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Structure identification by Mass Spectrometry Non-Targeted Analysis using the US EPA's CompTox Chemistry Dashboard

Antony Williams[1], Andrew D. McEachran[2], Chris Grulke[1], Seth Newton[3], Kristin Isaacs[3], Katherine Phillips[3], Nancy Baker[1] and Jon R. Sobus[3]

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2) *Oak Ridge Institute of Science and Education (ORISE) Research Participant, Research Triangle Park, NC*
3) *National Exposure Research Laboratory, U.S. Environmental Protection Agency, RTP, NC*

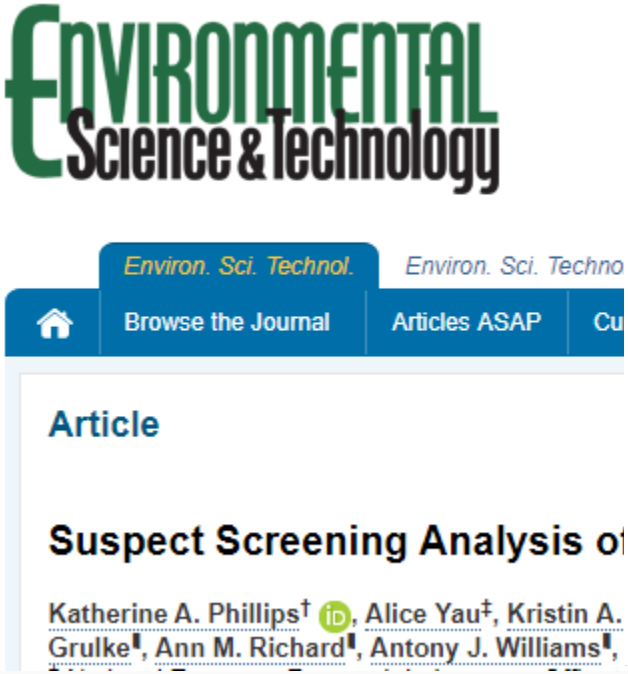
March 2018
ACS Spring Meeting, New Orleans

Two Years of Development for the CompTox Chemistry Dashboard

- The Chemistry Dashboard went online on April 1st 2016
- Two years later, with 10k users a week, it is fulfilling the promise with an underlying architecture for integrating CompTox data
- Used by our mass spectrometry team (in NERL) on a daily basis – suspect screening and non-targeted analysis

Published Many Times

EPA United States Environmental Protection Agency

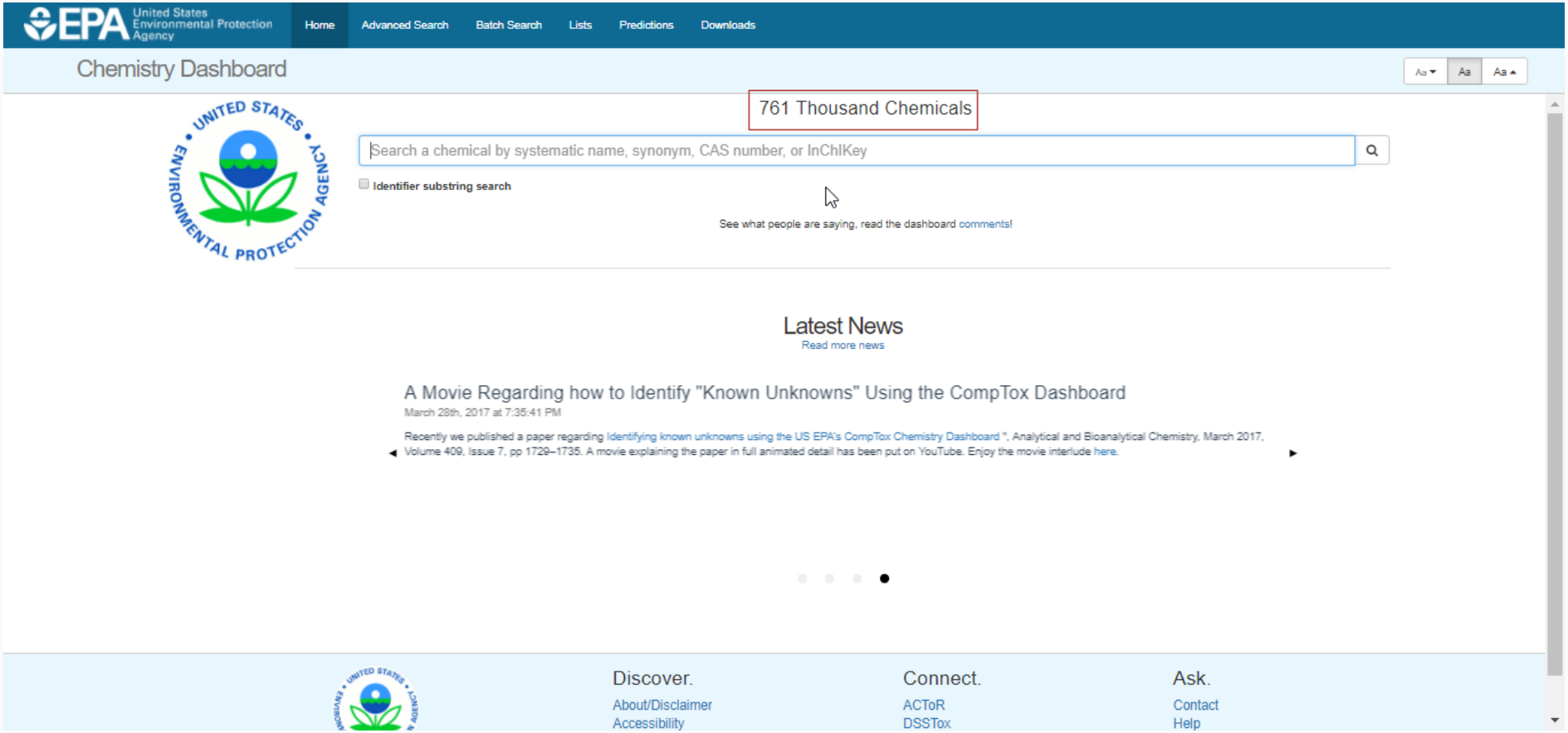


The CompTox Chemistry Dashboard

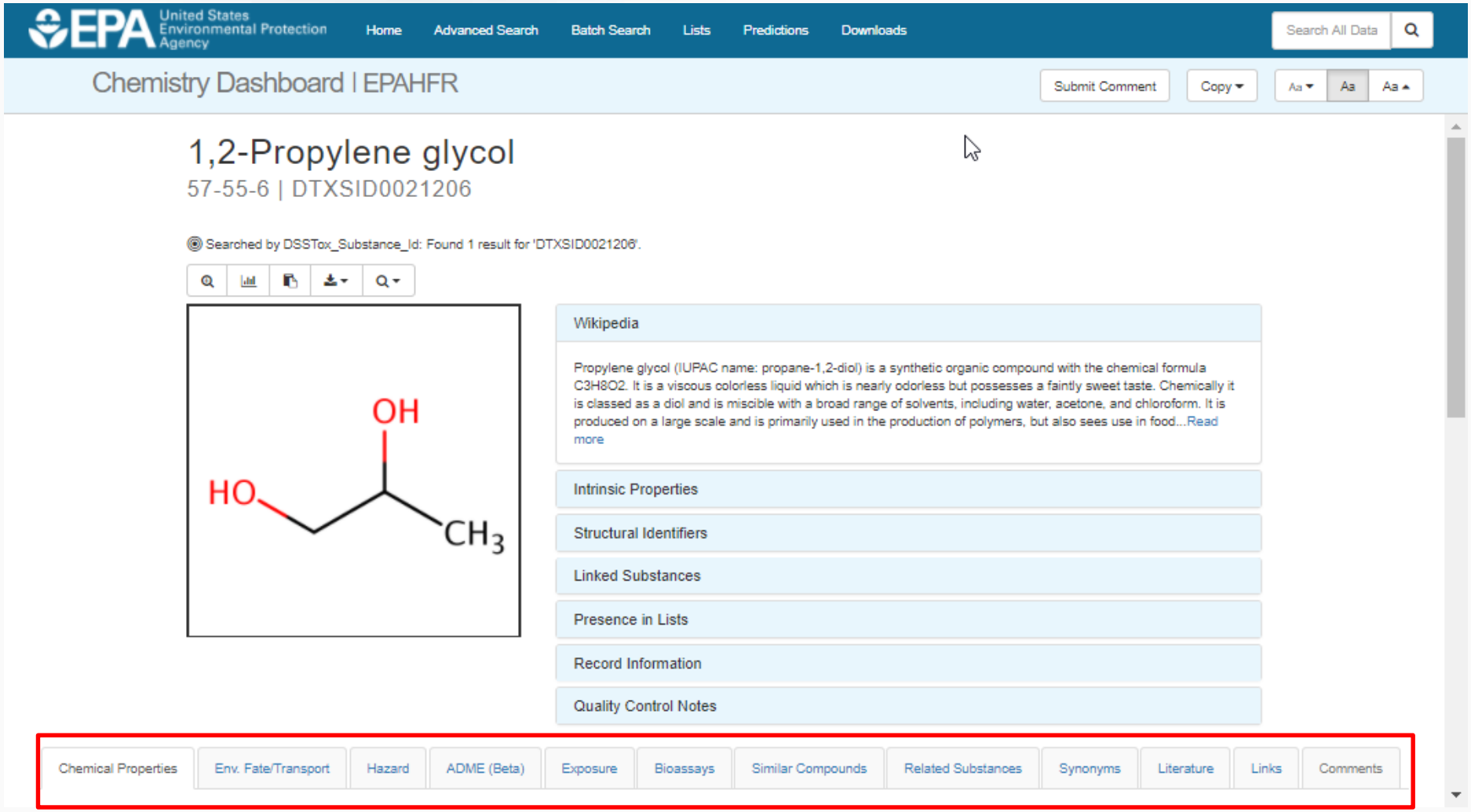
- A **publicly accessible website** delivering access:
  - ~760,000 chemicals with related property data
  - Experimental and predicted physicochemical property data
  - Experimental Human and Ecological hazard data
  - Integration to “biological assay data” for 1000s of chemicals
  - Information regarding consumer products containing chemicals
  - Links to other agency websites and public data resources
  - “Literature” searches for chemicals using public resources
  - “Batch searching” for thousands of chemicals
  - Real time prediction of physchem and toxicity endpoints

