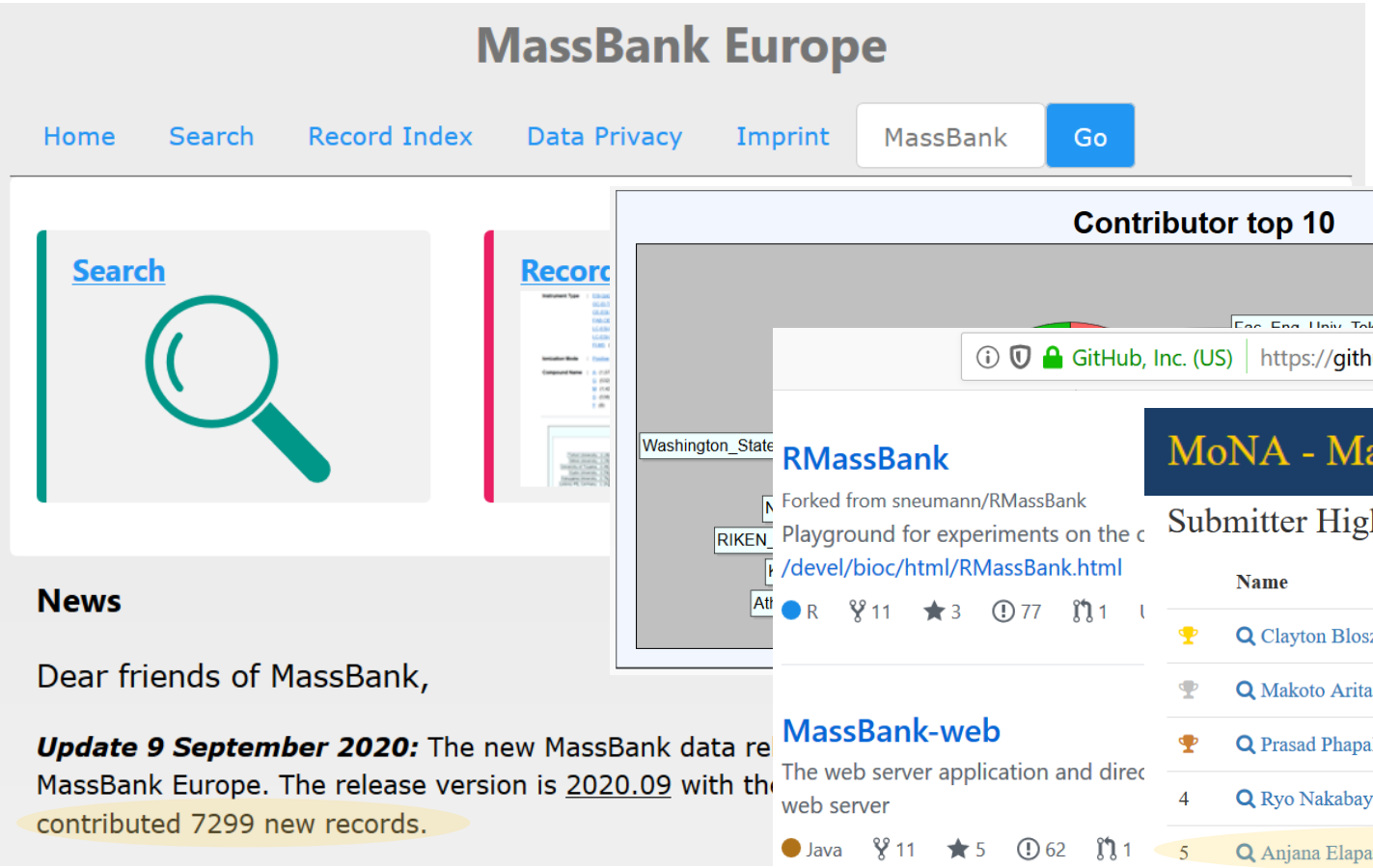


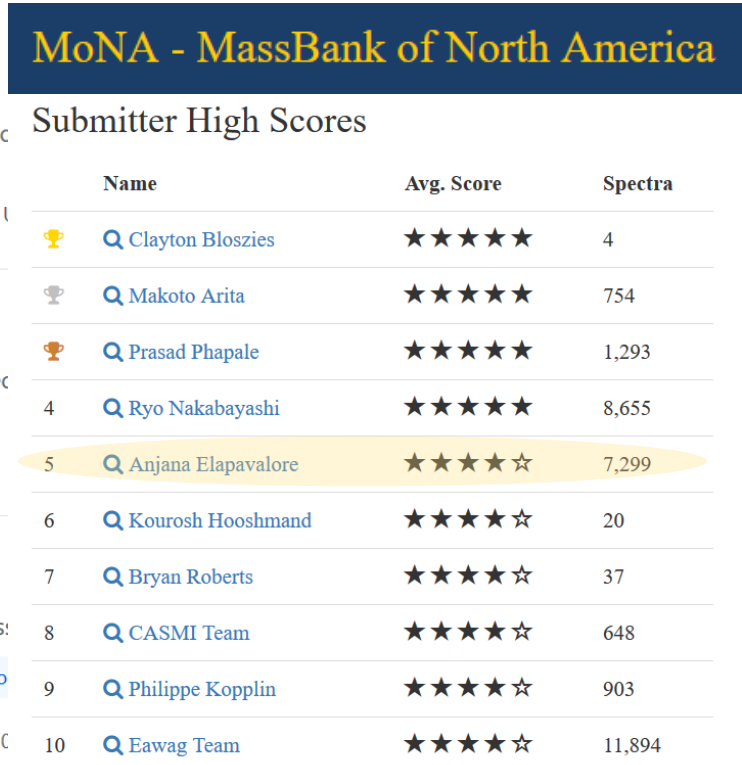
Pharma

Priority Lists

Our Toolkit: MassBank EU – Mass Spectra

http://massbank.eu/MassBank und https://github.com/MassBank/

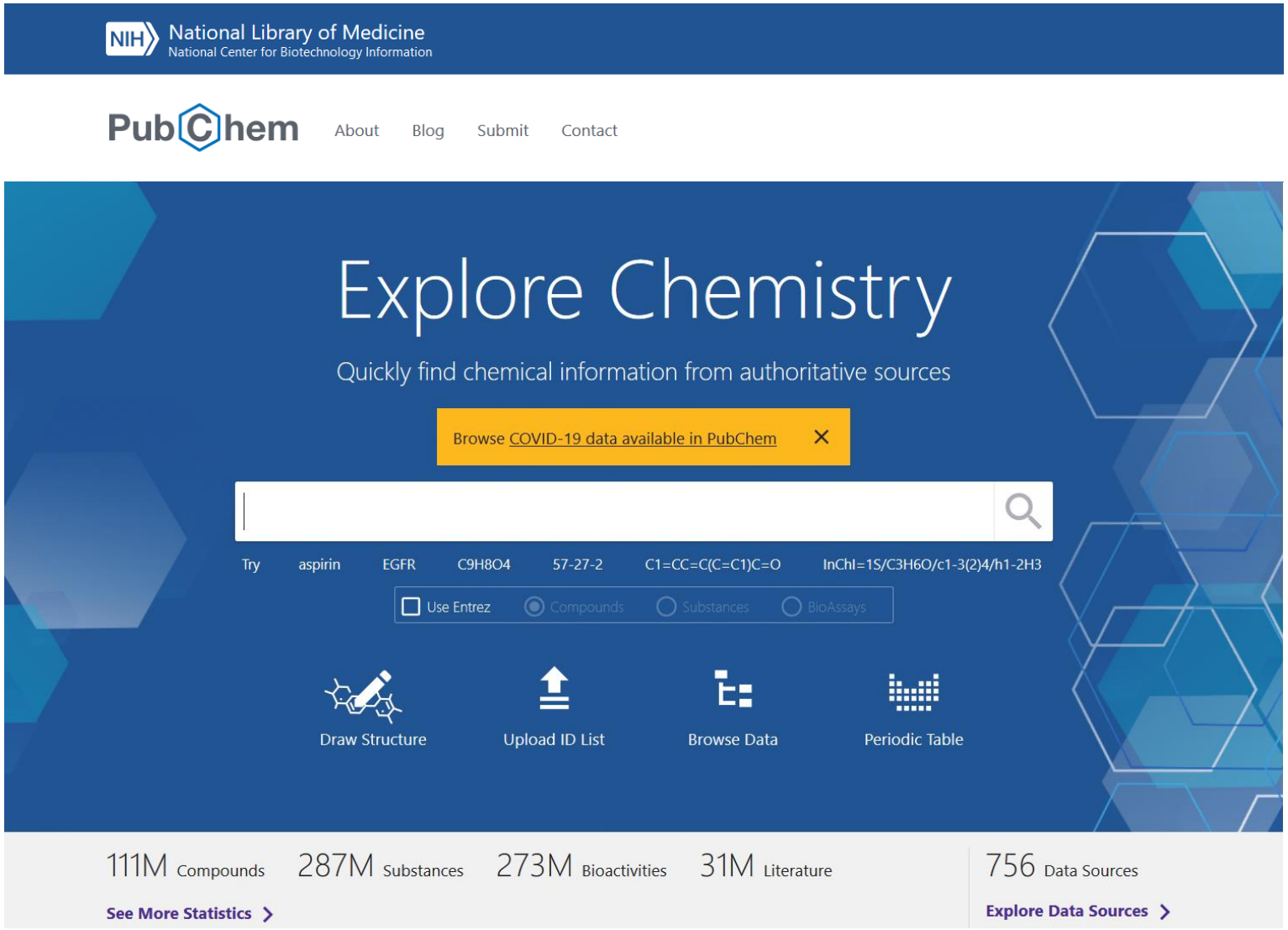




>88,100 spectra
~16,500 compounds
>47 contributors

Our Toolkit: PubChem – Finding the “known unknowns”

https://pubchem.ncbi.nlm.nih.gov/



Kim S, Chen J, Cheng T, et al. PubChem 2019 update: …. *Nucleic Acids Res*. 2019;47(D1):D1102–D1109. doi:10.1093/nar/gky1033

Our Toolkit: MetFrag – Annotating/Identifying Masses

MetFrag

In silico fragmentation for computer assisted identification of metabolite mass spectra

Database Settings

Database: PubChem Include references: ☑ Parent Ion: [M+H]+ Calculate

Neutral Mass: 253.966126 Search ppm: 5

Formula:

Identifiers:

Retrieve Candidates Download Candidates

Candidate Filter & Score Settings

Fragmentation Settings & Processing

Mzppm: 5

Mzabs: 0.001

Mode: [M+H]+

Tree depth: 2

Group candidates ☑

MS/MS Peak list

```
90.97445 681
106.94476 274
110.02750 110
115.98965 95
117.98540 384
124.93547 613
124.99015 146
125.99793 207
133.95592 777
143.98846 478
144.99625 352
```

Show Spectrum

Ruttkies, Schymanski, Wolf, Hollender, Neumann (2016) *J. Cheminf.*, 2016, DOI: 10.1186/s13321-016-0115-9

MetFrag + PubChem + MS/MS only

Status: 2010

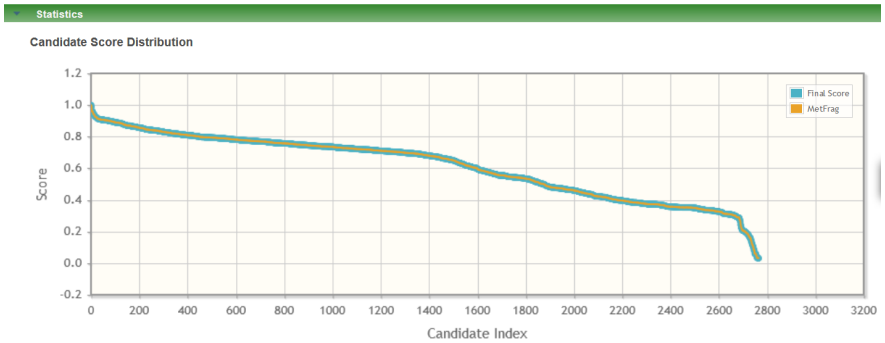
mz [M−H]⁻
213.9637
± 5 ppm

5 ppm
0.001 Da

PubChem

MetFrag

Ranked Candidates



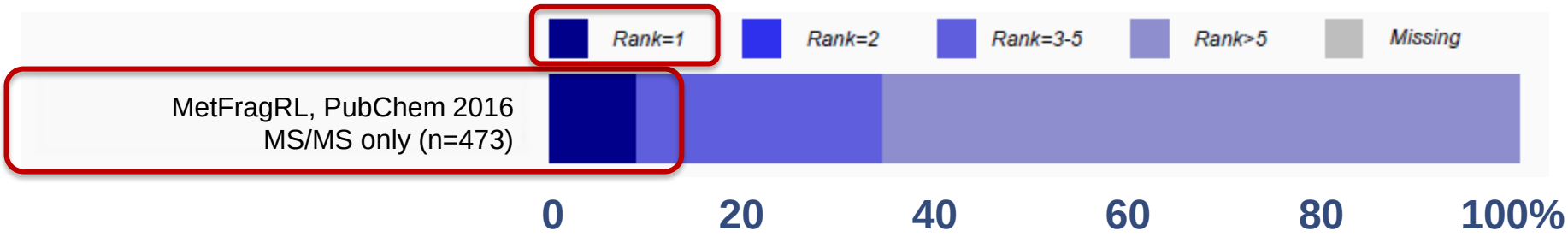
MS/MS

134.0054	339689
150.0001	77271
213.9607	632466

Ruttkies, Schymanski, Wolf, Hollender, Neumann (2016) *J. Cheminf.*, 2016, DOI: 10.1186/s13321-016-0115-9

