Community Resources Connecting Chemistry and Toxicity Knowledge to Environmental Observations

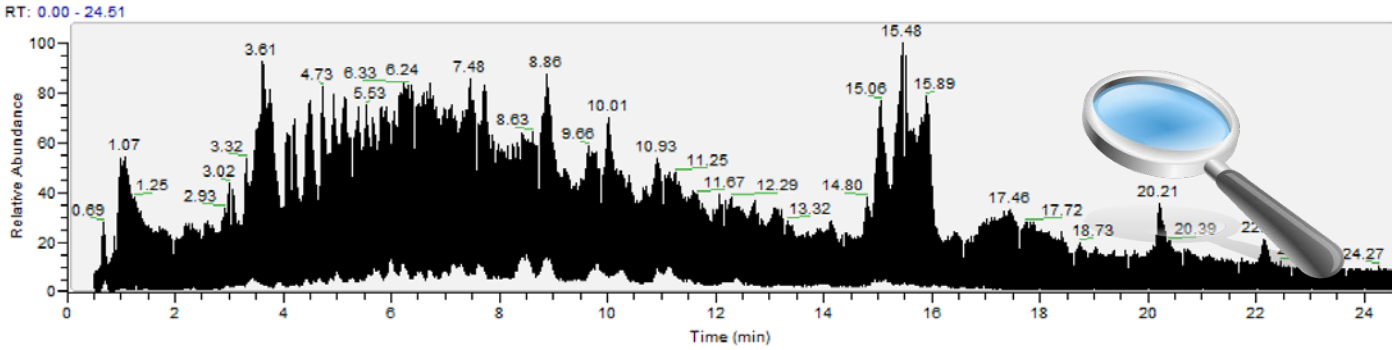

Image © www.seanoakley.com/

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University of Luxembourg
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Antony J. Williams
National Centre for Computational Toxicity (NCCT),
US Environmental Protection Agency (US EPA), NC, USA

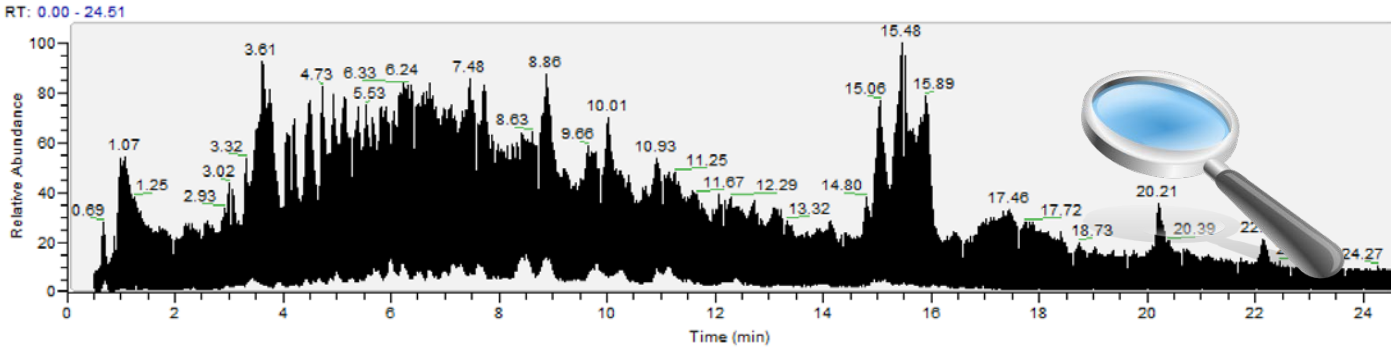
The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

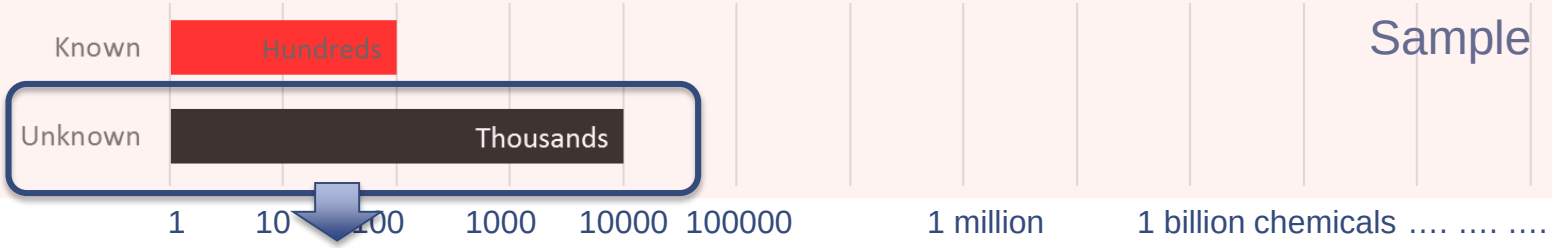
(European) Environmental Community (subset!)

