# The Tox21 10K Compound Library:
## *Collaborative Chemistry Advancing Toxicology*

*Dr. Ann M. Richard*
*Computational Chemistry & Cheminformatics Branch*
*Center for Computational Toxicology & Exposure*
*Office of Research & Development*
*U.S. Environmental Protection Agency, RTP, NC*

*This work was reviewed by the U.S. EPA and approved for presentation but does not necessarily reflect official Agency policy.*

*January 28, 2021*
*EPA's Computational Toxicology Communities of Practice Webinar*

Chemical Research in Toxicology

This is an open access article published under an ACS AuthorChoice License, which permits copying and redistribution of the article or any adaptations for non-commercial purposes.

ACS EDITOR'S CHOICE

pubs.acs.org/crt

Review

# The Tox21 10K Compound Library: Collaborative Chemistry Advancing Toxicology

Ann M. Richard,* Ruili Huang, Suramya Waidyanatha, Paul Shinn, Bradley J. Collins, Inthirany Thillainadarajah, Christopher M. Grulke, Antony J. Williams, Ryan R. Lougee, Richard S. Judson, Keith A. Houck, Mahmoud Shobair, Chihae Yang, James F. Rathman, Adam Yasgar, Suzanne C. Fitzpatrick, Anton Simeonov, Russell S. Thomas, Kevin M. Crofton, Richard S. Paules, John R. Bucher, Christopher P. Austin, Robert J. Kavlock, and Raymond R. Tice

Cite this: *Chem. Res. Toxicol.* 2020, XXXX, XXX, XXX-XXX

Publication Date: November 3, 2020

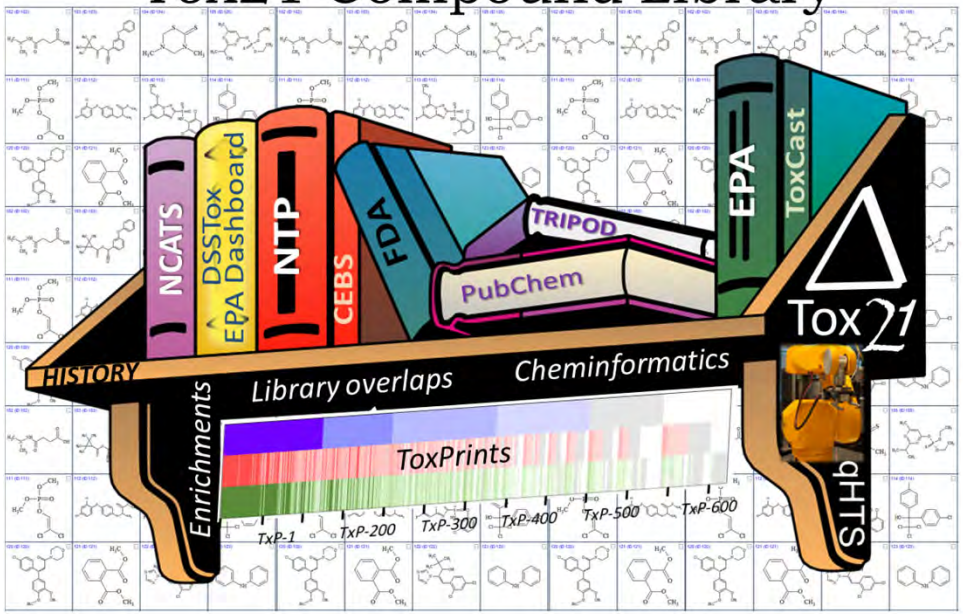
https://doi.org/10.1021/acs.chemrestox.0c00264

Copyright © 2020 American Chemical Society

RIGHTS & PERMISSIONS ACS Editors' Choice

Article Views 5170 | Altmetric 3 | Citations 1

Tox21 Compound Library



# First, a bit of …

# Toxicity Testing in the 21st Century

EPA United States Environmental Protection Agency

EPA, 2003

NATIONAL TOXICOLOGY PROGRAM

VISION

NTP, 2004

d at the National Institute of Health Sciences • NIH • DHHS

POLICY FORUM

NIH, 2004

MOLECULAR BIOLOGY

NIH Molecular

ers of high-quality compound libraries, small molecules can now be obtained on a large scale. At the same time, advances in robotics and informatics have made screening and analysis of such large compound libraries possible. Up to a million com-

EPA, 2007

FORUM

The ToxCast Program for Prioritizing Toxicity Testing of Environmental Chemicals

David J. Dix,[1] Keith A. Houck, Matthew T. Martin, Ann M. Richard, R. Woodrow Setzer, and Robert J. Kavlock

*National Center for Computational Toxicology (D343-03), Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711*

# Toxicity Testing in the 21st Century

EPA United States Environmental Protection Agency

EPA, 2003

NATIONAL TOXICOLOGY PR

VISION

NTP, 2004

POLICYFORUM

Science, 2008

TOXICOLOGY

**Transforming Environmental Health Protection**

We propose a shift from primarily in vivo animal studies to in vitro assays, in vivo assays with lower organisms, and computational modeling for toxicity assessments.

Francis S. Collins,[1*†] George M. Gray,[2*] John R. Bucher[3*]

In 2005, the U.S. Environmental Protection throughput screening (HTS) and other auto- tion, usually between 2 and 10 μM, and toler-

POLICY FORUM

NIH, 2004

MOLECULAR BIOLOGY

NIH Molecular

ers of high-quality compound libraries, small molecules can now be obtained on a large scale. At the same time, advances in robotics and informatics have made screening and analysis of such large compound libraries possible. Up to a million com-

EPA, 2007

FORUM

THE NATIONAL ACA

NAS, 2007

REPORT IN BRIEF

**Toxicity Testing in the 21st Century: A Vision and a Strategy**

Advances in molecular biology, biotechnology, and other fields are paving the way for major improvements in how scientists evaluate the health risks posed by potentially toxic chemicals found at low levels in the environment. These

# Toxicity Testing in the 21st Century

EPA United States Environmental Protection Agency

EPA, 2003

NATIONAL TOXICOLOGY PR
VISION

NTP, 2004

POLICYFORUM

Science, 2008

TOXICOLOGY

Transfor
Health F

Francis S. Collins,

PERSPECTIVE

PHARMACOLOGY

2011

The NCGC Pharmaceutical Collection:
A Comprehensive Resource of Clinically

POLICY FORUM

NIH

MOLECULAR BIOLOGY

NIH Molecular
Libraries Initiative

Review

2013

All EHP content is accessible to individuals with disabilities. A fully accessible (Section 508–compliant) HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1205784.

Improving the Human Hazard Characterization of Chemicals: A Tox21 Update

*Raymond R. Tice,[1] Christopher P. Austin,[2] Robert J. Kavlock,[3] and John R. Bucher[1]*

[1]Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, USA; [2]National Center for Advancing Translational Sciences, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, USA; [3]National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA

EPA, 2007

FORUM

THE NATIONAL ACA

NAS, 2007

REPORT IN BRIEF

**Toxicity Testing in the 21st Century:**
**A Vision and a Strategy**

Advances in molecular biology, biotechnology, and other fields are paving the way for major improvements in how scientists evaluate the health risks posed by potentially toxic chemicals found at low levels in the environment. These

# Toxicity Testing in the 21st Century

EPA United States Environmental Protection Agency

EPA, 2003

NATIONAL TOXICOLOGY PR
VISION

NTP, 2004

POLICYFORUM

Science, 2008

TOXICOLOGY

Transfor
Health F

Francis S. Collins,

PERSPECTIVE

PHARMACOLOGY

2011

The NCGC Pharmaceutical Collection:
A Comprehensive Resource of Clinically

POLICY FORUM

NIH

MOLECULAR BIOLOGY

NIH Molecular
Libraries Initiative

Review

2013

All EHP content is accessible to individuals with disabilities. A fully accessible (Section 508–compliant) HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1205784.

Improving the Hum

Raymond R. Tice,[1] Christoph

[1]Division of the National Toxicology
of Health and Human Services, Res
National Institutes of Health, Depart
Toxicology, Office of Research and

EPA, 2007

FORUM

The ToxCast Program for Prioritizing Toxicity Testin

FDA U.S. FOOD & DRUG ADMINISTRATION

2017

FDA'S PREDICTIVE
TOXICOLOGY ROADMAP

THE NATION

NAS,

Toxicity Testing in the 21st
A Vision and a Strate

Advances in molecular biology, biotechnology, and o
ing the way for major improvements in how scientists evalu
posed by potentially toxic chemicals found at low levels in t

*ALTEX* 2018 ; 35(2): 163–168. doi:10.14573/altex.1803011.

2018

The US Federal Tox21 Program: A Strategic and Operational Plan for Continued Leadership

Russell S. Thomas[1], Richard S. Paules[2], Anton Simeonov[3], Suzanne C. Fitzpatrick[4], Kevin M. Crofton[1], Warren M. Casey[5], Donna L. Mendrick[6]

# Tox21 Publications

Google Scholar

tox21

Articles

About 3,350 results (0.06 sec)

3,350 results

Any time
Since 2021
Since 2020
Since 2017
Custom range...

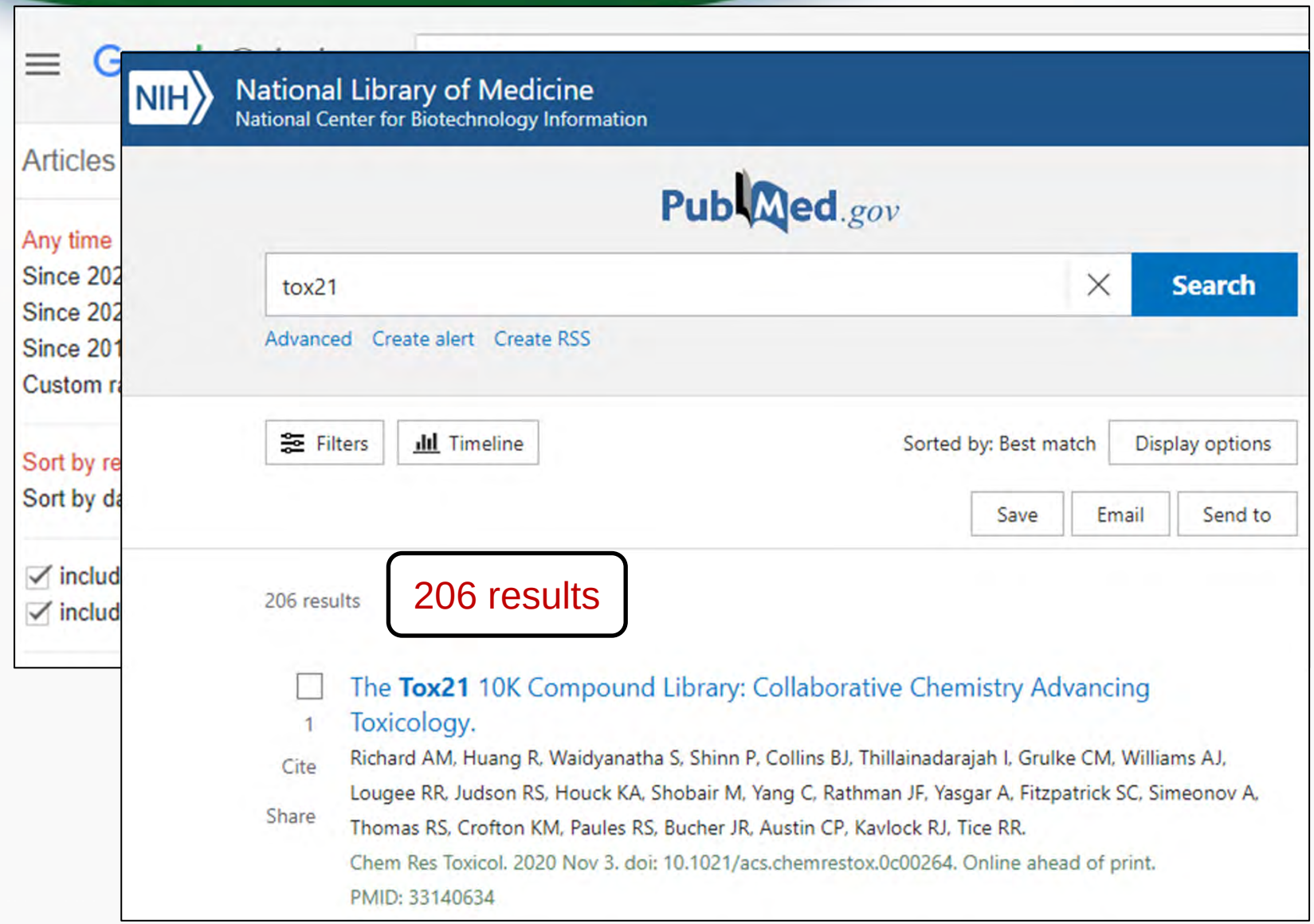
Sort by relevance
Sort by date

include patents
include citations

Improving the human hazard characterization of chemicals: a **Tox21** update
RR Tice, CP Austin, RJ Kavlock... - Environmental health ..., 2013 - ehp.niehs.nih.gov
Background: In 2008, the National Institute of Environmental Health Sciences/National Toxicology Program, the US Environmental Protection Agency's National Center for Computational Toxicology, and the National Human Genome Research Institute/National ...
Cited by 420 Related articles All 13 versions