Challenge: MetFrag + PubChem + MS/MS only

- MS/MS doesn't provide sufficient information alone …

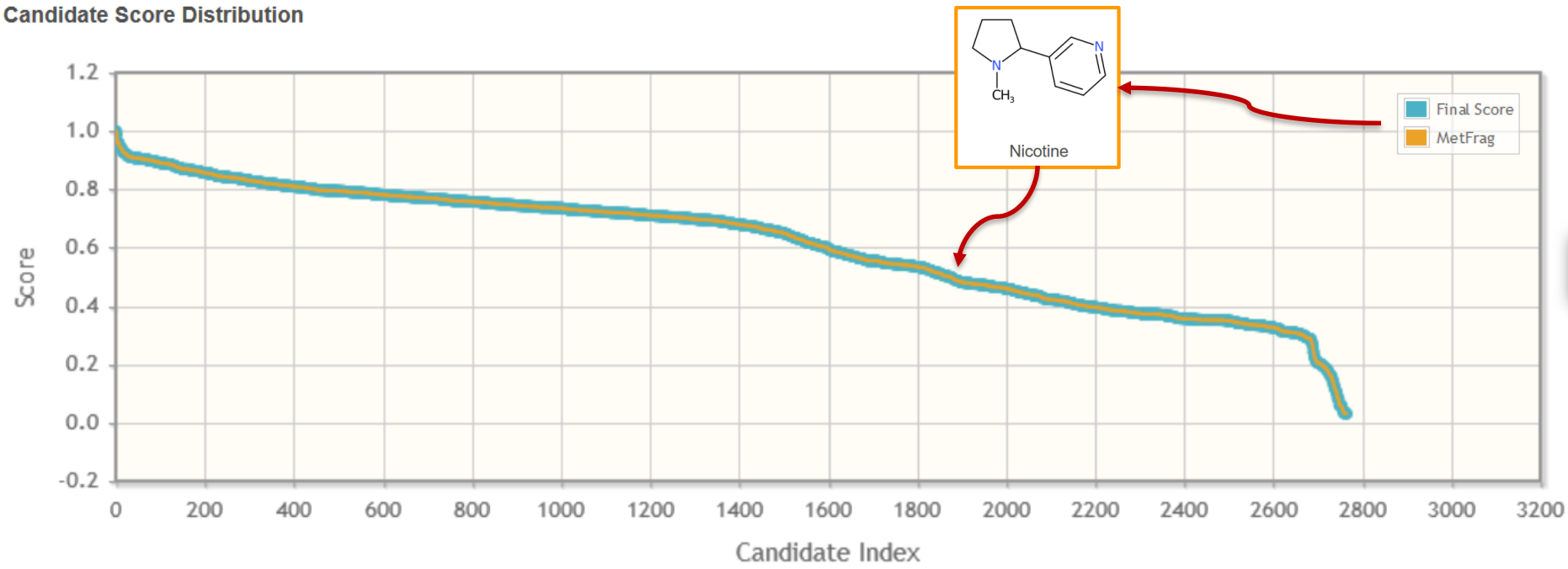


Ruttkies et al. (2016) DOI: 10.1186/s13321-016-0115-9, Bolton & Schymanski (2020), DOI: 10.5281/zenodo.3611238 & in prep.

MS/MS does not provide sufficient information alone…

MetFrag + PubChem

Statistics



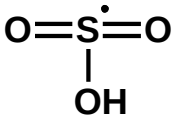
MetFrag + PubChem + Formula Search + https://massbank.eu/MassBank/RecordDisplay.jsp?id=EQ300804&dsn=Eawag

MetFrag – MS/MS and MORE!

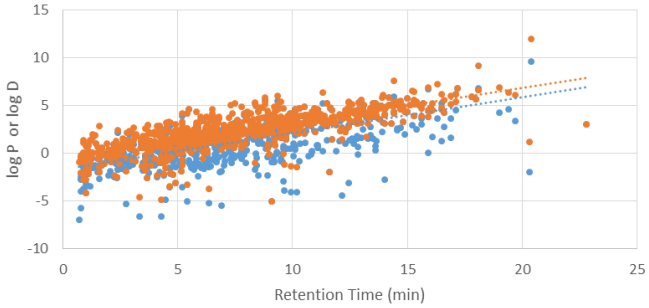
Status: 2016

mz [M-H]⁻
213.9637
± 5 ppm

Elements: C,N,S
5 ppm
0.001 Da



RT: 4.54 min
355 InChI/RTs



EPA Chemicals
or
PubChem

MetFrag

MoNA
MassBank of North America
MassBank.eu

References
Tox. Data
Data Sources
Exposure Info
MS-ready links

Literature Patents

Suspect Lists
?TOFF !DENT
norman suspects
EPA Chemicals

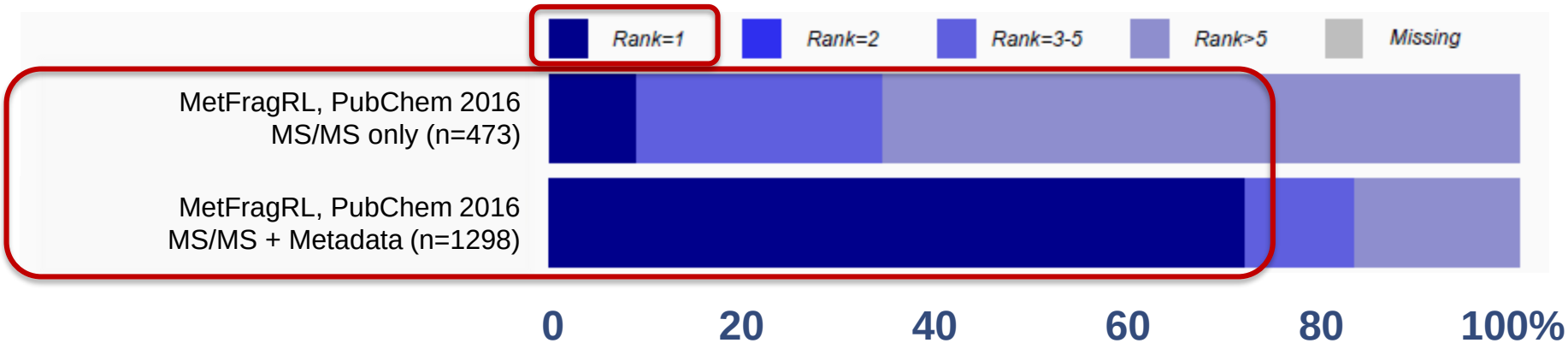
MS/MS

134.0054	339689
150.0001	77271
213.9607	632466

Ruttkies, Schymanski, Wolf, Hollender, Neumann (2016) *J. Cheminf.*, 2016, DOI: 10.1186/s13321-016-0115-9

MetFrag + PubChem + MS/MS + Metadata

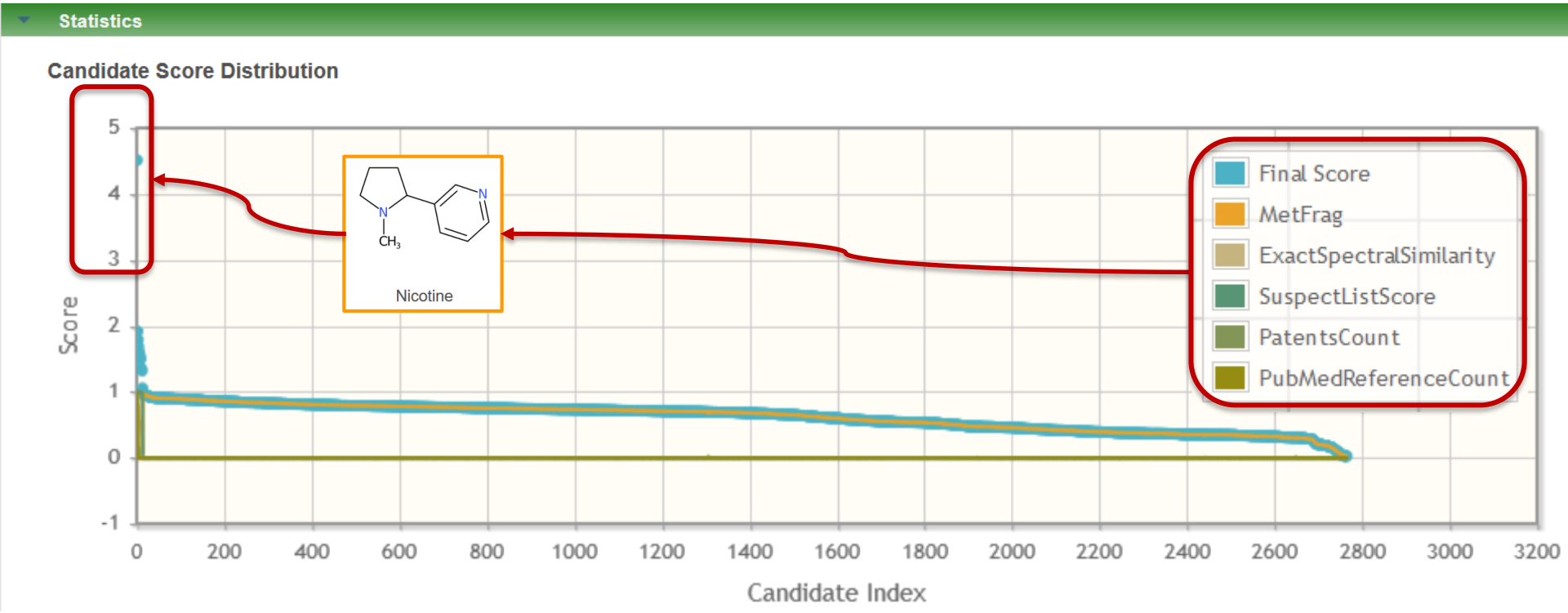
- Adding literature, references & RT boosts to ~71 % rank 1!



Ruttkies et al. (2016) DOI: 10.1186/s13321-016-0115-9, Bolton & Schymanski (2020), DOI: 10.5281/zenodo.3611238 & in prep.

Connecting multiple lines of evidence for identification

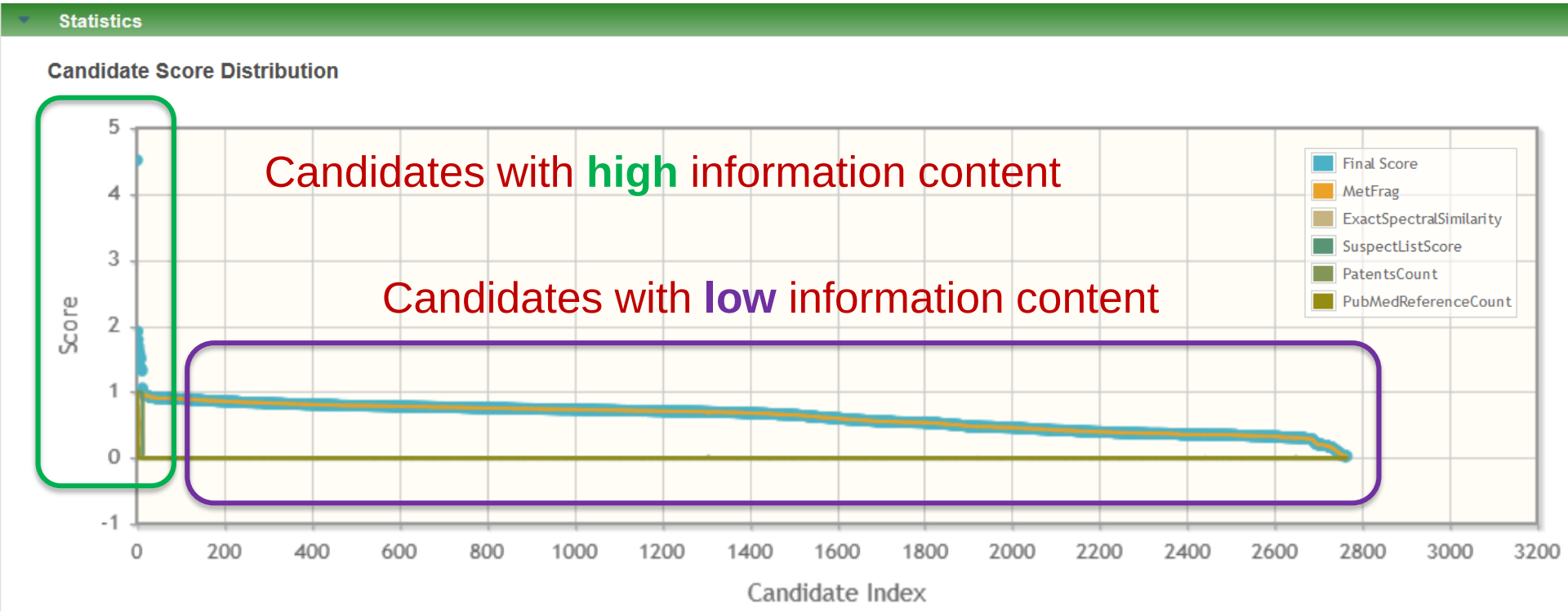
MetFrag | MassBank.eu | norman suspects | PubChem



MetFrag + PubChem + Formula + MoNA + SusDat + Pat + Refs + https://massbank.eu/MassBank/RecordDisplay.jsp?id=EQ300804&dsn=Eawag

Connecting multiple lines of evidence for identification

Challenge: the growing number of candidates …
Need: wide coverage and high efficiency!