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

Our (Community) Challenge: Identifying Chemicals

High resolution mass spectrometry



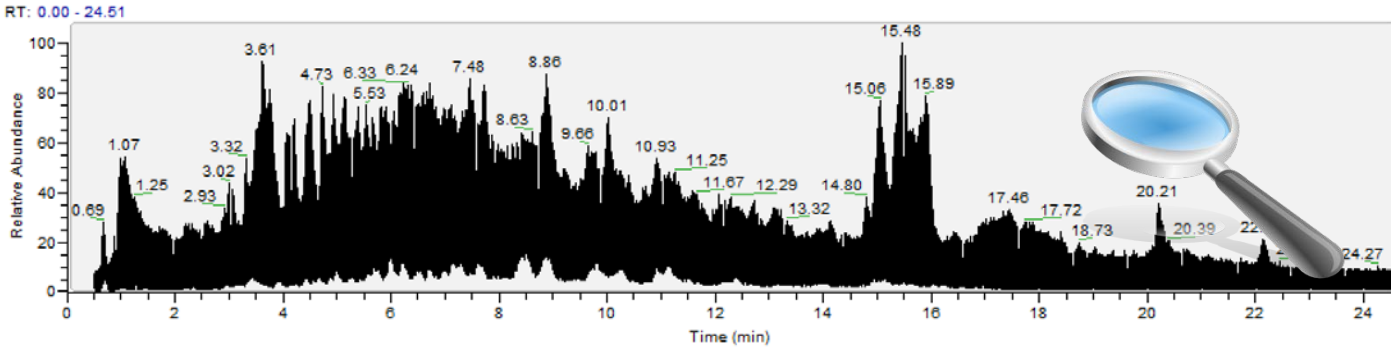


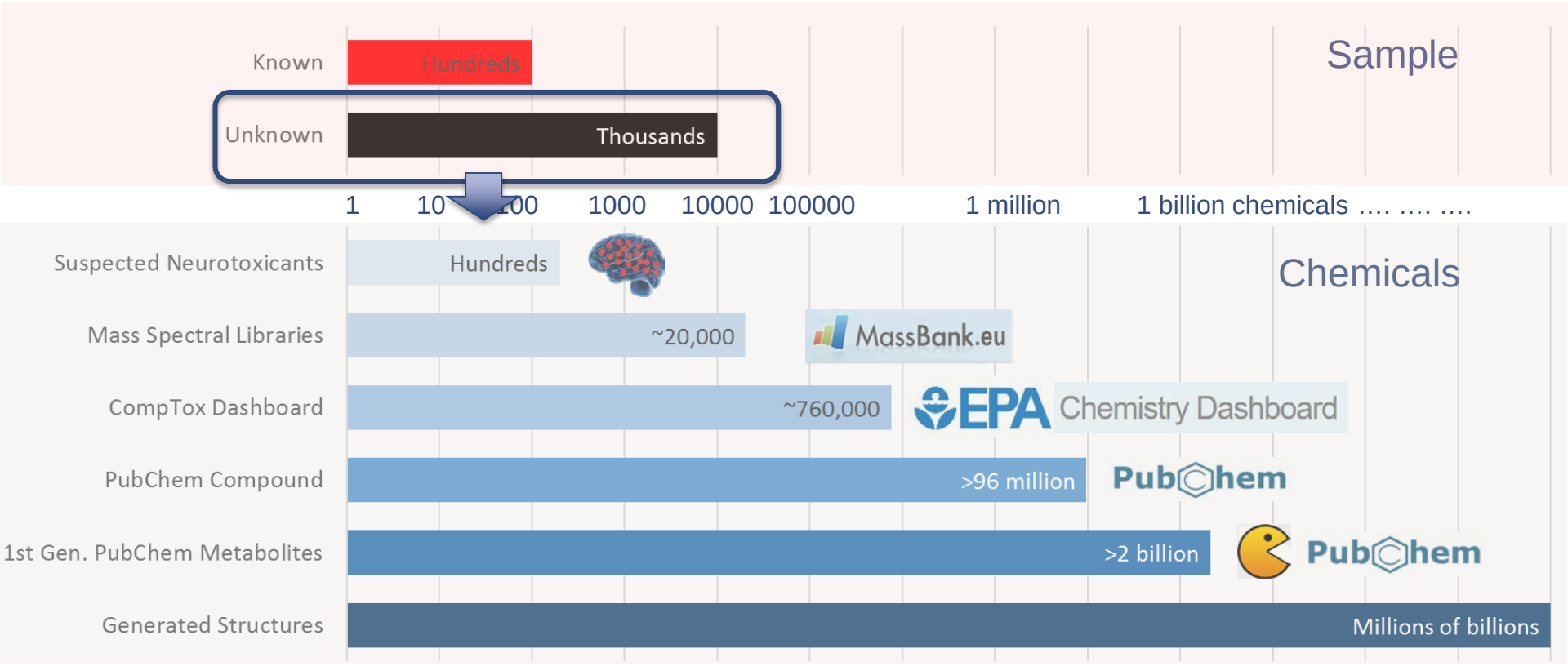
Data: Schymanski *et al* 2014, Environ. Sci. Technol. DOI: 10.1021/es4044374; Hollender *et al* 2017 DOI: 10.1021/acs.est.7b02184

Our (Community) Challenge: Identifying Chemicals

High resolution mass spectrometry

AND connecting chemical knowledge





Data: Schymanski *et al* 2014, DOI: 10.1021/es4044374; https://www.slideshare.net/EmmaSchymanski/small-molecules-in-big-data-analytica-munich

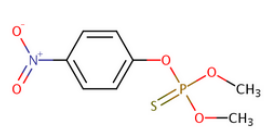
Suspected Neurotoxicants

Chemistry Dashboard | HUMANNEUROTOX

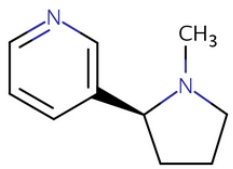
Description: A set of chemicals listed as neurotoxicants in the article "Developmental Neurotoxicity of Industrial Chemicals" by Grandjean and Landrigan, The Lancet, Volume 368, No. 9553, p2167–2178, 16 December 2006 (https://doi.org/10.1016/S0140-6736(06)69665-7). The authors list 5 of these chemicals additionally as developmental neurotoxins (arsenic and arsenic compounds; lead and lead compounds; methylmercury, toluene; polychlorinated biphenyls).

Number of Chemicals: 190

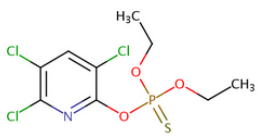
https://comptox.epa.gov/dashboard/chemical_lists/humanneurotox



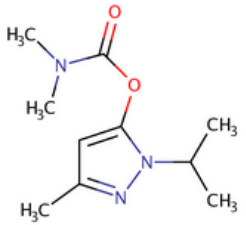
Methyl parathion
298-00-0



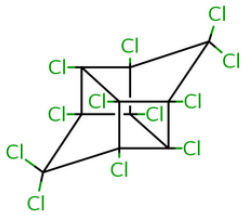
Nicotine
54-11-5



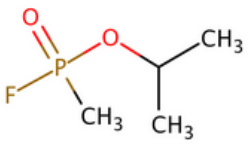
Chlorpyrifos
2921-88-2



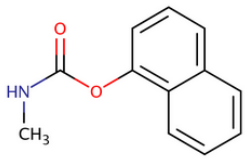
Isolane
119-38-0



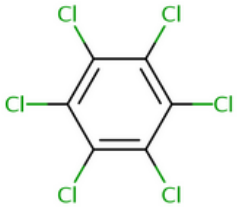
Mirex
2385-85-5



Sarin
107-44-8



Carbaryl
63-25-2



Hexachlorobenzene
118-74-1

Chemicals: Grandjean and Landrigan, 2006 DOI: 10.1016/S0140-6736(06)69665-7 and Legradi *et al.* (to be submitted)

Mass Spectral Libraries

MassBank.eu

http://massbank.eu/MassBank

https://github.com/MassBank/MassBank-data/

>46,000 spectra
32 contributors

MassBank norman High Resolution Mass Spectral Database

Home | Quick Search | Peak Search | Record Index | Statistics | Imprint/Data privacy MassBank ID: Go

European MassBank (NORMAN MassBank)

Mass Spectral Libraries

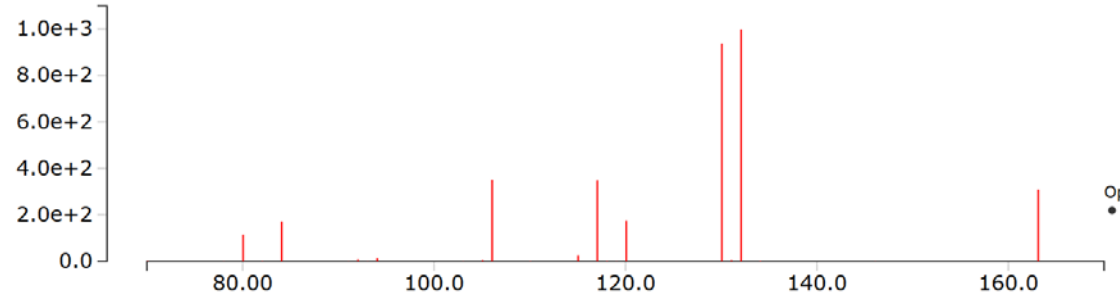
MassBank.eu

MassBank Record: EQ300804

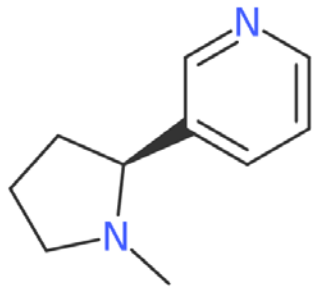
Home | Quick Search | Peak Search | Record Index | Statistics | Imprint/Data privacy MassBank ID: Go