[HTML] The **Tox21** robotic platform for the assessment of environmental chemicals–from vision to reality
MS Attene-Ramos, N Miller, R Huang, S Michael... - Drug discovery today, 2013 - Elsevier
Since its establishment in 2008, the US **Tox21** inter-agency collaboration has made great progress in developing and evaluating cellular models for the evaluation of environmental chemicals as a proof of principle. Currently, the program has entered its production phase ...
Cited by 152 Related articles All 7 versions

# Tox21 Publications



# Tox21 Publications

EPA United States Environmental Protection Agency

Articles

Any time
Since 202
Since 202
Since 201
Custom ra

Sort by re
Sort by da

include
include

NIH National Library of Medicine
National Center for Biotechnology Information

Tox21 Toxicology in the 21st Century

Search

OVERVIEW HIGHLIGHTS PROJECTS RESOURCES CONTACT

Tox21 > Publications

PUBLICATIONS

## Publications
2019

118 Tox21 Partner Publications thru 2019

The US Federal Tox21 Program: A Strategic and Operational Plan for Continued Leadership

Thomas, R.S., R.S. Paules, A. Simeonov, S.C. Fitzpatrick, K.M. Crofton, W.M. Casey, and D.L. Mendrick. The US Federal Tox21 Program: A Strategic and Operational Plan for Continued Leadership. ALTEX. Society ALTEX Edition, Kuesnacht, SWITZERLAND, 35(2): 163–168, (2018). https://doi.org/10.14573/altex.1803011

1

The next generation blueprint of computational toxicology at the U.S. Environmental Protection Agency

Thomas, R., T. Bahadori, T. Buckley, J. Cowden, C. Deisenroth, K. Dionisio, J. Frithsen, C. Grulke, M. Gwinn, J. Harrill, M. Higuchi, K. Houck, M. Hughes, S. Hunter, K. Isaacs, R. Judson, T. Knudsen, J. Lambert, M. Linnenbrink, T. Martin, S. Newton, S. Padilla, G. Patlewicz, K. Paul-Friedman, K. Phillips, A. Richard, R. Sams, T. Shafer, W. Setzer, I. Shah, J. Simmons, S. Simmons, A. Singh, J. Sobus, M. Strynar, A. Swank, R. Tornero-Velez, E. Ulrich, D. Villeneuve, J. Wambaugh, B. Wetmore, and

22

21.gov/all-publications/# The next generation blueprint of computational toxicology at the U.S.

Partner Agencies

United States Environmental Protection Agency

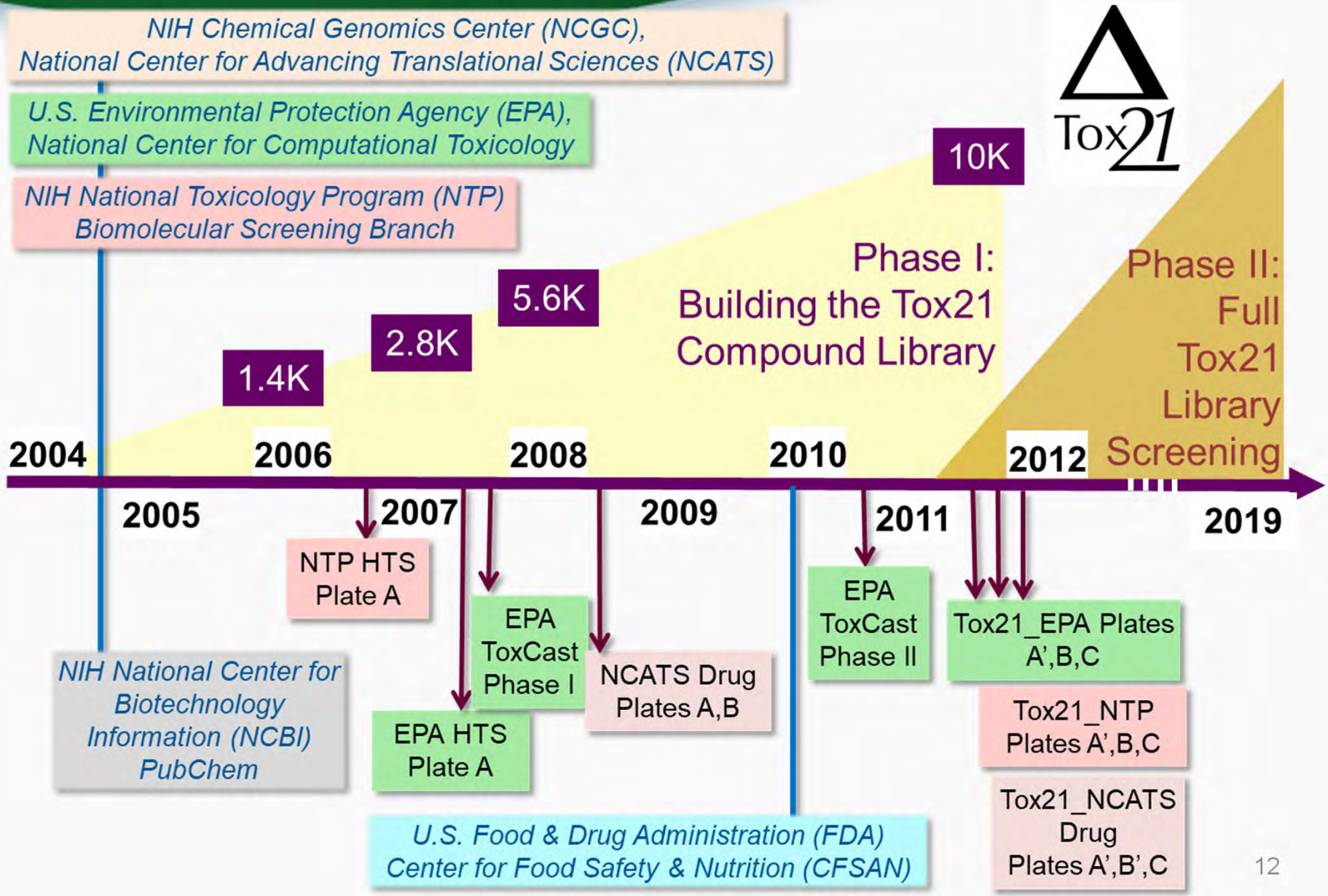
FDA U.S. FOOD & DRUG ADMINISTRATION

NIH National Center for Advancing Translational Sciences

NTP National Toxicology Program

# Let’s turn our attention to the Tox21 compound library …

# Building the Tox21 library



# Tox21 Partner Libraries

NCATS Pharmaceutical Collection (NPC)

- *Collection of "small molecule" drugs approved for human use*

→ NCATS (3764 total)

NTP Study Chemicals

- *NTP bioassay & genetox*
- *NICETM / ICVAM*
- *environmental/industrial*
- *known toxicants*

→ NTP (3115 total)

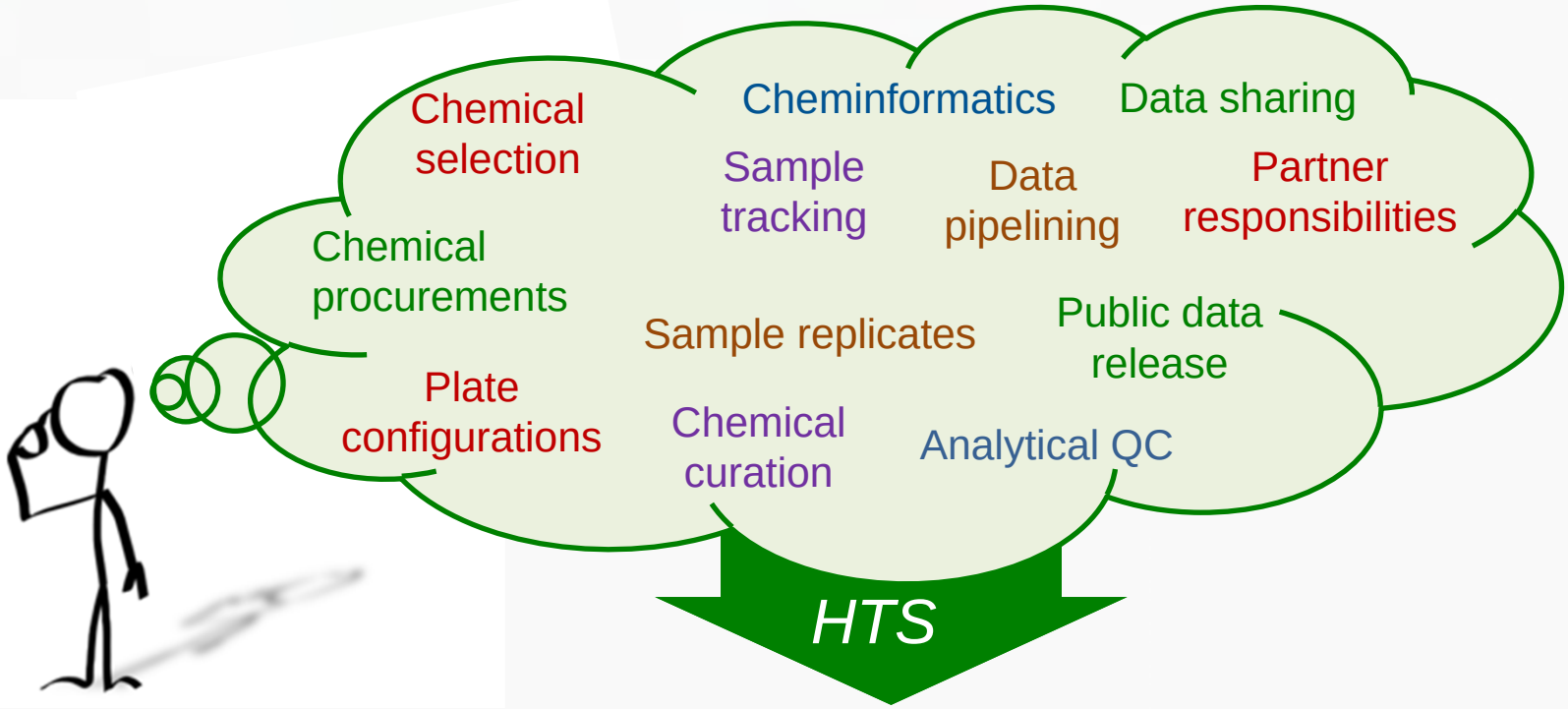
EPA's ToxCast library

- *environmental/industrial*
- *pesticides*
- *pharmaceutical*
- *known toxicants*
- *food-use, consumer products*

→ EPA (4078 total)