MetFrag + PubChem + Formula + MoNA + SusDat + Pat + Refs + https://massbank.eu/MassBank/RecordDisplay.jsp?id=EQ300804&dsn=Eawag

The 111 million PubChem Challenge …

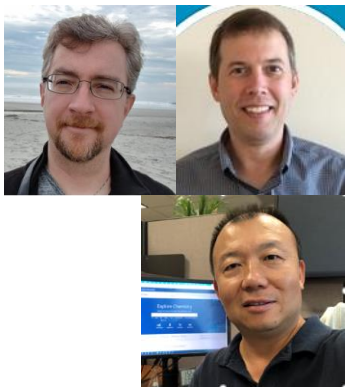
U.S. National Library of Medicine
National Center for Biotechnology Information

- PubChem Compound TOC ? 33,765,953
  - Agrochemical Information ? 2,002
  - Biologic Description ? 1,539,532
  - Biological Test Results ? 3,467,416
  - Biomolecular Interactions and Pathways ? 109,610
  - Chemical and Physical Properties ? 237,729
  - Classification ? 18,569,627
  - Diseases ?
  - Drug and Medication Information ? 15,955
  - Food Additives and Ingredients ? 7,447
  - Identification ? 5,746
  - Information Sources ? 20,654,780
  - Literature ? 1,668,437
  - Names and Identifiers ? 1,310,169
  - Patents ? 22,144,888
  - Pharmacology and Biochemistry ? 130,367
  - Related Records ? 5,297,096
  - Safety and Hazards ? 125,607
  - Spectral Information ? 761,478
  - Structures ? 5,926,225
  - Toxicity ? 114,554
  - Use and Manufacturing ? 108,745
  - Chemical Safety ? 122,739

111 million … OR … the most relevant / annotated?

Environmental Use Case:
PubChemLite tier0: 316 K

Exposomics Use Case:
PubChemLite tier1: 360 K



zenodo — Search — Upload — Communities — emma.schymanski@uni.lu

January 14, 2020 — Dataset — Open Access

PubChemLite tier0 and tier1

Bolton, Evan; Schymanski, Emma

Edit

New version

Communities

LCSB Environmental Cheminformatics Group — Remove

503 views — 482 downloads

See more details...

Database Settings

Database: PubChemLite_14Jan2020

Neutral Mass: 162.11576 Search ppm: 5

Formula: C10H14N2

Identifiers:

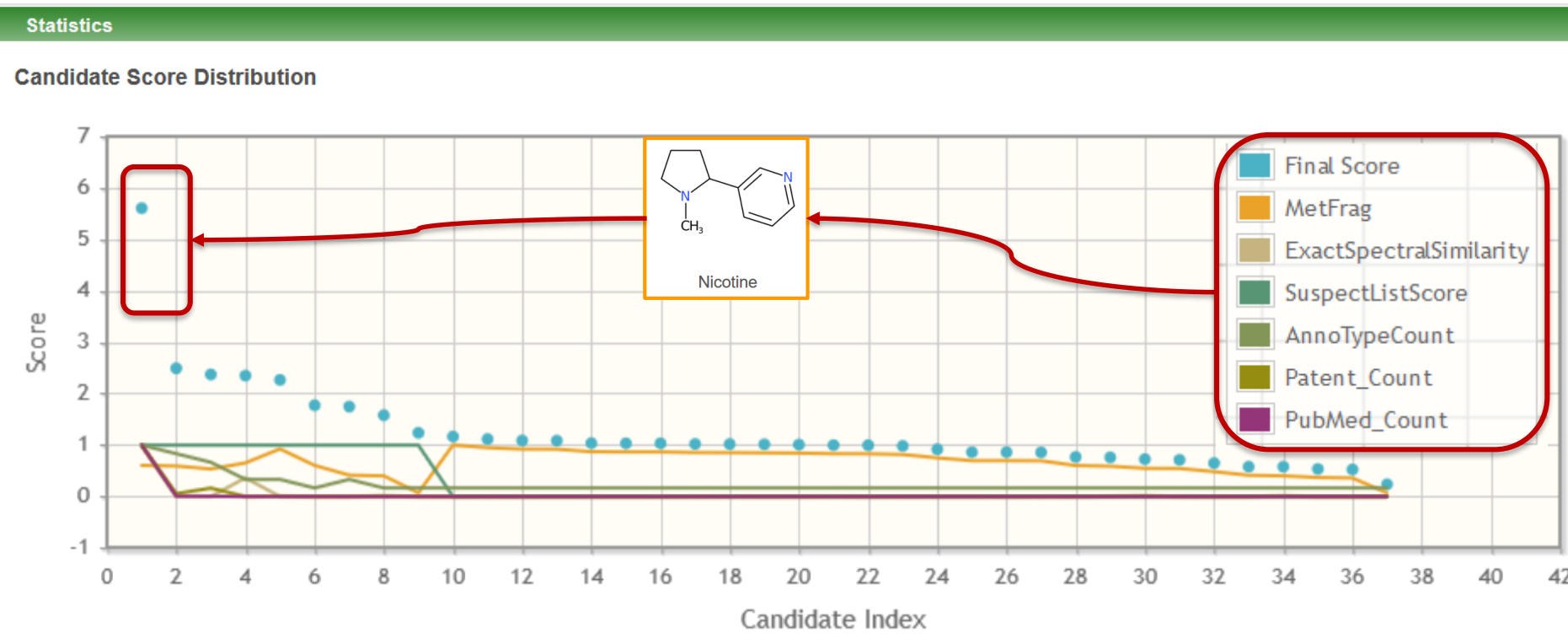
Retrieve Candidates — 37 Candidates

MetFrag

Bolton & Schymanski (2020). PubChemLite tier0 and tier1 (Version PubChemLite.0.2.0) DOI: 10.5281/zenodo.3611238

PubChemLite: tailor-made database + metadata

MetFrag MassBank.eu NORMAN suspects PubChem

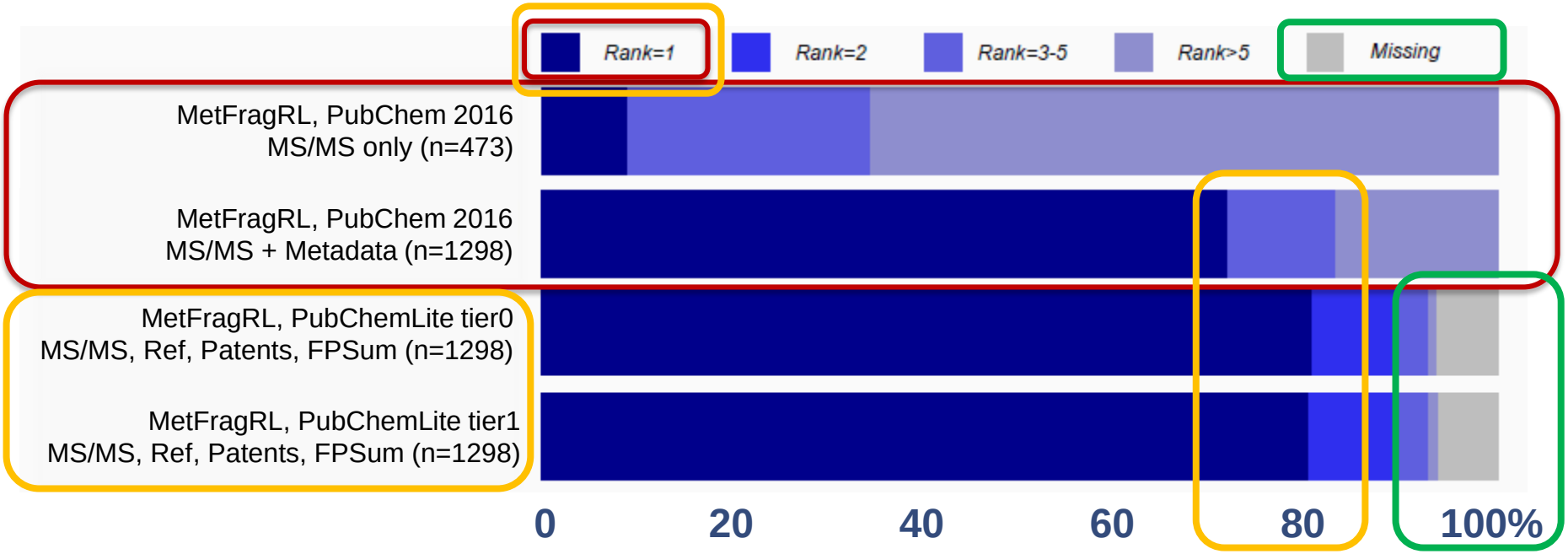


MetFrag+PubChemLite+Formula+MoNA+SusDat+Pat+Refs+Anno + https://massbank.eu/MassBank/RecordDisplay.jsp?id=EQ300804&dsn=Eawag

How does PubChemLite perform?

U.S. National Library of Medicine
National Center for Biotechnology Information

- 111 M => 300 K … how does this influence performance?

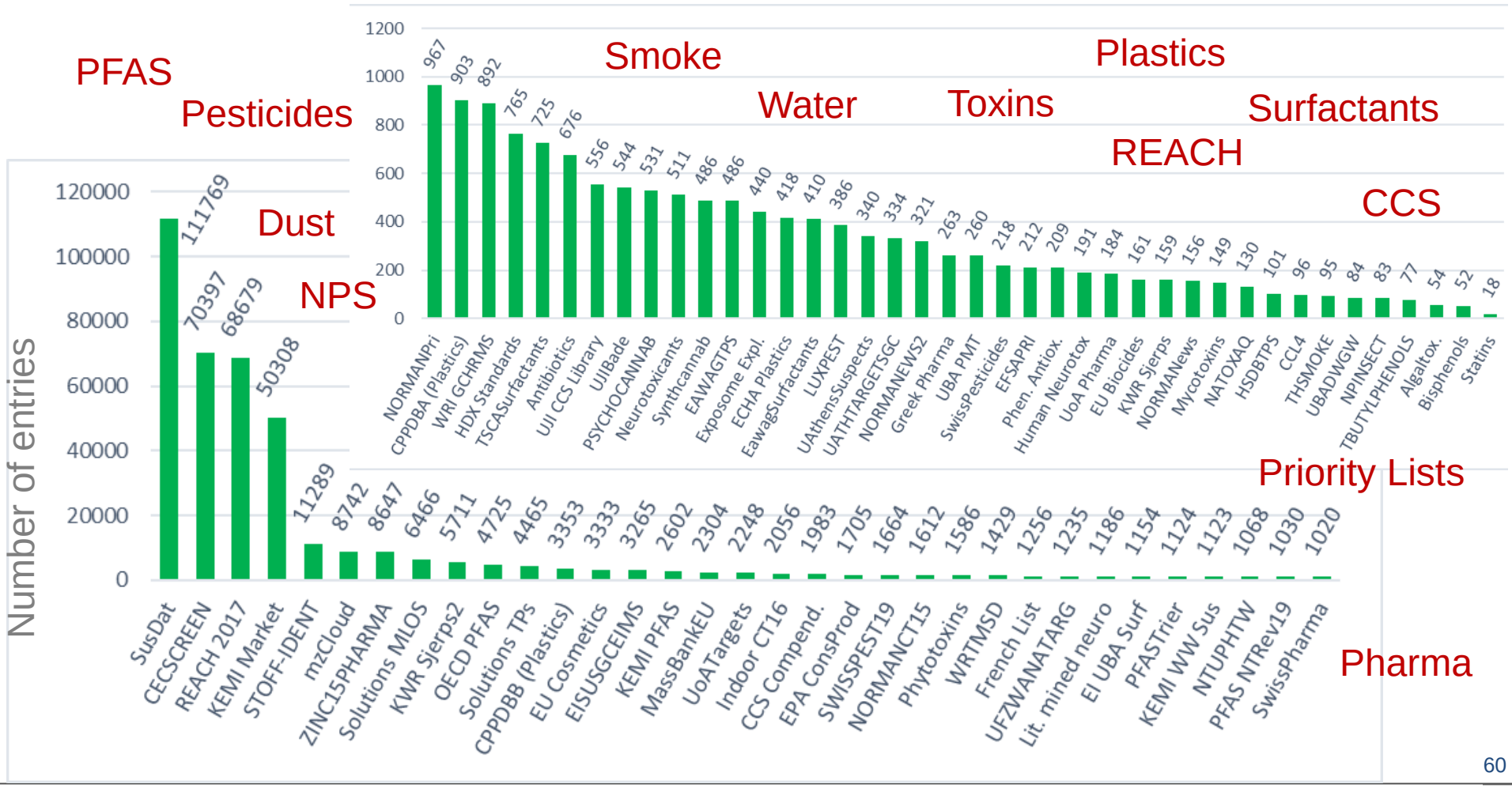


Ruttkies et al. (2016) DOI: 10.1186/s13321-016-0115-9, Bolton & Schymanski (2020), DOI: 10.5281/zenodo.3611238 & in prep.