Nicotine; LC-ESI-QFT; MS2; CE: 60; R=35000; [M+H]+

Mass Spectrum



Chemical Structure




```
ACCESSION: EQ300804
RECORD_TITLE: Nicotine; LC-ESI-QFT; MS2; CE: 60; R=35000; [M+H]+
DATE: 2015.08.25
AUTHORS: Beck B, Stravs M, Schymanski E, Singer H, Department of Environmental Chemistry, Eawag
LICENSE: CC BY
COPYRIGHT: Copy
PUBLICATION:
COMMENT: CONFID
COMMENT: EAWAG_
CH$NAME: Nicotine
CH$NAME: 3-[(2S)-1-methylpyrrolidin-2-yl]pyridine
CH$NAME: 3-[(2S)-1-methyl-2-pyrrolidinyl]pyridine
CH$COMPOUND_CLASS: N/A; Environmental Standard
CH$FORMULA: C10H14N2
CH$EXACT_MASS: 162.11570
CH$SMILES: n1cc(ccc1)[C@H]2
CH$IUPAC: InChI=1S/C10H14N2/
CH$LINK: CAS 54-11-5
CH$LINK: CHEBI 17688
CH$LINK: HMDB HMDB01934
CH$LINK: KEGG C00745
CH$LINK: PUBCHEM CID:89594
CH$LINK: INCHIKEY SNICXCGAK
CH$LINK: CHEMSPIDER 80863
AC$INSTRUMENT: Q Exactive Orbitrap Thermo Scientific
AC$INSTRUMENT_TYPE: LC-ESI-QFT
AC$MASS_SPECTROMETRY: MS_TYPE MS2
AC$MASS_SPECTROMETRY: IONIZATION ESI
AC$MASS_SPECTROMETRY: ION_MODE POSITIVE
AC$MASS_SPECTROMETRY: FRAGMENTATION_MODE HCD
AC$MASS_SPECTROMETRY: COLLISION_ENERGY 60 (nominal)
AC$MASS_SPECTROMETRY: RESOLUTION 35000
AC$CHROMATOGRAPHY: COLUMN_NAME XBridge C18 3.5um, 2.1x50mm, Waters