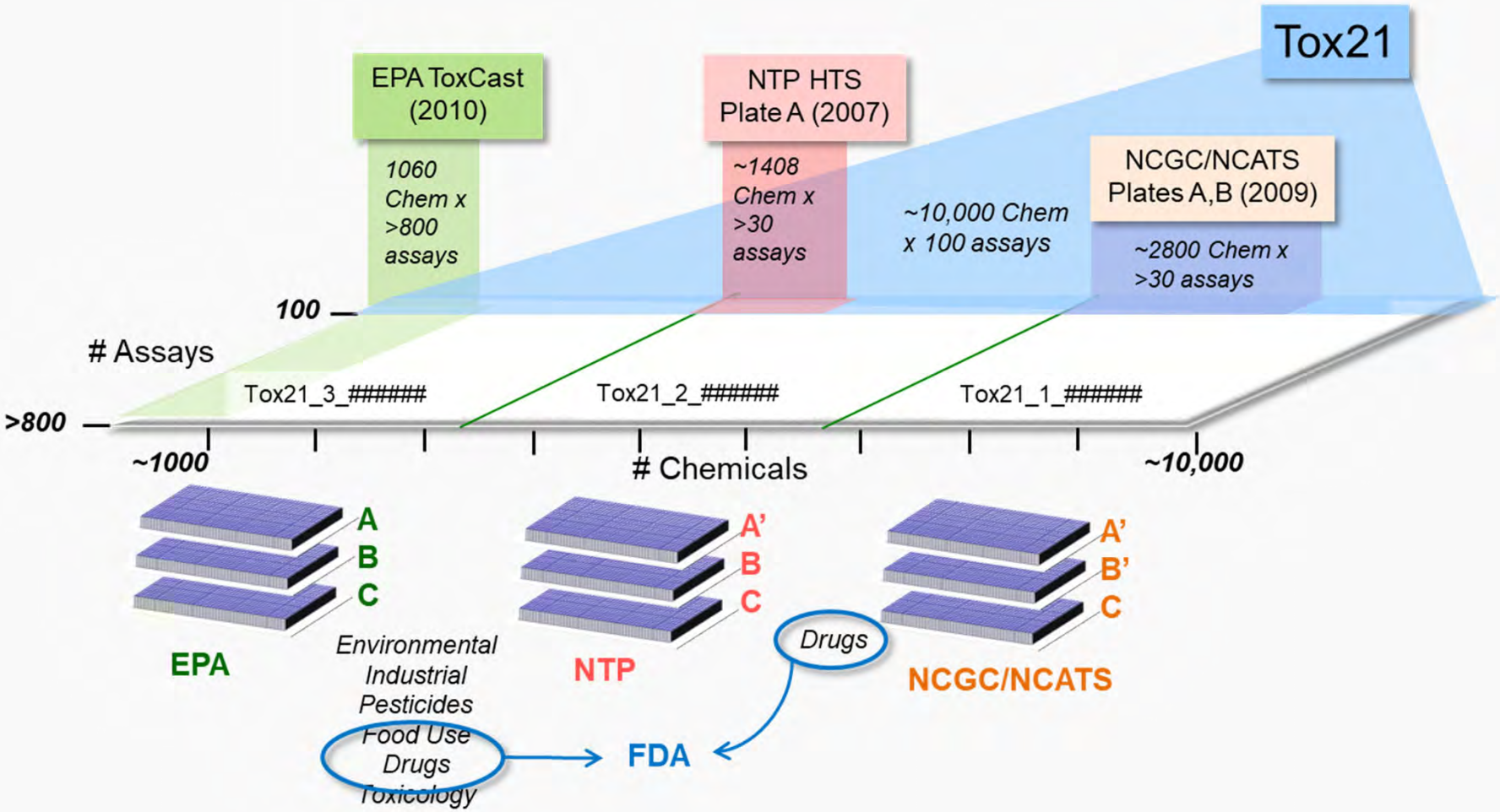
# Planning ahead

"By failing to prepare, you are preparing to fail." – *Benjamin Franklin*

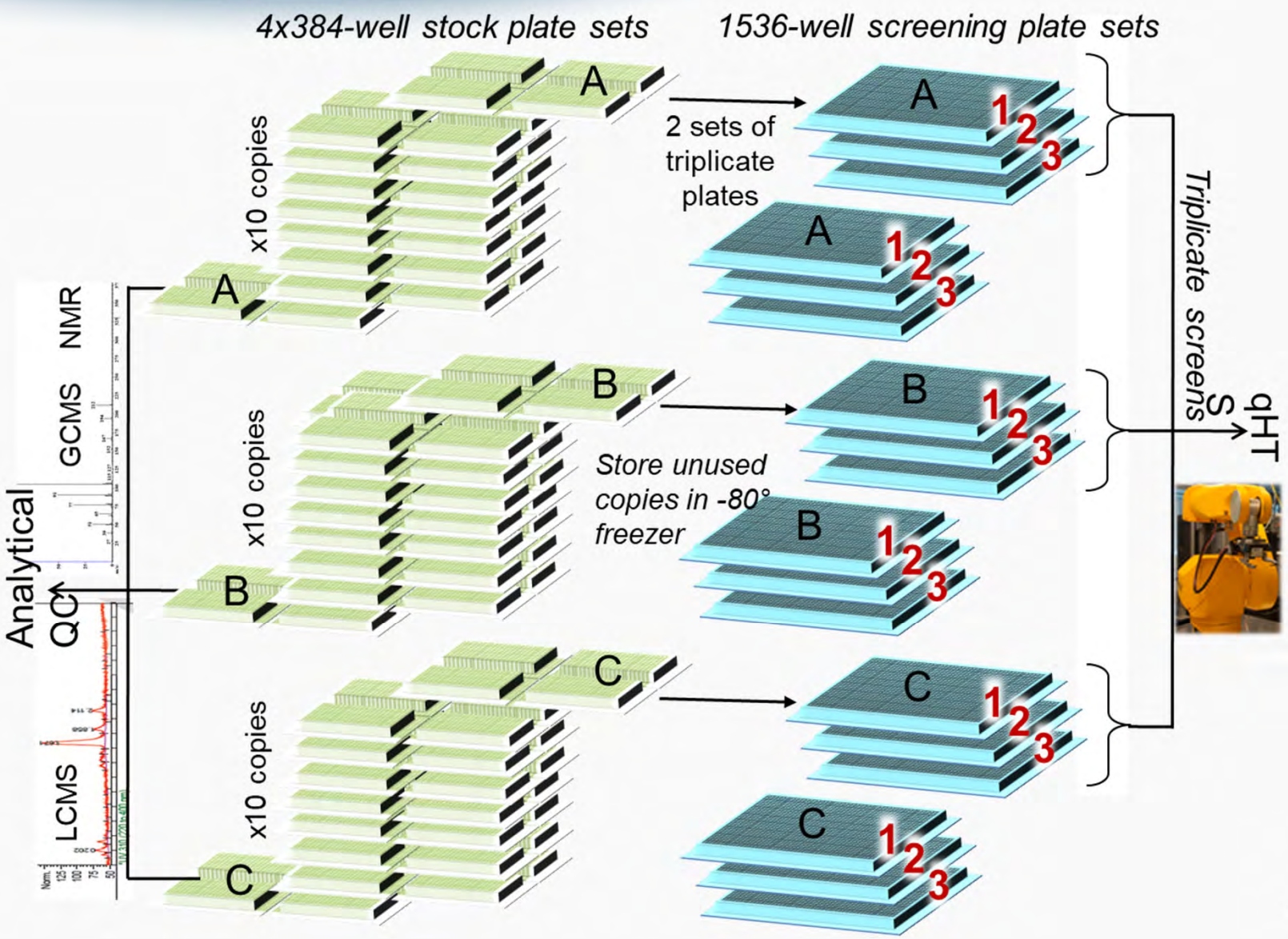



*Modeling, analyses, publications, scientific breakthroughs!*

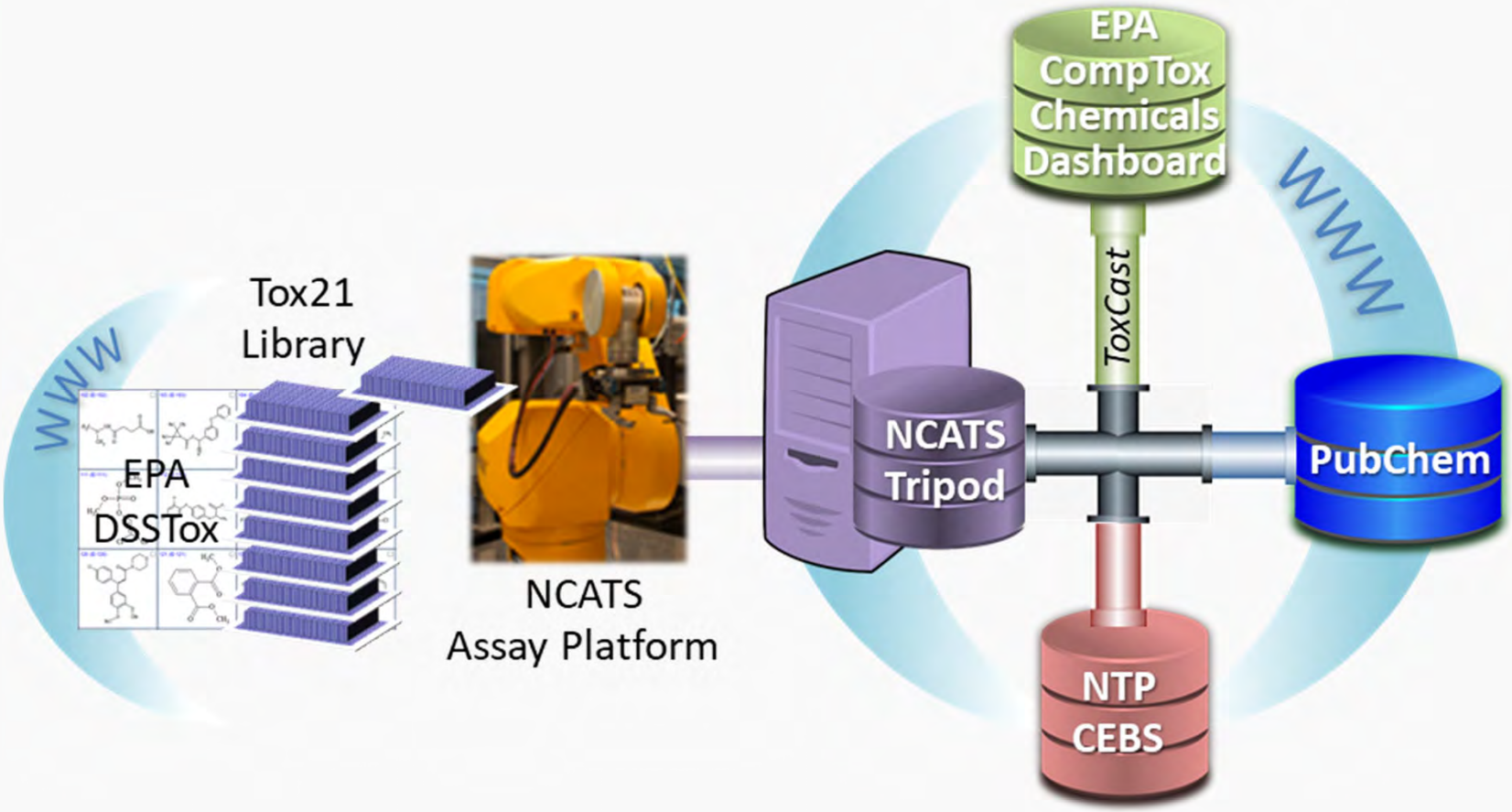
# Building the Tox21 library



# Processing each partner library



# Tox21 Public Data Release



# Tox21:EPA Public Data Release

EPA United States Environmental Protection Agency

Search EPA.gov

Environmental Topics

https://www.epa.gov/chemical-research/toxicology-testing-21st-century-tox21

**Related Topics:** Safer Chemicals Research

CONTACT US SHARE

## Toxicology Testing in the 21st Century (Tox21)

Toxicology in the 21st Century (Tox21) is a federal collaboration among EPA, NIH, including National Center for Advancing Translational Sciences and the National Toxicology Program at the National Institute of Environmental Health Sciences, and the Food and Drug Administration. Tox21 researchers aim to develop better toxicity assessment methods to quickly and efficiently test whether certain chemical compounds have the potential to disrupt processes in the human body that may lead to negative health effects. One of EPA's contributions to Tox21 are the chemical screening results from the Toxicity Forecaster (ToxCast). Learn more about the mission and goals of the Tox21 program.

Using a high-throughput robotic screening system housed at NCATS, researchers are testing 10,000 environmental chemicals (called the Tox21 10K library) for their potential to disrupt biological pathways that may result in toxicity. Screening results help the researchers prioritize chemicals for for further in-depth investigation. Learn more about NCATS role in the Tox21 collaboration.

# Tox21:EPA Public Data Release

https://comptox.epa.gov/dashboard

EPA United States Environmental Protection Agency

Home | Advanced Search | Batch Search | Lists | Predictions | Downloads | Share

## TOX21SL: Tox21 Screening Library

Search TOX21SL Chemicals

☐ Identifier substring search

### List Details

**Description:** TOX21SL is a list of unique DSSTox substances comprising the original screening library for the Tox21 program, a multi-federal agency collaborative among US EPA, the National Institutes of Health (NIH) National Toxicology Program (NTP) and National Center for Advances in Translational Science (NCATS), and the US Food and Drug Administration (FDA). EPA, NTP and NCATS partners contributed approximately equal size inventories to the library, whereas FDA contributed a small set of drugs. EPA's contribution to the original TOX21SL fully covered its ToxCast inventory, so retains significant overlap with the current ToxCast HTS inventory (TOXCAST). The NTP contribution was drawn from the NTP bioassay and research testing programs of chemicals of interest to environmental toxicology, and the NCATS contribution consisted primarily of marketed drugs. Tox21 compounds were selected based on a wide range of criteria, including, but not limited to: environmental hazard or exposure concern based on production volume (industrial chemicals) or occurrence data, availability of animal toxicity study data, food-additives, fragrances, toxicity reference chemicals, and drugs or known bioactive compounds. Chemicals in the original Tox21 program underwent screening at the intramural NCATS robotics testing facility. All HTS assay data generated in association with the Tox21 program are publicly available through PubChem (https://pubchem.ncbi.nlm.nih.gov/), as are the analytical chemistry quality control (QC) summary records generated in association with the Tox21 testing program. Tox21 assay data are also included in EPA's ToxCast data downloads (https://www.epa.gov/chemical-research/exploring-toxcast-data-downloadable-data).

For current information on the Tox21 program, see https://tox21.gov/page/home

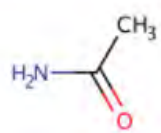
Update (Nov 20, 2018):

The following publication coauthored by Tox21 Federal Partner Leads lays out a strategic and operational plan for the Tox21 program from 2018 onward: https://www.ncbi.nlm.nih.gov/pubmed/29529324 The plan articulates areas of focused scientific investment, both in chemical and biological space, to which new Tox21 cross-partner projects will be directed. In keeping with the new strategic plan, the Tox21 testing library moving forward is being consolidated under EPA chemical management and includes the full, currently available EPA ToxCast chemical library as well as approx. 1300 newly added chemicals provided by the NTP that were in the original TOX21SL library. The full chemical library available to the Tox21 cross-partner projects as DMSO solutions currently exceeds 6400 chemicals, of which nearly 6000 were included in the original TOX21SL library. A snapshot of this active plating library list (dated 11/21/2018) can be accessed at EPACHEMINV_AVAIL.

