EPA United States Environmental Protection Agency

EPA's Research Initiatives on Non-Targeted Analyses of Environmental Chemicals

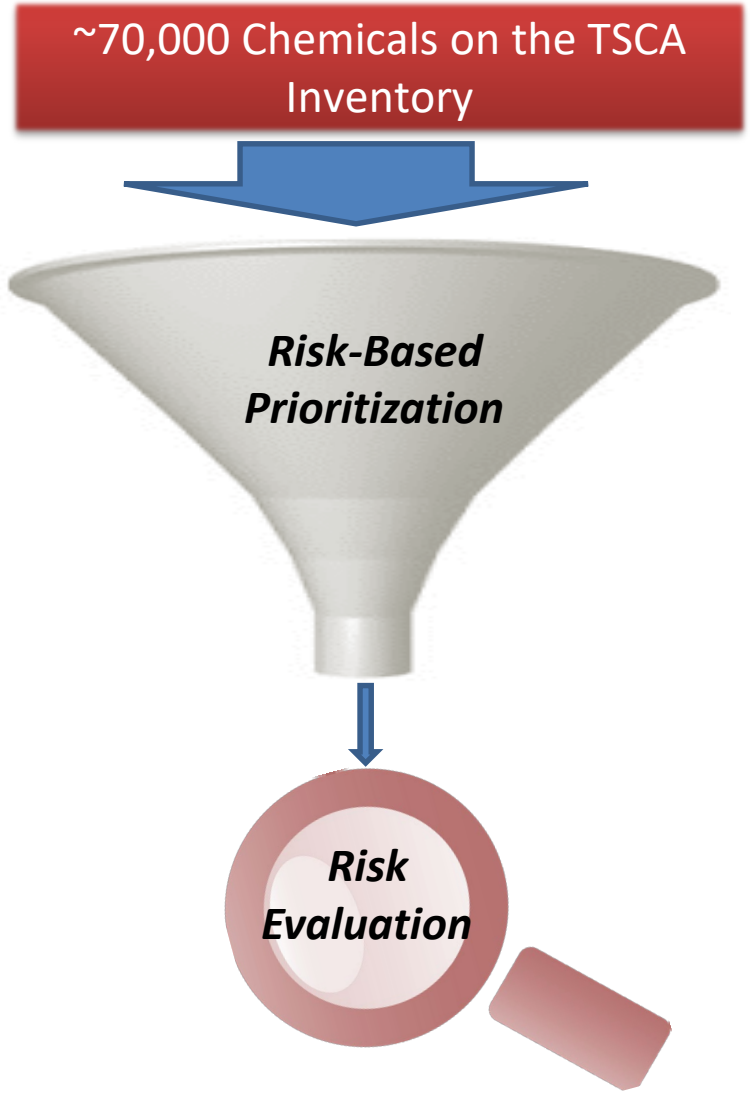
Jon Sobus[1], Elin Ulrich[1], Jarod Grossman[2], Alex Chao[2], Seth Newton[1], Antony Williams[1], Ann Richard[1], Chris Grulke[1], Andrew McEachran[2], Randolph Singh[2], Hussein Al-Ghoul[2], Louis Groff[2]

[1] Center for Computational Toxicology and Exposure
[2] ORAU/ORISE Participant

Office of Research and Development

Drivers for EPA Research Initiatives

- Many industrial & commercial chemicals are covered by the Toxic Substances Control Act (TSCA), which is administered by EPA.
- TSCA updated in June 2016 to allow *risk-based* evaluation of existing and new chemicals.
- Characterization of risk requires exposure and hazard data.
- EPA's Office of Research and Development (ORD) is developing new approach methodologies (NAMs) for rapid risk characterization.



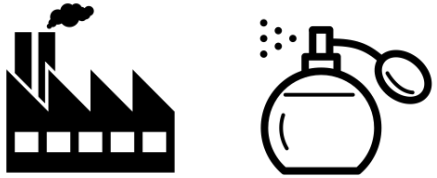
The Era of High-Throughput Assessments

United States Environmental Protection Agency

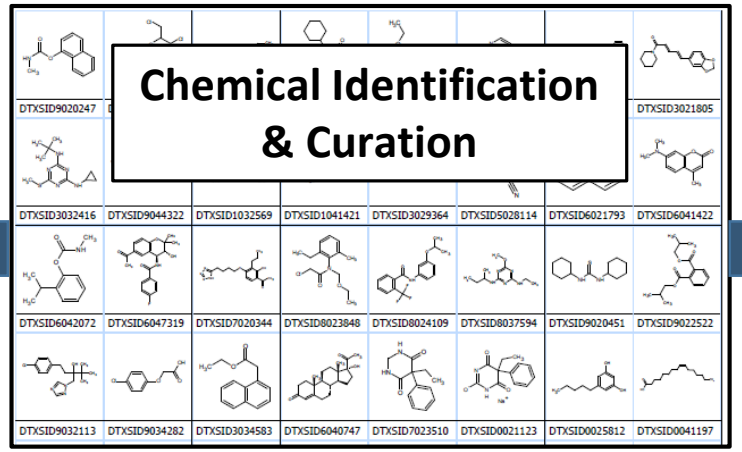
Exposure Forecasting (ExpoCast)

Toxicity Forecasting (ToxCast)

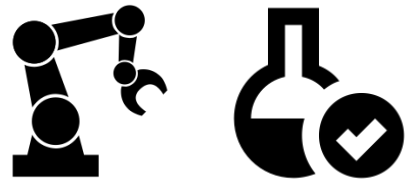
Production, Use & Scenario Data



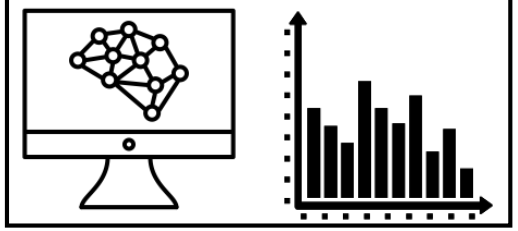
Chemical Identification & Curation



Procurement or Synthesis

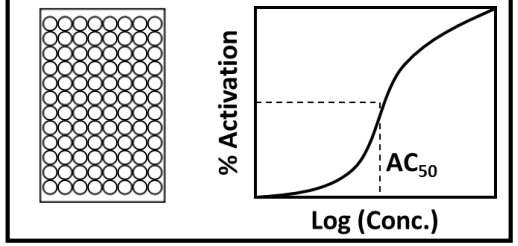


HT Exposure Prediction

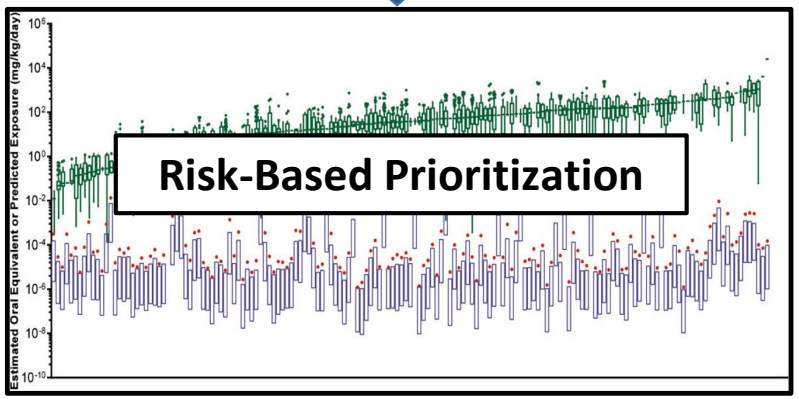


Extrapolation

HT Tox Assays



Risk-Based Prioritization



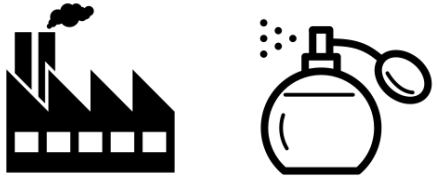
The Era of High-Throughput Assessments

United States Environmental Protection Agency

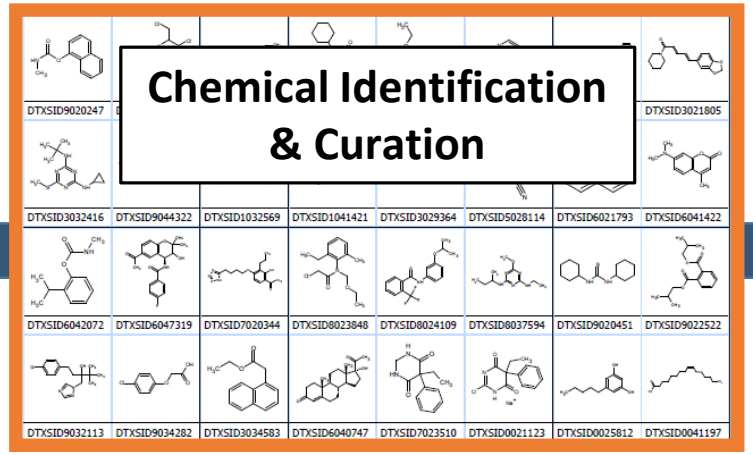
Exposure Forecasting (ExpoCast)

Toxicity Forecasting (ToxCast)