AC$CHROMATOGRAPHY: FLOW_GRADIENT 90/10 at 0 min, 50/50 at 4 min, 5/95 at 17 min
AC$CHROMATOGRAPHY: FLOW_RATE 200 ul/min
AC$CHROMATOGRAPHY: RETENTION_TIME 0.9 min
AC$CHROMATOGRAPHY: SOLVENT A water with 0.1% formic acid
AC$CHROMATOGRAPHY: SOLVENT B methanol with 0.1% formic acid
PK$NUM_PEAK: 24
PK$PEAK: m/z int. rel.int.
  70.065 454569.9 3
  78.0334 160392.5 1
  80.0494 14365987.5 115
  82.065 352108.2 2
  84.0807 21553065.2 172
  91.0541 243012.2 1
  92.0494 1173136.6 9
  93.0571 190301.4 1
  94.065 1842197.3 14
  103.054 194746.7 1
  105.0698 991130.4 7
  106.065 43816128.6 351
  110.0598 348436.9 2
  115.0541 3367681.5 27
  117.0571 43503063 349
  118.0649 392125 3
  119.0726 230767.3 1
  120.0806 21877380.1 175
  130.065 116905175 937
  131.073 880898.8 7
  132.0806 124509966.1 999
  134.0962 389380.4 3
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//
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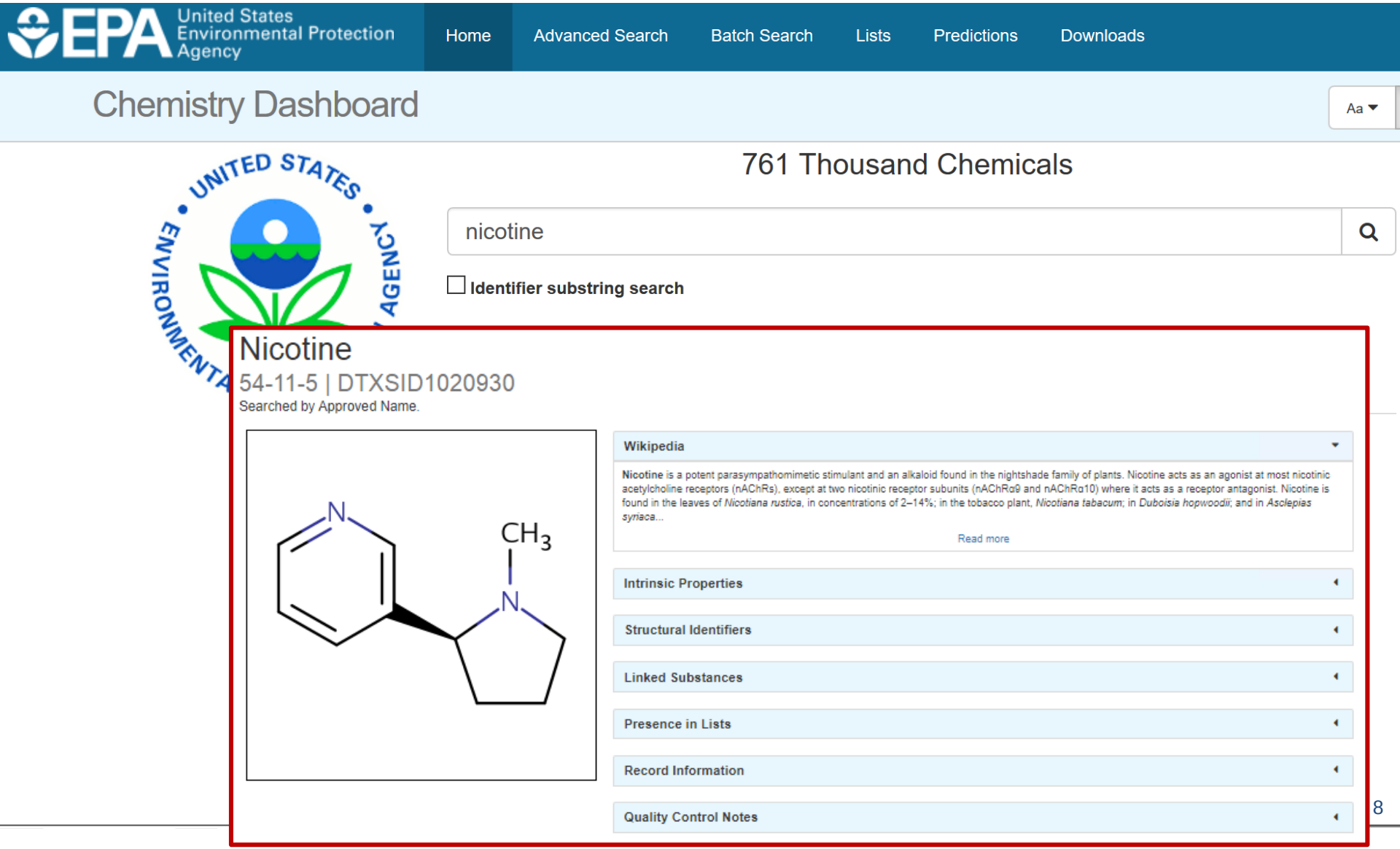
CompTox Chemistry Dashboard

https://comptox.epa.gov/dashboard/



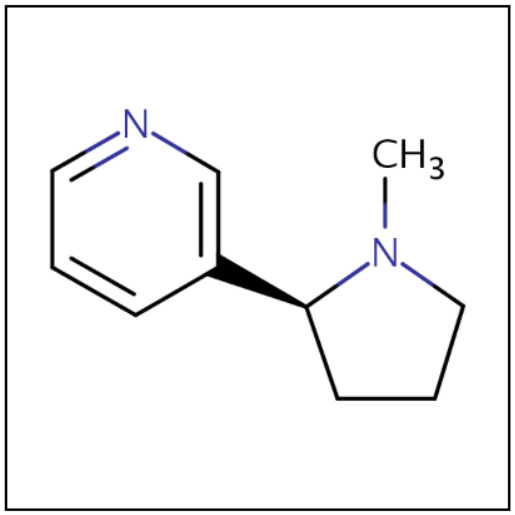
CompTox Chemistry Dashboard – Presence in Lists

https://comptox.epa.gov/dashboard/chemical_lists

Nicotine

54-11-5 | DTXSID1020930

Searched by Approved Name.



Wikipedia