CompTox Chemistry Dashboard

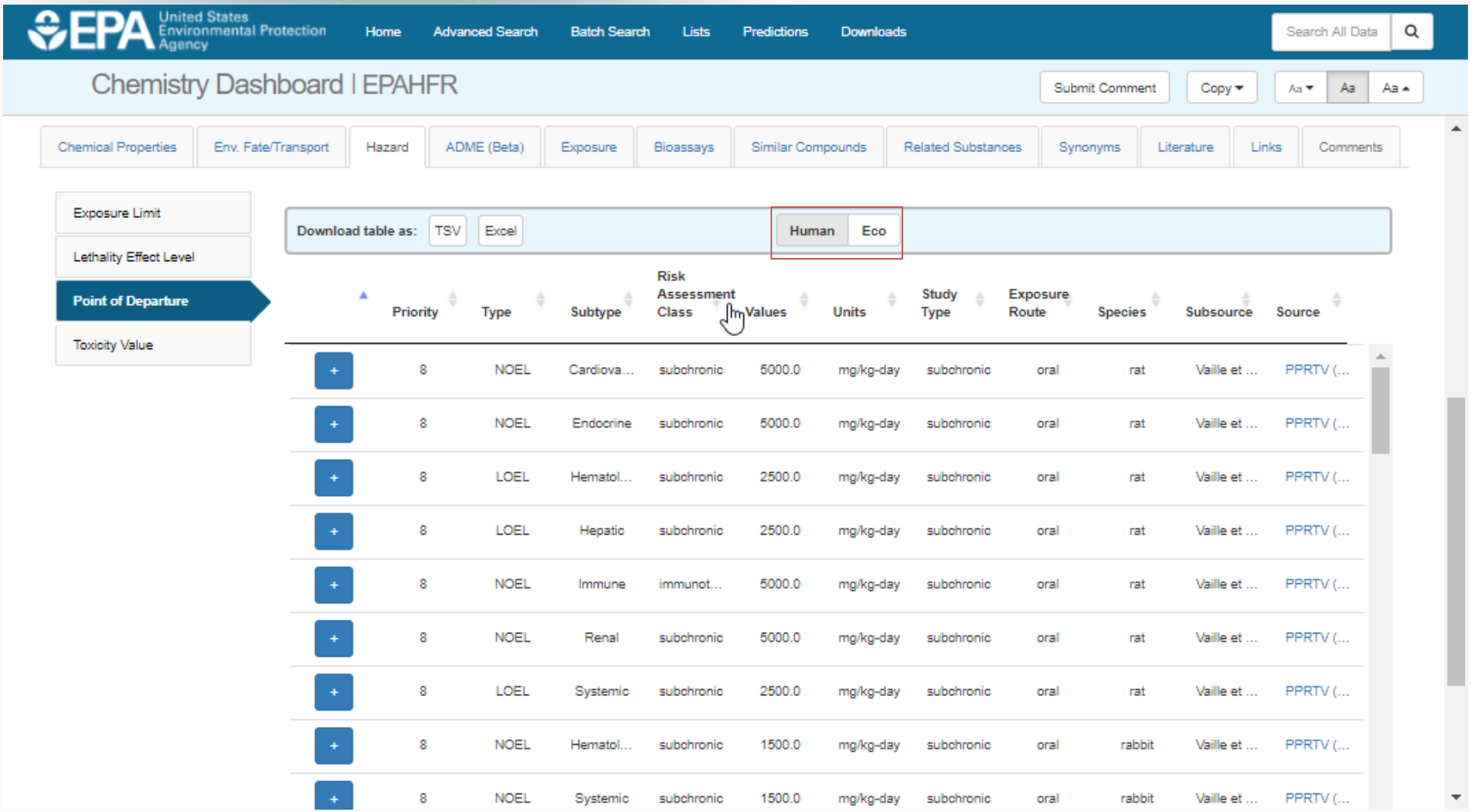
https://comptox.epa.gov/dashboard



Detailed Chemical Pages



Access to Chemical Hazard Data



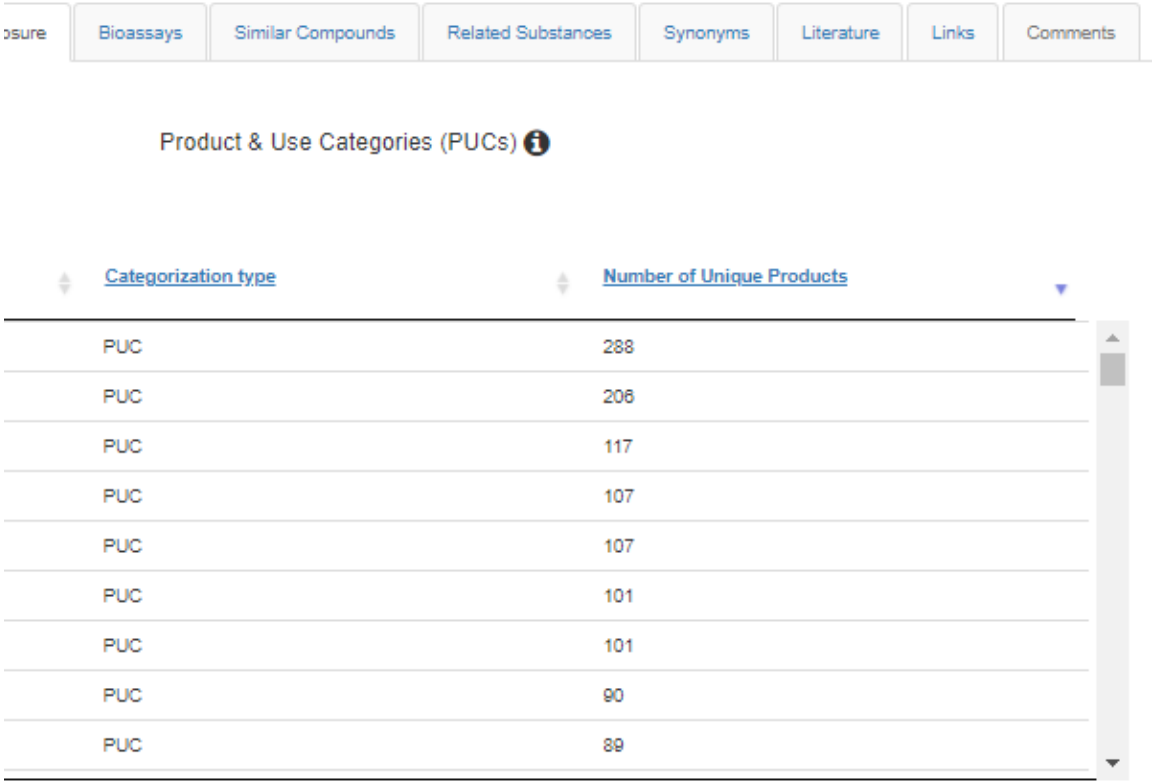
	Priority	Type	Subtype	Risk Assessment Class	Values	Units	Study Type	Exposure Route	Species	Subsource	Source
+	8	NOEL	Cardiova...	subchronic	5000.0	mg/kg-day	subchronic	oral	rat	Vaille et ...	PPRTV (...
+	8	NOEL	Endocrine	subchronic	5000.0	mg/kg-day	subchronic	oral	rat	Vaille et ...	PPRTV (...
+	8	LOEL	Hematol...	subchronic	2500.0	mg/kg-day	subchronic	oral	rat	Vaille et ...	PPRTV (...
+	8	LOEL	Hepatic	subchronic	2500.0	mg/kg-day	subchronic	oral	rat	Vaille et ...	PPRTV (...
+	8	NOEL	Immune	immunot...	5000.0	mg/kg-day	subchronic	oral	rat	Vaille et ...	PPRTV (...
+	8	NOEL	Renal	subchronic	5000.0	mg/kg-day	subchronic	oral	rat	Vaille et ...	PPRTV (...
+	8	LOEL	Systemic	subchronic	2500.0	mg/kg-day	subchronic	oral	rat	Vaille et ...	PPRTV (...
+	8	NOEL	Hematol...	subchronic	1500.0	mg/kg-day	subchronic	oral	rabbit	Vaille et ...	PPRTV (...
+	8	NOEL	Systemic	subchronic	1500.0	mg/kg-day	subchronic	oral	rabbit	Vaille et ...	PPRTV (...

In Vitro Bioassay Screening

ToxCast and Tox21

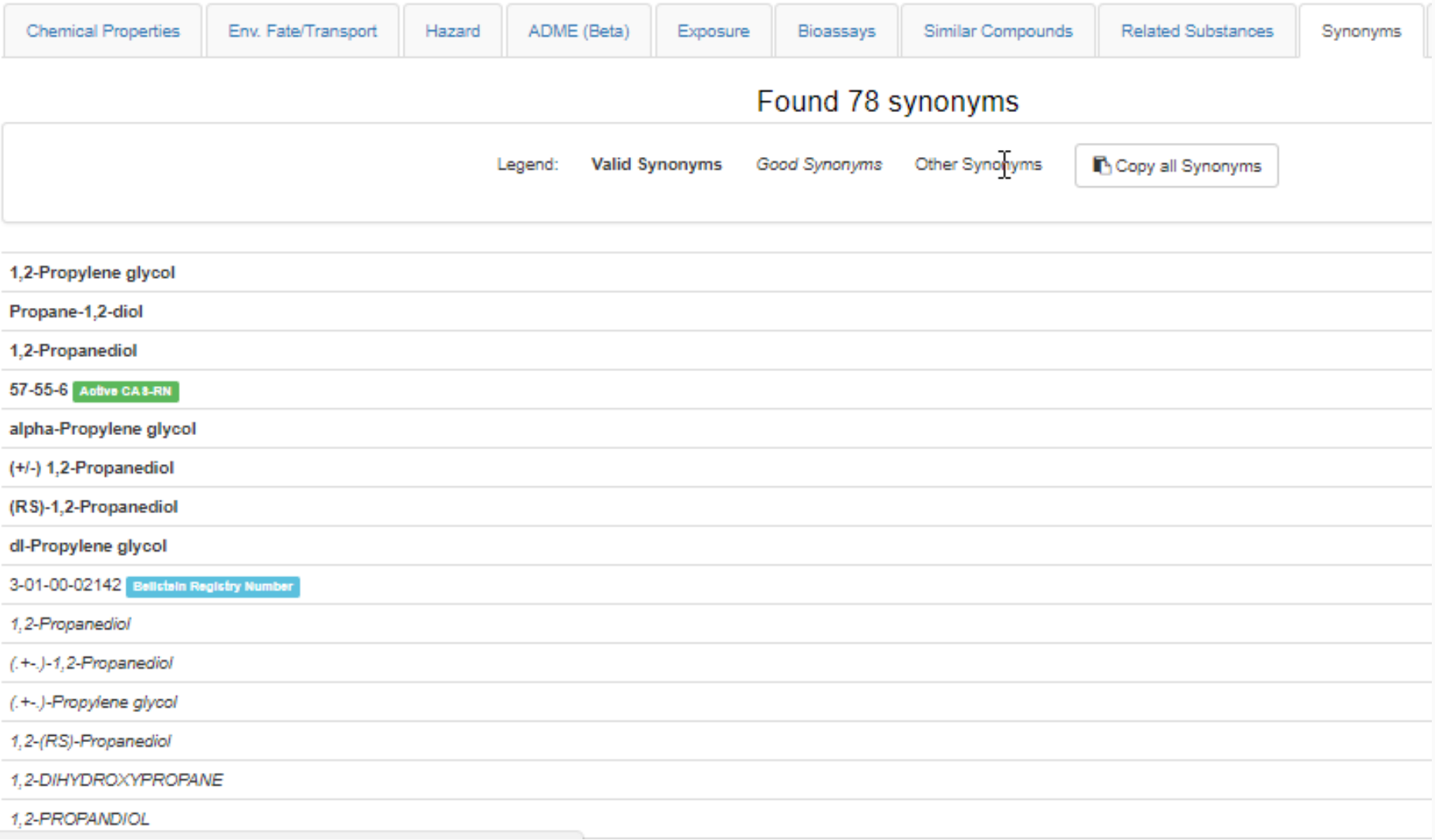
Sources of Exposure to Chemicals

- **Product & Use Categories**
- Chemical Weight Fraction
- Chemical Functional Use
- Monitoring Data
- Exposure Predictions
- Production Volume