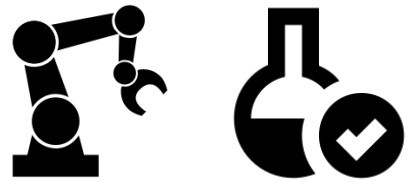
Production, Use & Scenario Data



Chemical Identification & Curation



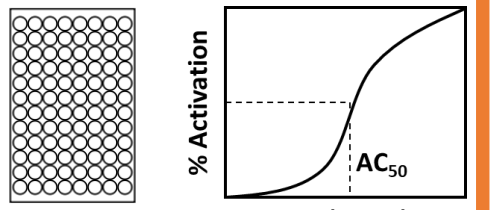
Procurement or Synthesis



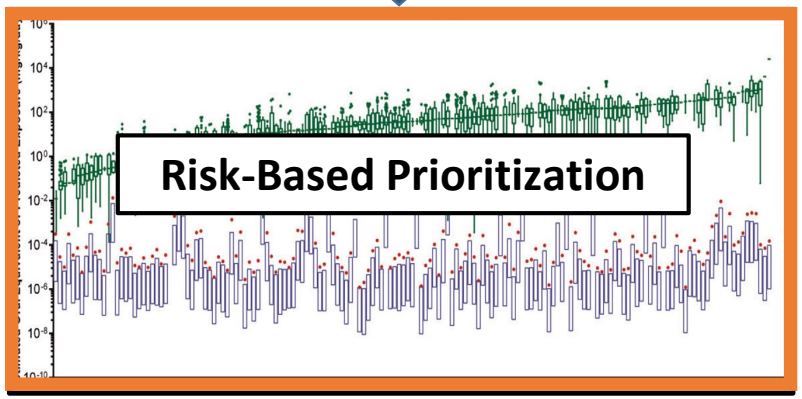
HT Exposure Prediction

Extrapolation

HT Tox Assays



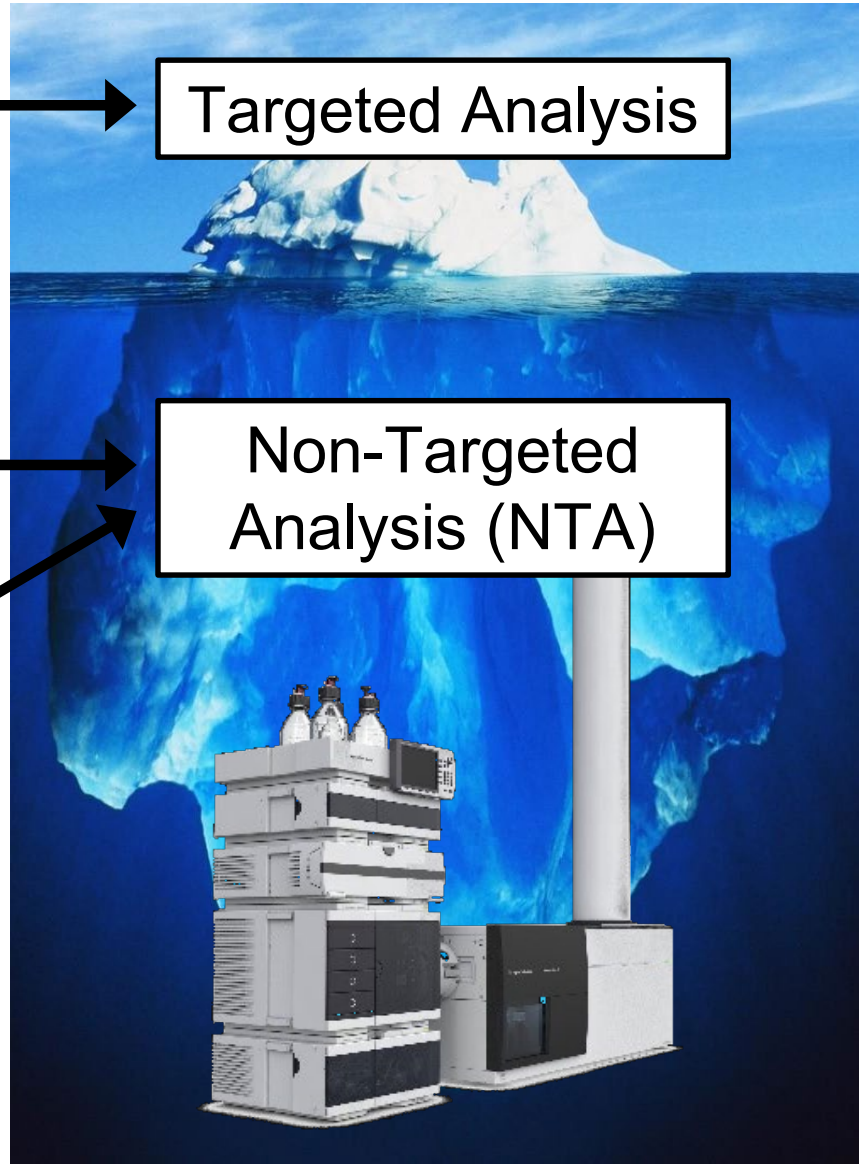
Risk-Based Prioritization



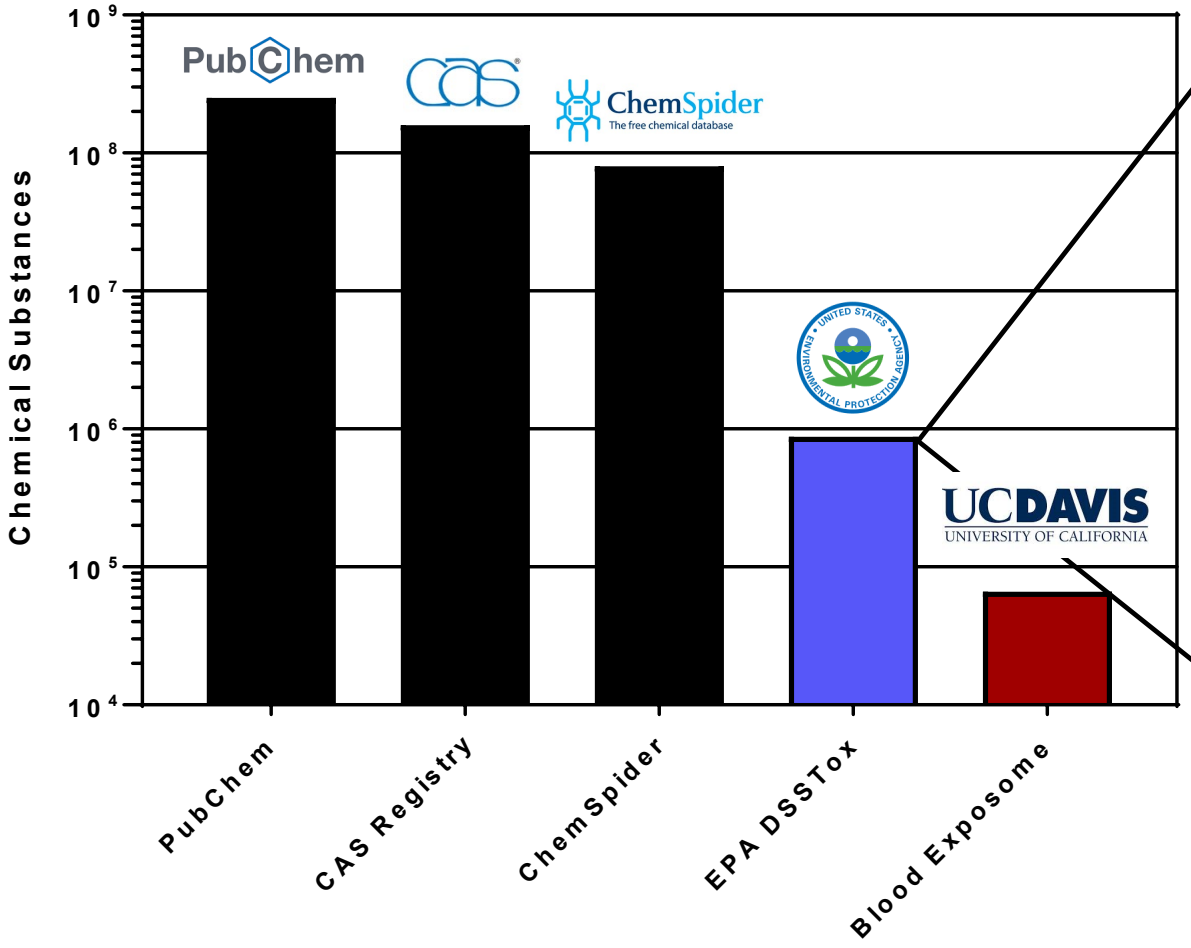
Guided and/or enhanced by Measurement Data!!