NORMAN Suspect List Exchange: Capturing Knowledge

- https://www.norman-network.com/nds/SLE/
- https://zenodo.org/communities/norman-sle
- https://pubchem.ncbi.nlm.nih.gov/classification/#hid=101

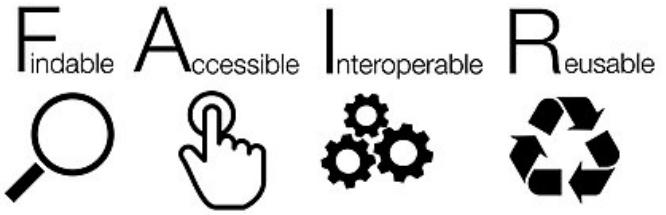
>73 lists!



Schymanski *et al*. (in prep.) https://www.norman-network.com/nds/SLE/

NORMAN-SLE on Zenodo

https://zenodo.org/communities/norman-sle/



zenodo

Search

emma.schymanski@uni.lu

Communities

NORMAN Suspect List Exchange

Remove

NORMAN Suspect Li

Recent uploads

Search NORMAN Suspect List Exchange

November 21, 2019 (NORMAN-SLE S61.0.1.2) | Dataset | Open A

S61 | UJICCSLIB | Collision Cross Sectior

Celma, Alberto; Fabregat-Safont, David; Ibàñe Félix; Sancho, Juan Vicente;

This is the collection associated with list S61 UJICCSl https://www.norman-network.com/nds/SLE/ A list of compounds (both positive and negative ionization mo instrument) pr

Uploaded on July 30, 2020

2 more version(s) exist for this record

1,049 views

1,166 downloads

See more details...

Publication date:
November 21, 2019

DOI:
DOI 10.5281/zenodo.3966751

Keyword(s):
Collision Cross Section | Ion Mobility | Suspect Screening | IMS-MS | CCS

Related identifiers:
Supplement to https://www.norman-network.com/nds/SLE/

New upload

NORMAN Suspect List Exchange

This is a public repository (under development) for suspect lists currently available on the NORMAN Suspect List Exchange: https://www.norman-network.com/?q=suspect-list-exchange

Read more

Curated by:
schymane

Curation policy:
This community will collect data that is

NORMAN-SLE on PubChem

U.S. National Library of Medicine
National Center for Biotechnology Information

https://pubchem.ncbi.nlm.nih.gov/source/NORMAN Suspect List Exchange

U.S. National Library of Medicine
National Center for Biotechnology Information

PubChem NORMAN Suspect List Exchange

Organization:	NORMAN Network (c/o Emma Schymanski)
Category:	Research and Development
URL:	https://www.norman-network.com/nds/SLE/
Contact Name:	Emma Schymanski
Address:	6 avenue du Swing, Belvaux, Luxembourg, 4367
Data Source ID:	23819
Data in PubChem:	144,980 Live Substances 11,208 Annotations 1 Classification
Last Updated:	2020/08/01

Huge thanks to Evan Bolton, Jian Zhang (Jeff), Paul Thiessen, Ben Shoemaker and the PubChem team for this!

NORMAN-SLE on PubChem

U.S. National Library of Medicine
National Center for Biotechnology Information

- https://pubchem.ncbi.nlm.nih.gov/classification/#hid=101

PubChem Classification Browser

Help

Browse PubChem data using a classification of interest, or search for PubChem records annotated with the desired classification/term (e.g., MeSH: phenylpropionates, or Gene Ontology: DNA repair). More...

Select classification NORMAN Suspect List Exchange

Search selected classification by Keyword | Enter desired search term | Search

Classification description (from NORMAN Suspect List Exchange)

The NORMAN Suspect List Exchange (NORMAN-SLE) is a central access point for NORMAN members (and others) to find suspect lists relevant for their environmental monitoring questions. More...

Data type counts to display None | Compound

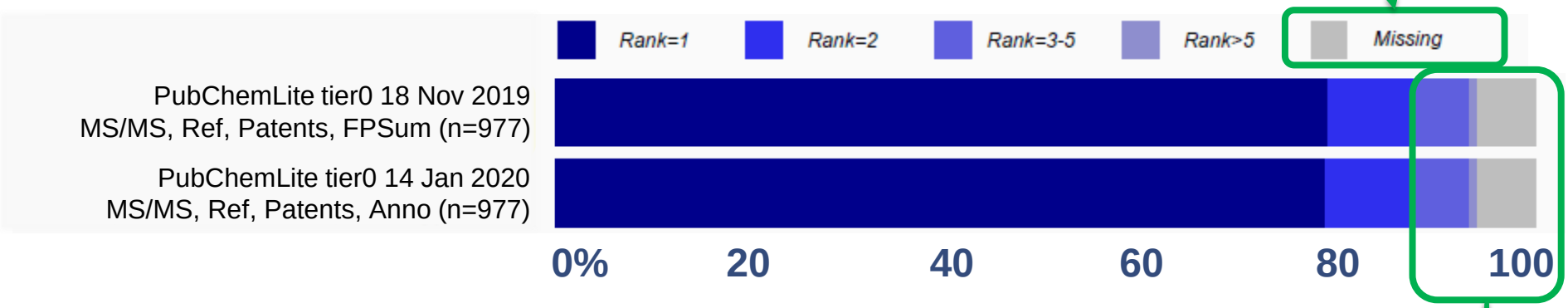
Display zero count nodes? Yes | No

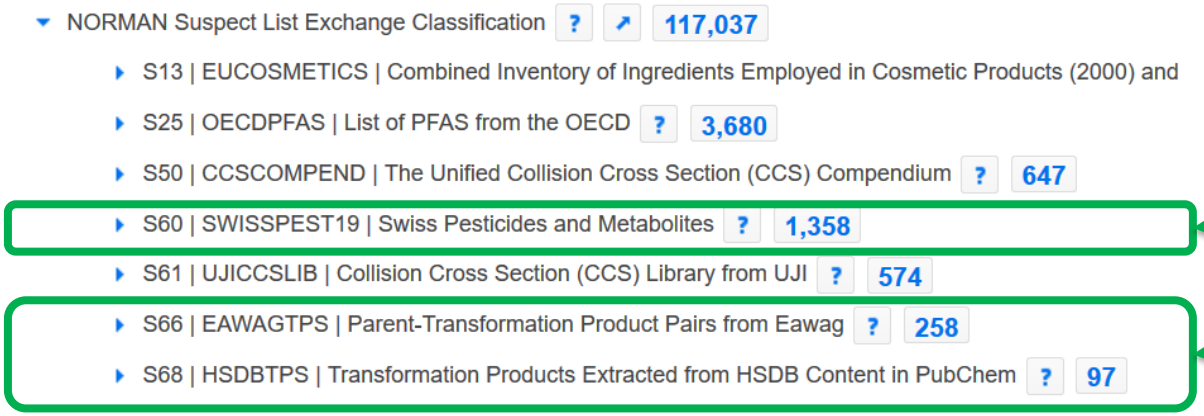
Browse NORMAN Suspect List Exchange Tree

- NORMAN Suspect List Exchange Classification ? 130,864
  - S13 | EUCOSMETICS | Combined Inventory of Ingredients Employed in Cosmetic Products (2000) and Revised Inventory (2006) ? 4,131
  - S25 | OECDPFAS | List of PFAS from the OECD ? 3,680
  - S50 | CCSCOMPEND | The Unified Collision Cross Section (CCS) Compendium ? 647
  - S60 | SWISSPEST19 | Swiss Pesticides and Metabolites from Kiefer et al 2019 ? 1,354
  - S61 | UJICCSLIB | Collision Cross Section (CCS) Library from UJI ? 574
  - S66 | EAWAGTPS | Parent-Transformation Product Pairs from Eawag ? 258

Missing Entries in PubChemLite

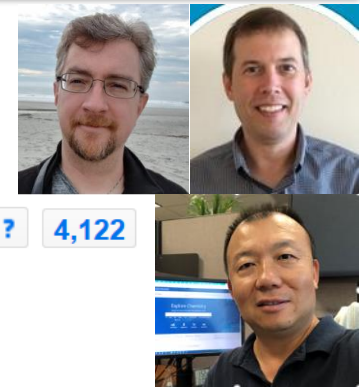
- Assessing the missing entries …





Ruttkies et al. (2016) DOI: 10.1186/s13321-016-0115-9, Bolton & Schymanski (2020), DOI: 10.5281/zenodo.3611238 & in prep.

Transformation Products: Filling the Data Gaps!



PubChem NORMAN Suspect List Exchange

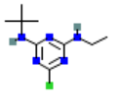
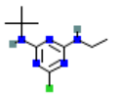
- NORMAN Suspect List Exchange Classification ? 117,037
  - S13 | EUCOSMETICS | Combined Inventory of Ingredients Employed in Cosmetic Products (2000) and Revised Inventory (2006) ? 4,122
  - S25 | OECDPFAS | List of PFAS from the OECD ? 3,680
  - S50 | CCSCOMPEND | The Unified Collision Cross Section (CCS) Compendium ? 647
  - S60 | SWISSPEST19 | Swiss Pesticides and Metabolites ? 1,358
  - S61 | UJICCSLIB | Collision Cross Section (CCS) Library from UJI ? 574
  - S66 | EAWAGTPS | Parent-Transformation Product Pairs from Eawag ? 258
  - S68 | HSDBTPS | Transformation Products Extracted from HSDB Content in PubChem ? 97
  - S69 | LUXPEST | Pesticide Screening List for Luxembourg ? 386
  - S72 | NTUPHTW | Pharmaceutically Active Substances from
- S00 | SUSDAT | Merged NORMAN Suspect List: SusDat ?
- S01 | MASSBANK | NORMAN Compounds in MassBank EU
- S02 | STOFFIDENT | HSWT/LfU STOFF-IDENT Database of W
- S03 | NORMANCT15 | NORMAN Collaborative Trial Targets an
- S04 | UJIBADE | Target List from UJI used in Bade et al 2015
- S05 | KWRSJERPS | KWR Drinking Water Suspect List ?
- S06 | ITNANTIBIOTIC | Antibiotic List from the ITN MSCA ANS
- S07 | EAWAGSURF | Eawag Surfactants Suspect List ? 17
- S08 | ATHENSSUS | University of Athens Surfactants and Susp
- S09 | PFASTRIER | PFAS Suspect List of fluorinated substance

PubChem Terbuthylazine (Compound)

8.5 Transformations

Page 3 of 25 items View More Rows & Details Download

SORT BY Please Choose One

Predecessor Image	Predecessor Name	Transformation	Successor Image	Successor Name	Evidence DOI
	Terbuthylazine	Mammalian metabolism		6-Chloro-1,3,5-triazine-2,4-diamine	10.5281/zenodo.382
	Terbutylazine	Deethylation		Terbutylazine-desethyl	10.1007/s13361-017-

PubChem Terbuthylazine (Compound)

Microbiocides, Algicides, Herbicides

S69 | LUXPEST | Pesticide Screening List for Luxembourg | DOI:10.5281/zenodo.3862688

▸ NORMAN Suspect List Exchange

Pesticides -> Herbicides -> Triazine herbicides -> Chlorotriazine herbicides

S66 | EAWAGTPS | Parent-Transformation Product Pairs from Eawag | DOI:10.5281/zenodo.3754448

▸ NORMAN Suspect List Exchange

7.2 Agrochemical Transformations

Terbutylazine has known environmental transformation products that include Terbutylazine-2-hydroxy, Terbutylazine-desethyl, and Terbutylazine-desethyl-2-hydroxy.