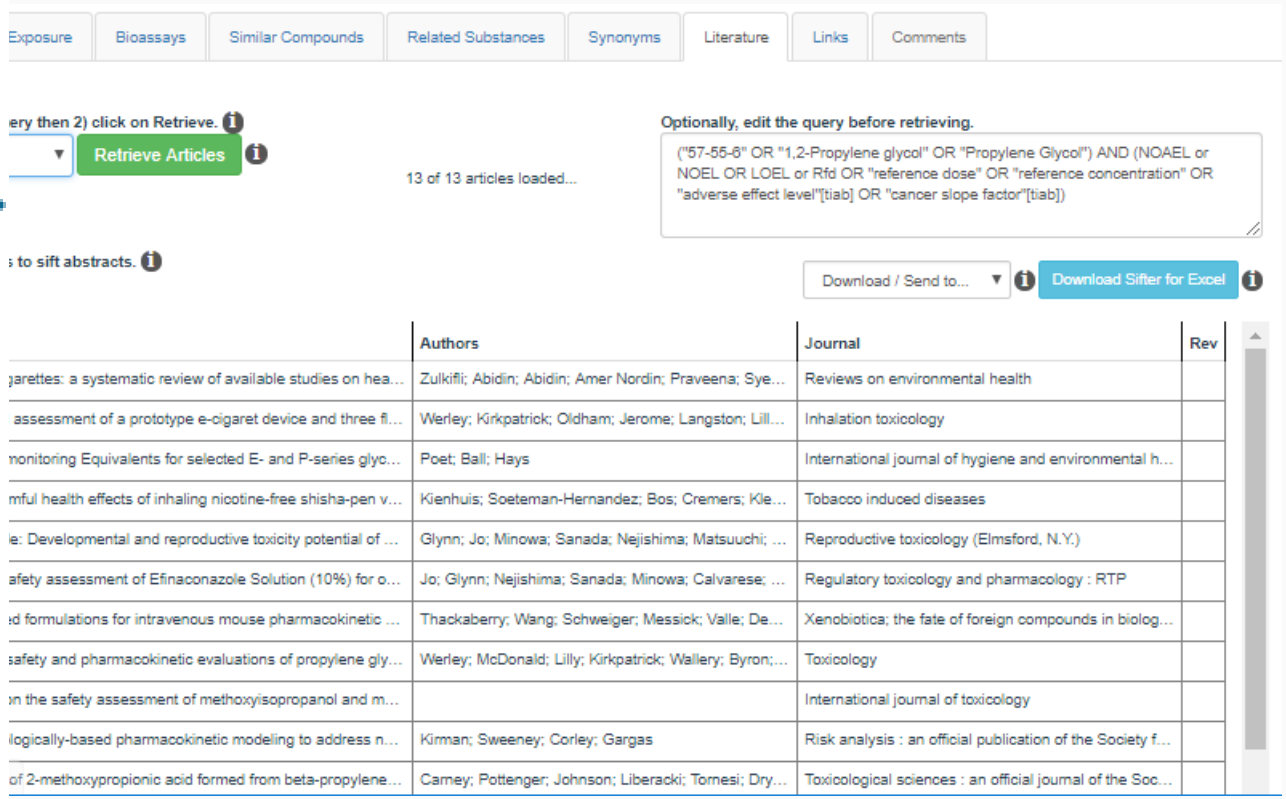
Identifiers to Support Searches

EPA United States Environmental Protection Agency

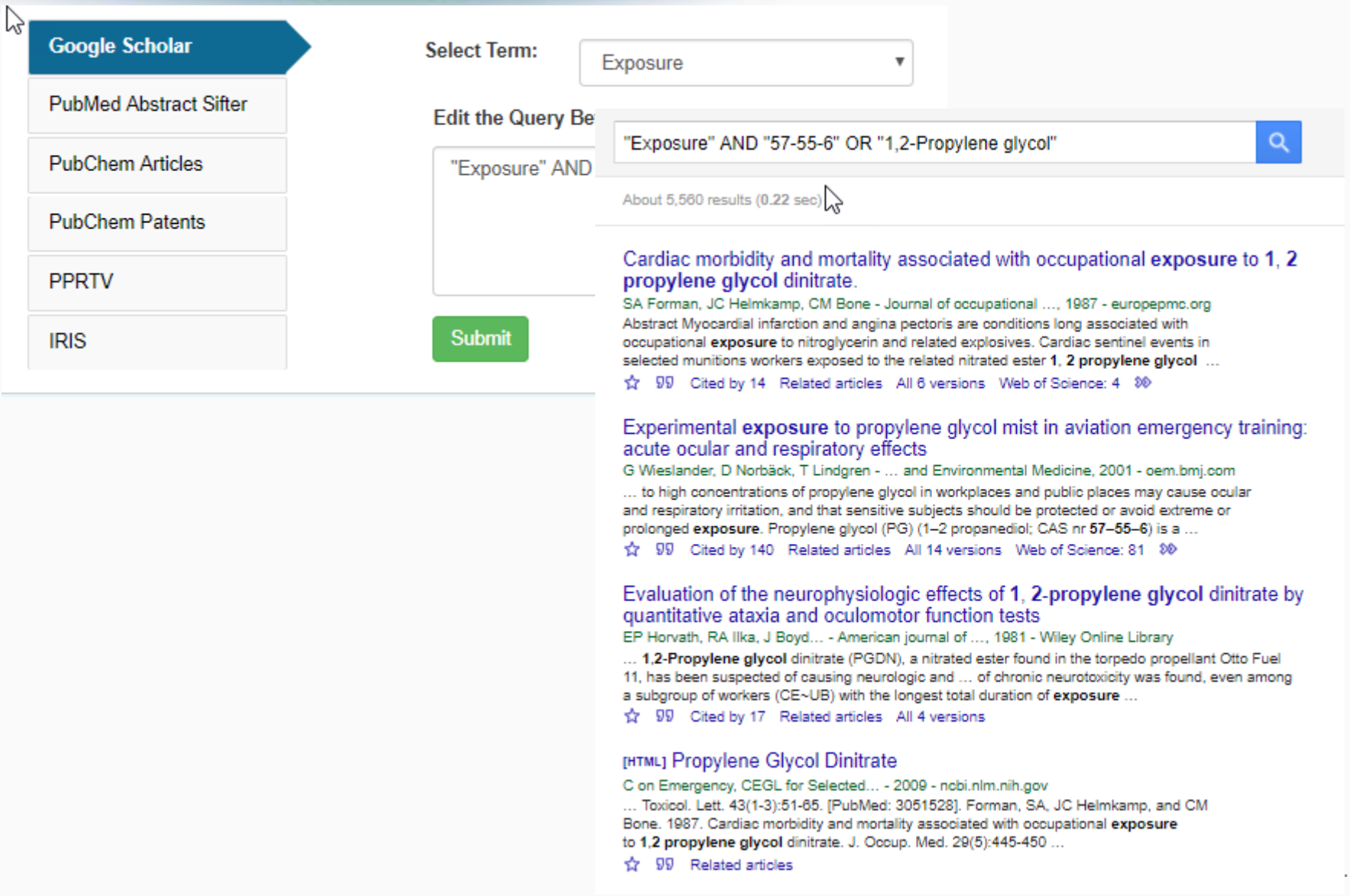


Literature Searches and Links

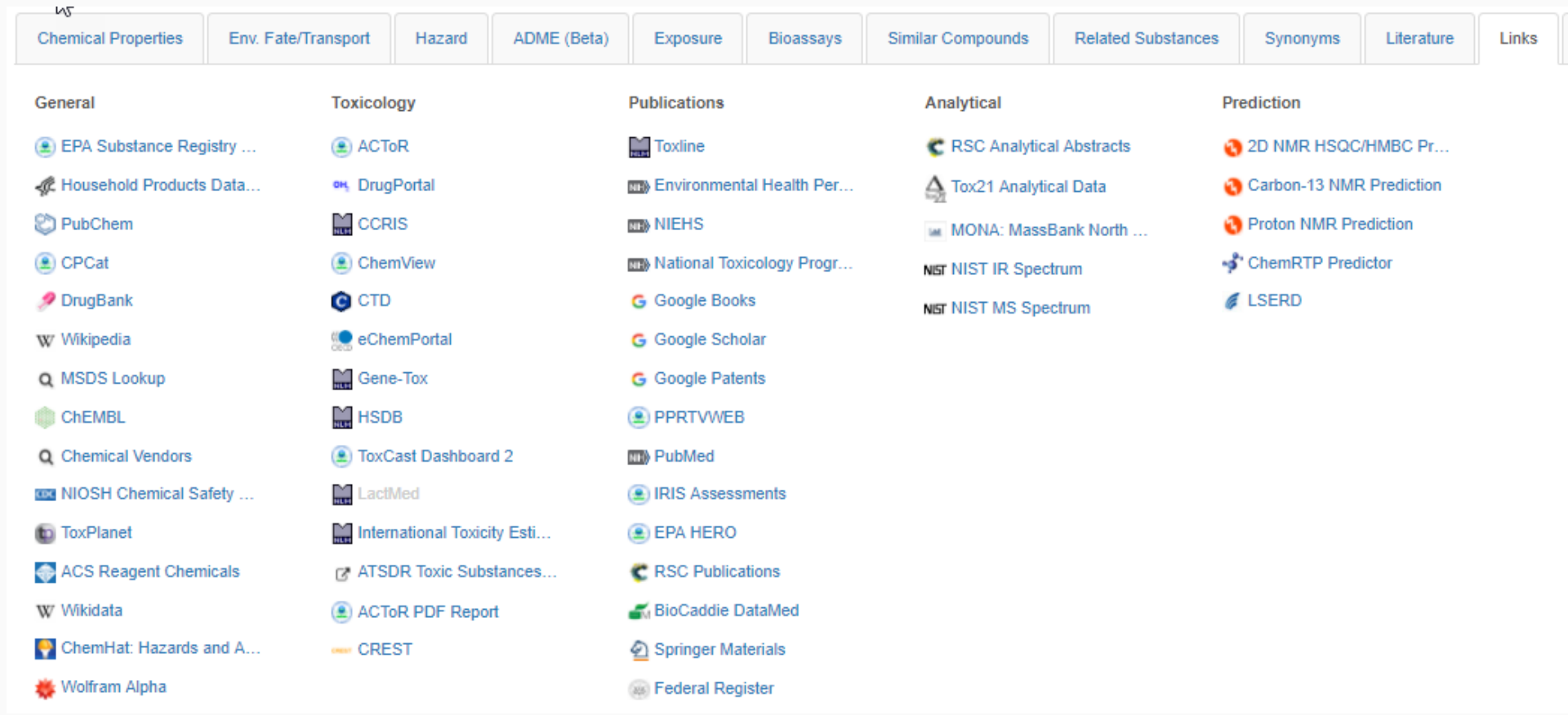
- Google Scholar
- **PubMed Abstract Sifter**
- PubChem Articles
- PubChem Patents
- PPRTV
- IRIS



Google Scholar



External Links to Data and Services



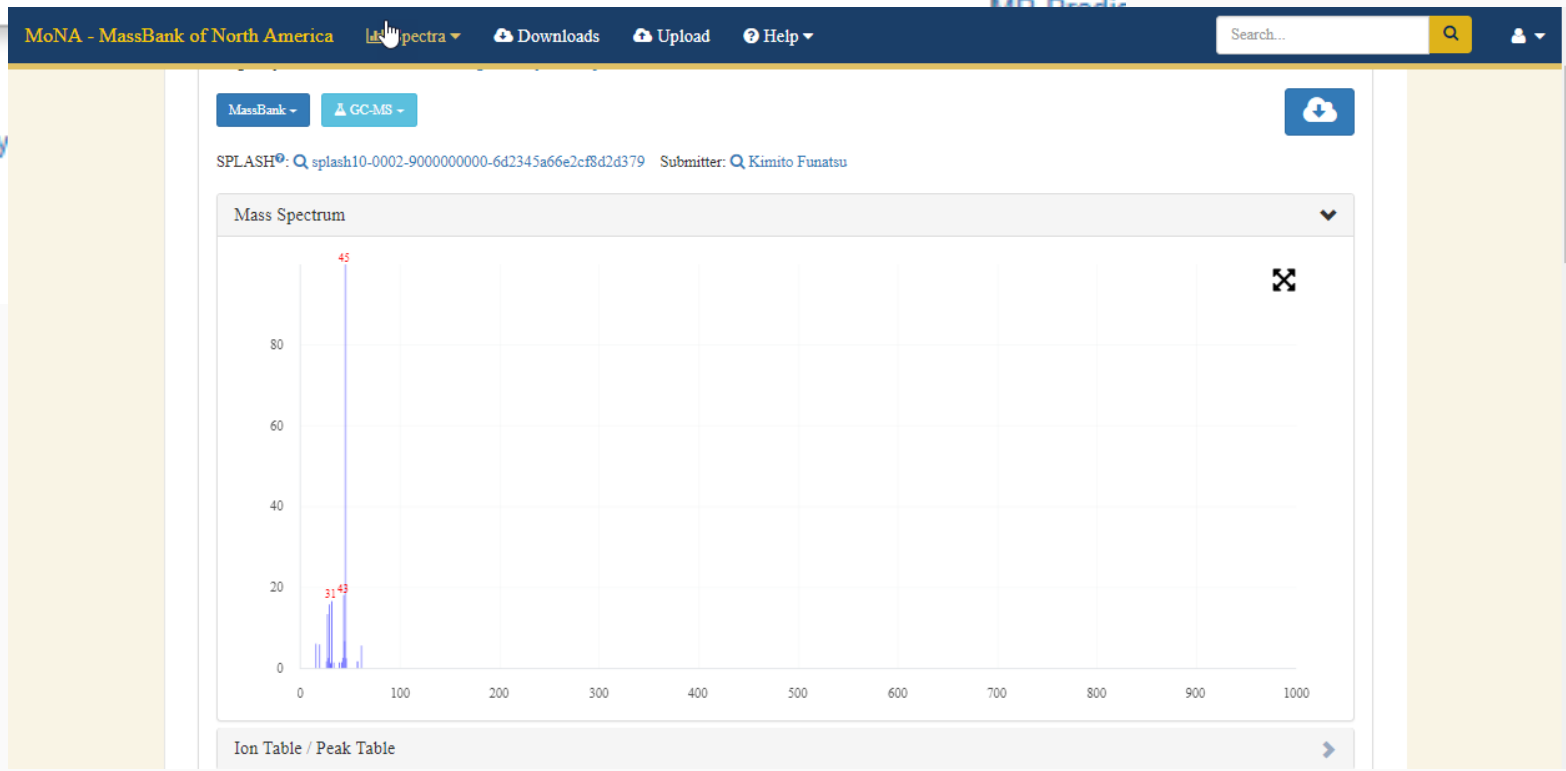
Mass Spec Data

EPA United States Environmental Protection Agency

Hazard | ADME (Beta) | Exposure | Bioassays | Similar Compounds | Related Subst

MassBank of America (MoNA) is a metadata-centric, auto-curating repository designed for efficient storage and querying of mass spectral records. It intends to serve as a the framework for a centralized, collaborative database of metabolite mass spectra, metadata and associated compounds. MoNA currently contains over 200,000 mass spectral records from experimental and in-silico libraries as well as from user contributions.

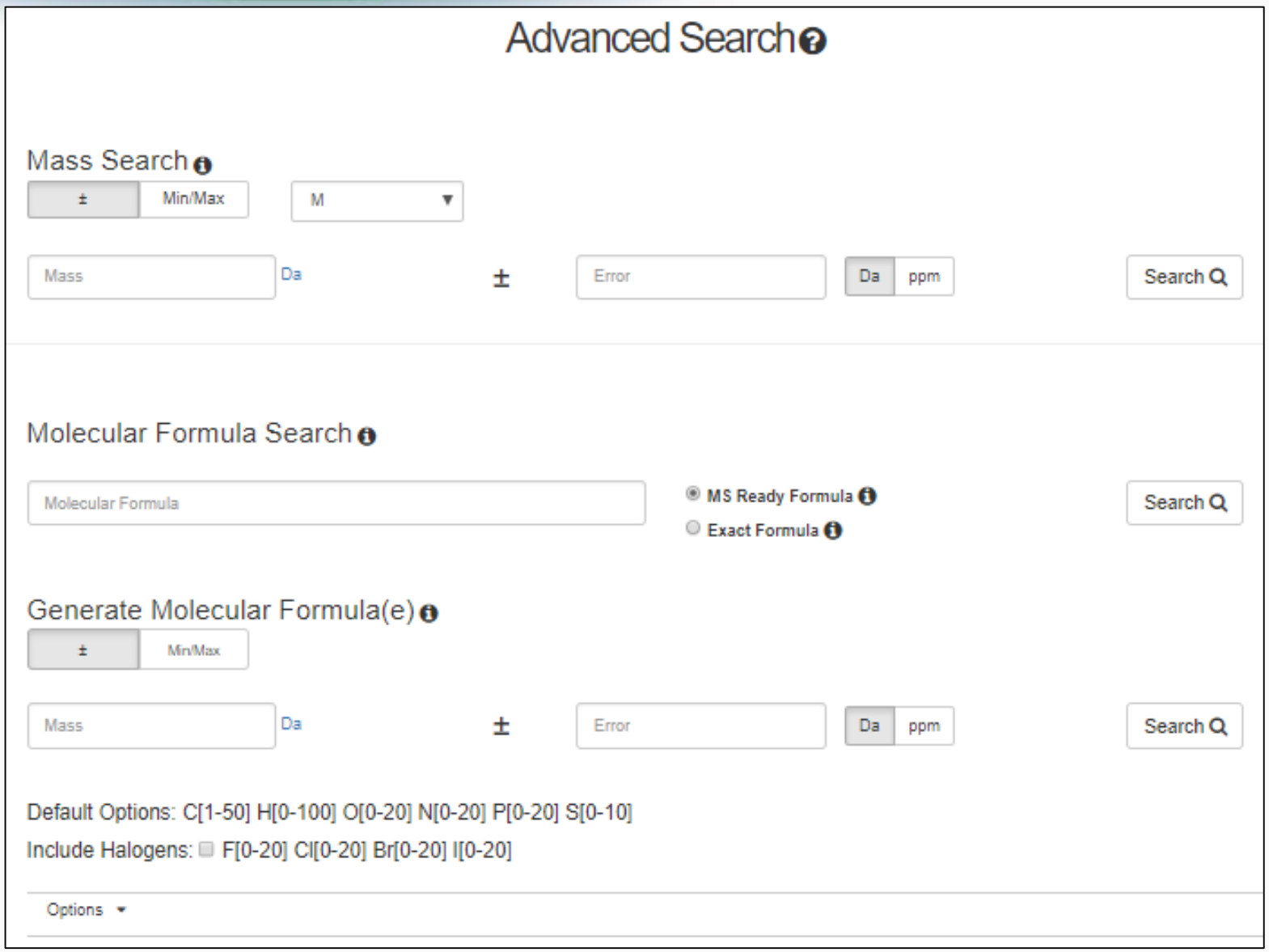
ications
oxline
nvironment
IEHS
ational Toxicology
oogle Books
oogle Scholar
QC/HMBC