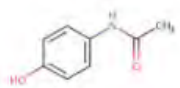
**Number of Chemicals:** 8947

**8947 chemicals**

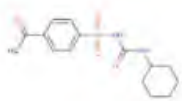
Select all | Download | Send to Batch Search | Default | DTXSID | CASRN | TOXCAST | Hide chemicals that are:



Acetamide
DTXSID:DTXSID7020005
CASRN:60-35-5
TOXCAST:17/864



Acetaminophen
DTXSID:DTXSID2020006
CASRN:103-90-2
TOXCAST:5/849

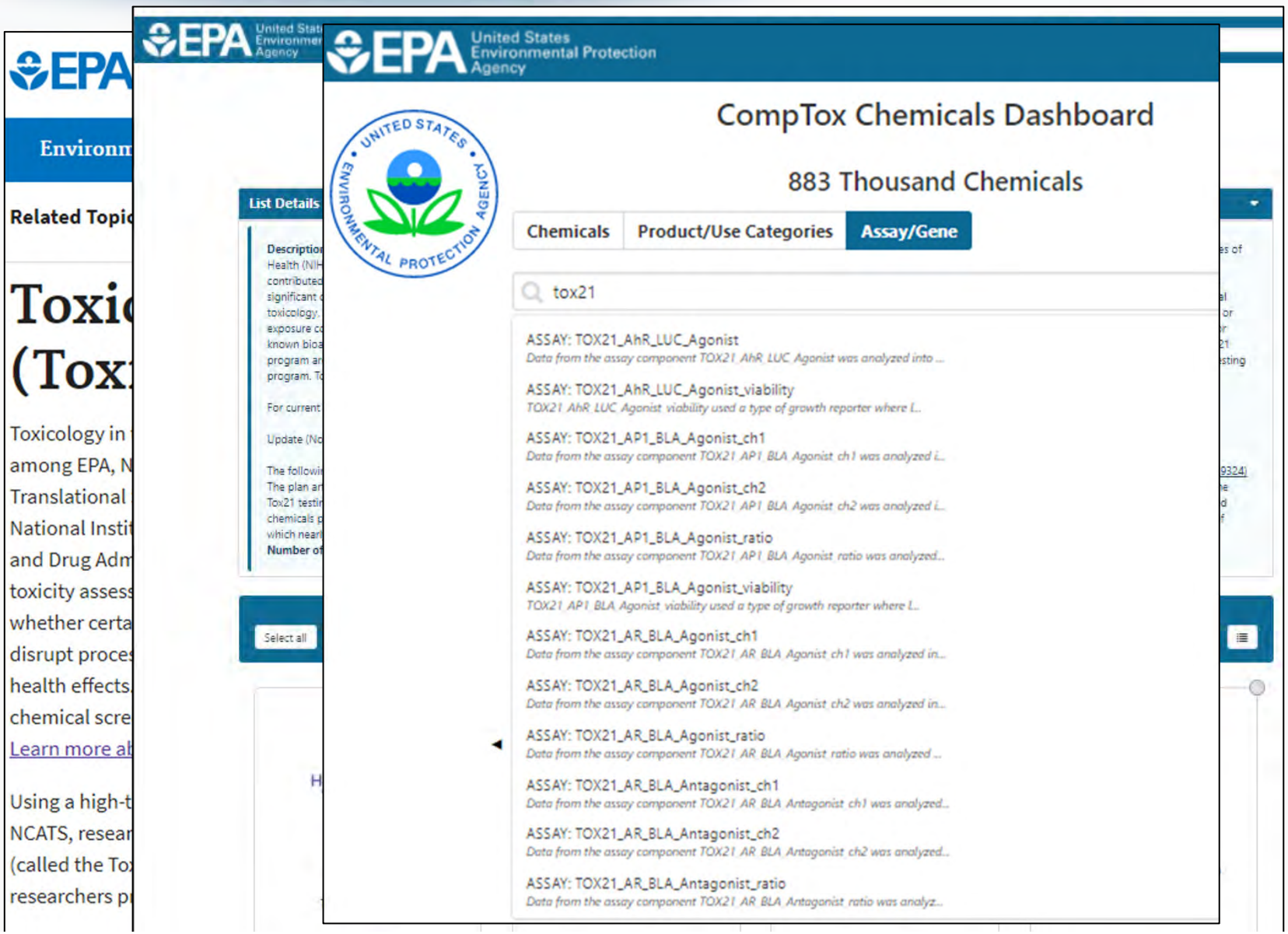


Acetohexamide
DTXSID:DTXSID7020007
CASRN:968-81-0
TOXCAST:7/403

Acetonitrile
DTXSID:DTXSID7020009
CASRN:75-05-8
TOXCAST:0/235

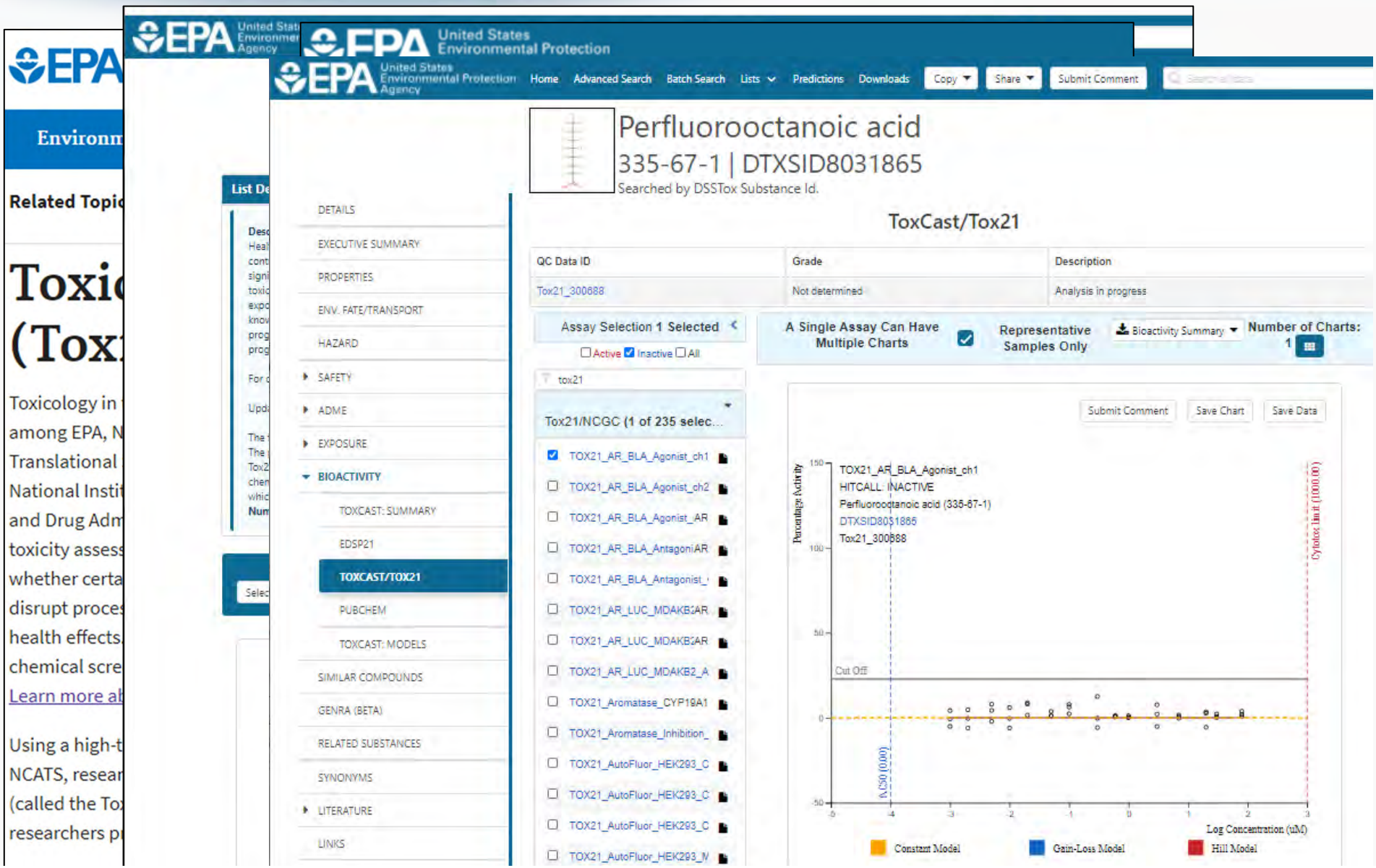
# Tox21:EPA Public Data Release

https://comptox.epa.gov/dashboard



# Tox21:EPA Public Data Release

https://comptox.epa.gov/dashboard



# Tox21:NCATS Public Data Release

https://ncats.nih.gov/tox21

National Center for Advancing Translational Sciences

Home > About NCATS > NCATS Programs & Initiatives > Toxicology in the 21st Century (Tox21)

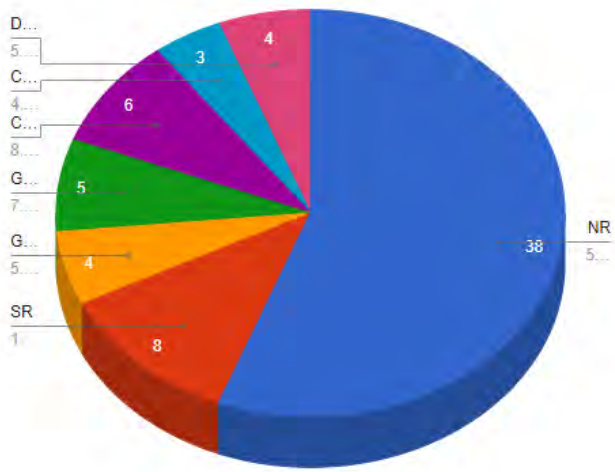
## Toxicology in the 21st Century (Tox21)

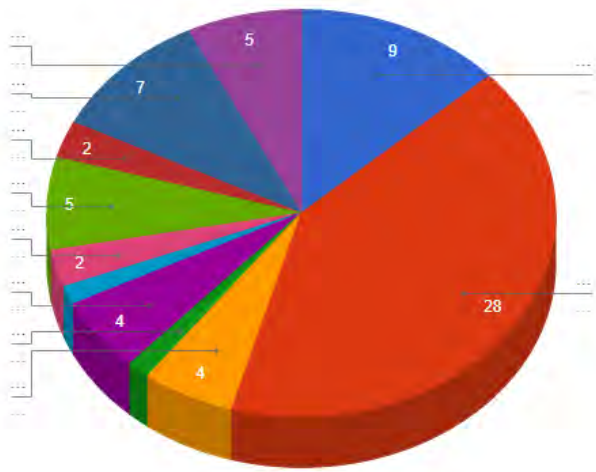
# Tox21:NCATS Public Data Release

https://ncats.nih.gov/tox21

https://tripod.nih.gov/tox21/

National Center for Advancing Translational Sciences | TOX21 PUBLIC DATA | SEARCH | REPLICATE | AGGREGATED | UPDATE | DOWNLOAD | SUBSCR



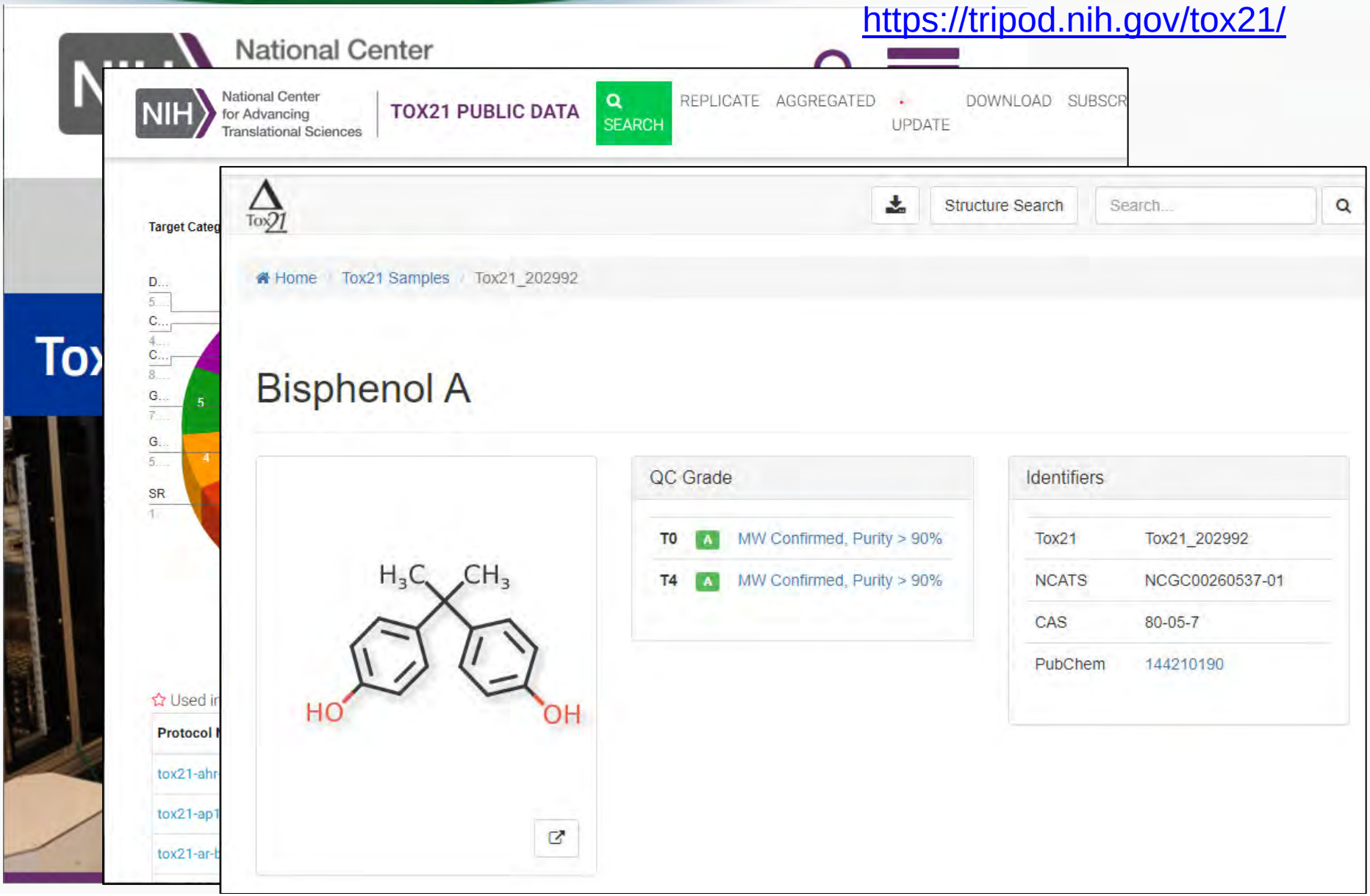

☆ Used in Tox21 Challenge

| Protocol Name | Assay Target | Target Category | Cell Line | Cell Type |
|---|---|---|---|---|
| tox21-ahr-p1 ☆ | AhR | NR | HepG2 | Liver |
| tox21-ap1-agonist-p1 | AP-1 agonist | SR | ME-180 | Cervical Cancer |
| tox21-ar-bla-agonist-p1 ☆ | AR-BLA agonist | NR | HEK293 | Kidney |