S66 | EAWAGTPS | Parent-Transformation Product Pairs from Eawag | DOI:10.5281/zenodo.3754448

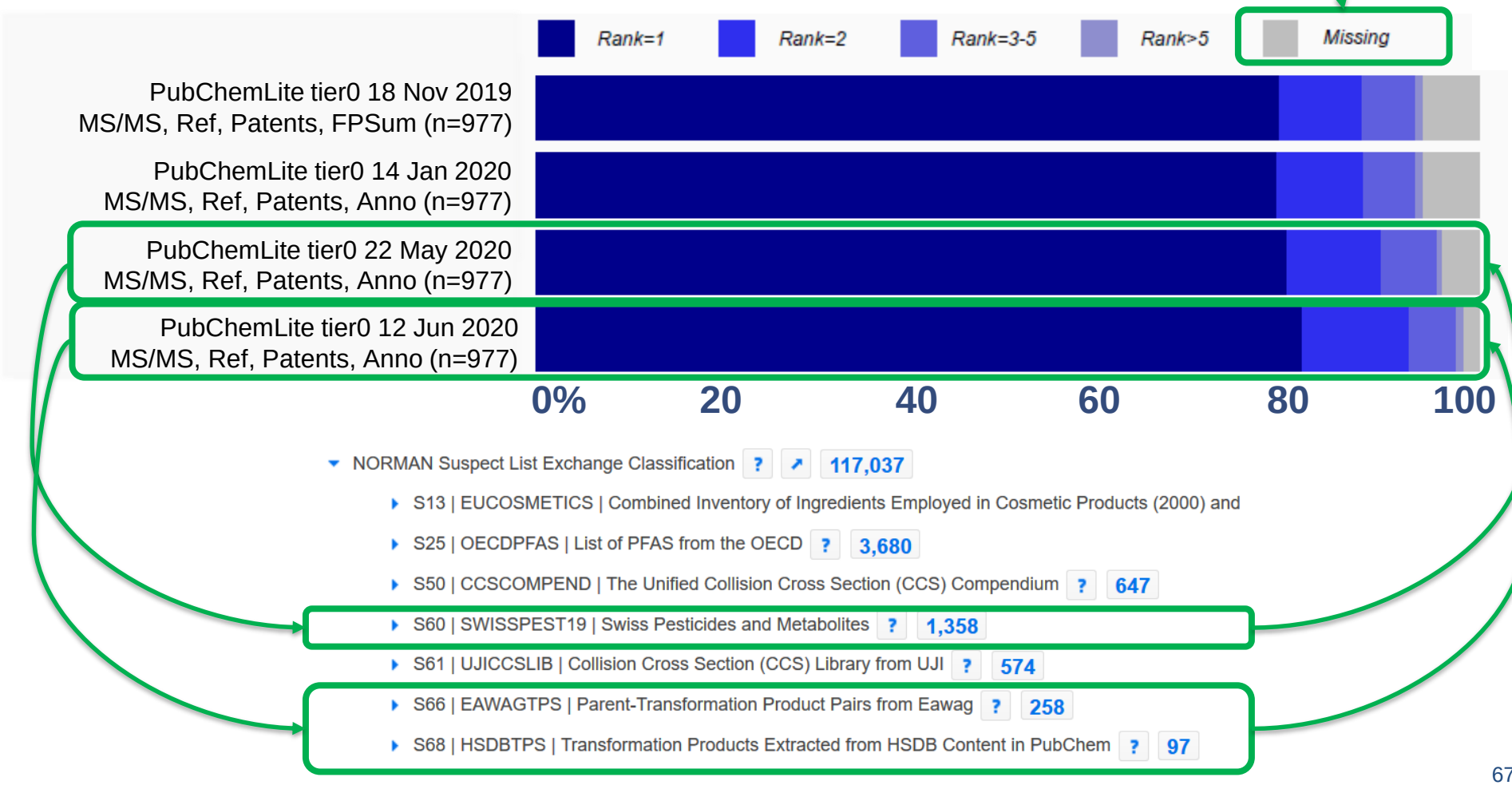
▸ NORMAN Suspect List Exchange

Terbutylazine has known environmental transformation products that include CSAA036479, CSAA04949, CSCD648241, CSCD692760, GS31398, MT1, GS 26379, MT13, GS 23158, Terbutylazine metabolite MT14, Terbutylazine metabolite MT23, and Terbutylazine metabolite MT24.

S60 | SWISSPEST19 | Swiss Pesticides and Metabolites from Kiefer et al 2019 | DOI:10.5281/zenodo.3544759

Missing Entries in PubChemLite

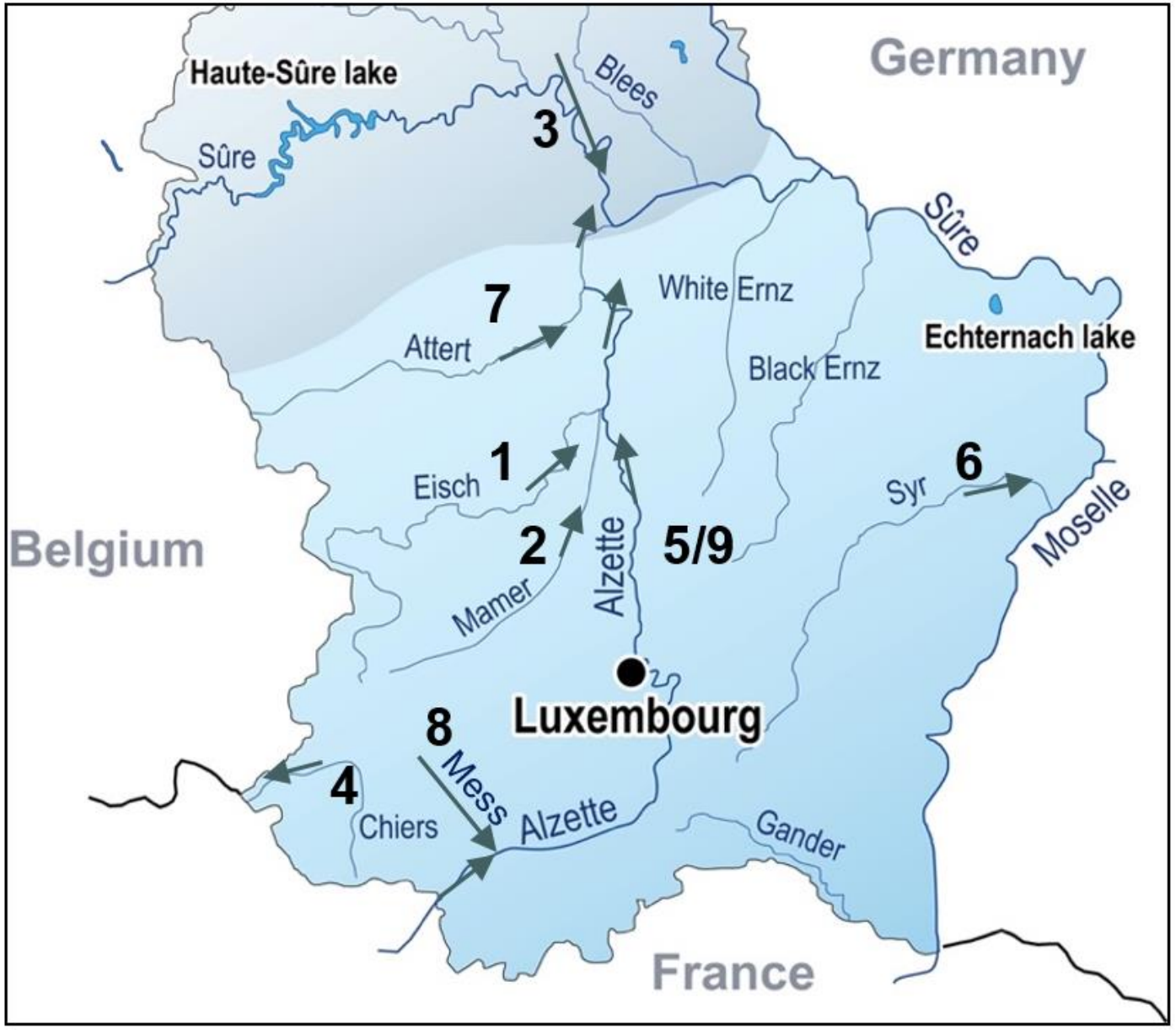
- Assessing the missing entries …



Ruttkies et al. (2016) DOI: 10.1186/s13321-016-0115-9, Bolton & Schymanski (2020), DOI: 10.5281/zenodo.3611238 & in prep.

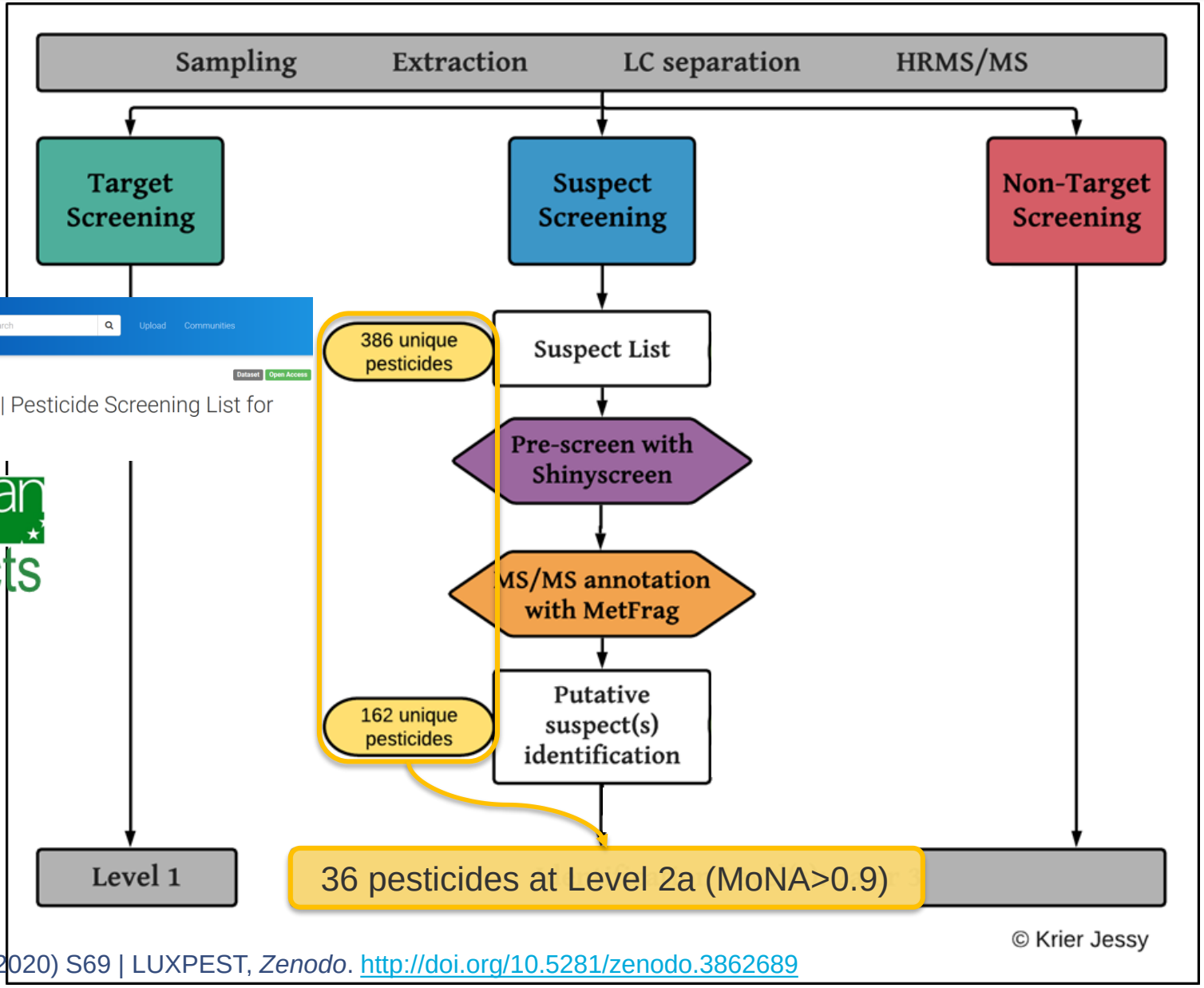
“Real Life” Application

THE GOVERNMENT
OF THE GRAND DUCHY OF LUXEMBOURG
Ministry of the Environment, Climate
and Sustainable Development



Jessy Krier (2020) Master’s Thesis, defended July 2020. Figure 34.

Suspect Screening for Lux-Relevant Pesticides

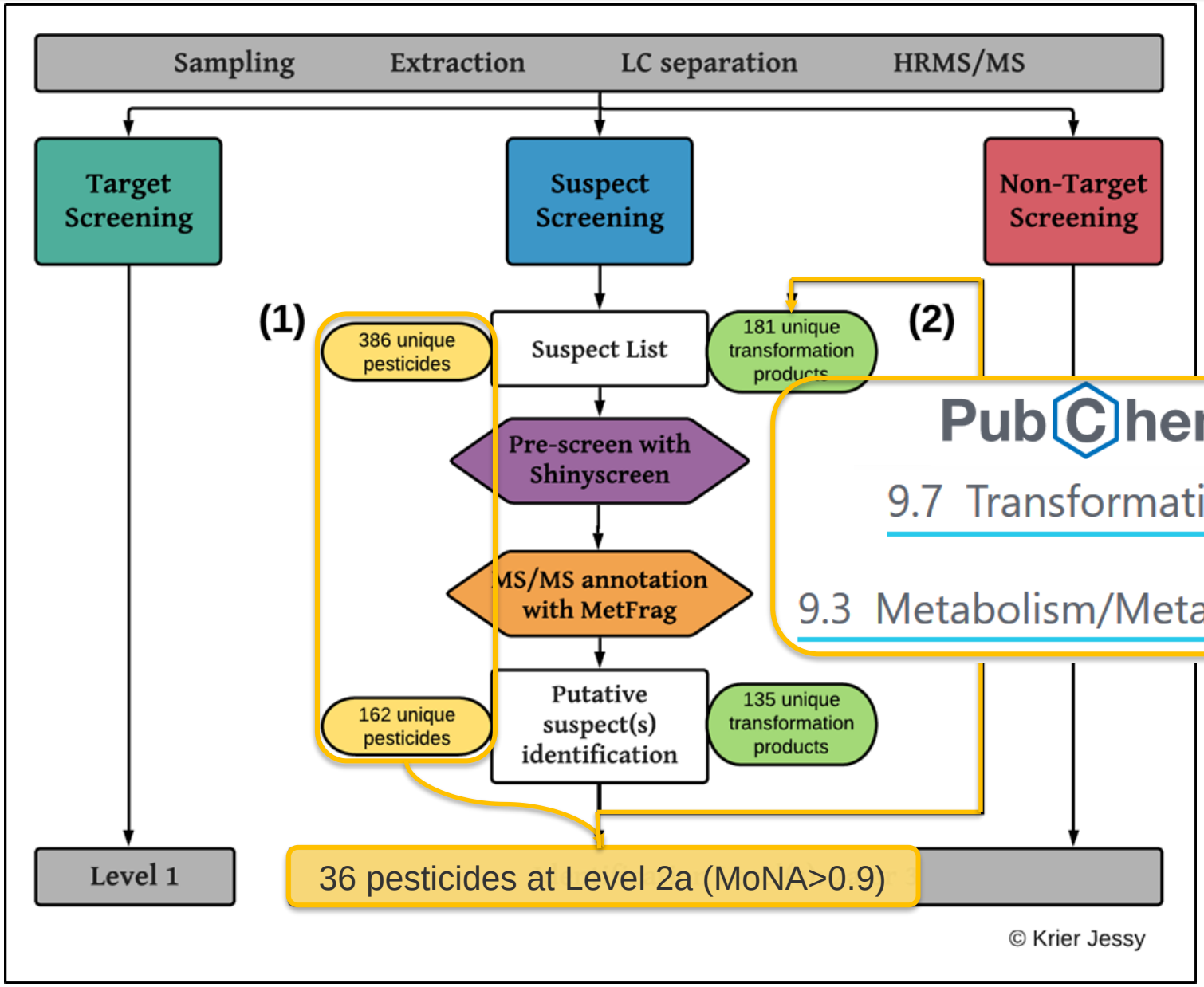


norman suspects

Jessy Krier (2020) S69 | LUXPEST, *Zenodo*. http://doi.org/10.5281/zenodo.3862689

Jessy Krier (2020) Master's Thesis, defended July 2020. Figure 8

Data-Driven TP/Metabolite Search



Jessy Krier (2020) Master's Thesis, defended July 2020. Figure 8.