Intrinsic Properties

Structural Identifiers

Linked Substances

Presence in Lists

Federal

TOX21SL: Tox21 Screening Library | NIOSH Skin Notation Profiles | NIOSH International Chemical Safety Cards | NIOSH Pocket Guide to Chemical Hazards | NIOSH IDLH Values | TOXCAST - EPA ToxCast Screening Library

US State

California Office of Environmental Health Hazard Assessment

International

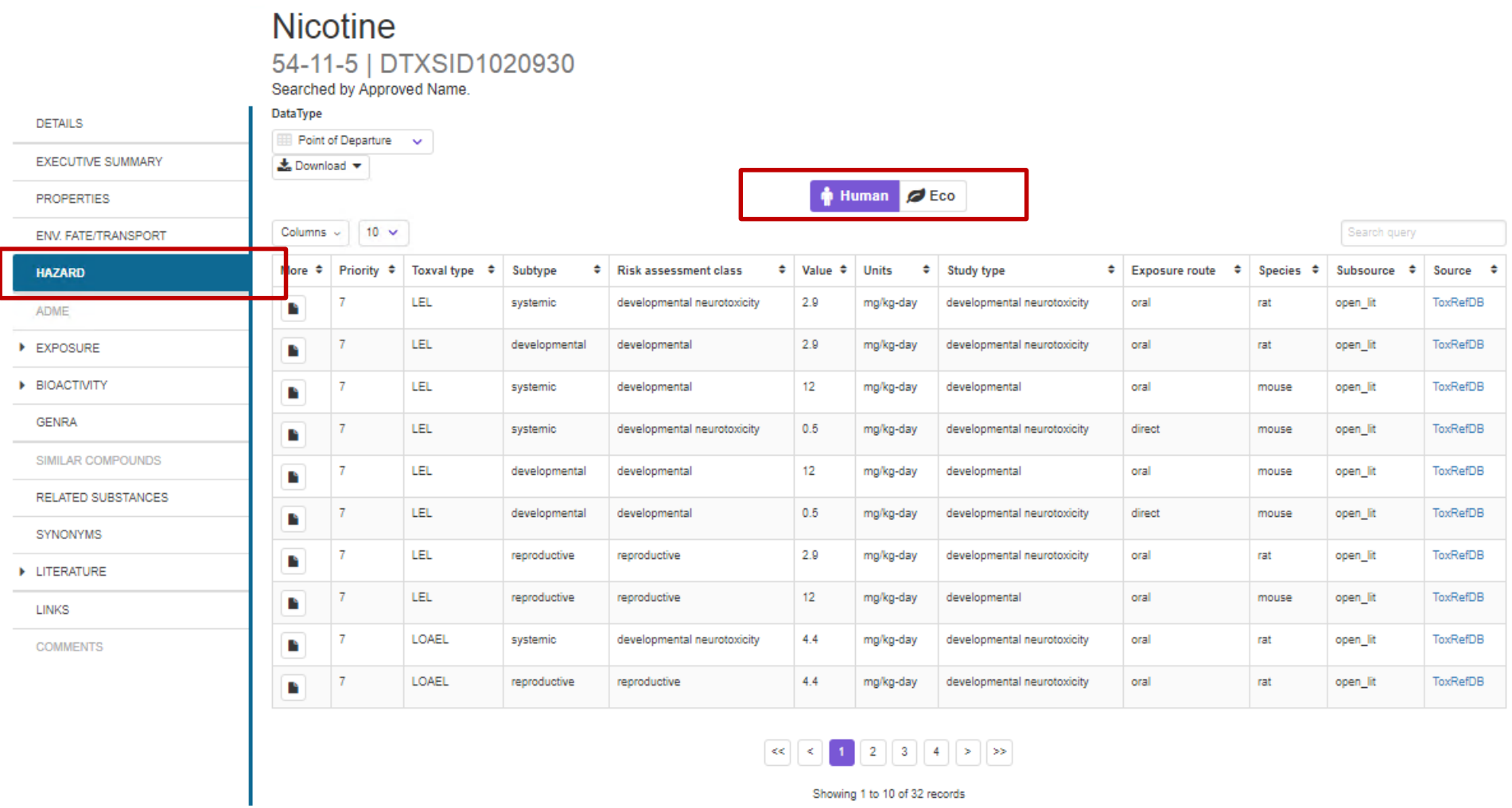
GENRA | Grace Patlewicz's Chemicals of Interest | Superfund Chemicals | REACH Dossier Chemicals | KEMI List of Substances on the Market

Other

DNT Screening Library | MassBank Reference Spectra Collection | NORMAN Collaborative Trial 2015 Targets and Suspects | STOFF-IDENT Database of Water-Relevant Substances | National Environmental Methods Index | EDSP Universe | 40CFR355 | TSCAACTIVE

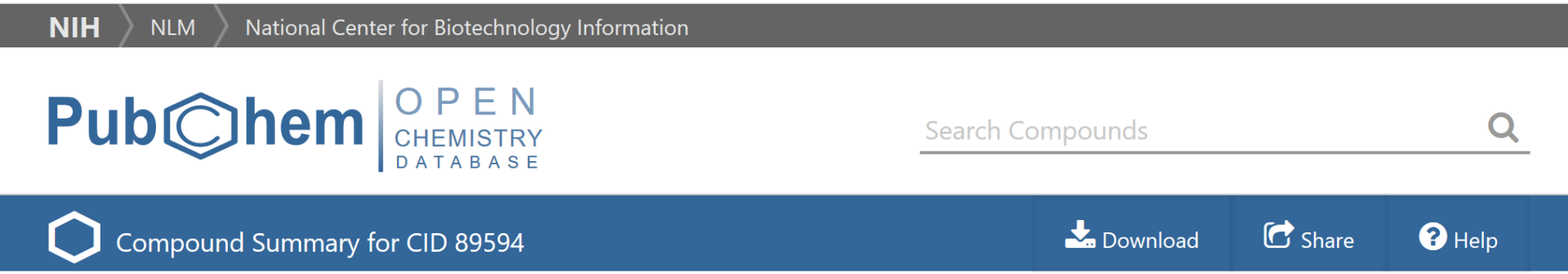
CompTox Chemistry Dashboard – Additional Data

https://comptox.epa.gov/dashboard/



PubChem

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



Connecting Resources in MetFrag

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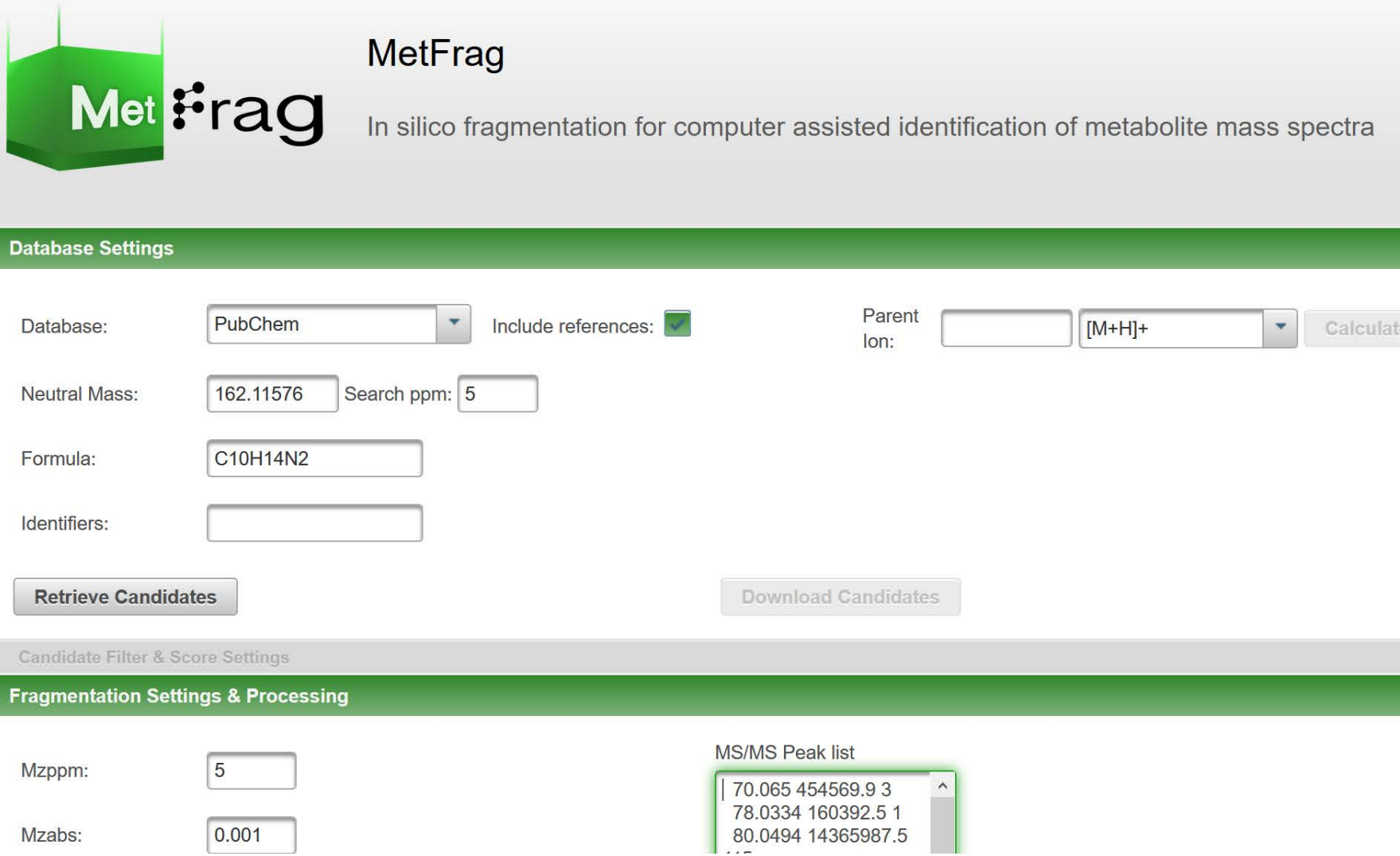
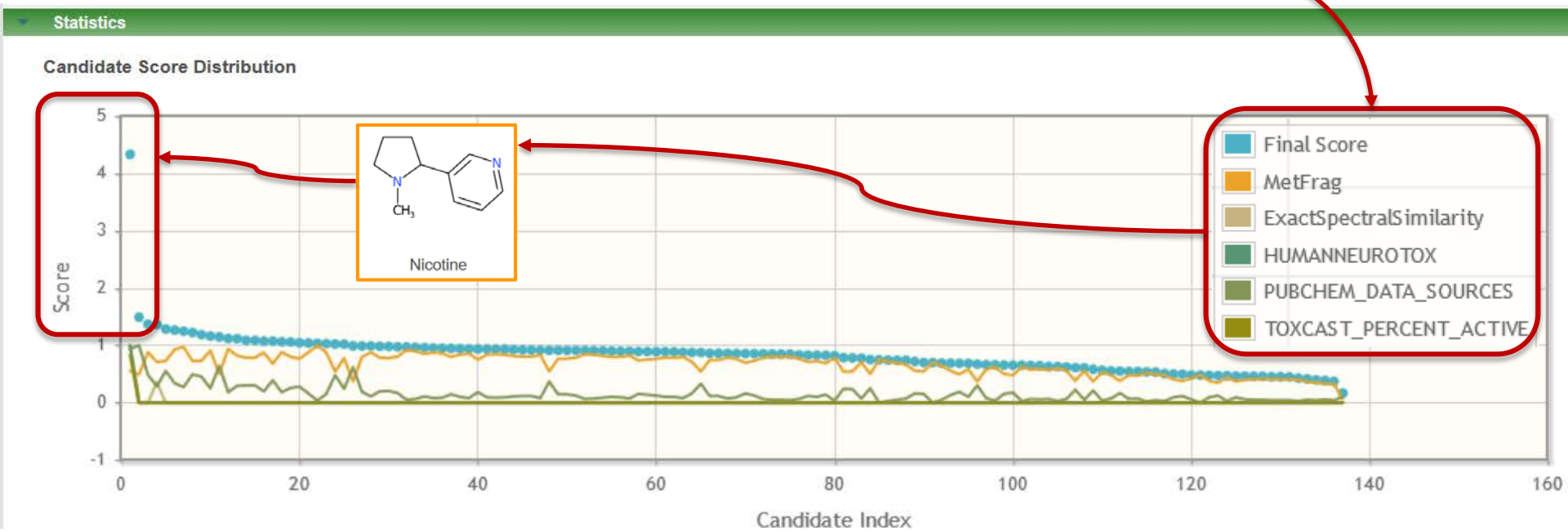