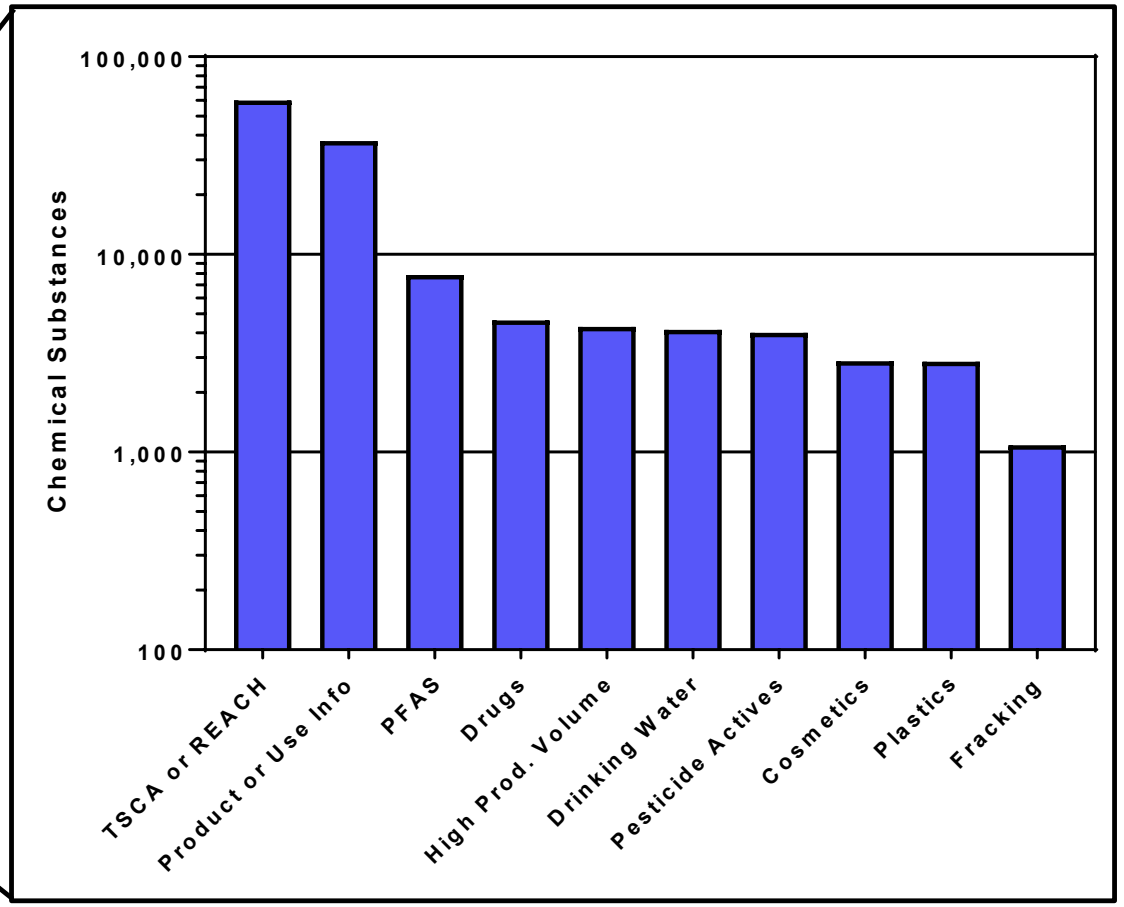
The Need for Chemical Measurement Data

- **Well-known chemicals**
  - 100s - 1,000s (e.g., NHANES)
  - Quality exposure data
- **Known but data-poor chemicals**
  - 1,000s - 1,000,000s (e.g., TSCA)
  - Limited exposure data
- **Chemicals not yet known to exist**
  - Unknown #
  - No exposure data