Dashboard for Structure ID

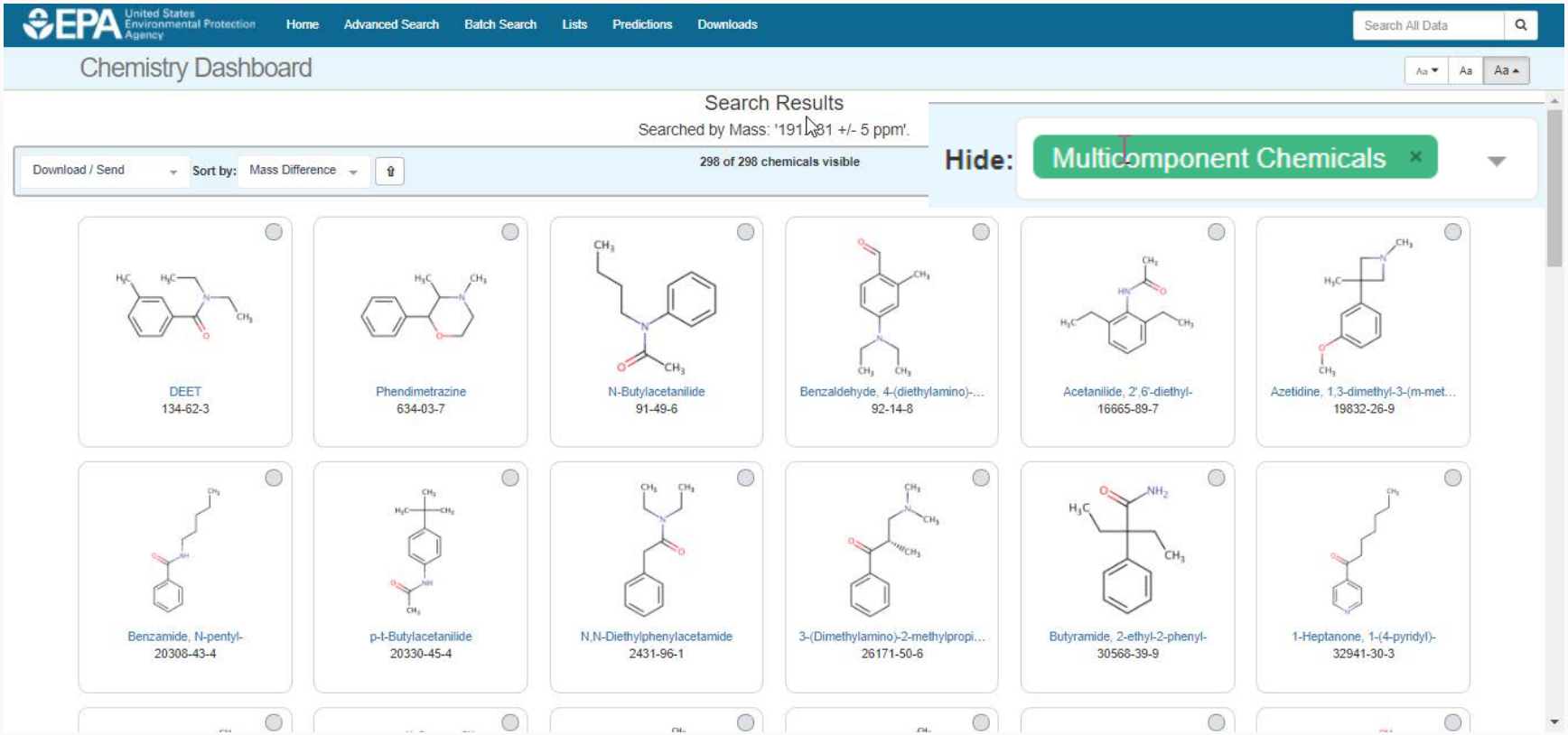
- Structure Identification using the dashboard
  - Formula/mass-based searching – 1 chemical at a time

Advanced Searches

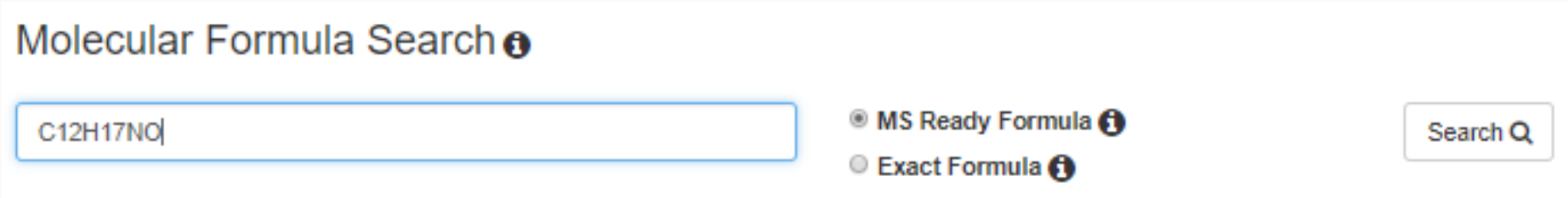


Advanced Searches
Mass Based Search

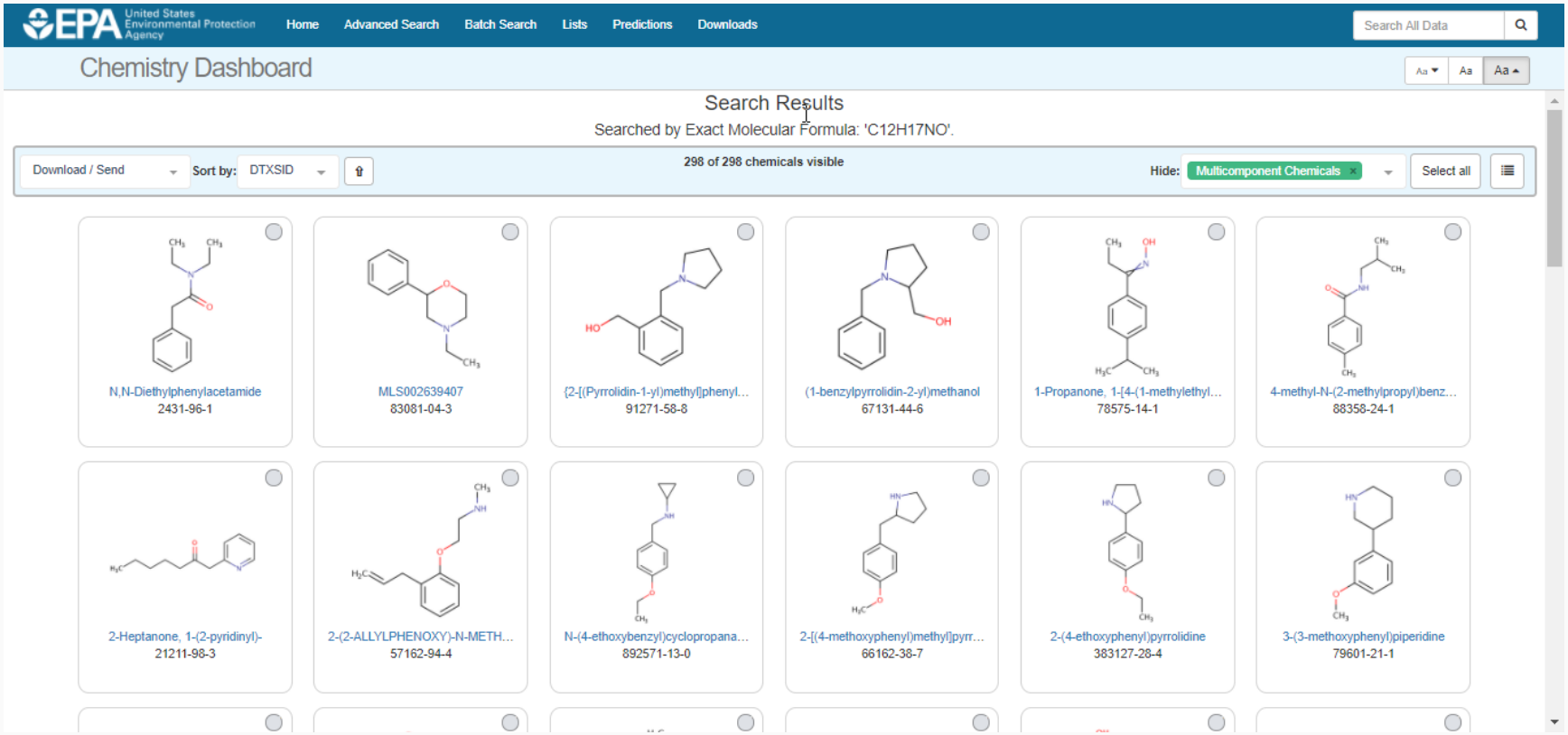
Advanced Searches



Formula Searches



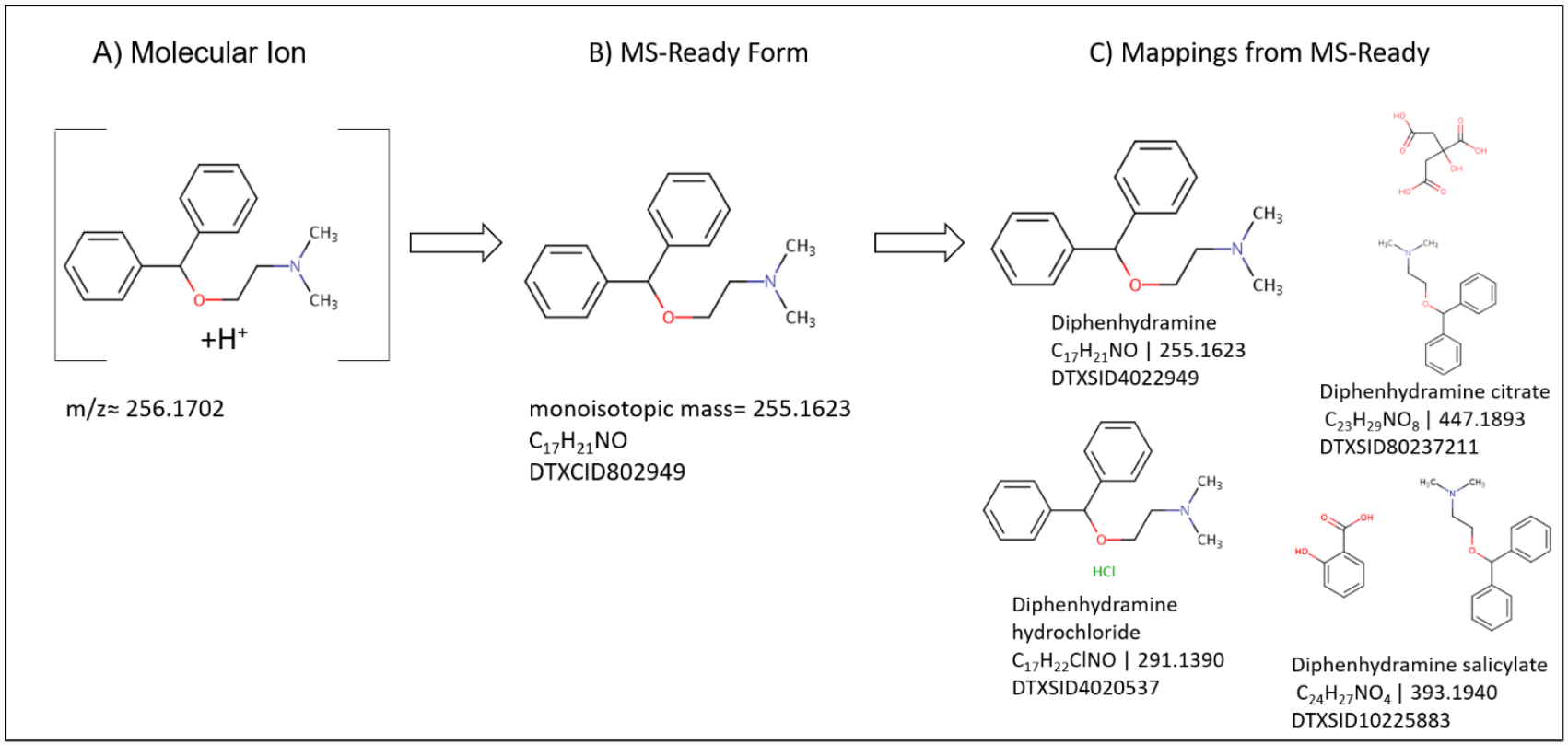
Exact Formula Search: C12H17NO
298 Chemicals