https://msbi.ipb-halle.de/MetFragBeta/ AND https://comptox.epa.gov/dashboard/dsstoxdb/batch_search (MetFrag Export)

Connecting Resources in MetFrag

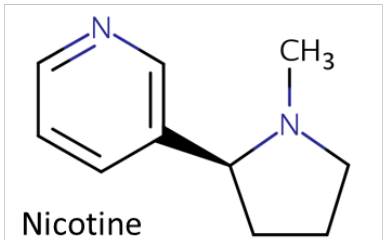
Combined evidence clearly highlights potential neurotoxicant among chemical candidates



https://msbi.ipb-halle.de/MetFragBeta/ ; https://comptox.epa.gov/dashboard/ ; https://massbank.eu ; http://normandata.eu/

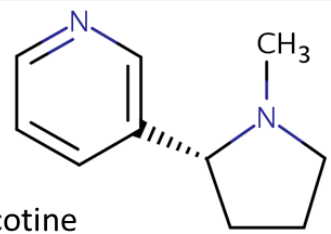
Metadata & Different Chemical Forms

LEGEND: Name, SMILES
DTXSID | InChIKey 1st Block
CAS | **Monoiso. Mass** | logP | **Sources**
Data on: **Toxicity | Exposure | Bioassays**



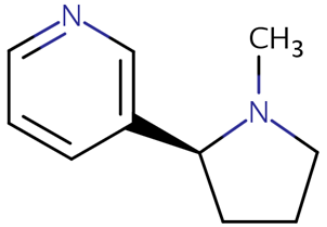
Nicotine

CN1CCC[C@H]1C1=CN=CC=C1
DTXSID1020930| SNICXCGAKADSCV
54-11-5 | **162.1157**| 0.929| **72**
Tox: **yes**| Expo: **yes**| Bioassay: **yes**



D-Nicotine

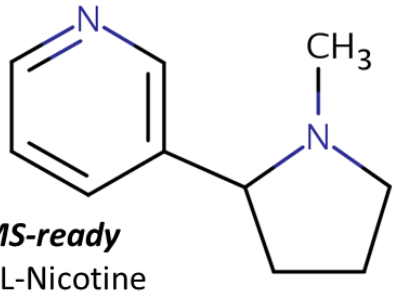
CN1CCC[C@@H]1C1=CN=CC=C1
DTXSID0046351| SNICXCGAKADSCV
25162-00-9 | **162.1157**| 0.929| **20**
Tox: **no**| Expo: **yes**| Bioassay: **yes**



HCl

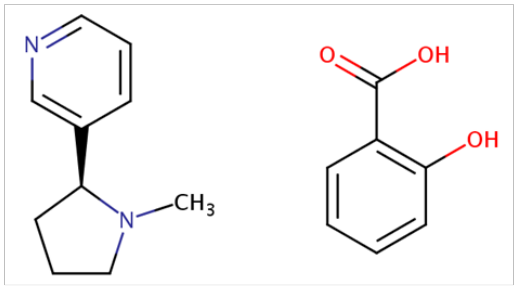
Nicotine hydrochloride

Cl.CN1CCC[C@H]1C1=CN=CC=C1
DTXSID6020931| HDJBTCAJIMNXEW
2820-51-1 | **198.0924** | 0.929| **9**
Tox: **no**| Expo: **yes**| Bioassay: **yes**



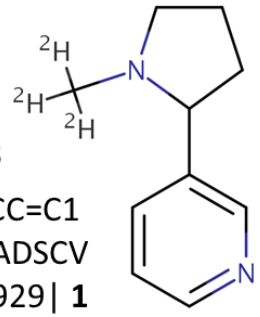