Literature Mining for Metabolites / TPs – and Curation

PubChem Terbuthylazine (Compound)

8.3 Metabolism/Metabolites

Metabolism of terbuthylazine in rats is similar to other chloro-s-triazine herbicides. The major routes of metabolism are hydrolysis of the chlorine moiety and mono- or didealkylation. Hydroxylation of one or both of the dealkylated amine groups may also occur.

USEPA; Reregistration Eligibility Decision (RED) Database for Terbuthylazine (5915-41-3). EPA 738-R-95-005 p.12 (March 1995). Available from, as of October 11, 2012: http://www.epa.gov/pesticides/reregistration/status.htm

▸ Hazardous Substances Data Bank (HSDB)

Urine and feces contained up to 25 and 15 identified metabolites, re
Degradation of the triazine ring did not occur. Ammeline and amme
dealkylated/hydroxylated metabolites common to all triazines, were

*USEPA; Reregistration Eligibility Decision (RED) Database for Terbuthylazine (
1995). Available from, as of October 11, 2012: http://www.epa.gov/pesticides/*

▸ Hazardous Substances Data Bank (HSDB)

In mammals, following oral administration, ...a de-ethyl metabolite fo
of products formed by oxidation of one methyl group of the tert-but

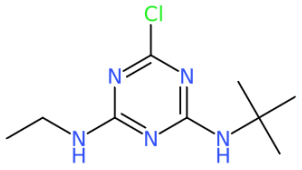
*Tomlin CDS, ed. Terbuthylazine (5915-41-3). In: The e-Pesticide Manual, Versi
Protection Council.*

▸ Hazardous Substances Data Bank (HSDB)

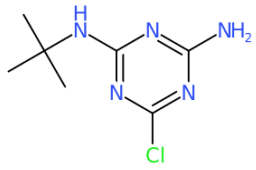
DEPICT D K

```
CCNC1=NC(=NC(=N1)Cl)NC(C)(C)C Terbutylazine CID:22206
NC1=NC(=NC(=N1)Cl)NC(C)(C)C desethyl-terbutylazine CID:108201
CCNC1=NC(=NC(=N1)Cl)N des-t-butyl-terbutylazine CID:13878
CCNC1=NC(=NC(=N1)O)NC(C)(C)C 2-hydroxy-terbutylazine CID:135495928
CCNC1=NC(=NC(=N1)Cl)NC(C)(C)C(O) (hydroxy-t-butyl)-Terbutylazine CID:779516
NC1=NC(=NC(=N1)Cl)N didealkyl-terbutylazine CID:18831
OC1=NC(=NC(=N1)Cl)N hydroxy-didesalkyl-terbutylazine CID:135438601
```

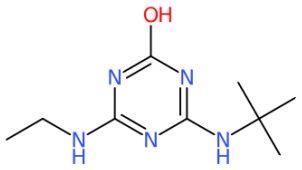
Color on White | No Annotation | Chiral Hydrogens (smart) | Do Not Abbreviate



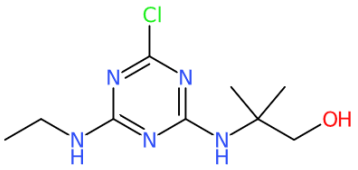
Terbutylazine CID:22206



desethyl-terbutylazine CID:108201



2-hydroxy-terbutylazine CID:135495928



(hydroxy-t-butyl)-Terbutylazine CID:779516

https://www.simolecule.com/cdkdepict/depict.html

Living Data Connections

zenodo Search Upload Communities emma.schymanski@uni.lu

June 11, 2020

Dataset Open Access

Edit

New version

S68 | HSDBTPS | Transformation Products Extracted from HSDB Content in PubChem

LCSB-ECI; Krier, Jessy; Schymanski, Emma; PubChem Team; Bolton, Evan; Thiessen, Paul; Zhang, Jeff

This is the collection
PubChem on the NOR

https://www.norman-

HSDBTPS is a list of r
HSDB (Hazardous Su
10.5281/zenodo.382

Entries automatically

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Current repository **pubchem** | Current branch **master** | Fetch origin Last fetched 2 minutes ago

Changes 2 | History

No branches to compare

Update extractAnnotations.R
Emma Schymanski • Jun 9, 2020

HSDB Ref Info
Emma Schymanski • Jun 8, 2020

added new CIDs to HSDBTPS
Emma Schymanski • Jun 8, 2020

Update PCLite_eval_support.R
Emma Schymanski • Jun 8, 2020

Added S69 LUXPEST
Emma Schymanski • May 28, 2020

Update PCLite_eval_support.R
Emma Schymanski • May 25, 2020

Update user_PCLite_eval.R
Emma Schymanski • May 20, 2020

Update PCLite_eval_support.R

added new CIDs to HSDBTPS
Emma Schy
Added newly
annotations\tp
annotations\tp
annotations\tp
...\S68_HSDBTI
annotations\tp

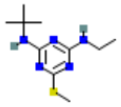
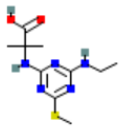
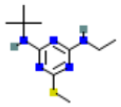
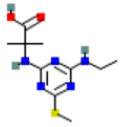
Preview

Predecessor_CID
13450
13450

8.5 Transformations

19 items View More Rows & Details Download

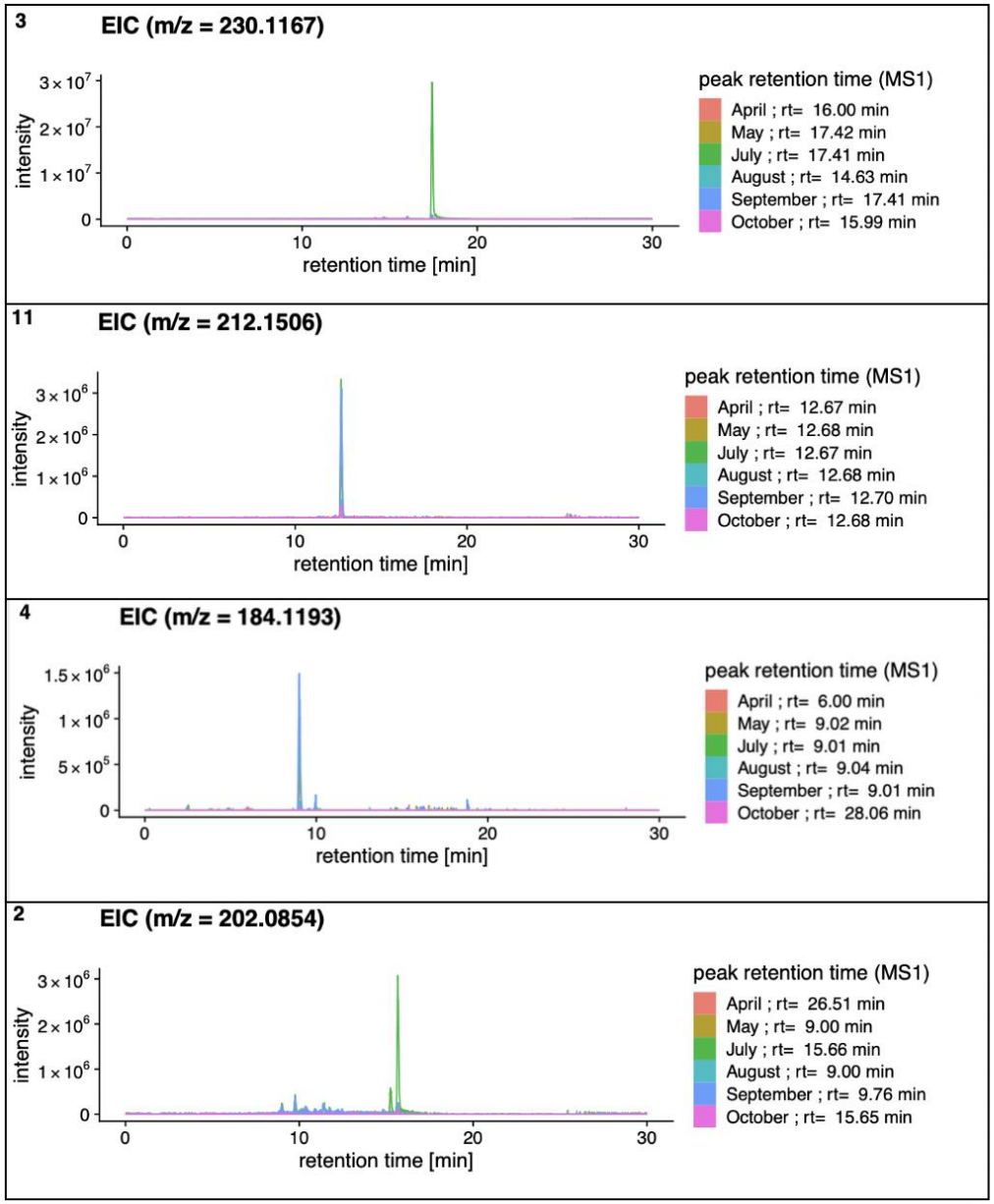
SORT BY Please Choose One

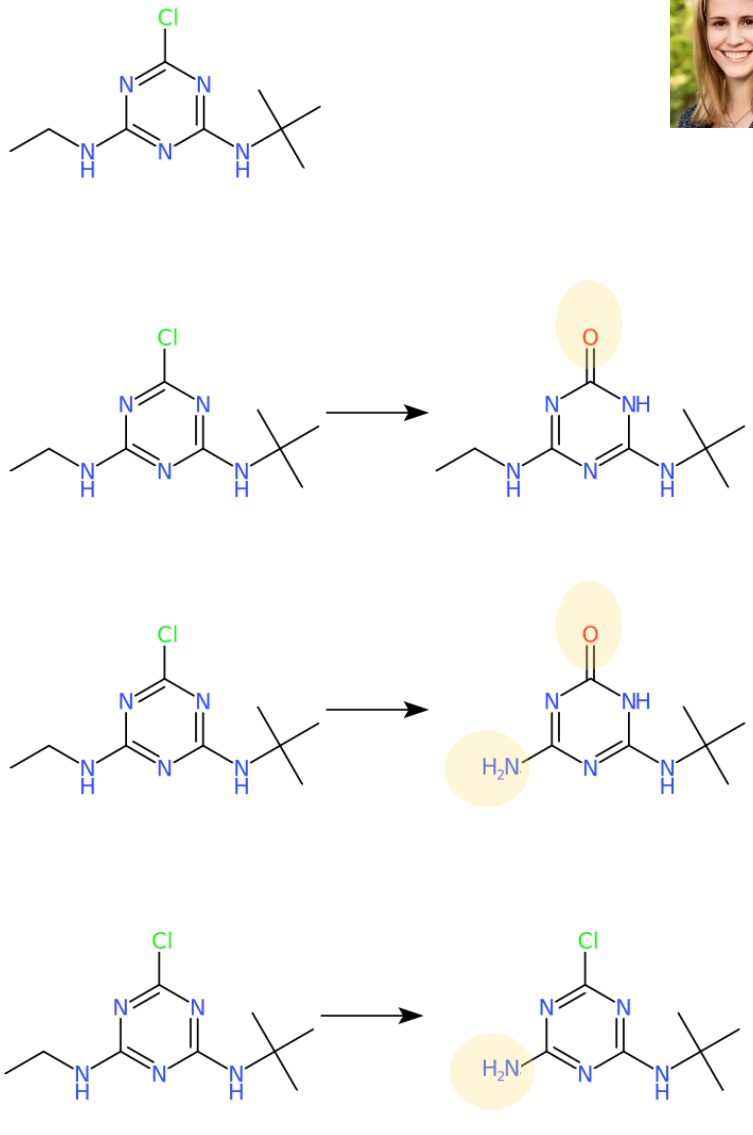
Predecessor Image	Predecessor Name	Transformation	Successor Image	Successor Name	Evidence DOI
	Terbutryn	Mammalian metabolism		2-[[4-(Ethylamino)-6-methylsulfanyl-1,3,5-triazin-2-yl]amino]-2-methylpropanoic acid	10.1002/bms.1200506
	Terbutryn	Mammalian metabolism		2-[[4-(Ethylamino)-6-methylsulfanyl-1,3,5-triazin-2-yl]amino]-2-methylpropanoic acid	10.5281/zenodo.38274

https://git-r3lab.uni.lu/eci/pubchem/

LCSB-ECI & PubChem Team. DOI 10.5281/zenodo.3890392

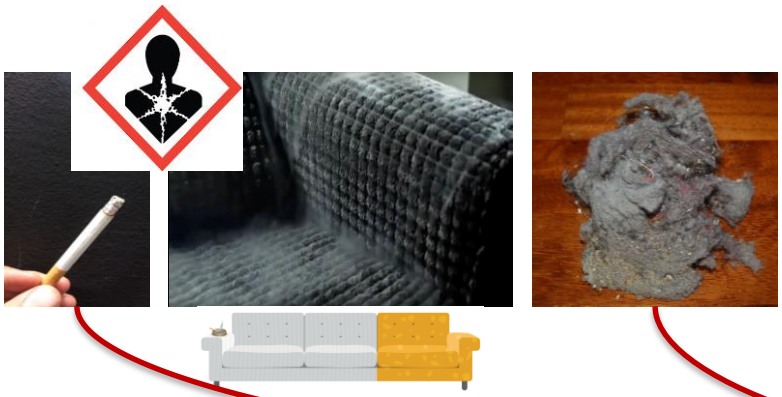
Pesticides & TPs over time (tent. IDs)