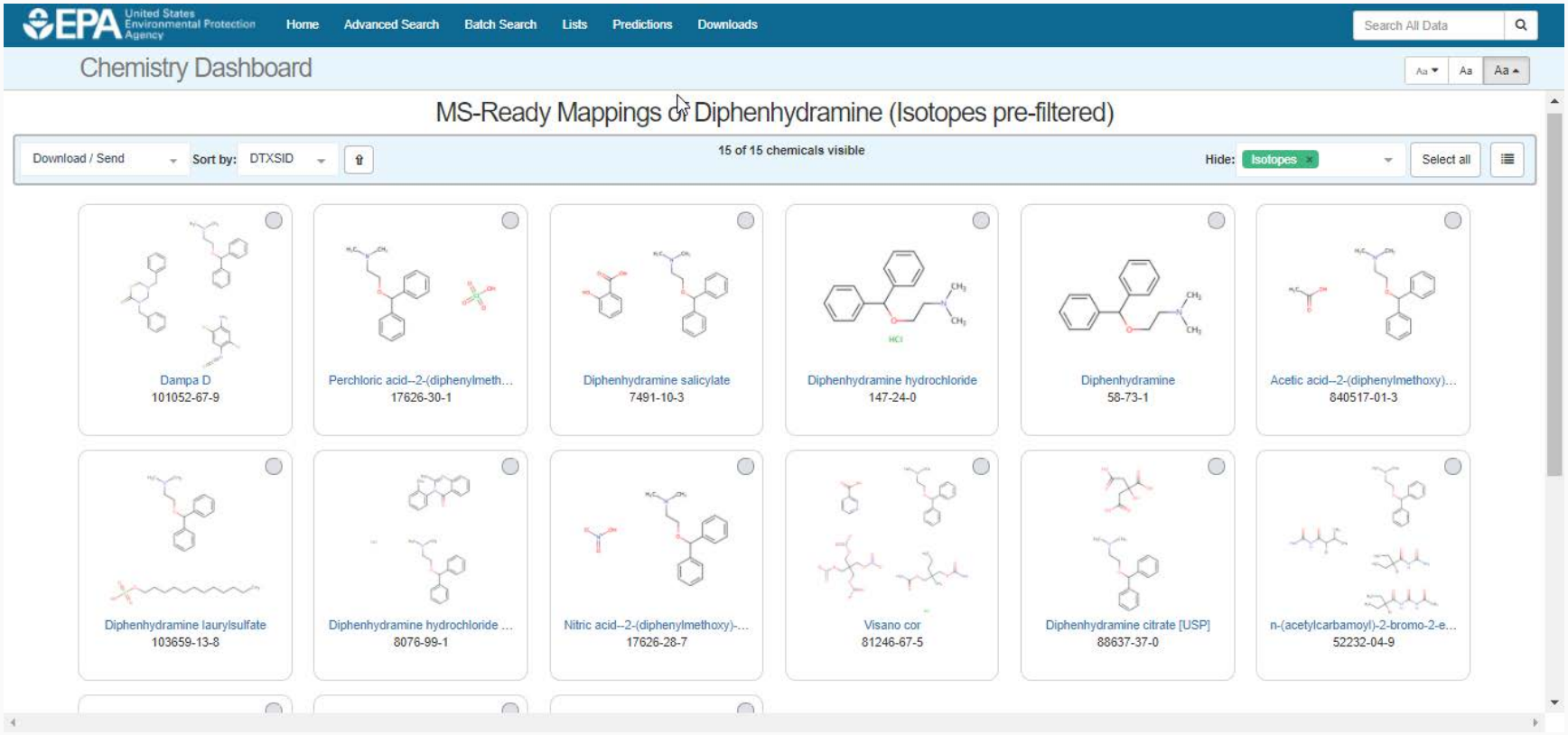
Dashboard for Structure ID

- Structure Identification using the dashboard
  - Formula/mass-based searching – 1 chemical at a time
  - Distilling structures into “MS-Ready form”

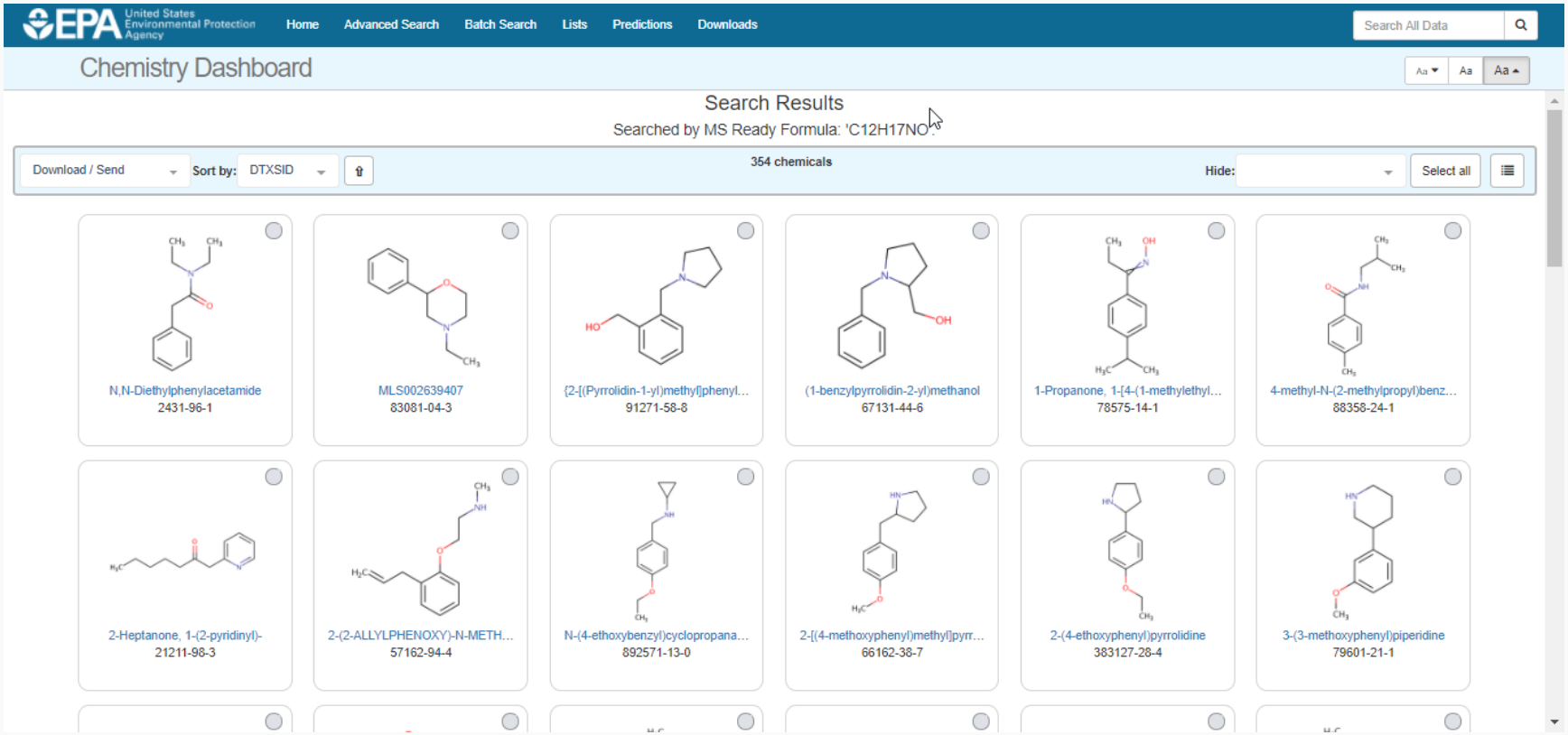
Specific Data-Mappings "MS-Ready Structures"



Diphenhydramine
15 Total MS-Ready Mappings



“MS Ready” Formula Search C12H17NO 354 Chemicals



Dashboard for Structure ID

- Structure Identification using the dashboard
  - Formula/mass-based searching – 1 chemical at a time
  - Distilling structures into “MS-Ready form”
  - Ranking based on metadata

Identifying Known Unknowns by reference ranking

Journal of The American Society for Mass Spectrometry
January 2012, Volume 23, Issue 1, pp 179–185 | Cite as

Table 1

Searching ChemSpider by Elemental Composition then Sorting by Number of Associated References

Class of compounds	Number compounds in class	Position of compound sorted in descending order by number of references					
		#1	#2	#3	#4	#5	>#5
Drugs	45	43	1	1			
Pesticides	8	7	1				
Toxins	2	2					
Polymer antioxidants	15	15					
Polymer UV stabilizers	10	8	1	1			

Data source ranking using the Dashboard

Anal Bioanal Chem
DOI 10.1007/s00216-016-0139-z

RAPID COMMUNICATION

Identifying known unknowns using the US EPA's CompTox Chemistry Dashboard

Andrew D. McEachran[1] · Jon R. Sobus[2] · Antony J. Williams[3]

	Mass-based searching		Formula-based searching	
	Dashboard	ChemSpider	Dashboard	ChemSpider
Average rank position	1.3	2.2[a]	1.2	1.4
Percent in #1 position	85%	70%	88%	80%

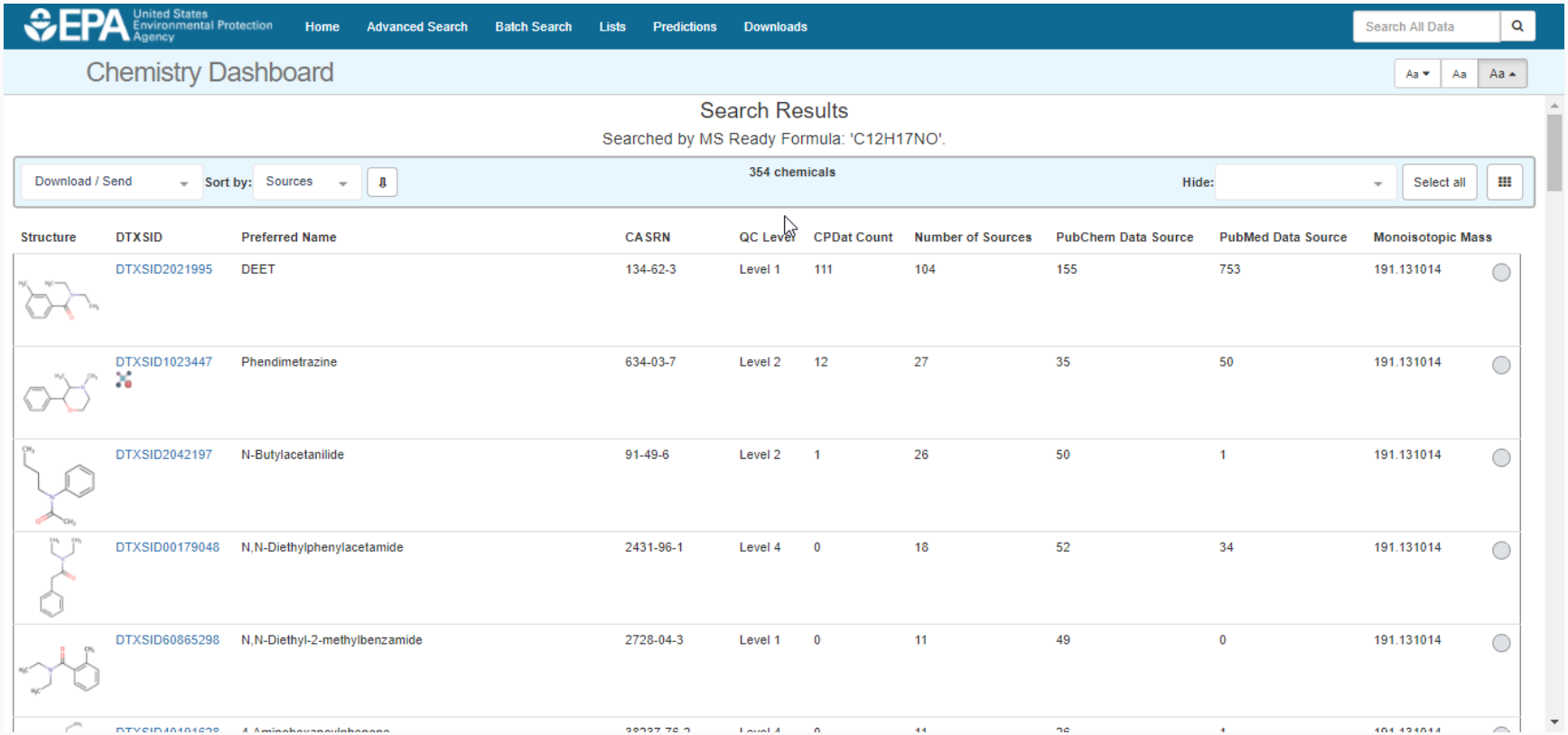
[a] Average rank in ChemSpider shown here does not include an outlier where the rank was 201, when added the average rank position is 3.5

DOI: 10.1007/s00216-016-0139-z

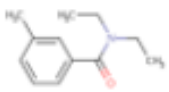
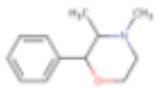
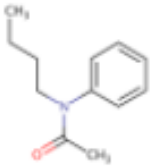
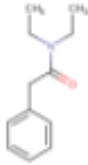
Additional Metadata Ranking

- US EPA CompTox Chemistry Dashboard Data Sources
- “CPDat” Consumer Product Database
- PubChem Data Source Count
- PubMed Reference Count