MS-ready
DL-Nicotine

CN1CCCC1C1=CN=CC=C1
DTXSID3048154 | SNICXCGAKADSCV
22083-74-5 | **162.1157**| 0.953| 9
Tox: **yes**| Expo: **no**| Bioassay: **yes**



Benzoic acid, 2-hydroxy-, compd. with
3-[(2S)-1-methyl-2-pyrrolidinyl]pyridine (1:1)

OC(=O)C1=C(O)C=CC=C1.CN1CCC[C@H]1C1=CN=CC=C1
DTXSID5075319| AIBWPBUAKCMKNS
29790-52-1| **300.1474**| 0.929| **6**
Tox: **no**| Expo: **yes**| Bioassay: **no**

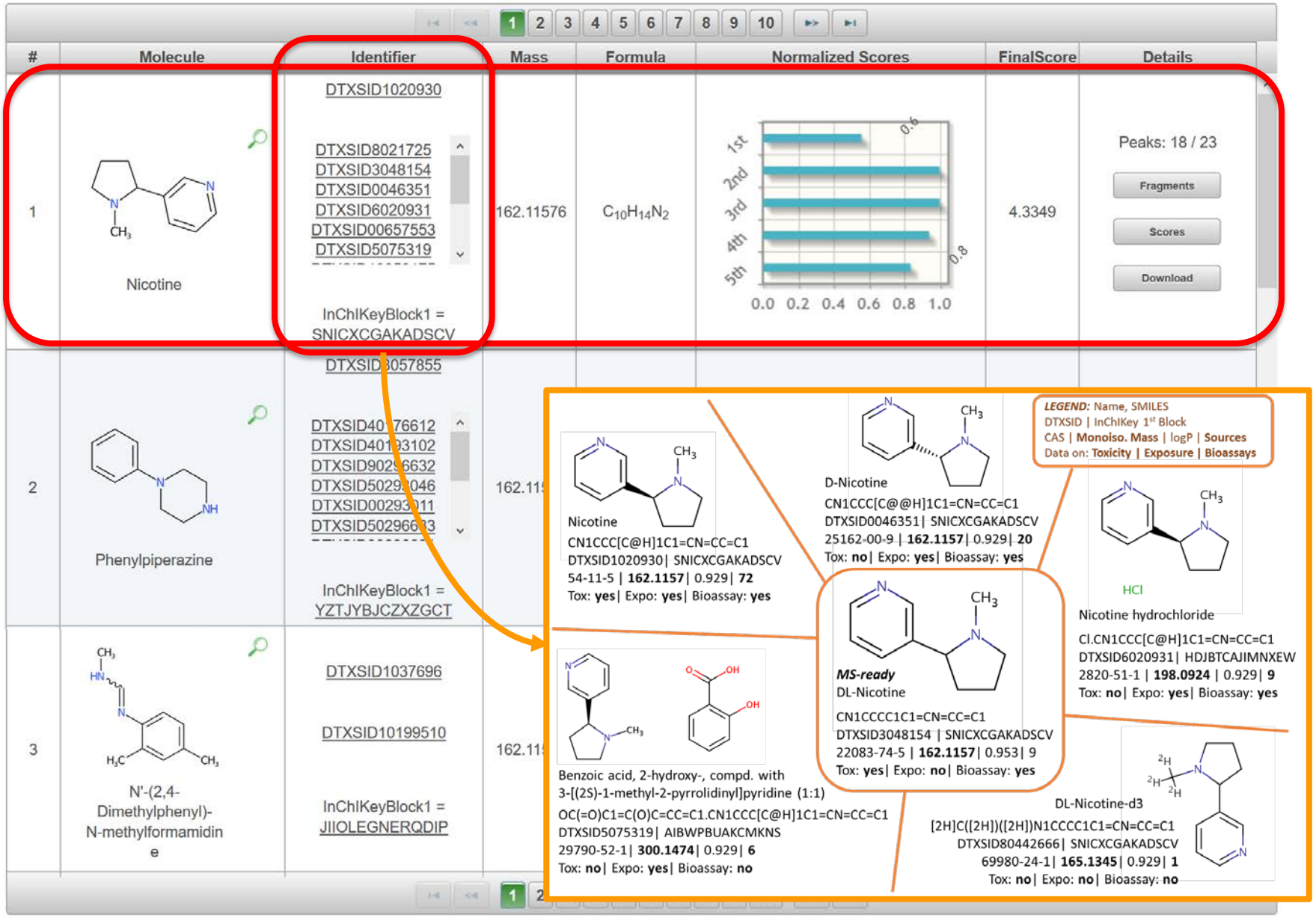


DL-Nicotine-d3

[2H]C([2H])([2H])N1CCCC1C1=CN=CC=C1
DTXSID80442666| SNICXCGAKADSCV
69980-24-1| **165.1345**| 0.929| **1**
Tox: **no**| Expo: **no**| Bioassay: **no**

Schymanski & Williams, 2017, ES&T51 (10), pp 5357–5359. DOI: 10.1021/acs.est.7b01908

Connecting Resources in MetFrag

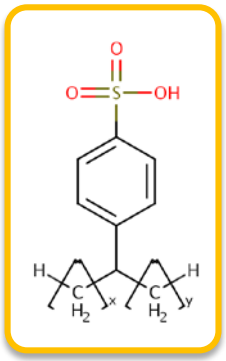


Example from: Schymanski & Williams, 2017, ES&T, 51 (10), pp 5357–5359. DOI: 10.1021/acs.est.7b01908

Connecting and Enhancing Open Resources

- Sharing knowledge is a win-win situation

2014



MassBank.eu

NORMAN suspects

EPA Chemistry Dashboard

2015: found in waters across Europe

2016: 1 datapoint cross-annotates 3072 in GNPS

Hits in GNPS MassIVE datasets:

Surfactants: http://goo.gl/7sY9Pf

2017: Early-Warning System is born