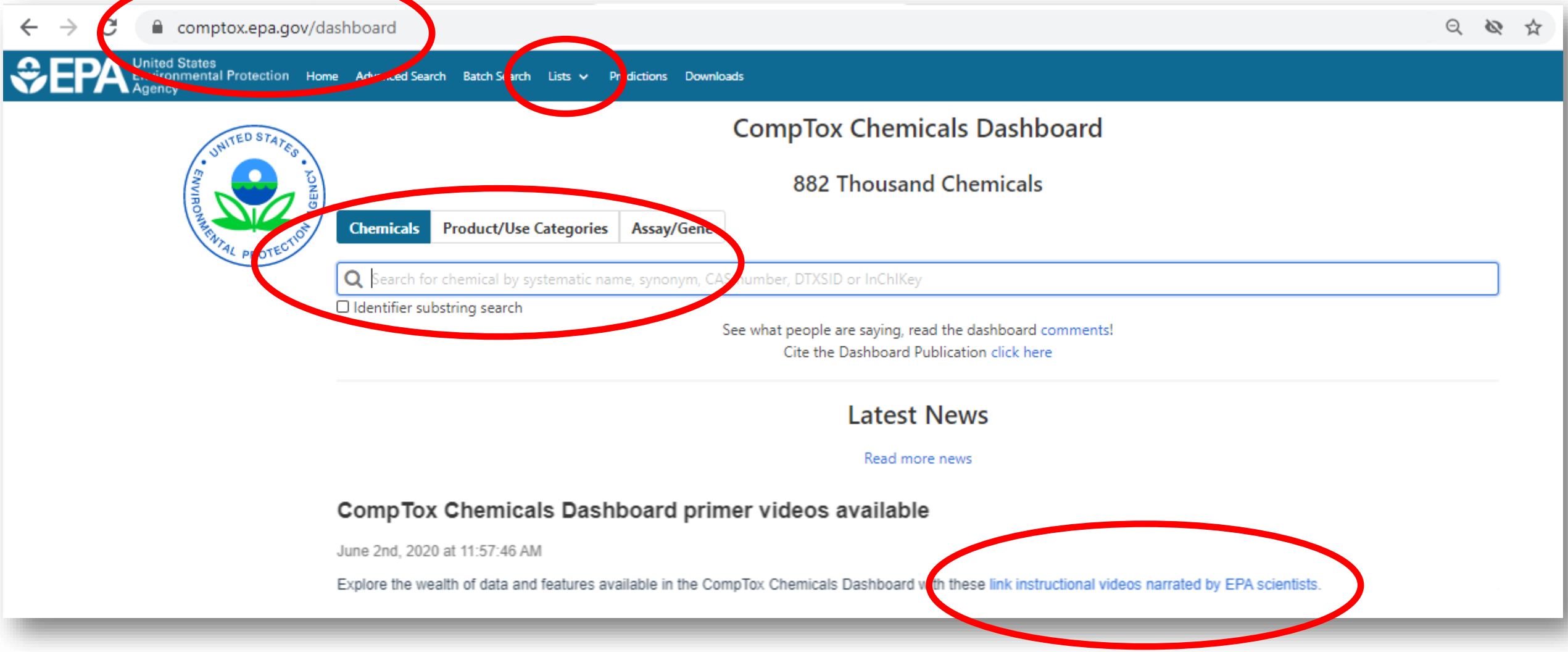


Compilations of Known Chemicals

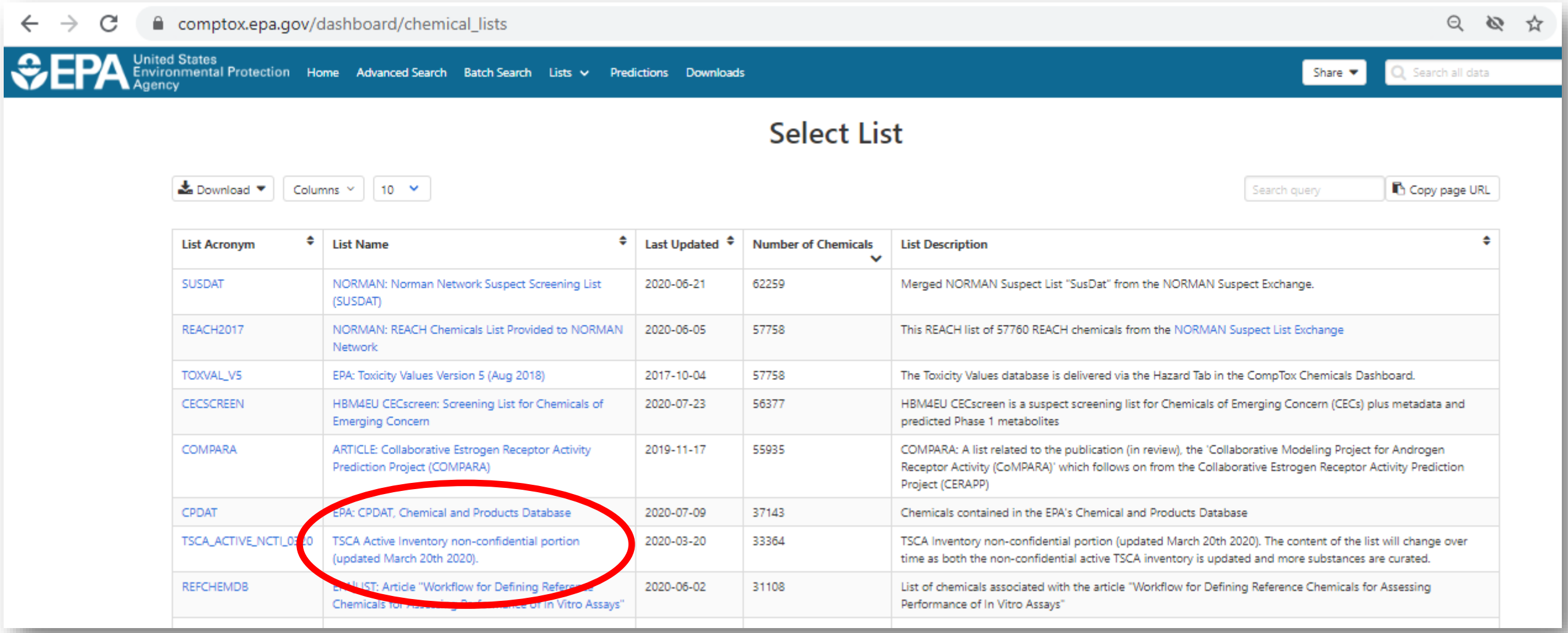




Accessing DSSTox Chemistry Data

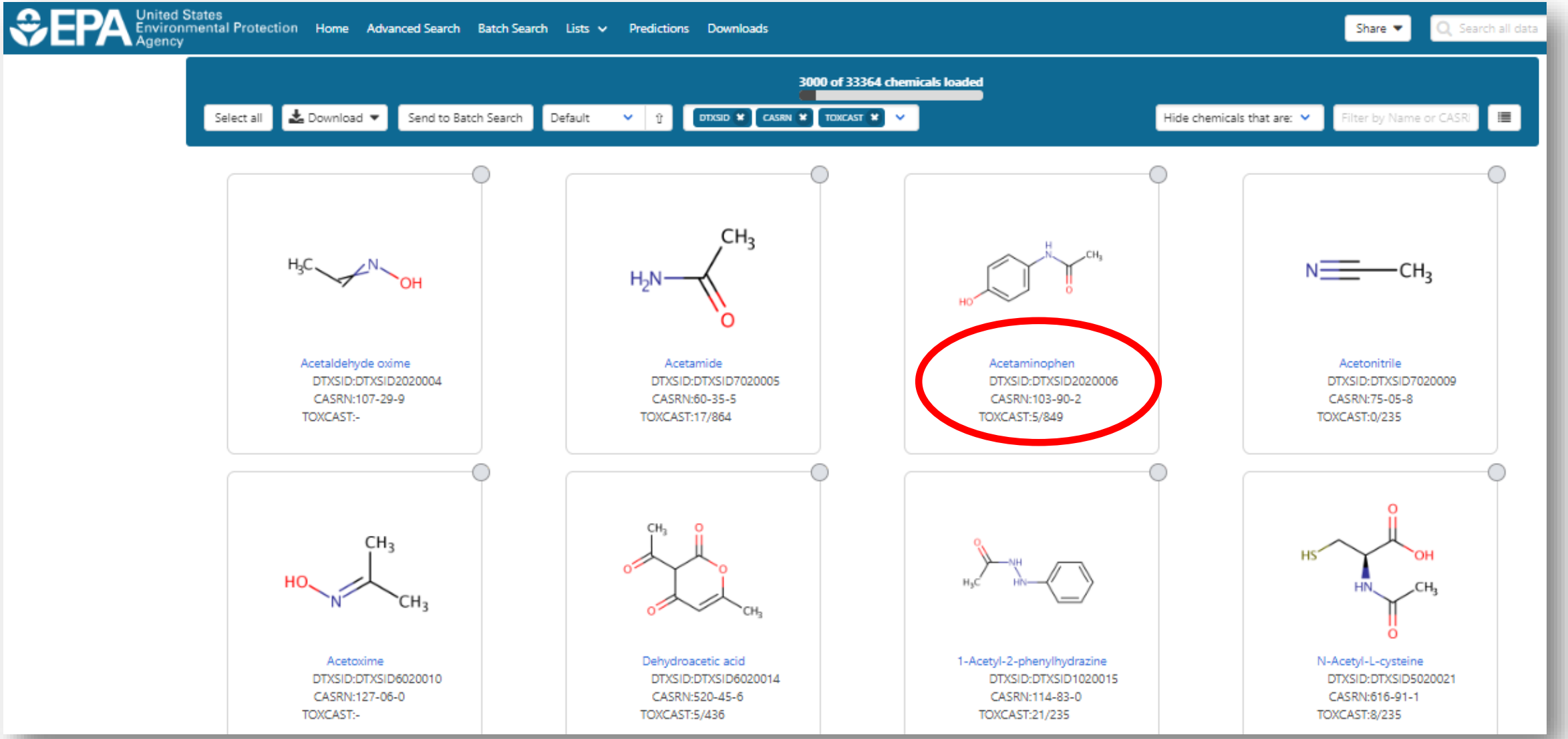


Accessing Chemical Lists

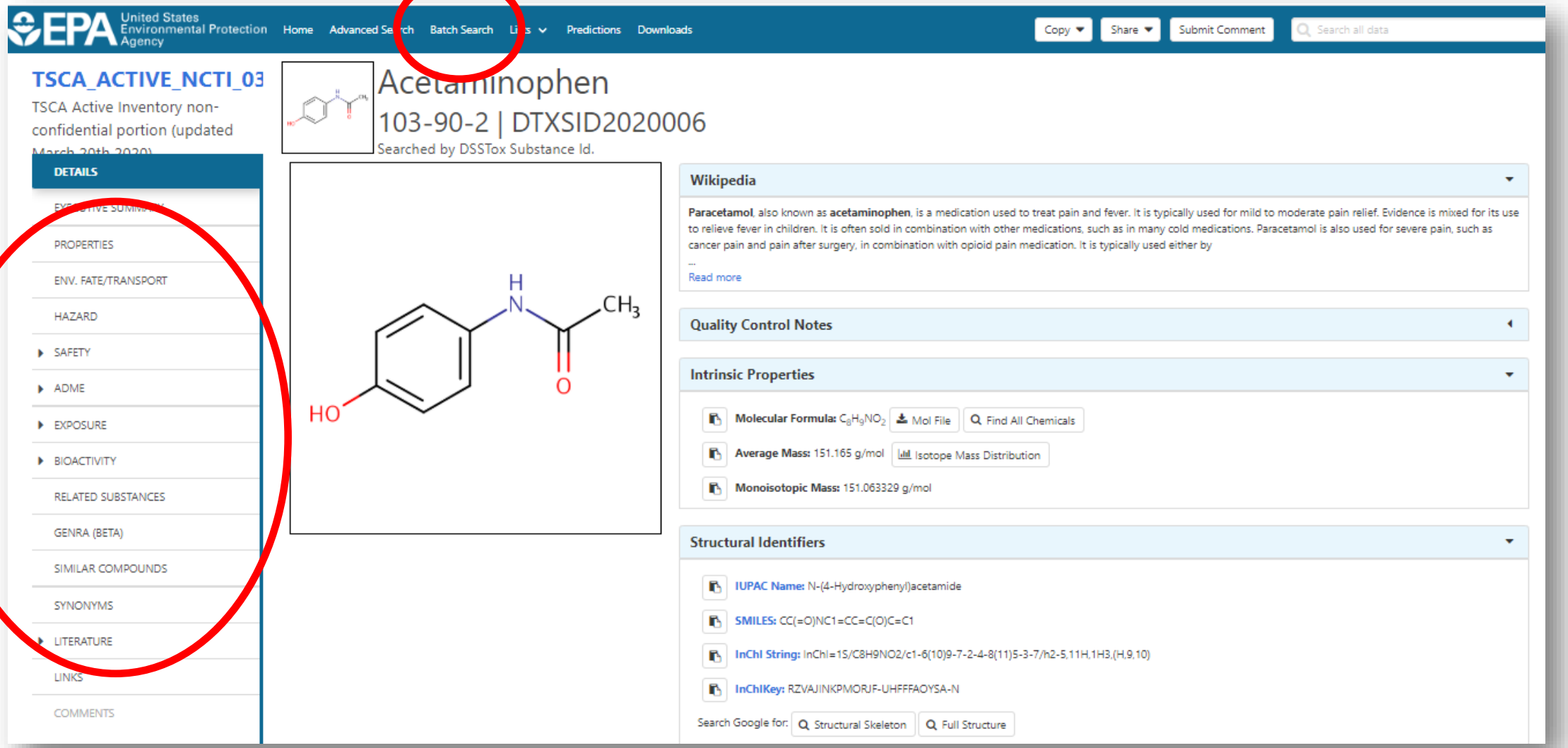


List Acronym	List Name	Last Updated	Number of Chemicals	List Description
SUSDAT	NORMAN: Norman Network Suspect Screening List (SUSDAT)	2020-06-21	62259	Merged NORMAN Suspect List "SusDat" from the NORMAN Suspect Exchange.
REACH2017	NORMAN: REACH Chemicals List Provided to NORMAN Network	2020-06-05	57758	This REACH list of 57760 REACH chemicals from the NORMAN Suspect List Exchange
TOXVAL_V5	EPA: Toxicity Values Version 5 (Aug 2018)	2017-10-04	57758	The Toxicity Values database is delivered via the Hazard Tab in the CompTox Chemicals Dashboard.
CECSCREEN	HBM4EU CECscreen: Screening List for Chemicals of Emerging Concern	2020-07-23	56377	HBM4EU CECscreen is a suspect screening list for Chemicals of Emerging Concern (CECs) plus metadata and predicted Phase 1 metabolites
COMPARA	ARTICLE: Collaborative Estrogen Receptor Activity Prediction Project (COMPARA)	2019-11-17	55935	COMPARA: A list related to the publication (in review), the 'Collaborative Modeling Project for Androgen Receptor Activity (CoMPARA)' which follows on from the Collaborative Estrogen Receptor Activity Prediction Project (CERAPP)
CPDAT	EPA: CPDAT, Chemical and Products Database	2020-07-09	37143	Chemicals contained in the EPA's Chemical and Products Database
TSCA_ACTIVE_NCTI_03[illegible]20	TSCA Active Inventory non-confidential portion (updated March 20th 2020).	2020-03-20	33364	TSCA Inventory non-confidential portion (updated March 20th 2020). The content of the list will change over time as both the non-confidential active TSCA inventory is updated and more substances are curated.
REFCHEMDB	[illegible]IST: Article "Workflow for Defining Reference Chemicals for [illegible] of In Vitro Assays"	2020-06-02	31108	List of chemicals associated with the article "Workflow for Defining Reference Chemicals for Assessing Performance of In Vitro Assays"