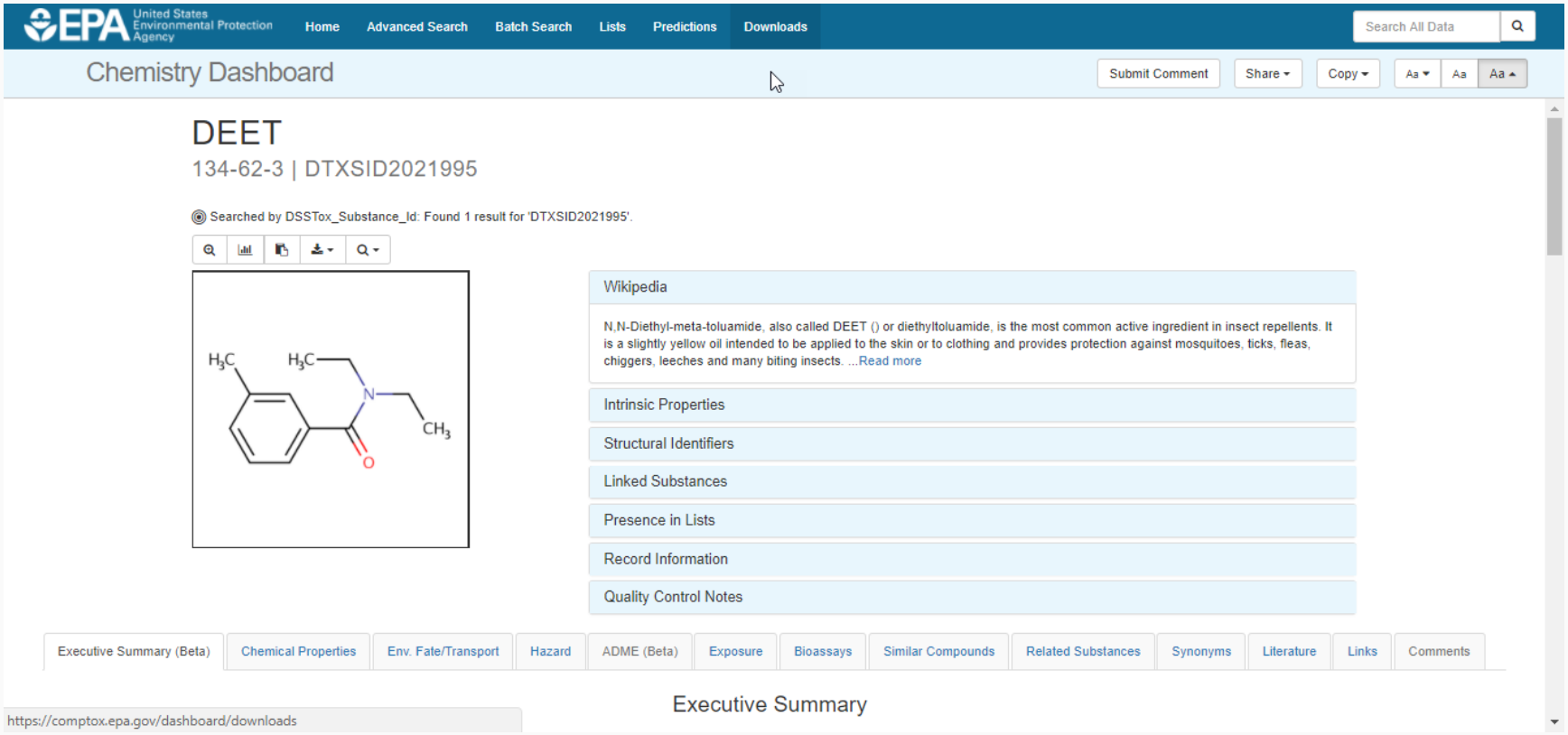
Additional Metadata Ranking C12H17NO: 354 Chemicals



Additional Metadata Ranking
C12H17NO: 354 Chemicals

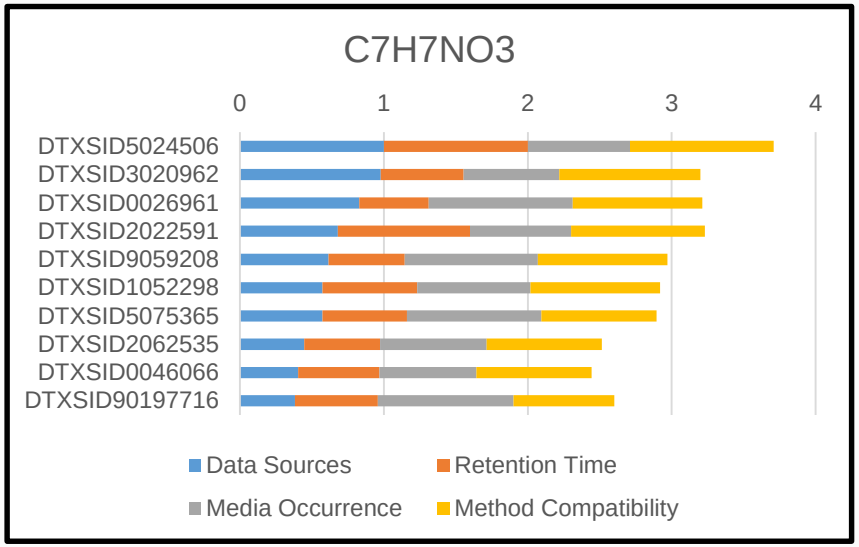
Structure	DTXSID	Preferred Name	CPDat Count	Number of Sources	PubChem Data Source	PubMed Data Source
	DTXSID2021995	DEET	111	104	155	753
	DTXSID1023447	Phendimetrazine	12	27	35	50
	DTXSID2042197	N-Butylacetanilide	1	26	50	1
	DTXSID00179048	N,N-Diethylphenylacetamide	0	18	52	34

Top Ranked Chemical



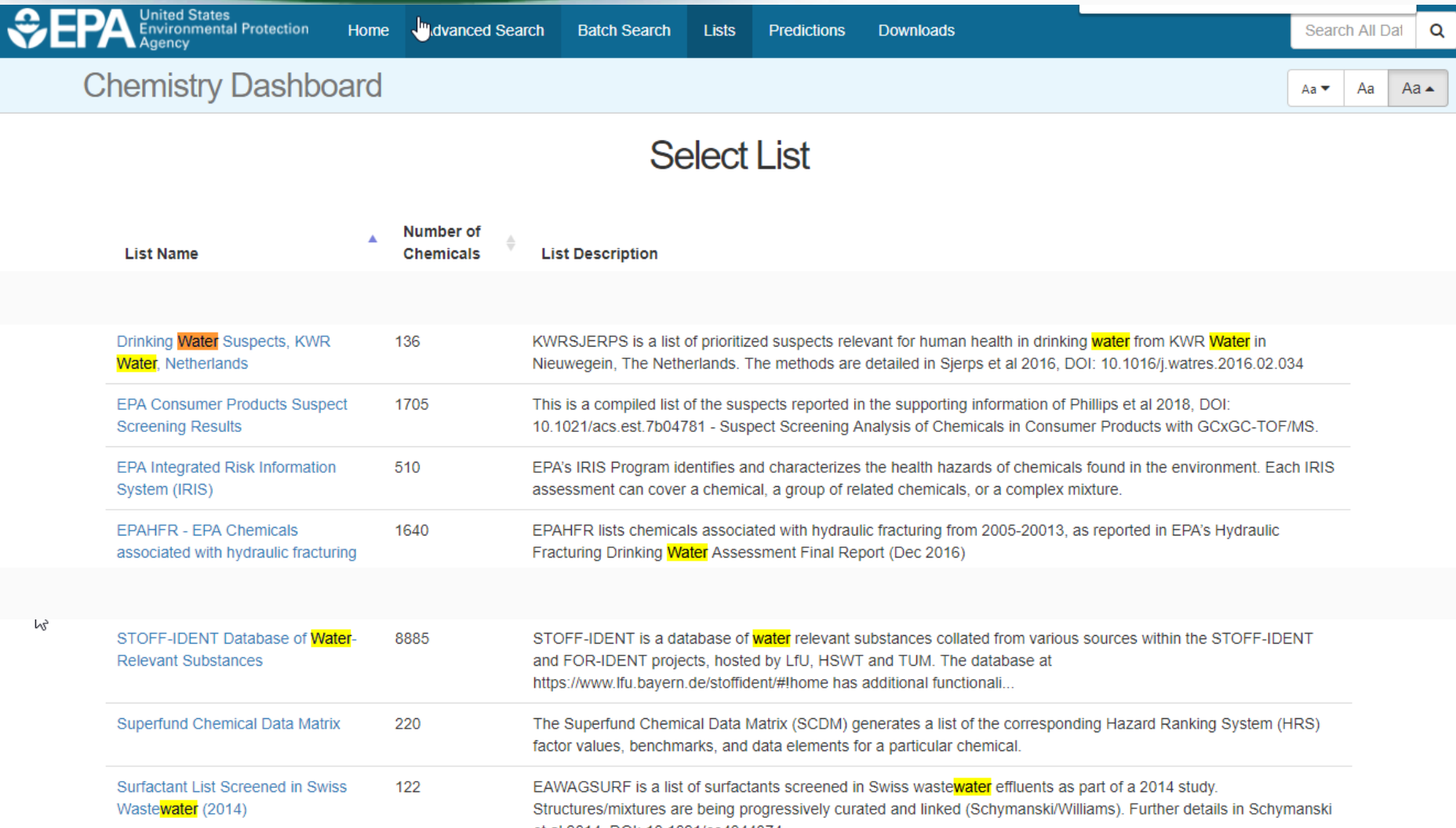
Additional data streams in development

- US EPA CompTox Chemistry Dashboard Data Sources
- “CPDat” Consumer Product Database
- PubChem Data Source Count
- PubMed Reference Count
- Retention Time Prediction $SC_{TOTAL} = SC_{DS} + SC_{PM} + SC_{RT} + SC_{MO} + \cdots$
- Predicted Environmental Media Occurrence
- Presence in Lists



“Chemicals Detected in Water”

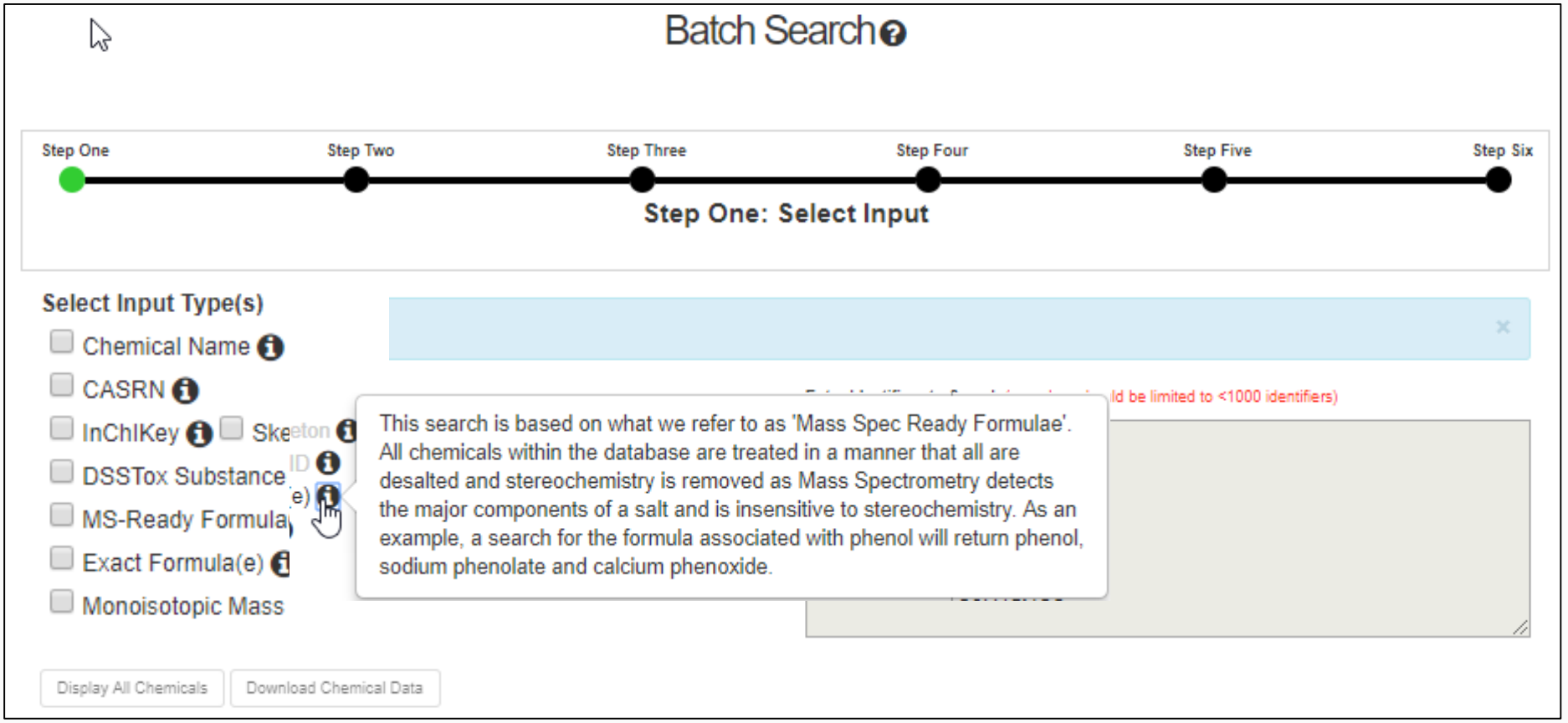
EPA United States Environmental Protection Agency



Dashboard for Structure ID

- Structure Identification using the dashboard
  - Formula/mass-based searching – 1 chemical at a time
  - Distilling structures into “MS-Ready form”
  - Ranking based on metadata
  - Batch searching of formulae and masses