# Tox21:NCATS Public Data Release

https://ncats.nih.gov/tox21

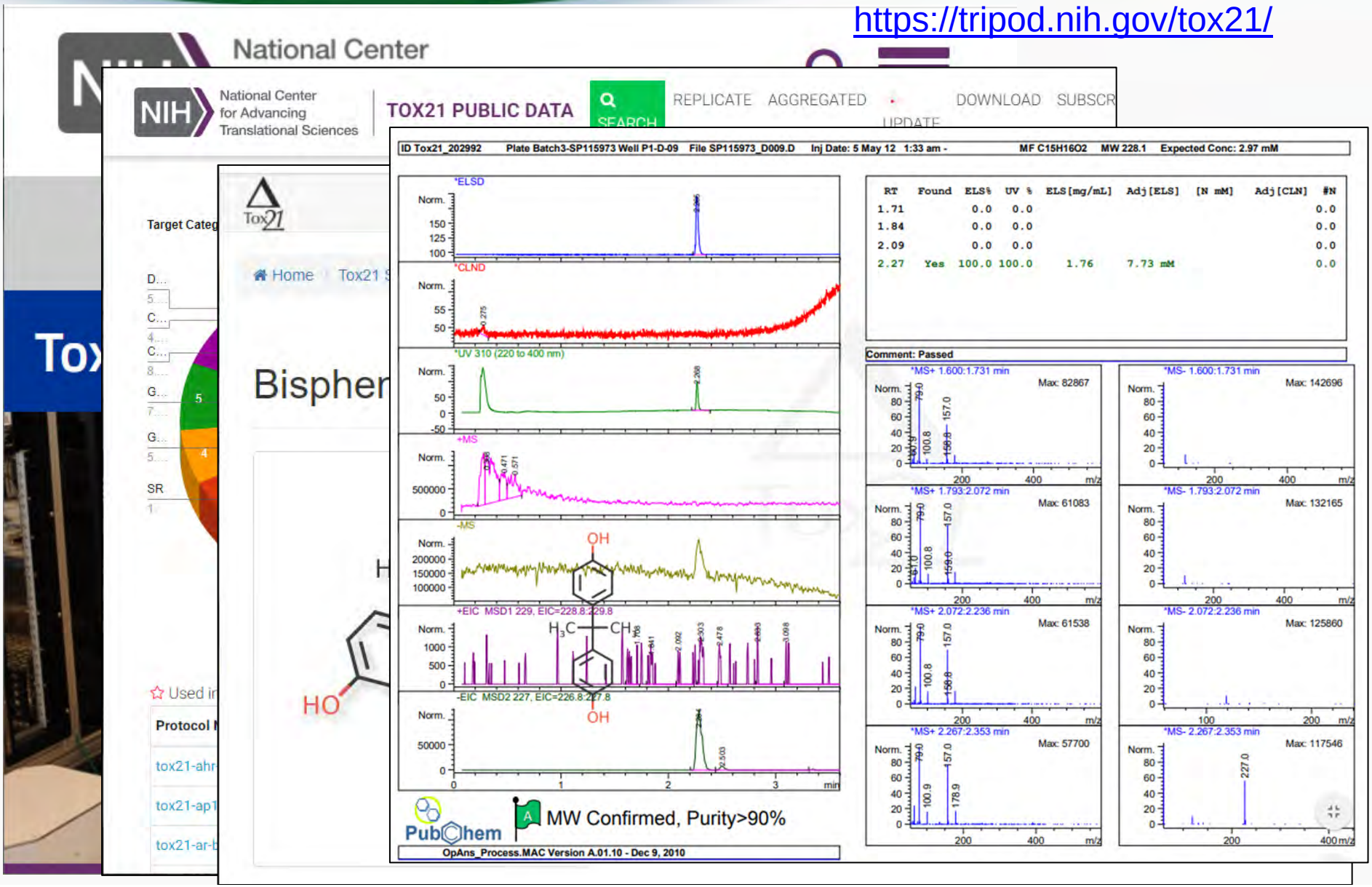
https://tripod.nih.gov/tox21/



# Tox21:NCATS Public Data Release

https://ncats.nih.gov/tox21

https://tripod.nih.gov/tox21/



# Tox21:NCATS Public Data Release

EPA United States Environmental Protection Agency

https://ncats.nih.gov/tox21

https://tripod.nih.gov/tox21/

National Center

NIH National Center for Advancing Translational Sciences

TOX21 PUBLIC DATA SEARCH REPLICATE AGGREGATED UPDATE DOWNLOAD SUBSCR

ID Tox21_202992 Plate Batch3-SP115973 Well P1-D-09 File SP115973_D009.D Inj Date: 5 May 12 1:33 am - MF C15H16O2 MW 228.1 Expected Conc: 2.97 mM

Target Categ

Tox21

Home

Bispl

Used in

Protocol

tox21-ahr

tox21-ap1

tox21-ar-b

NIH National Library of Medicine
National Center for Biotechnology Information

PubChem About Blog Submit Contact

https://pubchem.ncbi.nlm.nih.gov/#query=tox21

SEARCH FOR

tox21

Treating this as a text search.

DATA SOURCE

Tox21

Governmental Organizations

The Toxicology in the 21st Century (Tox21) program aims to develop better toxicity assessment methods to quickly and efficiently test whether certain chemical compounds have the potential to disrupt processes in the human body that may lead to negative health effects.

Last Updated: 2020/02/20

Compounds (11,267) Substances (14,469) BioAssays (226) Literature (186)

Searching chemical names and synonyms including IUPAC names and InChIKeys across the compound collection. Note that annotations text from compound summary pages is not searched. Read More...

11,267 results Filters SORT BY Relevance Download

# Tox21:NTP Public Data Release

https://ntp.niehs.nih.gov/whatwestudy/tox21/

National Toxicology Program
U.S. Department of Health and Human Services

Search the NTP Website | SEARCH

What We Study | How We Work | Data & Resources | Publications | Who We Are

Home » What We Study » Tox21

**What We Study**

- Health Effects Assessments
- Highlighted Research Topics
- NICEATM: Alternative Methods
- NTP Laboratory Research
- Testing Program
- Tox21
  - History of Tox21
  - High-Throughput Transcriptomics & the S1500+ Gene Set Strategy
  - Research Phases
  - Selected Publications

## Tox21

SHARE THIS: 9

https://ntp.niehs.nih.gov/go/tox21

### Toxicology in the 21st Century (Tox21)

**Robotic arm used for Tox21 testing**

Thousands of chemical substances exist in the world, but only a small fraction of these have been adequately assessed for their potential toxicity to humans. The Toxicology in the 21st Century program, or Tox21, is a unique collaboration between several federal agencies to develop new ways to rapidly test whether substances adversely affect human health. Substances assayed in Tox21 include a diverse range of products such as: commercial chemicals, pesticides, food additives/contaminants, and medical compounds.

The following four government agencies bring their unique expertise, resources, and tools to the Tox21 collaboration:

**On This Page**

- Toxicology in the 21st Century (Tox21)
- Goals of the Tox21 Program
- Research Phases
- Contact

**Related Links**

- Biomolecular Screening Branch (BSB)
- Tox21: Chemical Testing in the 21st Century
- United States Federal Government Collaboration

# Tox21:NTP Public Data Release

https://ntp.niehs.nih.gov/whatwestudy/tox21/

National Toxicology Program
U.S. Department of Health and Human Services

Search the NTP Website | SEARCH

What We Study | How We Work | Data & Resources | Publications | Who We Are

Home » What We Study » Tox21 » **Tox21 Toolbox**

- What We Study
- Health Effects Asse
- Highlighted Resea Topics
- NICEATM: Alternat Methods
- NTP Laboratory Re
- Testing Program
- Tox21
  - History of Tox2
  - High-Throughp Transcriptomic S1500+ Gene S Strategy
  - Research Phas
  - Selected Publi

- **Tox21**
- History of Tox21
- High-Throughput Transcriptomics & the S1500+ Gene Set Strategy
- Research Phases
- Selected Publications
- Tox21 Toolbox

## Tox21 Toolbox

SHARE THIS:

https://ntp.niehs.nih.gov/go/tbox

The Tox21 Toolbox contains data-analysis tools for accessing and visualizing Tox21 quantitative high-throughput screening (qHTS) 10K library data, as well as integrating with other publicly available data.

**On This Page**

- NIEHS/NTP Tools
- External Tools

### NIEHS/NTP Tools

- **Tox21 Data Analysis** tools facilitate the analysis and visualization of Tox21 data.
  - BMDExpress 2 allows users to perform genomic dose-response analyses, with the goal of identifying gene set/pathway-level potency estimates.
- **Tox21 Data Visualization** tools provide quick, easy-to-use Tox21 qHTS data access, visualization, and clustering.
  - Tox21 Curve Browser (beta version) lets users visualize the concentration-response curves of compounds of interest, with the ability to superimpose assay results per compound for easy comparison.
  - Tox21 Activity Profiler (beta version) lets users prioritize

Let’s take

at the library

# Tox21 Partner Libraries

NCATS Pharmaceutical Collection (NPC)

- *Collection of "small molecule" drugs approved for human use*

NCATS
(3764 total)

NTP Study Chemicals

- *NTP bioassay & genetox*
- *NICETM*
- *environmental/industrial*
- *known toxicants*

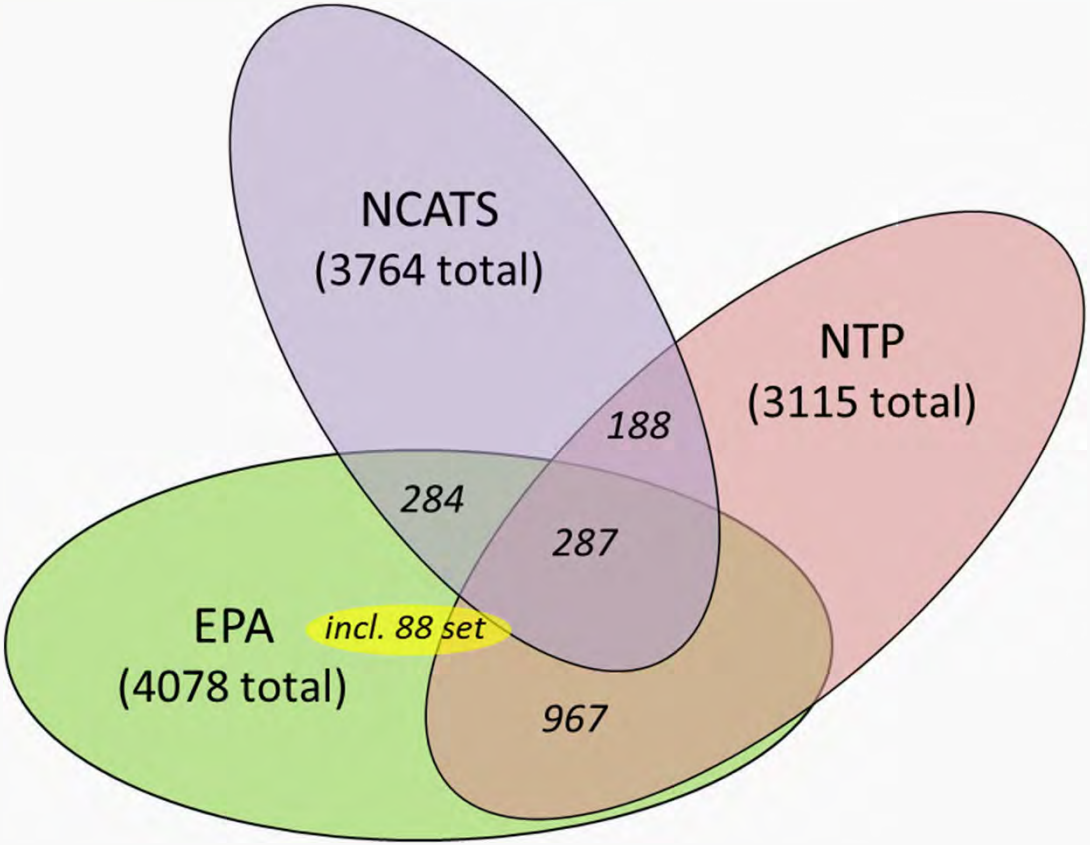
NTP
(3115 total)