Jessy Krier (2020) Master's Thesis, defended July 2020. Modified from Figure 33.

More Examples? Thirdhand Smoke (THS) in Dust



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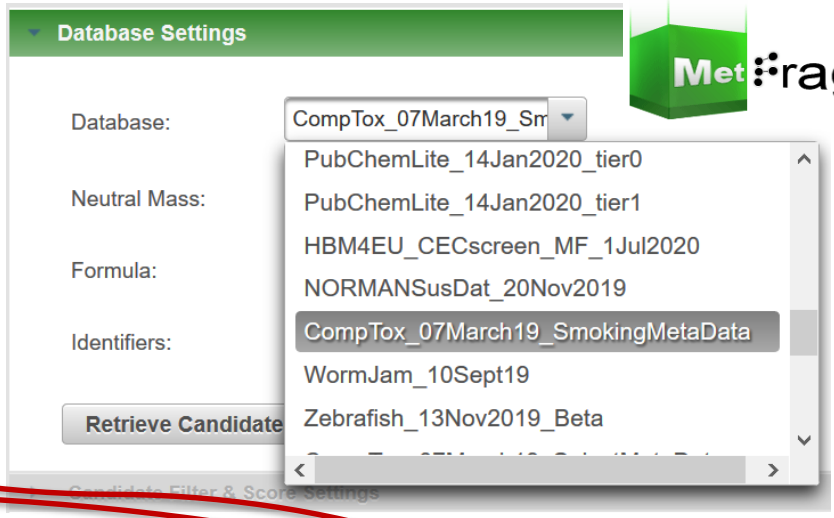
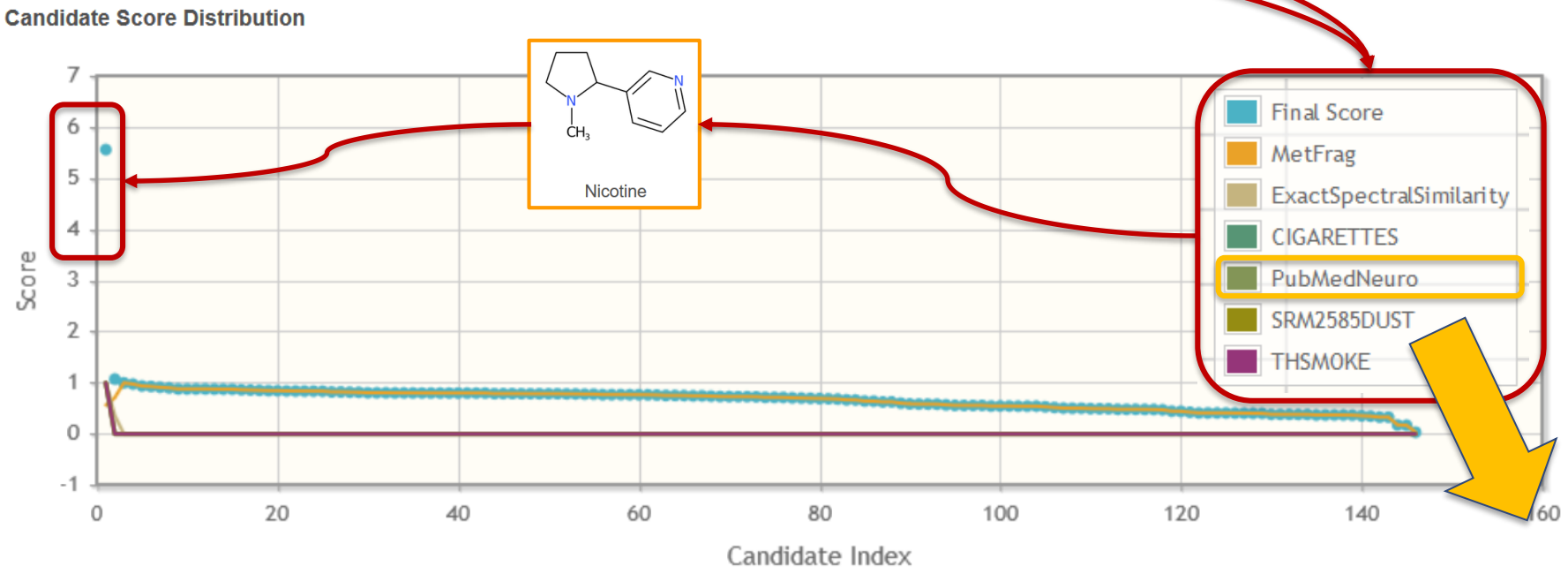


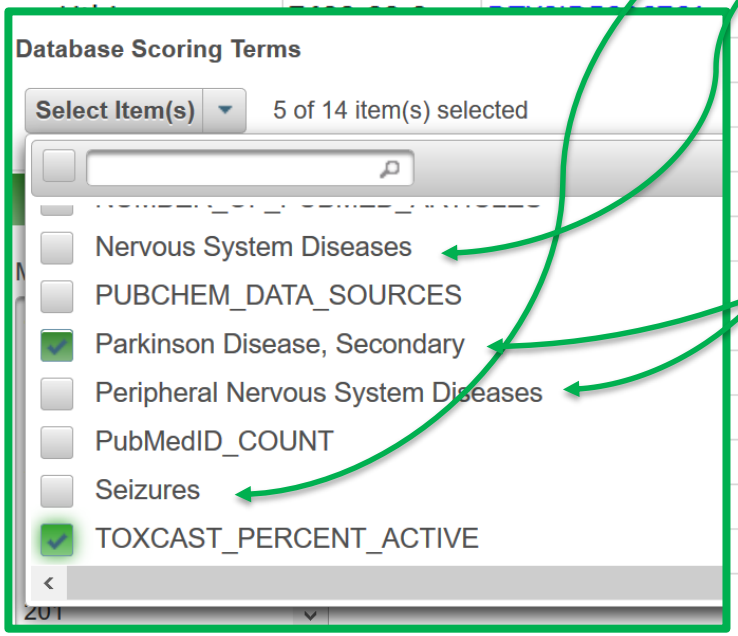


Schymanski, EL, Torres, S, & Ramirez, N. (2020). Thirdhand Smoke in House Dust. Zenodo. http://doi.org/10.5281/zenodo.3613472

New MetaData: Disease-Specific Reference Counts

S37 LitMinedNeuro: DOI: [10.5281/zenodo.3242298](https://doi.org/10.5281/zenodo.3242298)

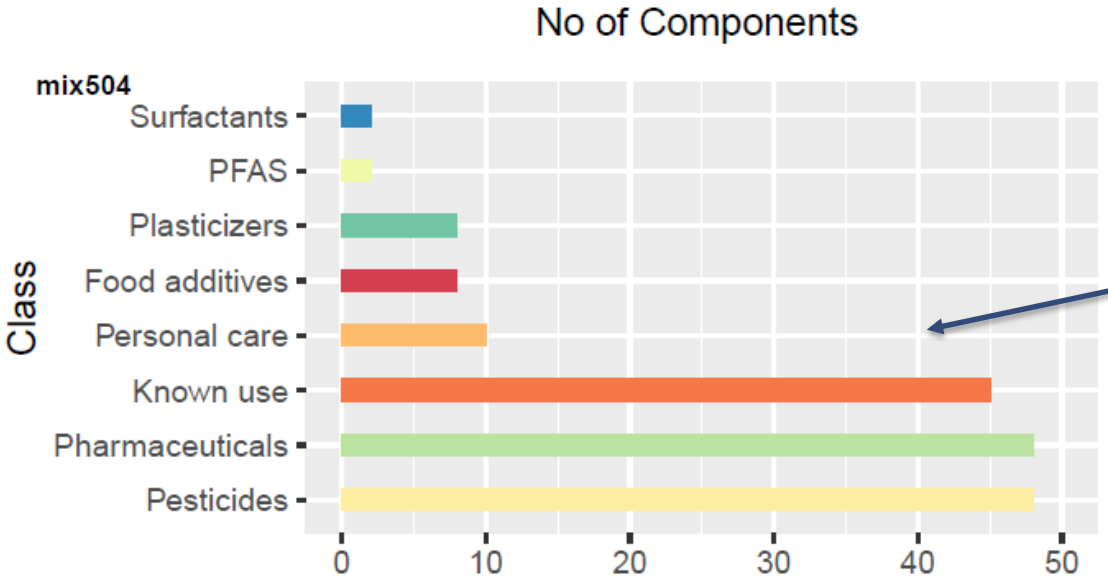
Chemical	CAS RN	DSSToxID	PMID Ct	Seizures	Nervous System Diseases	Peripheral Nervous System Diseases	Brain Diseases	Muscular Diseases	Basal Ganglia Diseases	Parkinson Disease, Secondary	Coma	Hallucinations	Tremor	Memory Disorders	Central Nervous
Cisplatin	15663-27-1	DTXSID4024983	1032	20	47	140	13	0	4	1	1	0	1	2	4
Ethanol	64-17-5	DTXSID9020584	768	100	23	11	18	26	1	3	20	6	17	54	2
Lead	7439-92-1	DTXSID2024161	740	28	107	68	102	4	2	2	1	3	4	19	30
			689	30	50	9	22	5	36	13	25	6	93	12	15
			666	32	10	3	65	6	10	18	45	5	18	4	2
			638	1	24	0	11	0	6	289	0	0	5	0	1
			567	17	59	125	15	5	1	1	5	3	2	1	8
			560	37	24	25	16	9	3	1	9	3	8	4	6
			555	6	6	1	10	6	153	51	4	4	11	1	0
			530	151	16	0	8	0	2	3	3	8	6	12	11
			489	8	3	0	3	2	2	0	9	4	1	0	5
			485	4	43	217	9	14	0	0	0	0	0	1	2
			477	13	41	1	105	4	0	0	1	0	1	13	12
			464	150	26	15	3	2	0	0	8	4	6	2	10
			451	17	25	1	79	4	0	1	5	0	1	9	18
			450	6	79	22	23	2	3	5	2	2	38	7	25

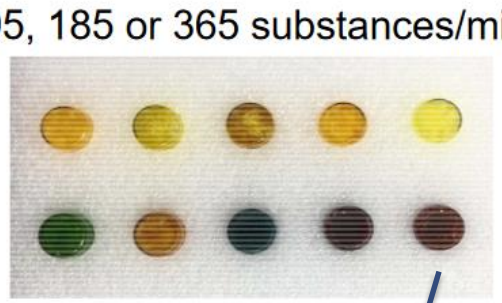


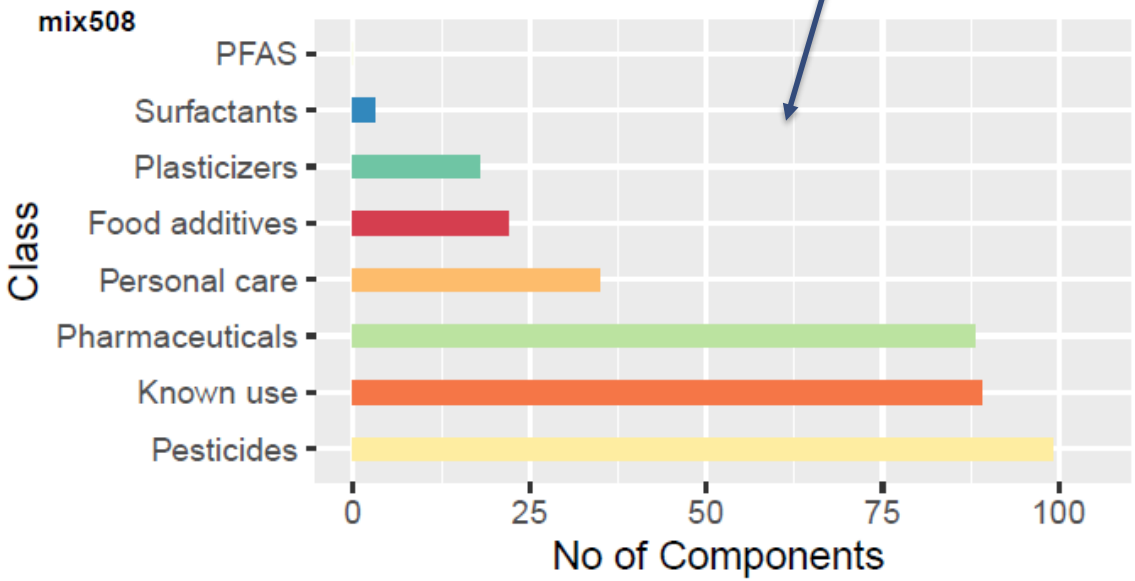
Schymanski *et al.* DOI: [10.1039/C9EM00068B](https://doi.org/10.1039/C9EM00068B) (Perspective) Environ. Sci.: Processes Impacts, 2020.