NORMAN NEWS

2018: Highlighted in

Science

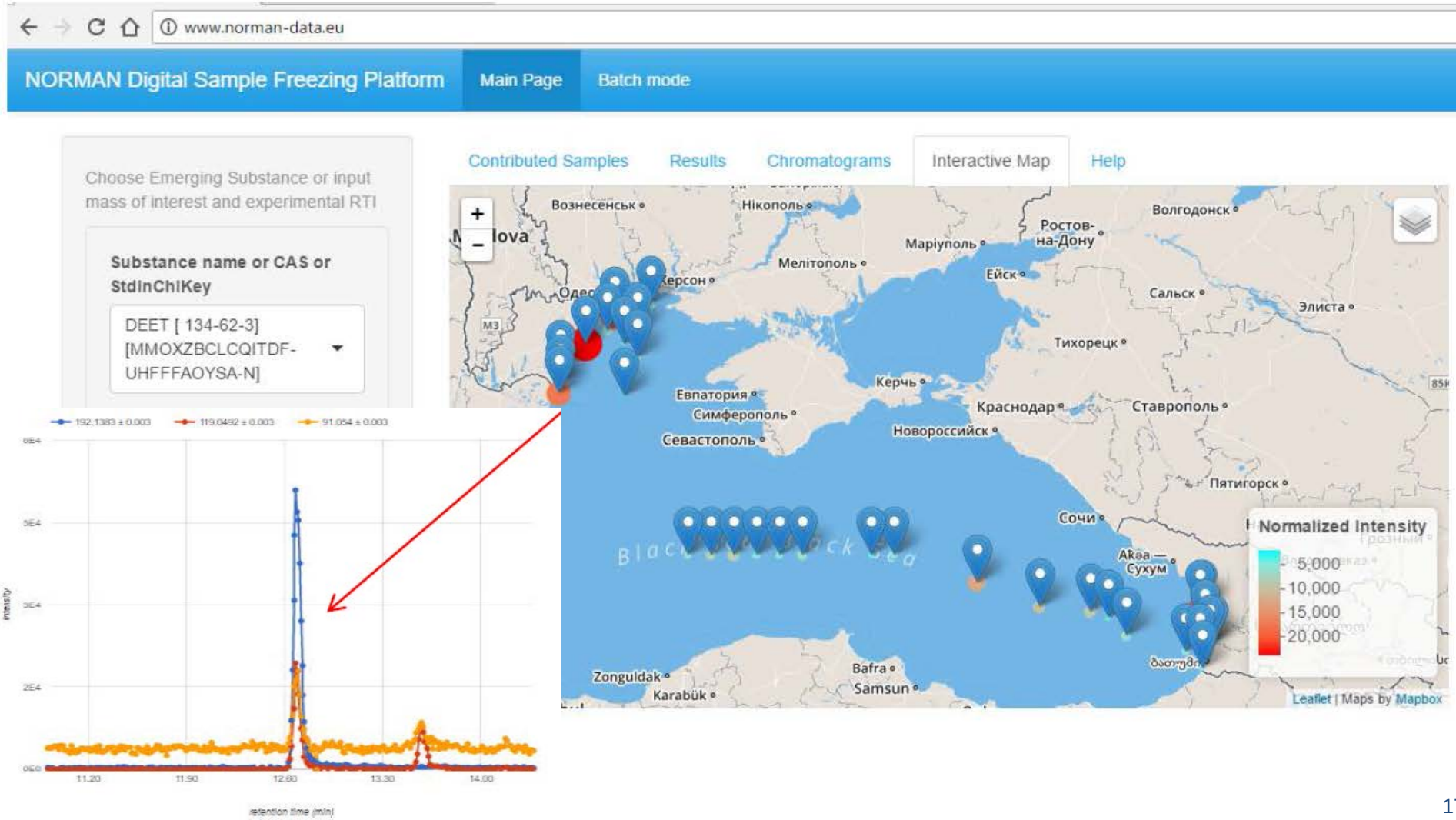
CHEMISTRY

Early warning about emerging contaminants

https://www.slideshare.net/EmmaSchymanski/small-molecules-in-big-data-analytica-munich

NORMAN Digital Sample Freezing Platform

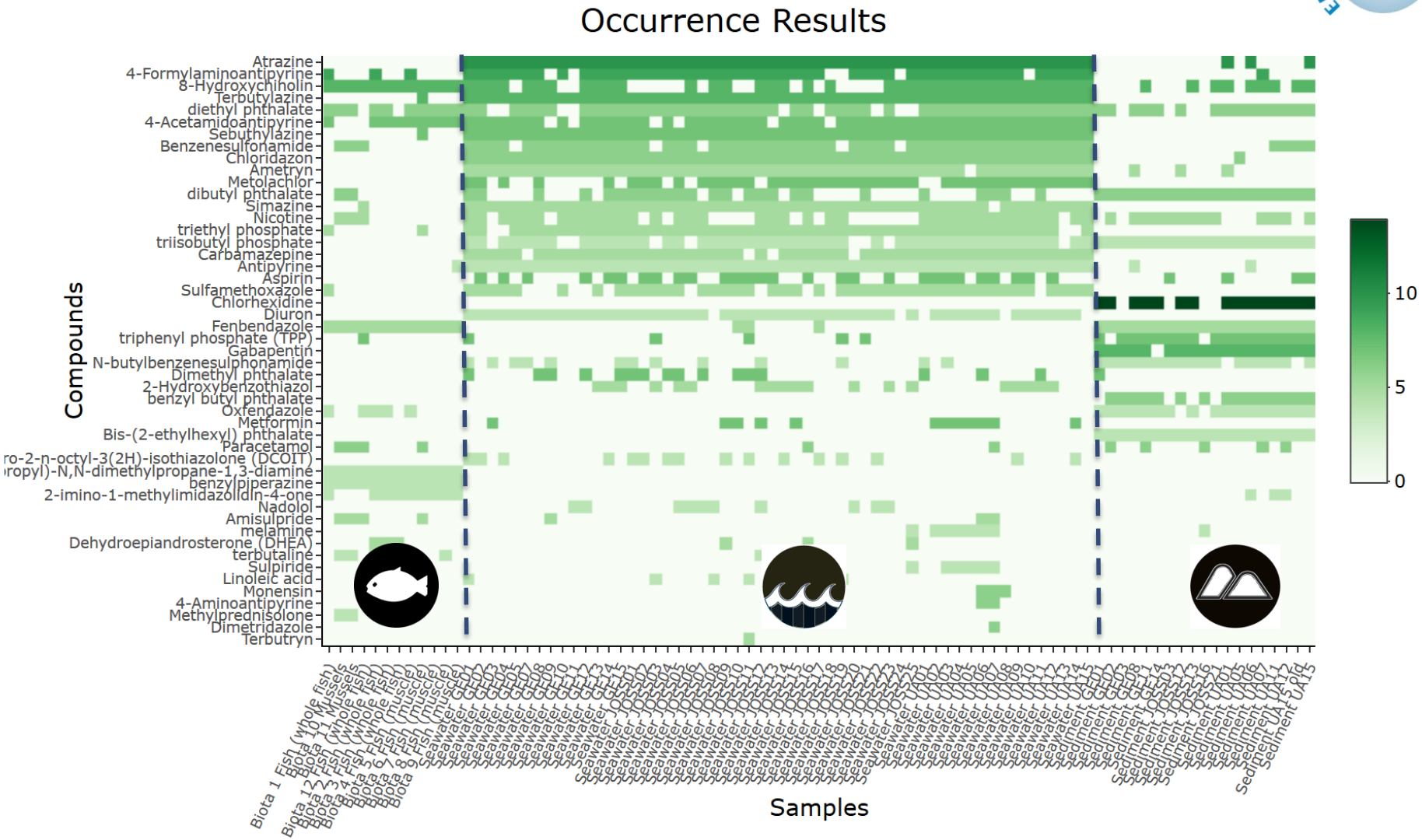
"Live" retrospective screening of known and unknown chemicals in European samples (various matrices)



http://norman-data.eu/ AND Aligizakis *et al*, in prep.

NORMAN Digital Sample Freezing Platform

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

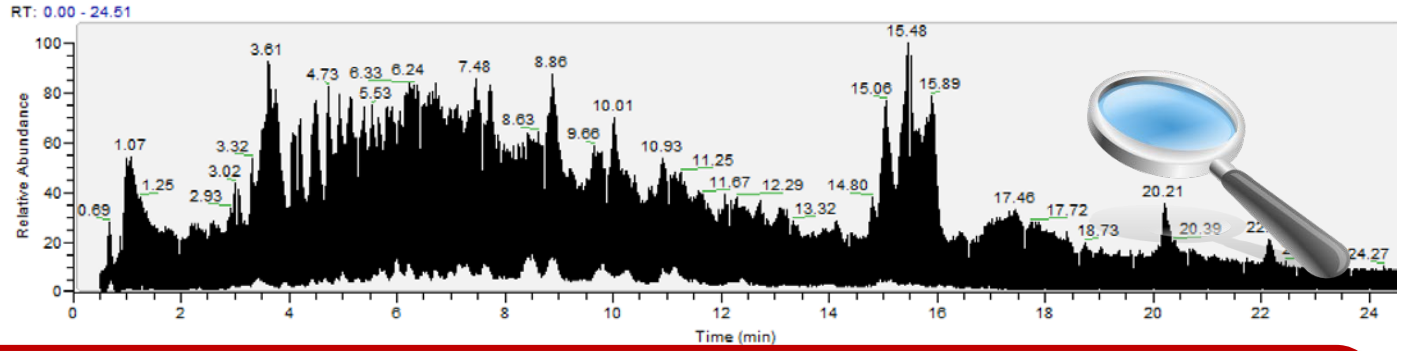


Interactive heatmap available at http://norman-data.eu/NORMAN-REACH

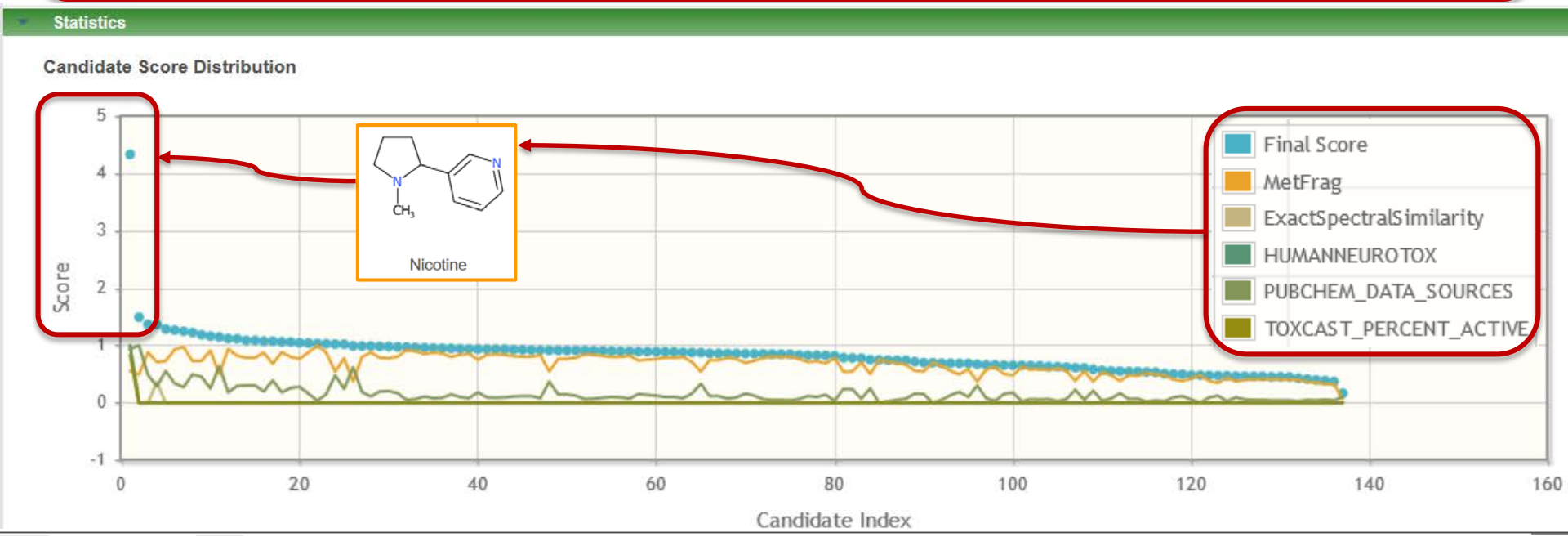
Community Challenges … and Solutions

High resolution mass spectrometry

AND connecting chemical knowledge



MetFrag · MassBank.eu · norman suspects · PubChem · EPA Chemistry Dashboard



Data: Schymanski *et al* 2014, DOI: 10.1021/es4044374; https://www.slideshare.net/EmmaSchymanski/small-molecules-in-big-data-analytica-munich

Thank you

emma.schymanski@uni.lu

ART2 CURE

MassBank consortium

norman

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licensed under Creative Commons License CC BY-NC-ND