EPA's ToxCast library

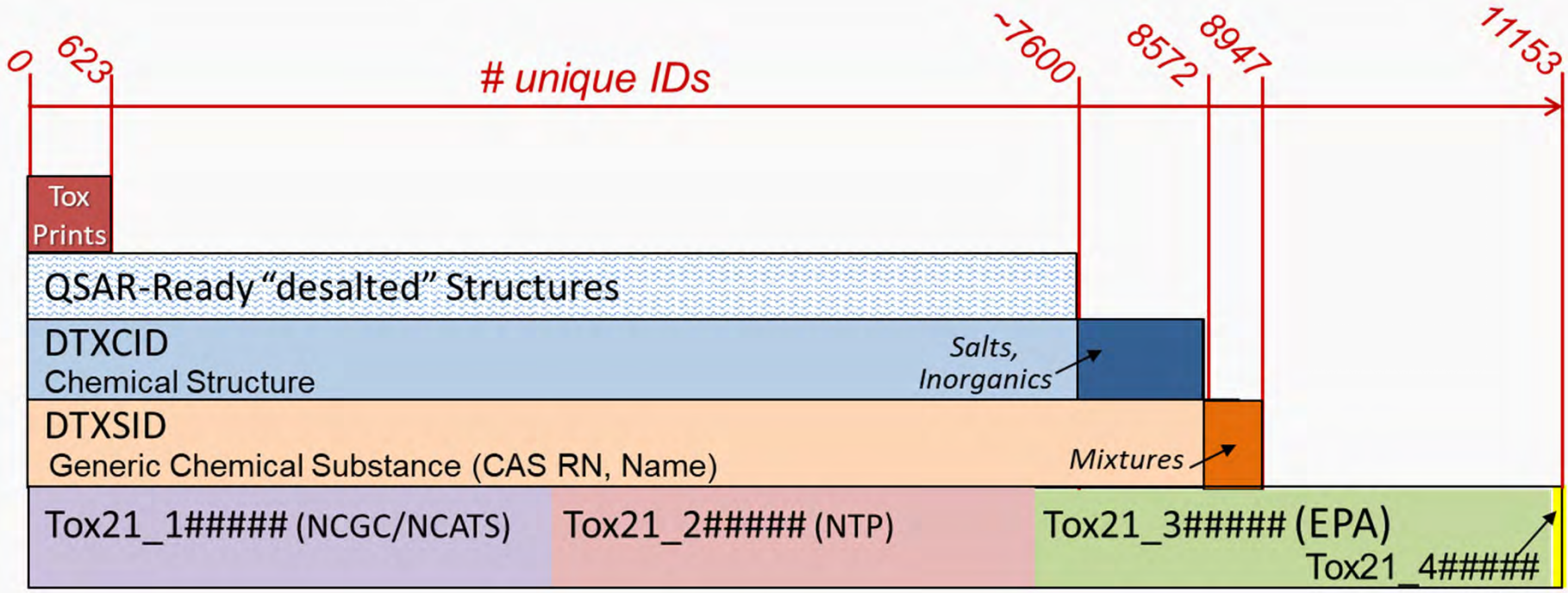
- *environmental/industrial*
- *pesticides*
- *pharmaceutical*
- *known toxicants*

EPA
(4078 total)

# Tox21 Partner Library Overlaps



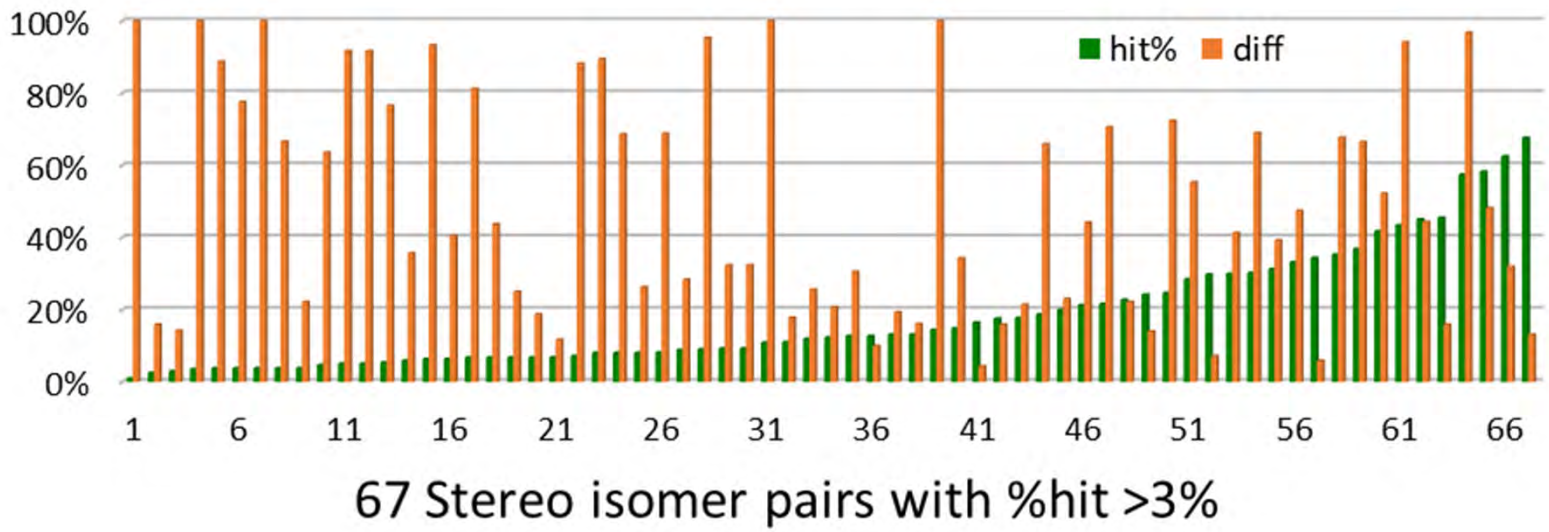
# Tox21 Cheminformatics



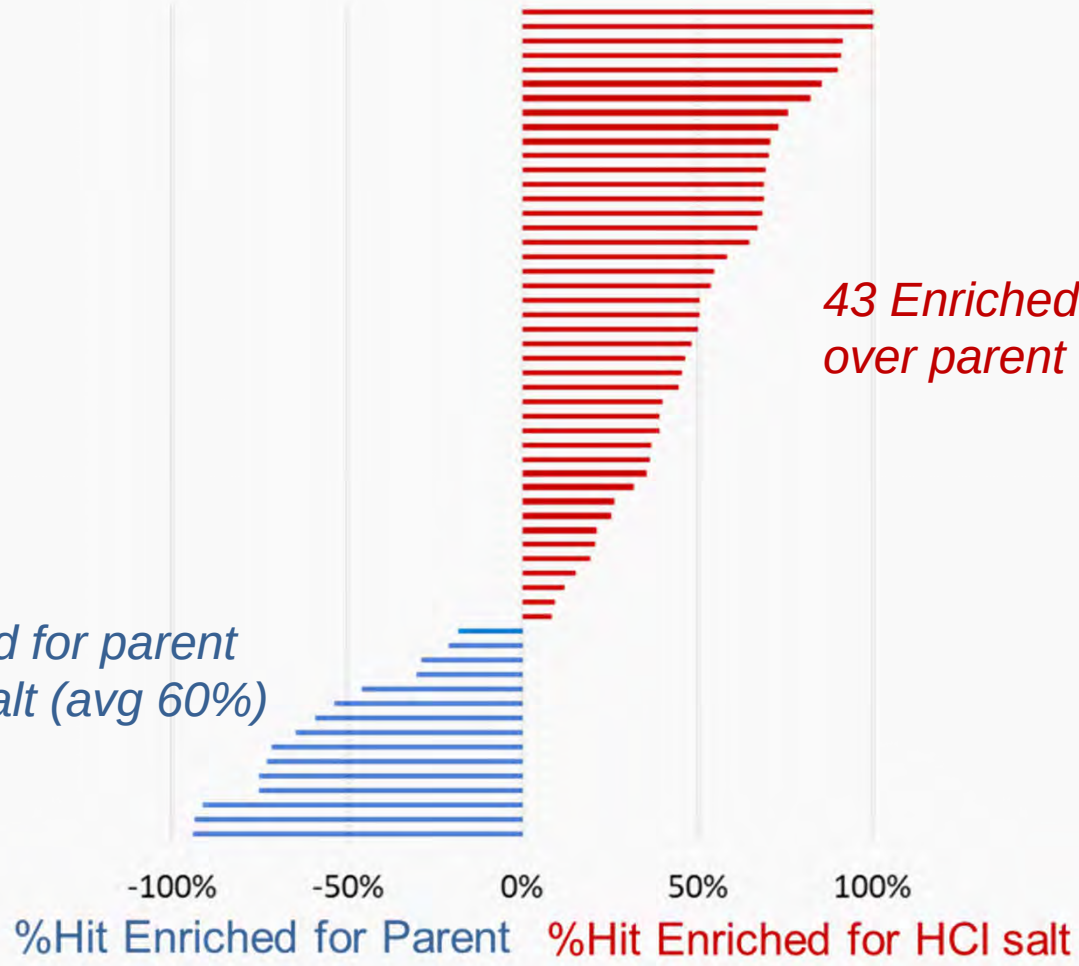
DSSTox
Cheminformatics

What sorts of questions can we ask of the Tox21 chemical-assay landscape?

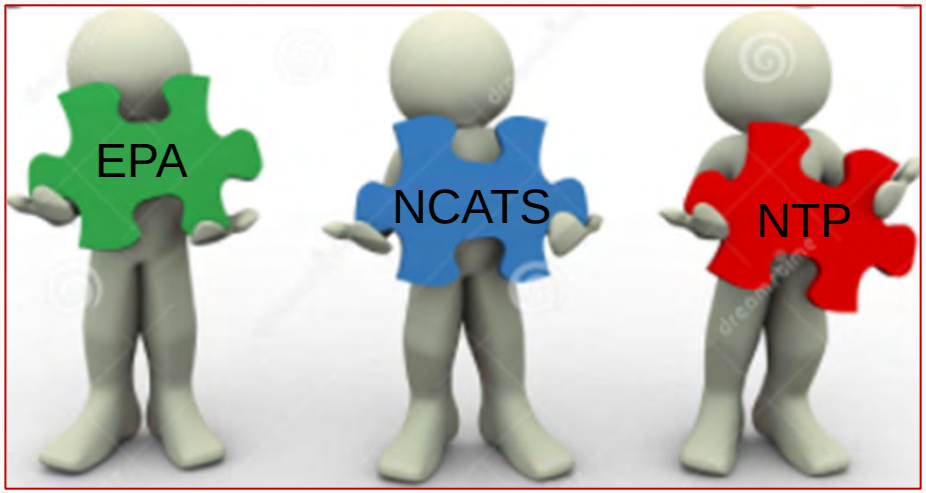
# Does stereochemistry matter?



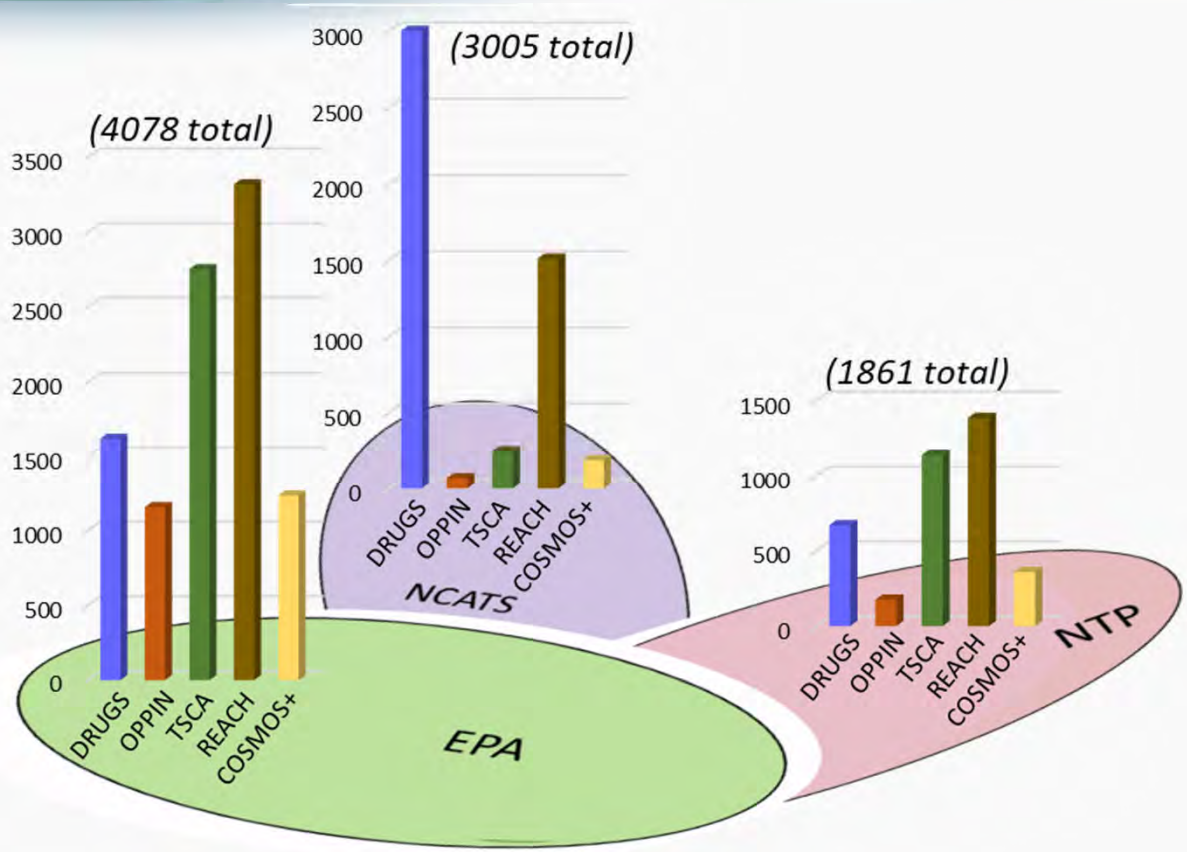
# Does salt form matter?