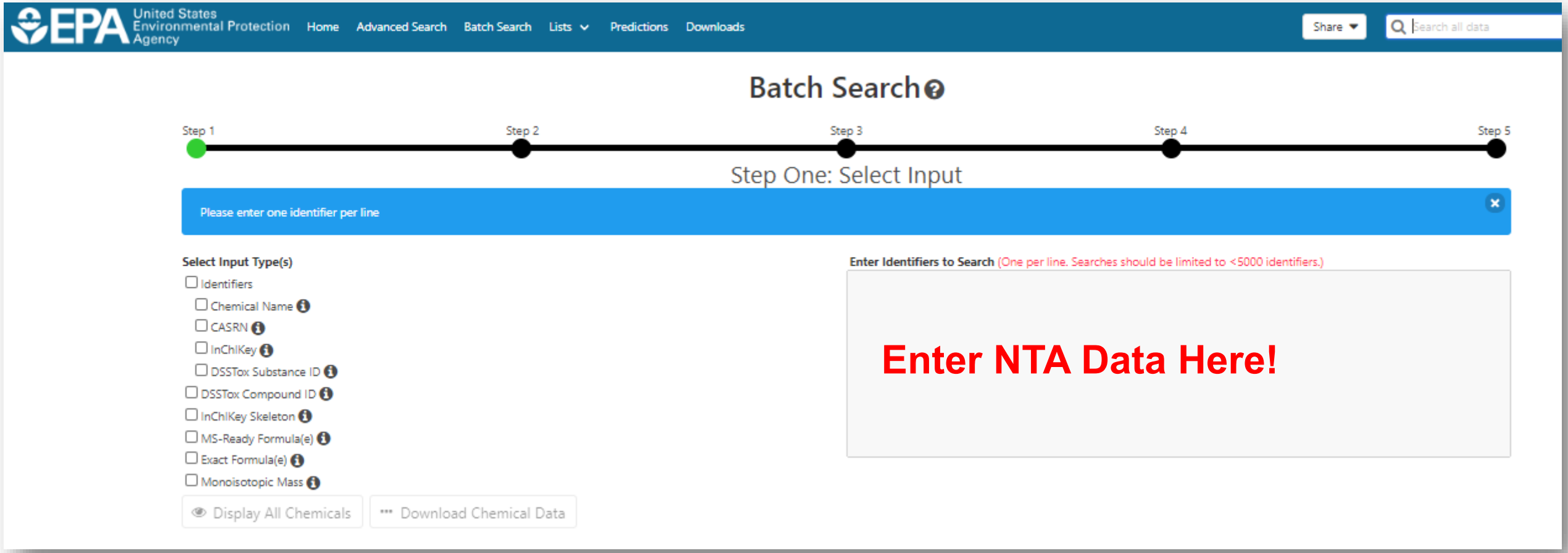
Accessing Specific Chemicals



Accessing Chemical-Specific Info



Accessing Chemical Info via Batch Search



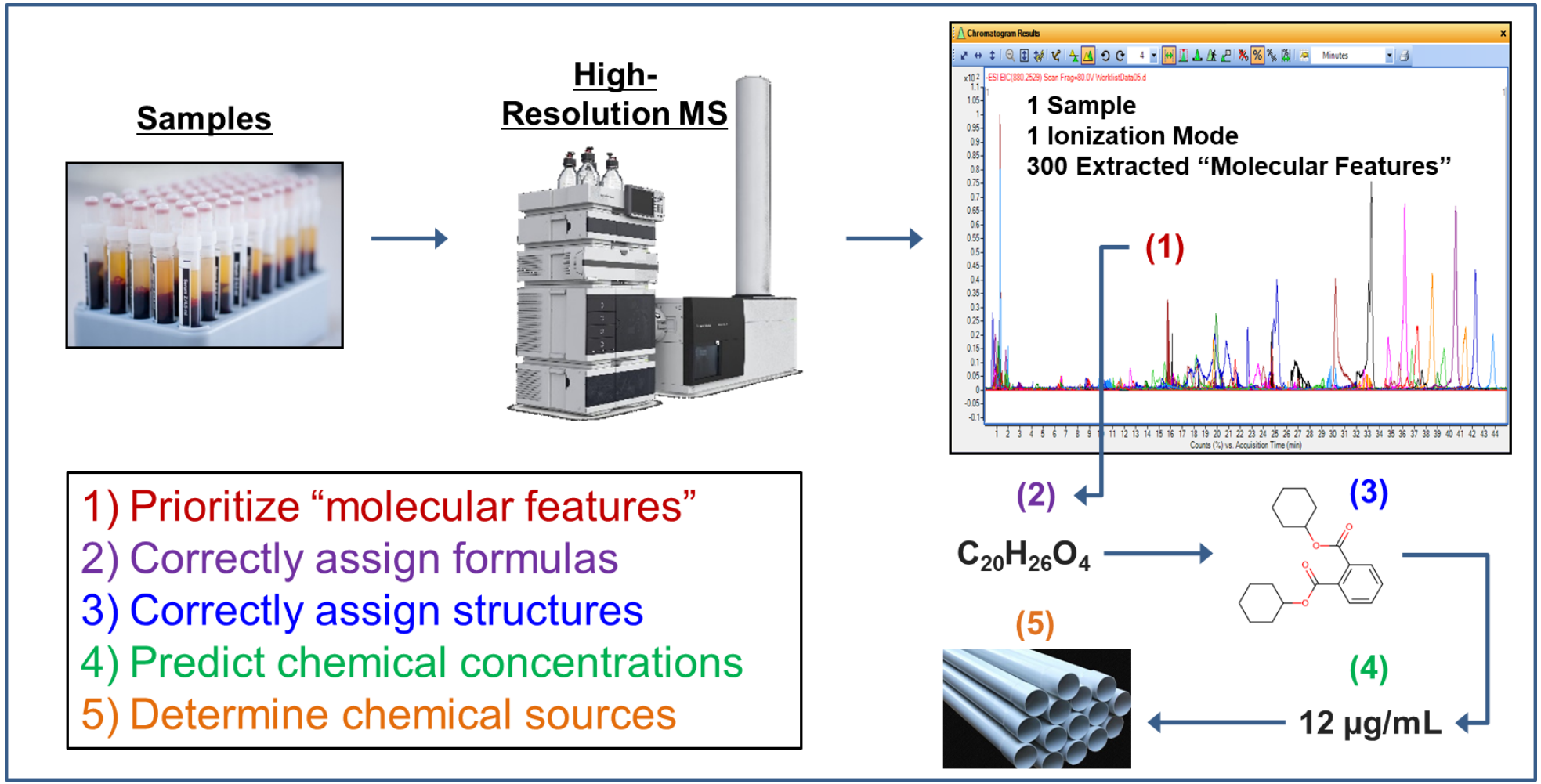
What's So Great About NTA?

Rapidly screen for "knowns"

Discover "unknowns"

Uncover historical exposures

Generate source fingerprints…



Example NTA Application Using Brita Filters

Environmental Pollution 234 (2018) 297–306

Contents lists available at ScienceDirect

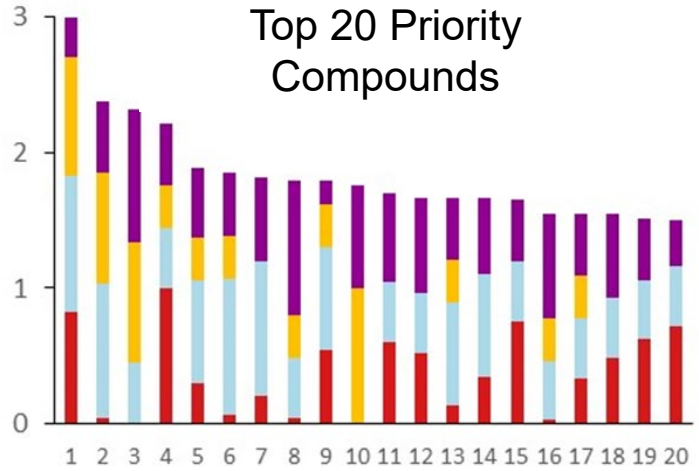
Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Suspect screening and non-targeted analysis of drinking water using point-of-use filters☆