Batch Search



Batch Search

Select Input Type(s)

- [ ] Chemical Name
- [ ] CASRN
- [ ] InChIKey
- [ ] Skeleton
- [ ] DSSTox Substance ID
- [x] MS-Ready Formula(e)
- [ ] Exact Formula(e)
- [ ] Monoisotopic Mass

Enter Identifiers to Search (searches should be limited to <1000 identifiers)

C6H12O3
C7H7N3
C8H11NO
C7H5NOS
C9H15NO
C11H12O
C9H8O3
C6H12O5
C9H15NO2

Metadata

- [ ] Curation Level Details
- [x] Data Sources
- [x] Assay Hit Count
- [ ] Include links to ACToR reports - SLOW! (BETA)
- [x] NHANES/Predicted Exposure
- [x] Include ToxVal Data Availability
- [x] Number of PubMed Articles
- [ ] Abstract Sifter Input File (Beta)
- [ ] MetFrag Input File(Beta)
- [x] IRIS
- [x] PPRTV
- [x] PubChem Data Sources
- [ ] ToxPrint fingerprints

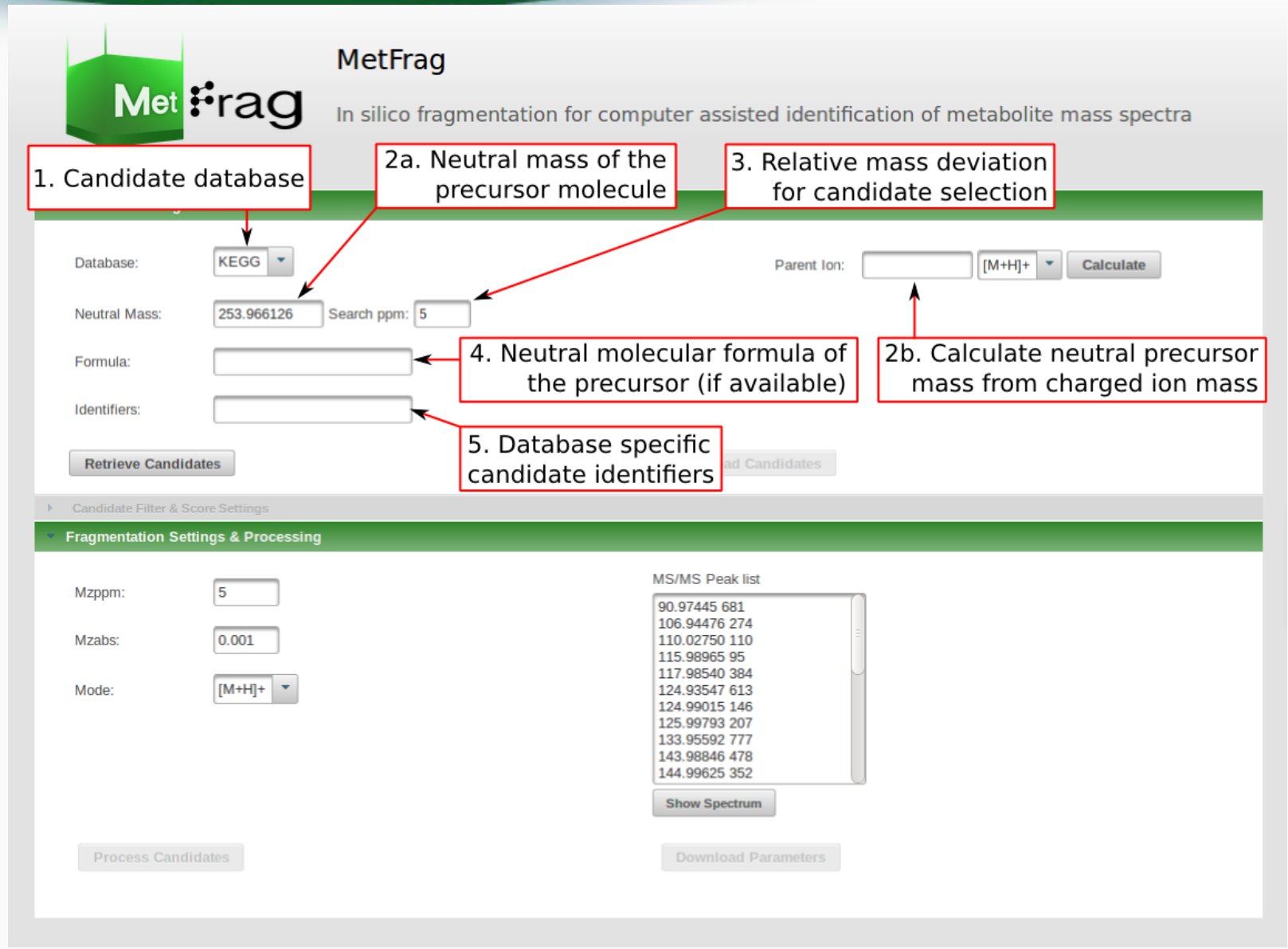
- [ ] NIOSH IDLH Values
- [ ] NIOSH International Chemical Safety Cards
- [ ] NIOSH Pocket Guide to Chemical Hazards
- [ ] NIOSH Skin Notation Profiles
- [ ] NORMAN Collaborative Trial 2015 Targets and Suspects
- [ ] Norman Network PFAS (KEMI Report)
- [ ] NORMAN Network Priority List
- [ ] NormaNEWS: Norman Early Warning System
- [ ] PFAS list provided by X.Trier et al
- [ ] Pharmaceutical List with EU, Swiss and US Consumption Data
- [ ] Provisional Peer Reviewed Toxicity Values
- [ ] Stockholm Convention on Organic Pollutants
- [x] STOFF-IDENT Database of Water-Relevant Substances
- [ ] Superfund Chemical Data Matrix
- [x] Surfactant List Screened in Swiss Wastewater (2014)

Excel Output

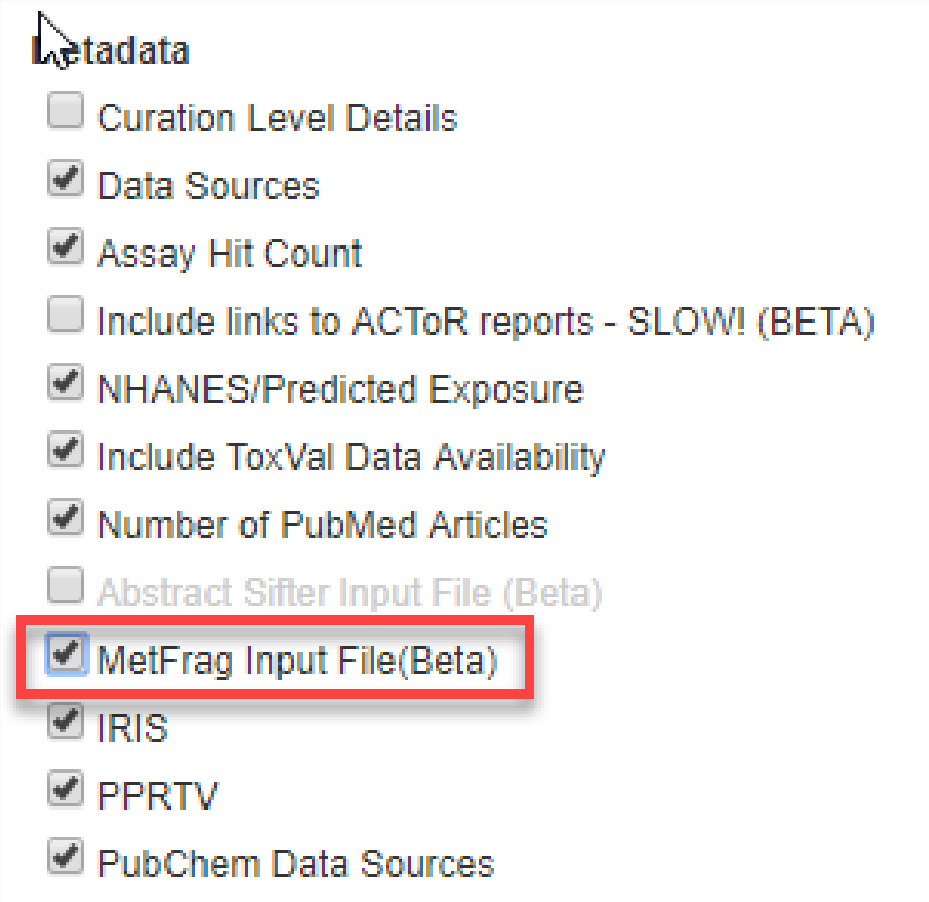
INPUT	FOUND_BY	DTXCID_IN	DATA_SOU	TOXVAL_D	TOXCAST_	TOXCAST_	NUMBER_C	PUBCHEM_	STO
C6H12O3	MS Ready I	DTXCID701	91	Y	0.36	2/562	24	83	Y
C6H12O3	MS Ready I	DTXCID003	67	Y	0.36	1/276	376	80	Y
C6H12O3	MS Ready I	DTXCID106	65	Y	4.42	5/113	6	77	Y
C6H12O3	MS Ready I	DTXCID105	45	Y	0.0	0/163	3	94	-
C6H12O3	MS Ready I	DTXCID901	38	Y	-	-	14	110	Y
C6H12O3	MS Ready I	DTXCID402	34	Y	0.0	0/113	-	53	Y
C6H12O3	MS Ready I	DTXCID202	31	Y	-	-	-	36	Y
C6H12O3	MS Ready I	DTXCID202	30	-	2.54	7/276	-	54	-
C6H12O3	MS Ready I	DTXCID109	26	Y	-	-	-	46	-
C6H12O3	MS Ready I	DTXCID202	24	Y	0.0	0/113	-	47	-
C6H12O3	MS Ready I	DTXCID303	22	Y	-	-	-	89	-
C6H12O3	MS Ready I	DTXCID302	20	Y	-	-	2	25	Y
C6H12O3	MS Ready I	DTXCID407	19	Y	-	-	12	62	-
C6H12O3	MS Ready I	DTXCID704	17	Y	-	-	-	64	-
C6H12O3	MS Ready I	DTXCID704	16	Y	-	-	3	49	-