# What do each of the Tox21 partner libraries contribute to the whole?

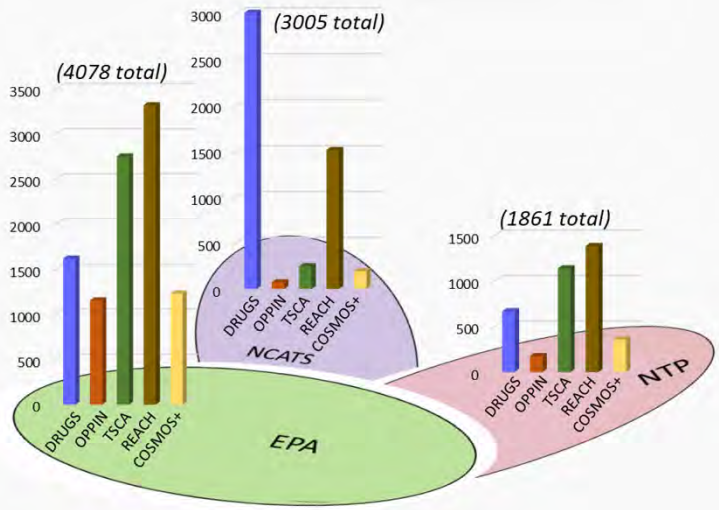


# Regulatory Use-List Coverage

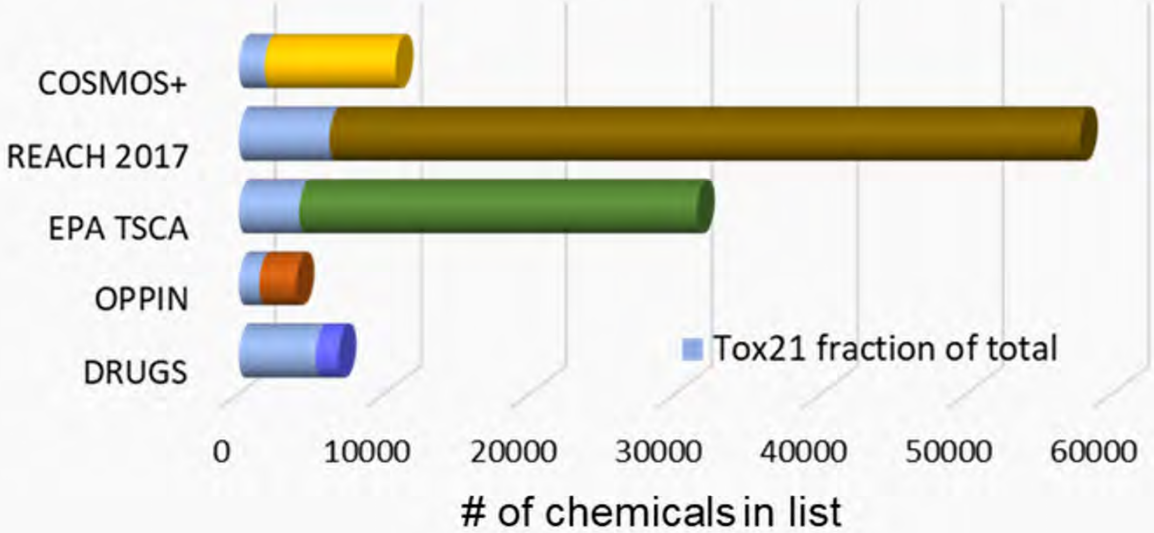



| | |
|---|---|
| **Drugs** | List membership on DrugBank, NCATS, ToxCast donated drugs |
| **OPPIN** | EPA Pesticide Inventory |
| **TSCA** | EPA Toxics Substances Control Act (industrial, environmental) |
| **REACH** | Regulated chemicals in Europe (industrial, environmental, product use) |
| **COSMOS+** | COSMOSDB & EFSAOFT (cosmetics, food-use, toxicity) |

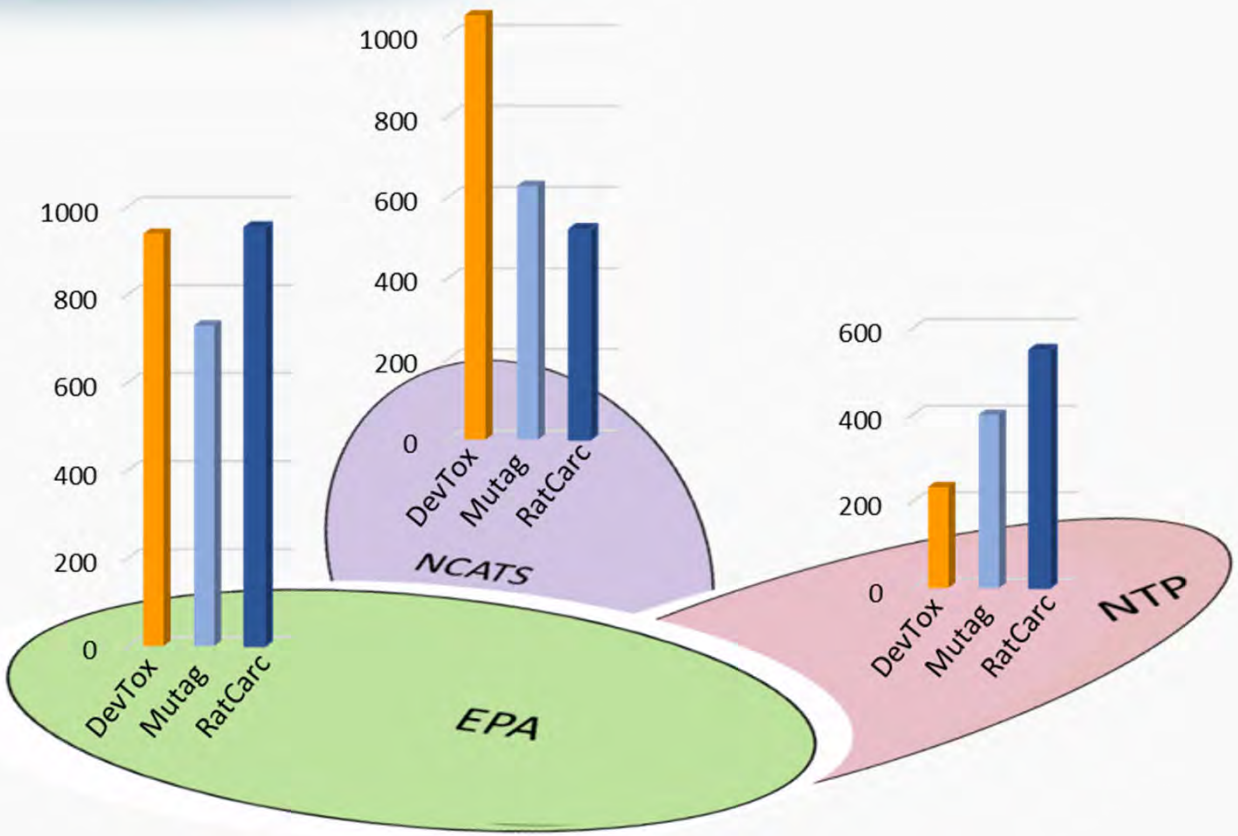
# Regulatory Use-List Coverage




| LIST OVERLAPS | DRUGS | OPPIN | TSCA | REACH | COSMOS+ |
|---|---|---|---|---|---|
| DRUGS | **5293** | 630 | 1991 | 3478 | 962 |
| OPPIN | 630 | **1402** | 736 | 1087 | 416 |
| TSCA | 1991 | 736 | **4141** | 3880 | 1608 |
| REACH | 3478 | 1087 | 3880 | **6218** | 1631 |
| COSMOS+ | 962 | 416 | 1608 | 1631 | **1783** |