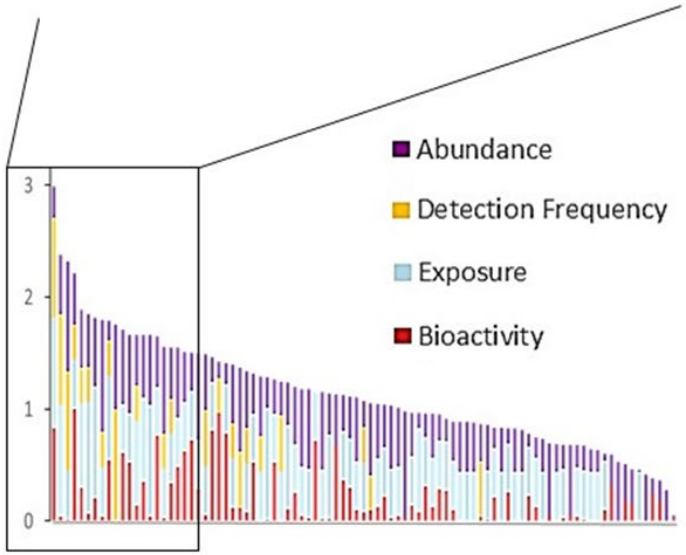
Seth R. Newton [a, *], Rebecca L. McMahen [a, b], Jon R. Sobus [a], Kamel Mansouri [b, c, 1], Antony J. Williams [c], Andrew D. McEachran [b, c], Mark J. Strynar [a]

[a] United States Environmental Protection Agency, National Exposure Research Laboratory, Research Triangle Park, NC 27709, United States
[b] Oak Ridge Institute for Science and Education Research Participant, 109 T.W. Alexander Drive, Research Triangle Park, NC 27709, United States
[c] United States Environmental Protection Agency, National Center for Computational Toxicology, Research Triangle Park, NC 27709, United States



#	Compound	ToxPi Score
1	1,2-Benzisothiazolin-3-one*	2.99
2	Diethyleneglycol	2.38
3	N-[3-(Dimethylamino)propyl] methacrylamide	2.32
4	Nonylparaben	2.22
5	Dipentyl phthalate	1.89
6	2-[2-(2-Butoxyethoxy) ethoxy]ethanol*	1.85
7	N,N-Dimethyldodecan-1-amine*	1.81
8	Sucralose	1.80
9	PFOS*	1.79
10	2-(2-Ethoxyethoxy) ethyl acetate*	1.76
11	TDCPP*	1.71
12	Zearalanol	1.67
13	PFOA*	1.66
14	Butylparaben	1.66
15	Noristerat	1.65
16	p-Synephrine	1.55
17	Alprostadil	1.55
18	Sclareol	1.55
19	PFDA*	1.51
20	Simvastatin	1.50

*Confirmed with standard

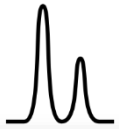


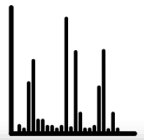
Top 100 Priority Compounds

Building an NTA Research Program

United States Environmental Protection Agency

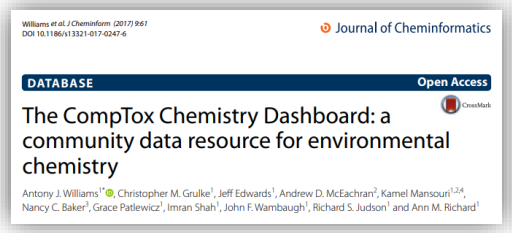
Data, Tools & Informatics





Semi Quant. Methods

EPA NTA WebApp

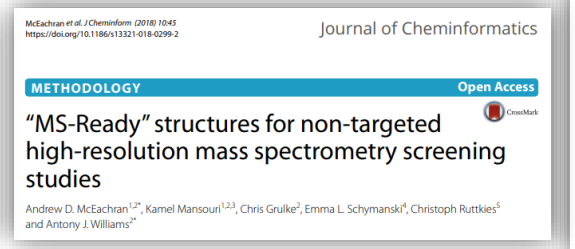

Journal of Cheminformatics

DATABASE Open Access

The CompTox Chemistry Dashboard: a community data resource for environmental chemistry

Antony J. Williams, Christopher M. Grulke, Jeff Edwards, Andrew D. McEachran, Kamel Mansouri, Nancy C. Baker, Grace Patlewicz, Imran Shah, John F. Wambaugh, Richard S. Judson and Ann M. Richard

Chemicals Dashboard

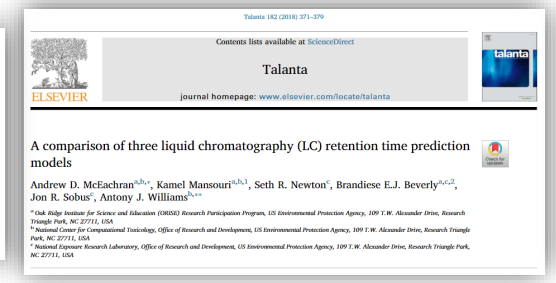

Journal of Cheminformatics

METHODOLOGY Open Access

"MS-Ready" structures for non-targeted high-resolution mass spectrometry screening studies

Andrew D. McEachran, Kamel Mansouri, Chris Grulke, Emma L. Schymanski, Christoph Ruttkies and Antony J. Williams

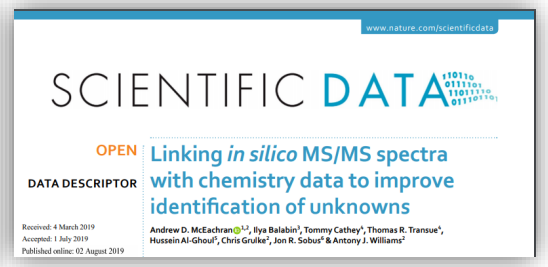
"MS Ready" Structures


Talanta

A comparison of three liquid chromatography (LC) retention time prediction models

Andrew D. McEachran, Kamel Mansouri, Seth R. Newton, Brandiese E.J. Beverly, Jon R. Sobus, Antony J. Williams

RT Models


SCIENTIFIC DATA

OPEN DATA DESCRIPTOR

Linking *in silico* MS/MS spectra with chemistry data to improve identification of unknowns

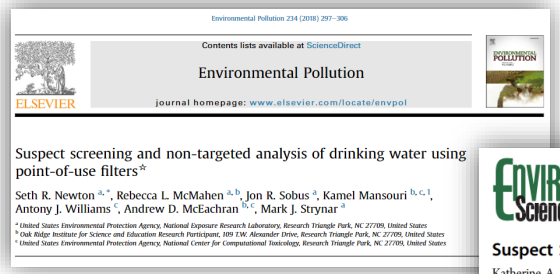
Andrew D. McEachran, Ilya Balabin, Tommy Cathey, Thomas R. Transue, Hussein Al-Ghoul, Chris Grulke, Jon R. Sobus & Antony J. Williams

In Silico Spectra

2016… 2017… 2019… 2020…

NTA Applications

Brita Filters


Environmental Pollution

Suspect screening and non-targeted analysis of drinking water using point-of-use filters

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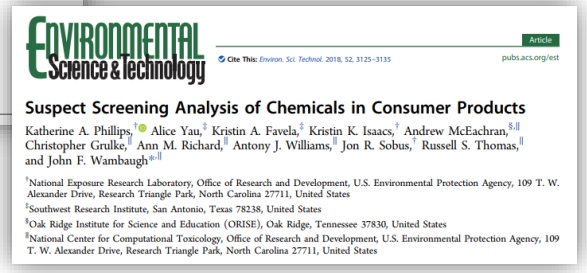
Consumer Products


Environmental Science & Technology

Suspect Screening Analysis of Chemicals in Consumer Products

Katherine A. Phillips, Alice Yau, Kristin A. Favela, Kristin K. Isaacs, Andrew McEachran, Christopher Grulke, Ann M. Richard, Antony J. Williams, Jon R. Sobus, Russell S. Thomas, and John F. Wambaugh

Model Organisms

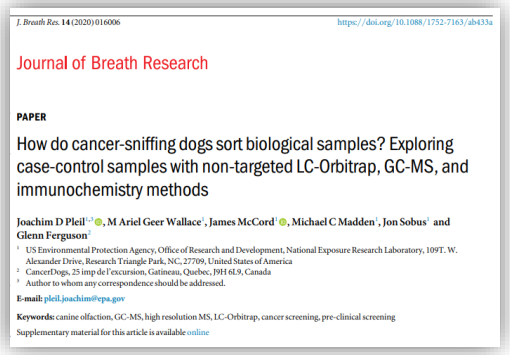

SOT Society of Toxicology academic.oup.com/toxsci

Tox Spotlight

Triclosan-Selected Host-Associated Microbiota Perform Xenobiotic Biotransformations in Larval Zebrafish

Chelsea A. Weitekamp, Drake Phelps, Adam Swank, James McCord, Jon R. Sobus, Tara Catron, Scott Keely, Nichole Brinkman, Todd Zurlinden, Emily Wheaton, Mark Strynar, Charlene McQueen, Charles E. Wood, and Tamara Tal