Batch Search Integration to MetFrag

http://c-ruttkies.github.io/MetFrag/projects/metfragweb/

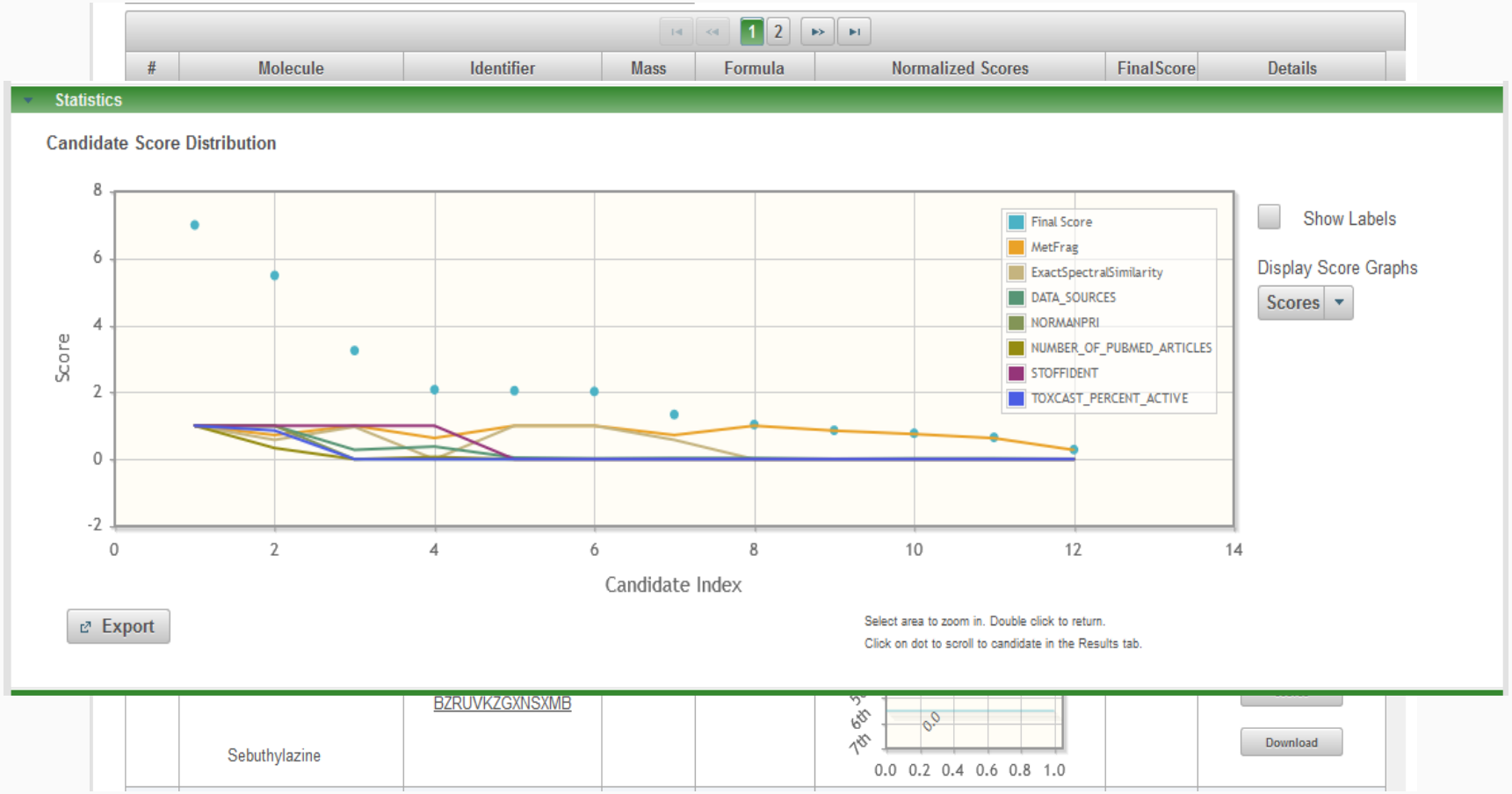


MetFrag Input File

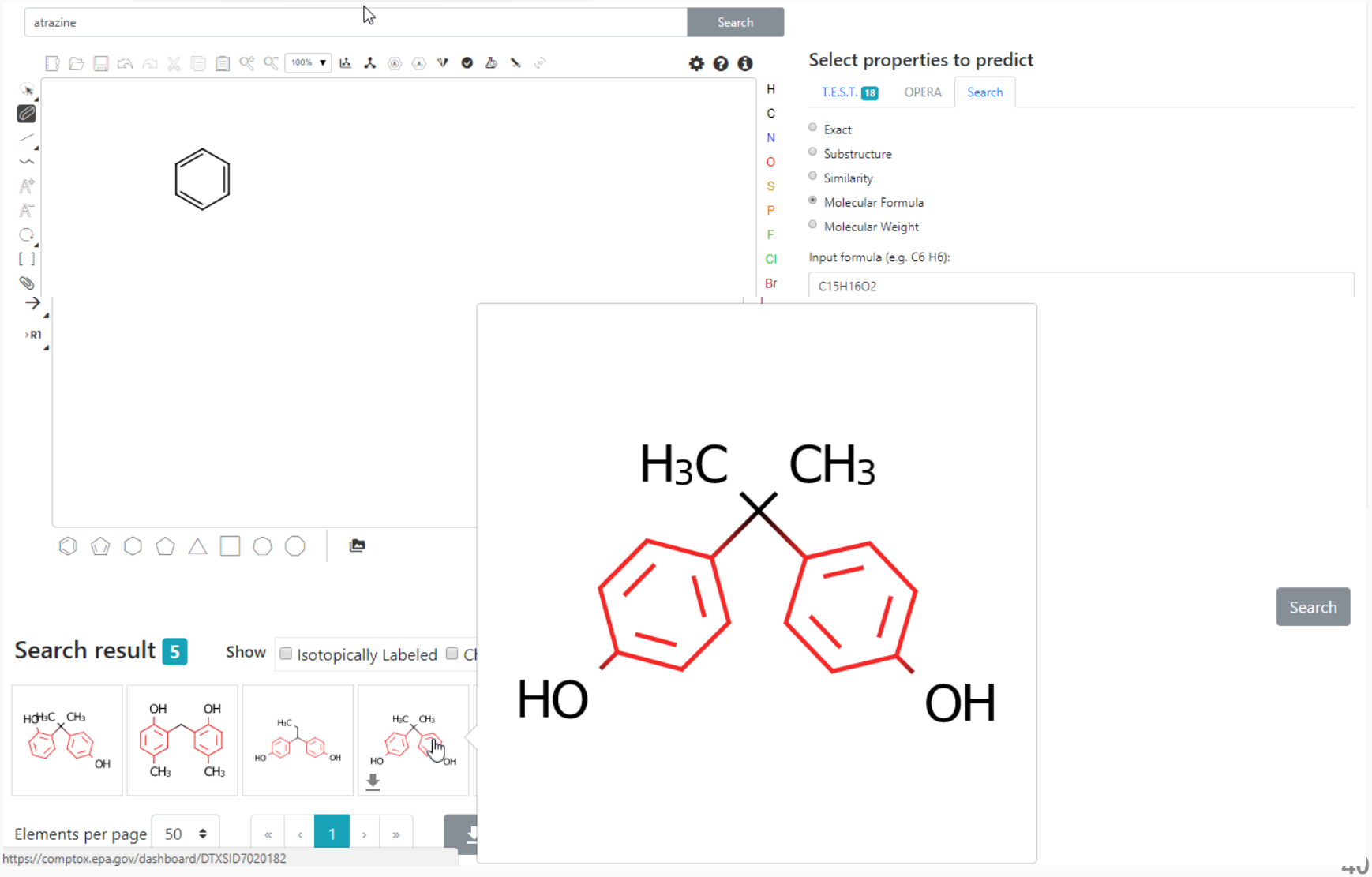


Batch Search Integration to MetFrag

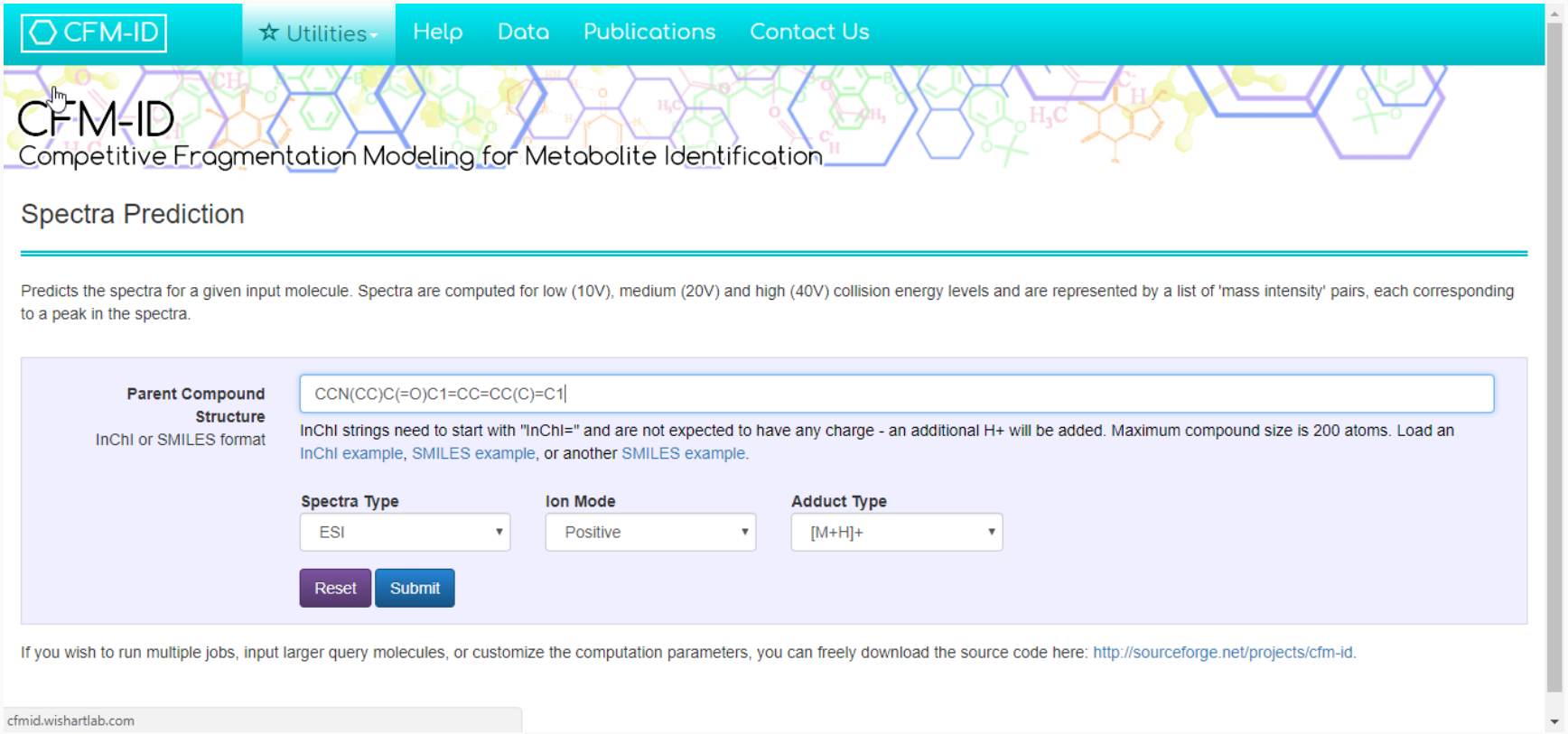
http://c-ruttkies.github.io/MetFrag/projects/metfragweb/



Future Work: Combined Substructure/Formula Searching

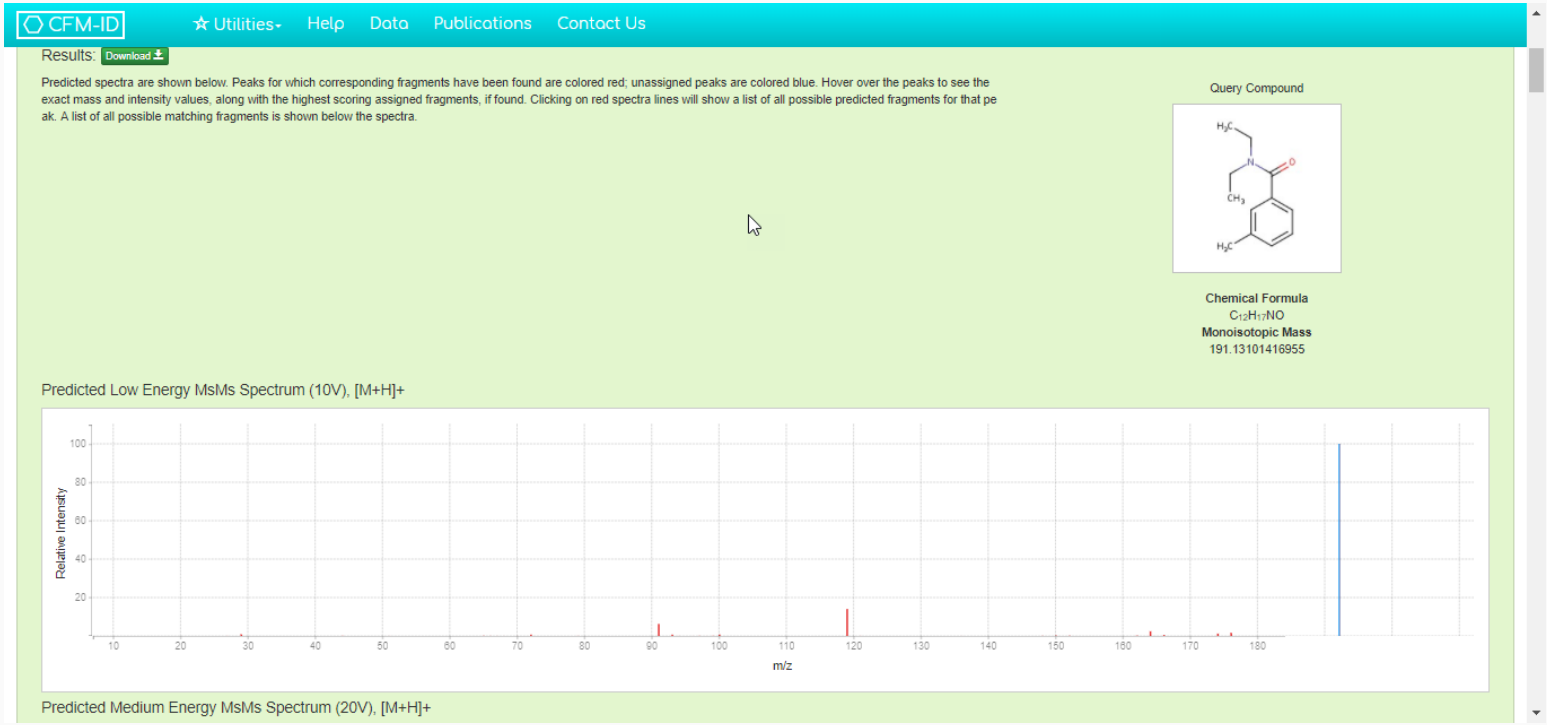


Future Work: Searching Against Predicted Spectra



Future Work: Searching Against Predicted Spectra

- CFM-ID predicted spectra generated for 700,000 chemicals
  - Positive ion, Negative ion, Electron Impact
  - Three energies



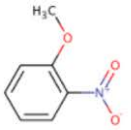
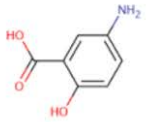
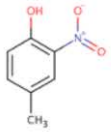
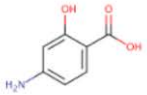
Future Work
Scoring scheme into results

EPA United States Environmental Protection Agency

Search Results

Searched by molecular formula: Found 188 results.

Download as: TSV Excel SDF

ID	Structure	Preferred Name	CAS-RN	QC Level	CPCat Count	Number of S...	PubChem D...	Monoisotopic Mass	Identification Score
DTXSID3020962 ToxCast™		1-Methoxy-2-nitrobenzene	91-23-6	Level 2: Expert curate...	0	58	111	153.042593	3.6
DTXSID5024506 ToxCast™		5-Aminosalicylic acid	89-57-6	Level 2: Expert curate...	2	57	193	153.042593	3.3
DTXSID0026961 ToxCast™		4-Methyl-2-nitrophenol	119-33-5	Level 2: Expert curate...	0	46	93	153.042593	3.3
DTXSID2022591		Aminosalicylic acid	65-49-6	Level 1: Expert curate...	0	40	177	153.042593	2.5

Data Sources PubMed Ct Media Occurr CPDat Ct

$$SC_{TOTAL} = SC_{DS} + SC_{PM} + SC_{RT} + SC_{MO} + \cdots$$

Conclusion

- The CompTox Chemistry Dashboard provides access to data for ~760,000 chemicals
- High quality curated data and rich metadata facilitates mass spec analysis
- “MS-Ready” processed data enables structure identification

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