Future Perspectives

- Rapid classification / interpretation of large collections







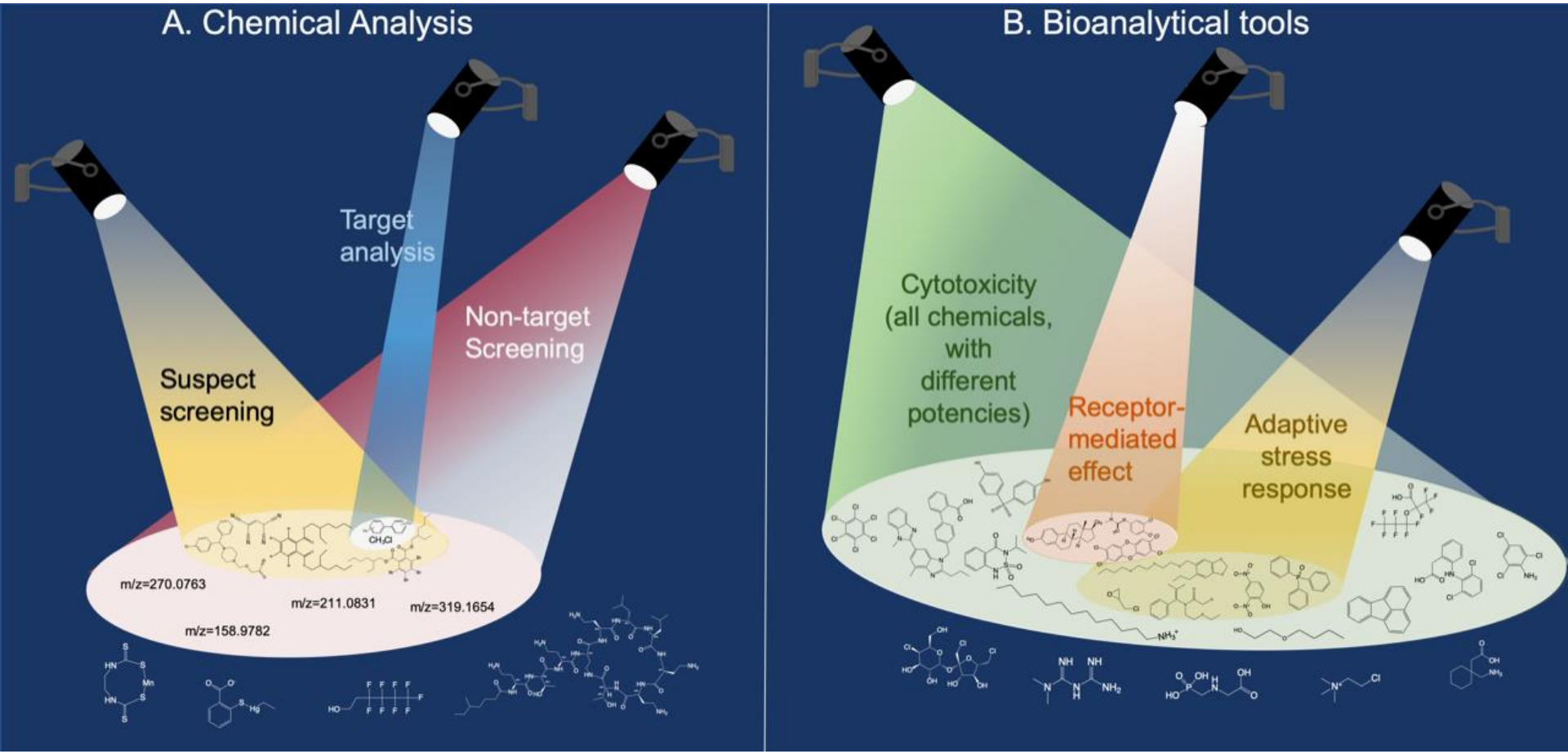
ENTACT: Elin Ulrich *et al.* 2018, https://www.epa.gov/sites/production/files/2018-06/documents/comptox_cop_6-28-18.pdf and

Ulrich, EM, et al. (2019) Anal Bioanal Chem. DOI: 10.1007/s00216-018-1435-6

Classification Figures:

Anjana Elapavalore, ECI (Master's thesis)

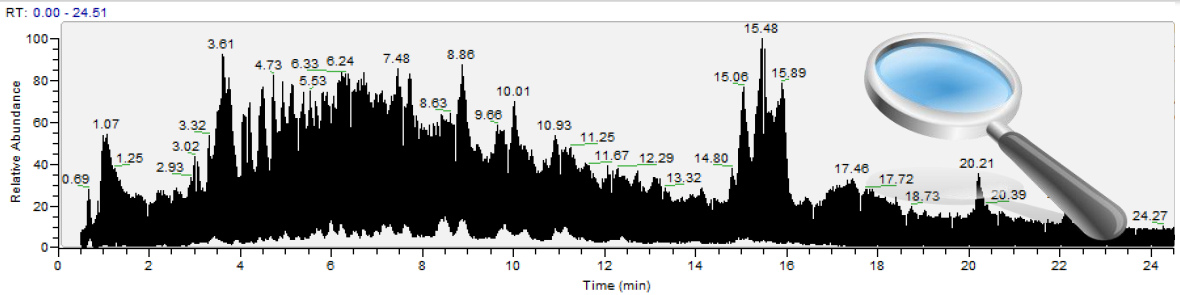
Next Big Challenge: Connection to Effects!



Modified from Escher, Stapleton, Schymanski (2020). Science. DOI: 10.1126/science.aay6636

Take Home Messages

- Challenge:
  Increase ***% identified***
  Improve ***interpretation***



More? Check out our presentations at: https://zenodo.org/communities/lcsb-eci/

Take Home Messages

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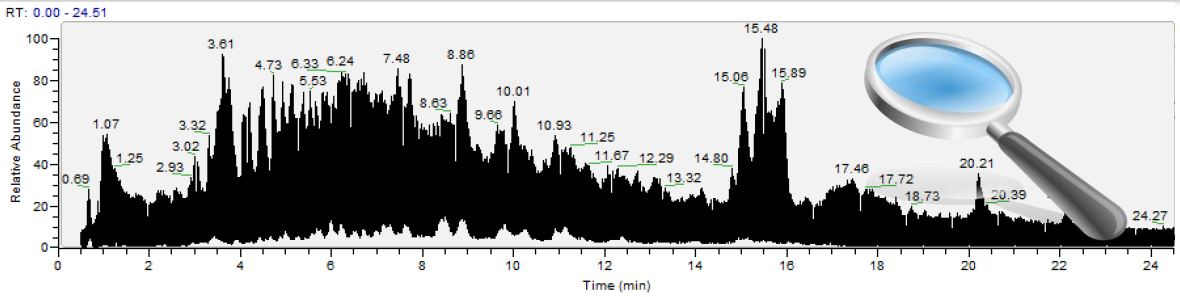
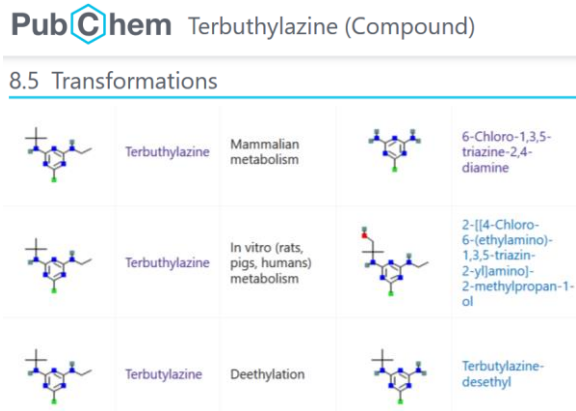
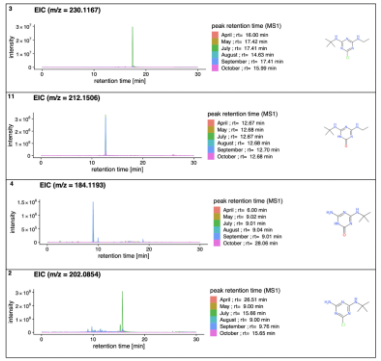
  Improve ***interpretation***



- ***"Environmental Cheminformatics" is …***
  - Capturing expert knowledge
    Machine and ***human*** readable
  - ***Connecting*** this to environmental observations
  - Identifying and ***closing knowledge gaps***
  - Supporting ***interpretation*** of complex data





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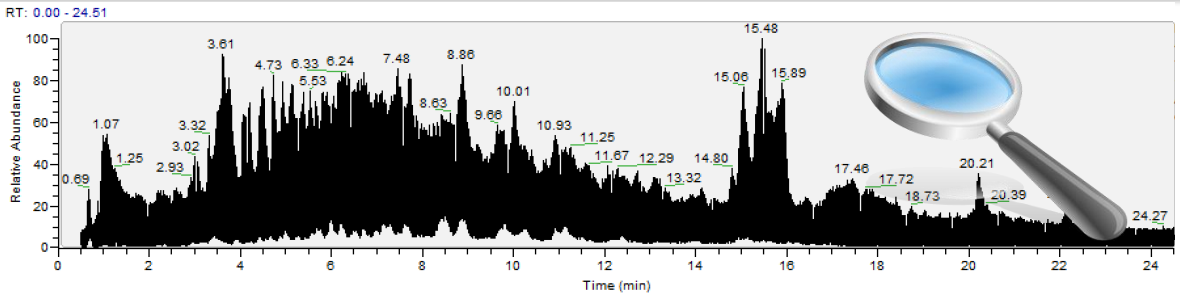

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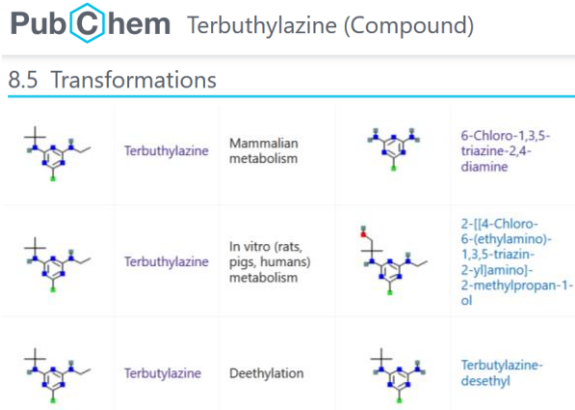

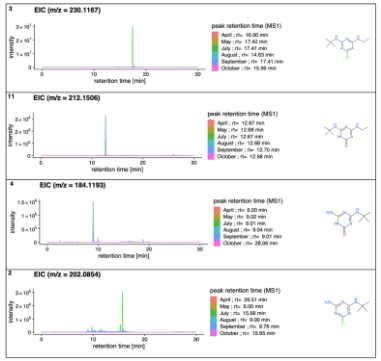

- Finally … information in the public domain helps ***everybody***
  - You never know when it will help you ☺

Acknowledgements

Luxembourg National Research Fund

U.S. National Library of Medicine
National Center for Biotechnology Information

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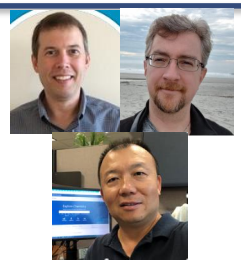
Ministry of the Environment, Climate and Sustainable Development



Evan Bolton, Paul Thiessen, Jeff (Jian) Zhang, PubChem Team

Christoph Ruttkies, Steffen Neumann, MetFrag Team

Simone Witzmann, Vero Briche, Rick Helmus, Jessy Krier Todor Kondic, Emma Schymanski, Anjana Elapavalore, Hiba Mohammed Taha; Mira Narayanan, Corey Griffith, Lorenzo Favilli, German Preciat, Adelene Lai, Randolph Singh

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Further Information:

https://pubchem.ncbi.nlm.nih.gov/

https://git-r3lab.uni.lu/eci/shinyscreen

https://git-r3lab.uni.lu/eci/pubchem/

https://ipb-halle.github.io/MetFrag/

https://www.norman-network.com/nds/SLE/

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