Hospital Masks


Journal of Breath Research

PAPER

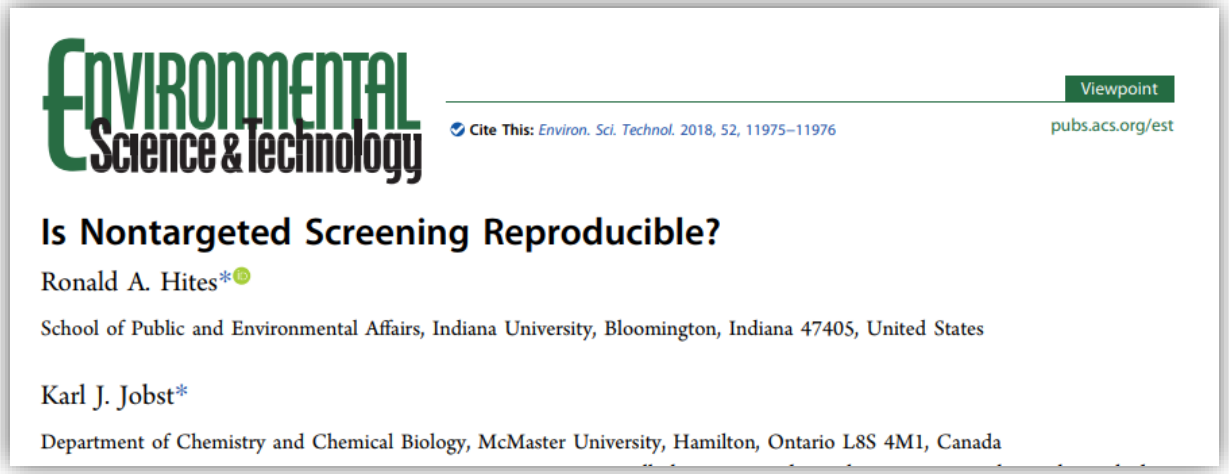
How do cancer-sniffing dogs sort biological samples? Exploring case-control samples with non-targeted LC-Orbitrap, GC-MS, and immunochemistry methods

Joachim D Pleil, M Ariel Geer Wallace, James McCord, Michael C Madden, Jon Sobus and Glenn Ferguson

Recycled Products

Human Placentas

NTA State-of-the-Science



Environmental Science & Technology

Viewpoint

Cite This: *Environ. Sci. Technol.* 2018, 52, 11975−11976

pubs.acs.org/est

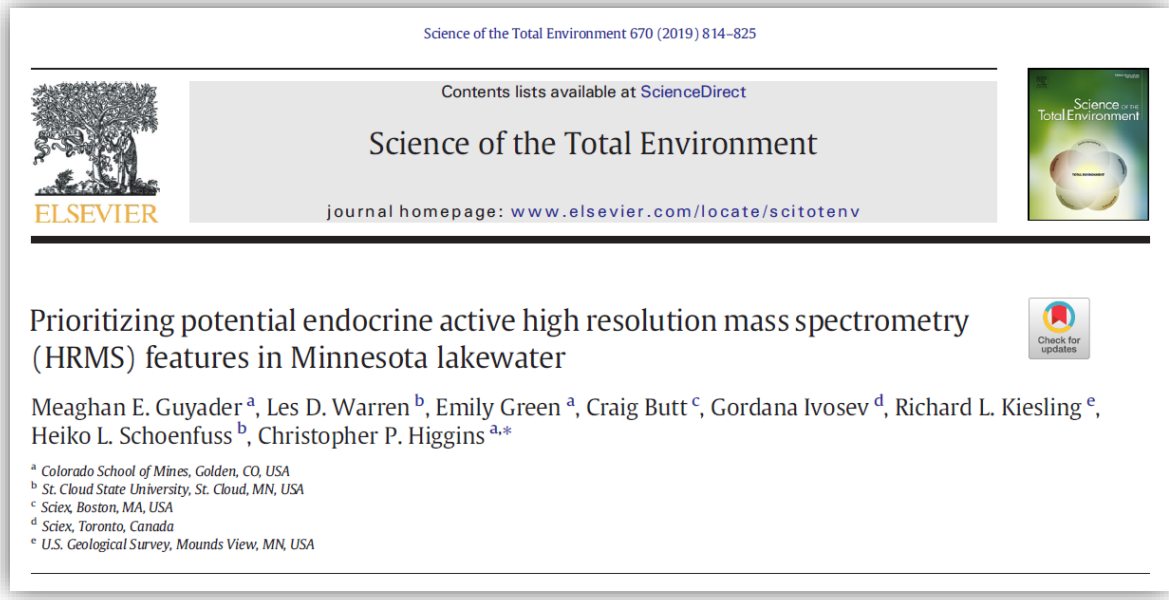
Is Nontargeted Screening Reproducible?

Ronald A. Hites*

School of Public and Environmental Affairs, Indiana University, Bloomington, Indiana 47405, United States

Karl J. Jobst*

Department of Chemistry and Chemical Biology, McMaster University, Hamilton, Ontario L8S 4M1, Canada



Science of the Total Environment 670 (2019) 814–825

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

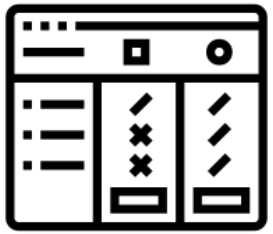
Prioritizing potential endocrine active high resolution mass spectrometry (HRMS) features in Minnesota lakewater

Meaghan E. Guyader [a], Les D. Warren [b], Emily Green [a], Craig Butt [c], Gordana Ivosev [d], Richard L. Kiesling [e], Heiko L. Schoenfuss [b], Christopher P. Higgins [a,*]

[a] Colorado School of Mines, Golden, CO, USA
[b] St. Cloud State University, St. Cloud, MN, USA
[c] Sciex, Boston, MA, USA
[d] Sciex, Toronto, Canada
[e] U.S. Geological Survey, Mounds View, MN, USA

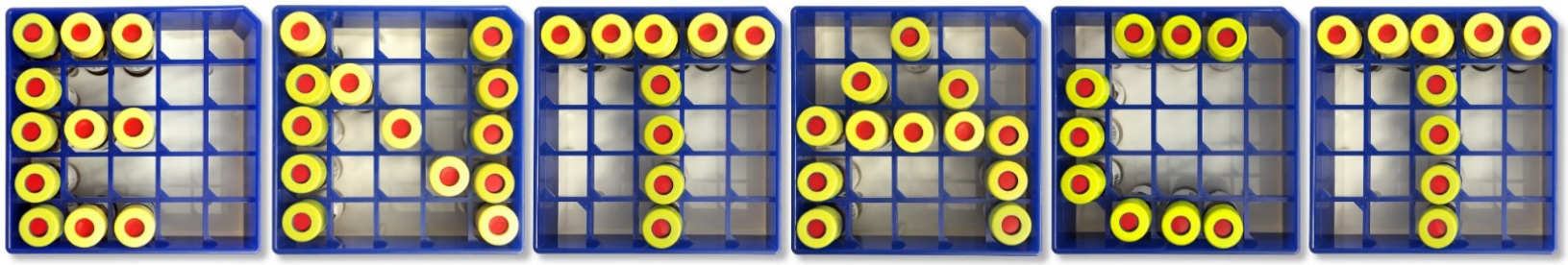
"*No single analytical technique is suitable for the analysis of all compounds, and successful nontargeted screening will require the development of multiplatform approaches, facilitated and validated through interlaboratory collaborations*."

"*The novelty of nontarget analysis, particularly its current lack of implementation by regulatory agencies, has prevented the establishment of streamlined quality assurance and quality control (QA/QC) procedures.*"



Science Questions for Research Community

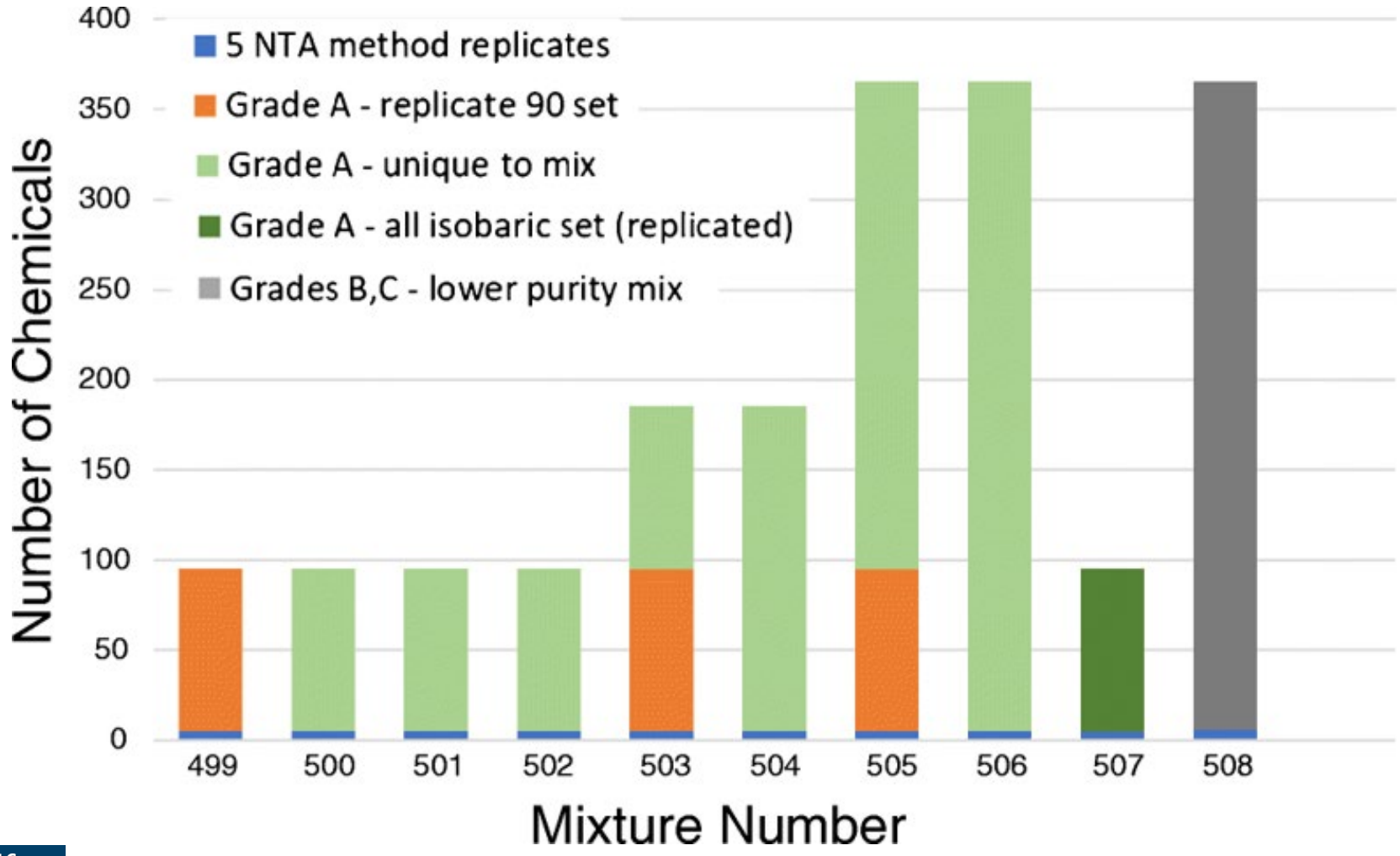
- How variable are tools and results from lab to lab?
- Are some methods/workflows better than others?
- How does sample complexity affect performance?
- What chemical space does a given method cover?
- How sensitive are specific instruments/methods?



EPA's Non-Targeted Analysis Collaborative Trial

Design of ENTACT Mixtures

~1200 Unique ToxCast Chemicals:



~30 Collaborators:

1st: Blinded analysis

2nd: Unveiling of chemicals

3rd: Unblinded evaluation

Ulrich et al. 2019. doi: 10.1007/s00216-018-1435-6

Who is Working on ENTACT?

Contractors:

University of Alberta
Emory University
Duke University
Oregon State University
San Diego State University
Pacific Northwest National Laboratory

19 Blind submissions

15 Unblinded submissions

Vendors:

The Scripps Research Institute
Agilent Technologies
Thermo Scientific
Leco
AB SCIEX
Waters

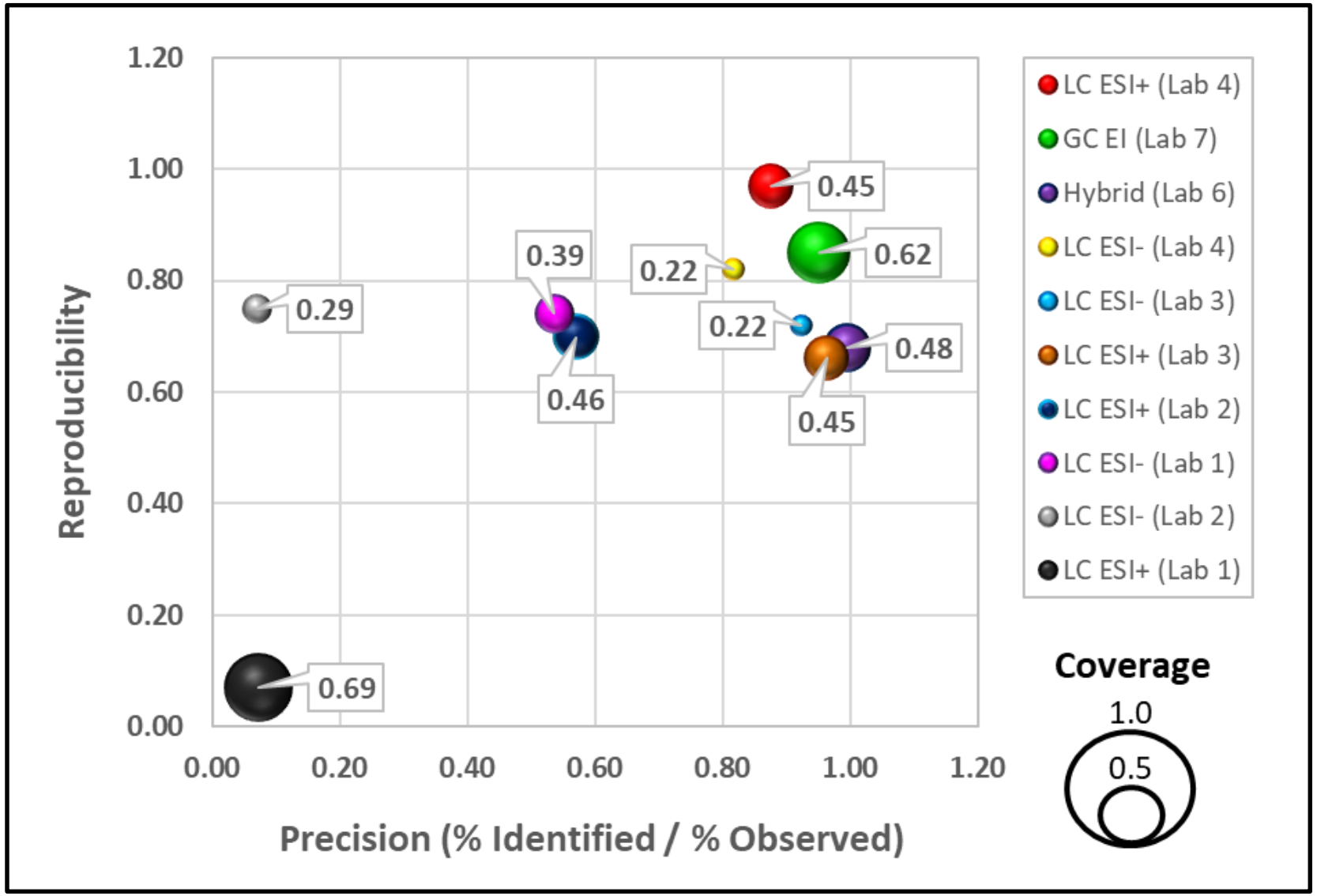
General Participants:

Université du Luxembourg
University of Florida
Wisconsin State Laboratory of Hygiene, University of Wisconsin-Madison
NIST
NC State University
Recetox
Cornell University
UW Tacoma
Mount Sinai
University of Birmingham
DTSC Department of Toxic Substances Control
eawag aquatic research
United States Environmental Protection Agency
FIU

Processing ENTACT Data Submissions

- Individual methods treated separately (if appropriate)
- One candidate mass/formula/compound per feature
- Confidence level revised as needed (with consensus)
- Matching to spiked substances by mass, formula & structure
- "**Observed**" if structure or formula (no spiked isomers) match
- "**Identified**" if structure match
- "**Reproducible**" if correctly ID'd >50% of the time
  - For compounds spiked >1 time and identified ≥1 time

Method Comparison: Total Performance



Metrics (all %):

X-Axis →
How often correct?

Y-Axis →
How consistent?

Bubble Size →
How much coverage?

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Overall Summary

- Regulatory drivers necessitate NAMs for rapid risk characterization
- Measurement data are needed to inform and evaluate NAMs
- Targeted measurement methods can’t keep pace with needs of NAMs
- NTA methods may meet needs, but require development and validation
- EPA/ORD is working to:
  - Develop tools to support NTA studies
  - Apply NTA methods to identify and prioritize chemicals based on anticipated risk
  - Evaluate NTA state-of-the-science via ENTACT

Additional Resources

- ENTACT
  - Dust Analysis: doi: 10.1007/s00216-020-02658-w
  - Evaluation of *in silico* spectra: doi: 10.1007/s00216-019-02351-7
  - APCI vs. ESI: doi: 10.1007/s00216-020-02716-3
- EPA NTA Workflow
  - CompTox Chemicals Dashboard: doi: 10.1186/s13321-017-0247-6
  - MS-Ready Structures: doi: 10.1186/s13321-018-0299-2
  - Risk prioritization framework: doi: 10.1038/s41370-017-0012-y
- EPA NTA Applications
  - Consumer products: doi: 10.1021/acs.est.7b04781
  - House dust: doi: 10.1016/j.envint.2015.12.008
  - Drinking water: doi: 10.1016/j.envpol.2017.11.033

Additional Resources

- POSTER → ID: 3430230
  TITLE: Suspect screening analysis of recycled consumer products

- PRESENTATION → ID: 3430216
  TITLE: Predicting chromatography-tandem mass spectrometry amenability to improve non-targeted analysis

Contributing Researchers

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