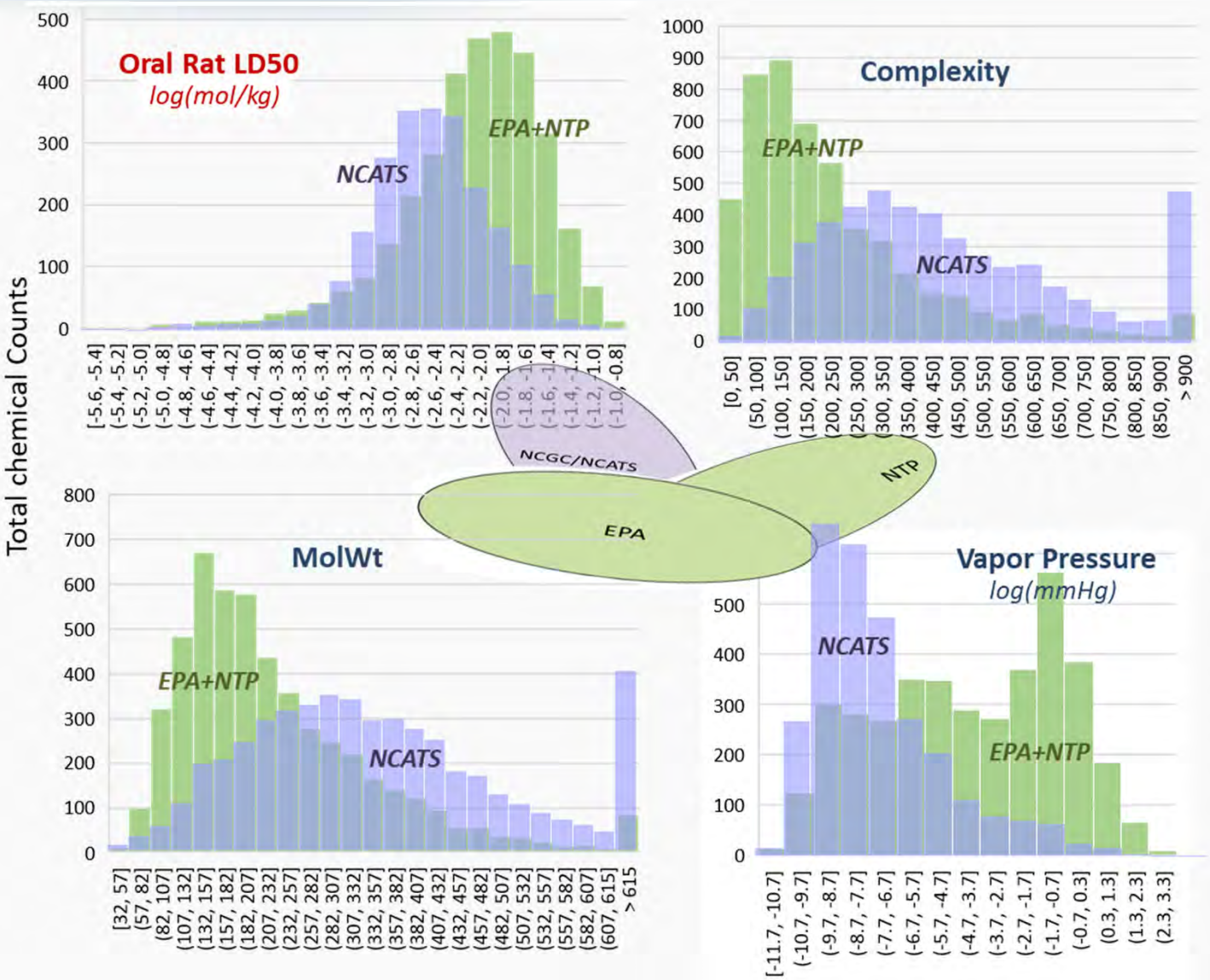
# Toxicity Endpoint Coverage



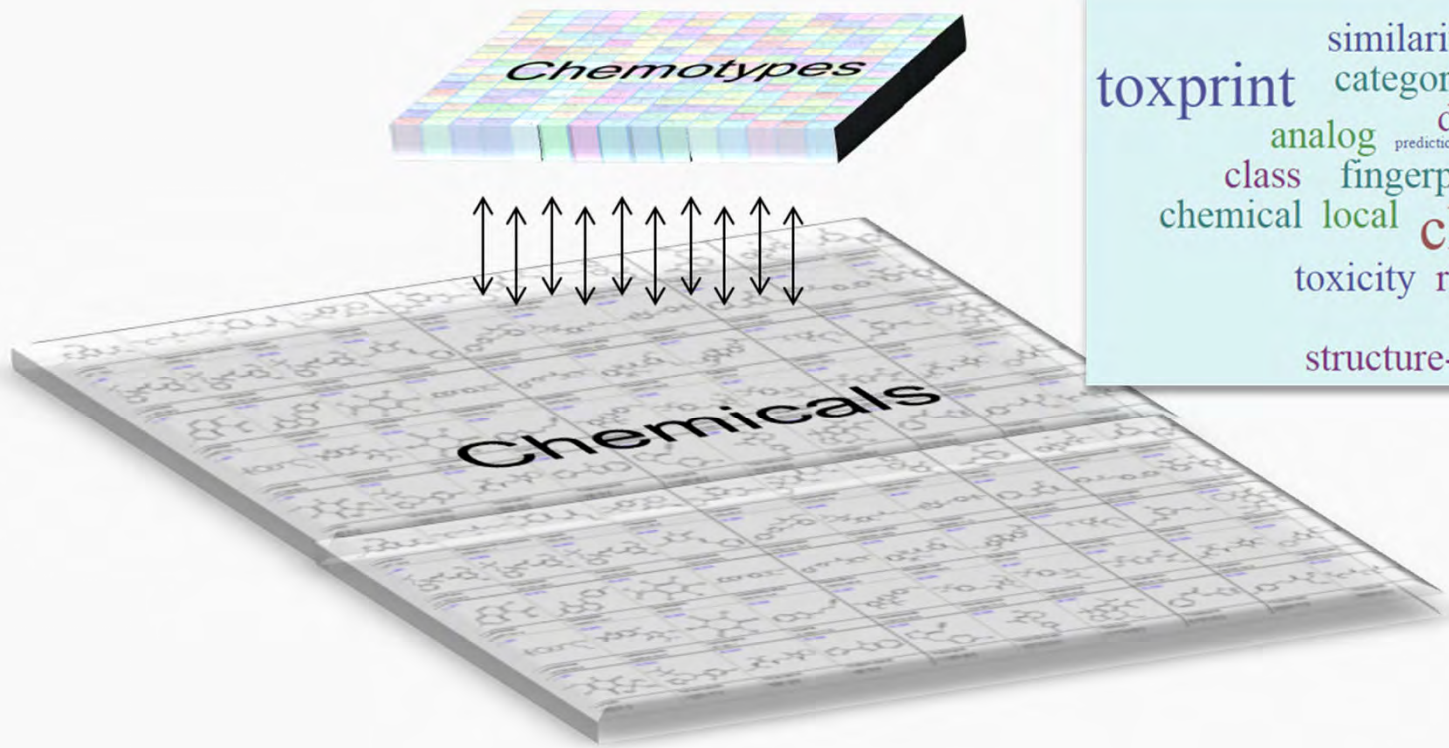

| | |
|---|---|
| **DevTox** | Developmental Toxicity (predicted from EPA T.E.S.T. model*) |
| **Mutag** | Mutagenicity (predicted from EPA T.E.S.T. model*) |
| **RatCarc** | Rodent Carcinogenicity (predicted from LHASA Derek Nexus) |

** EPA T.E.S.T. model predictions downloaded from EPA's CompTox Chemicals Dashboard, https://comptox.epa.gov/dashboard*

# Expanded Property distributions:
## *Drugs vs. "Environmental"*



# “Chemotype” (CT) profiling of the Tox21 library

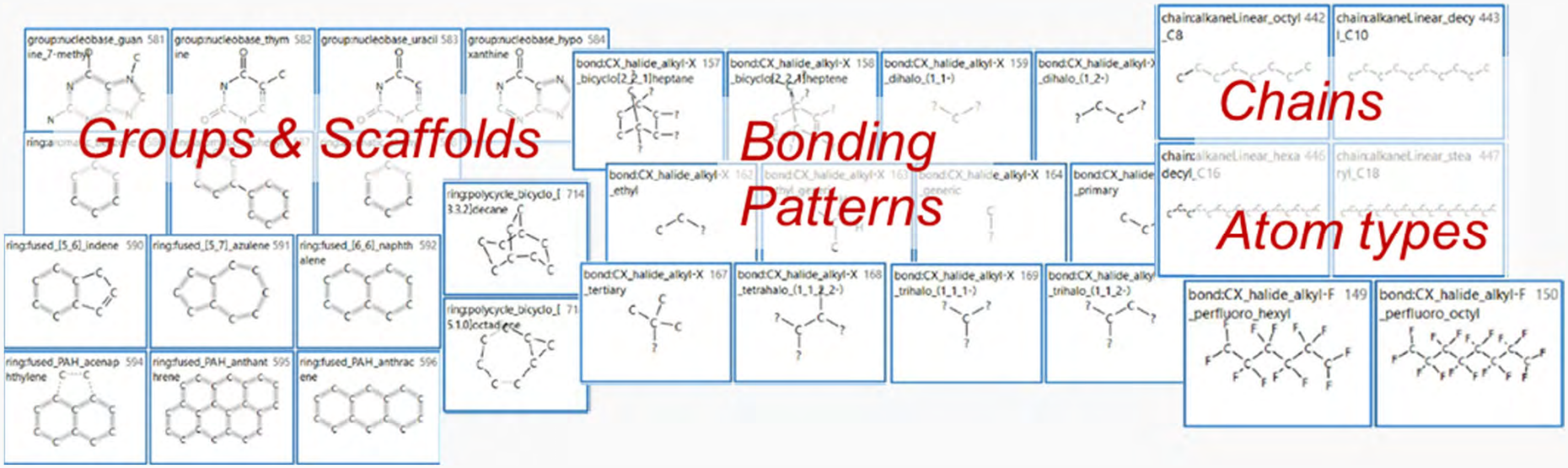



similarity data-mining
toxprint categories atoms
diversity bonds
analog prediction global machine-learning
class fingerprint modeling
chemical local chemotypes
toxicity read-across
scaffolds
structure-alerts coverage

# ToxPrints: A public set of chemotypes

http://www.toxprint.org

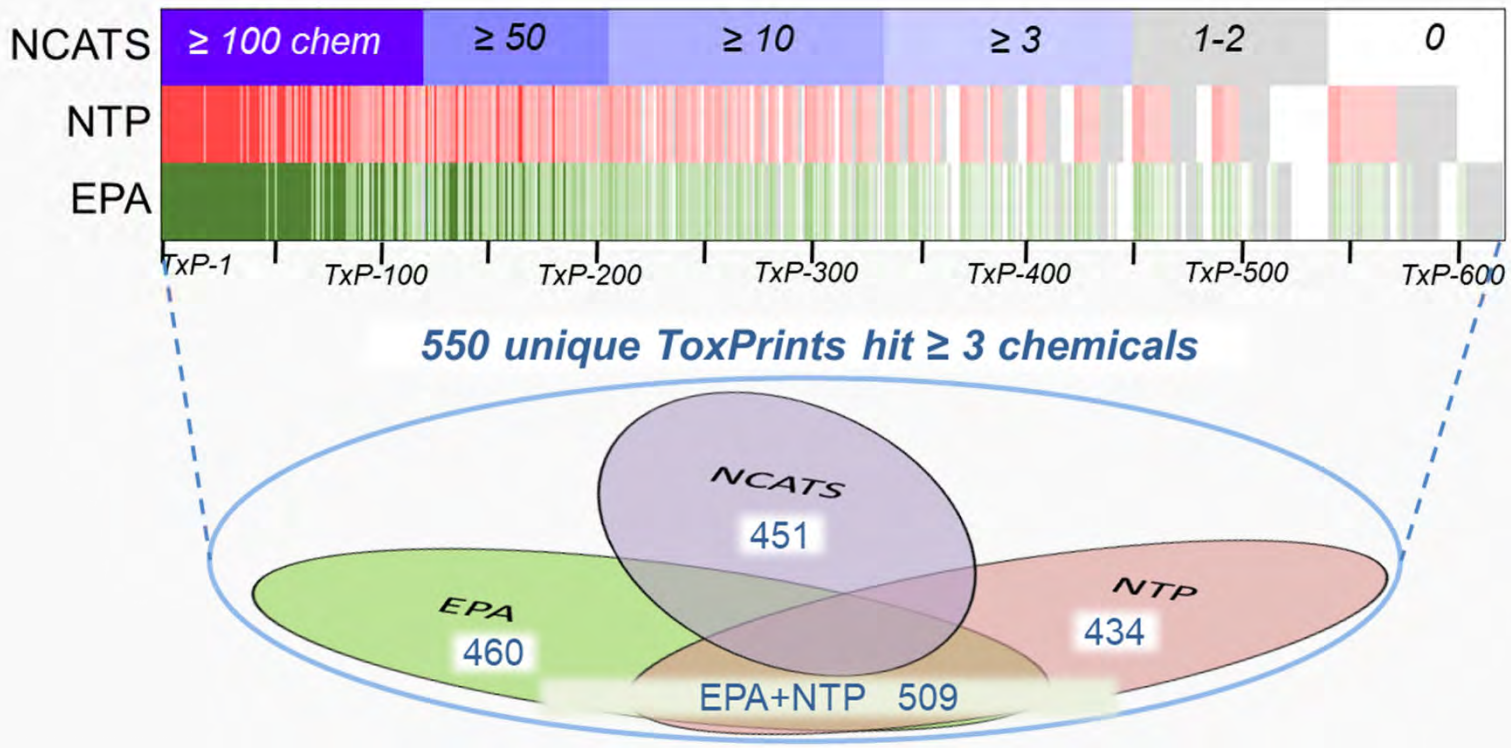
729 structural features important to EPA & FDA's "chemical exposure" landscape and safety assessment workflow

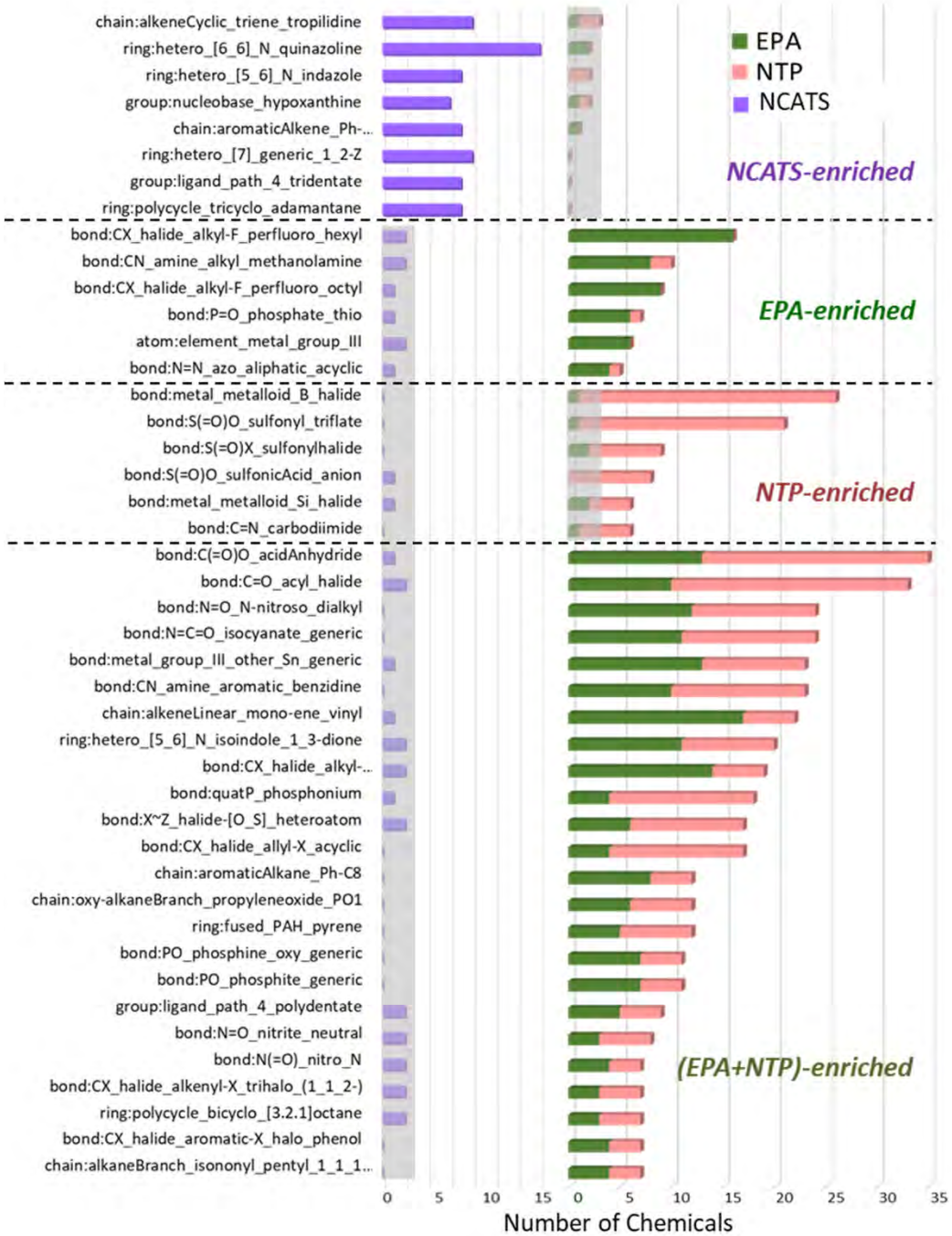



*Yang et al. (2015). New publicly available chemical query language, CSRML, to support chemotype representations for application to data mining and modeling. Journal of chemical information and modeling, 55(3), 510-528.*

# Tox21 Library Profiling:
## *Structural Diversity & Coverage*

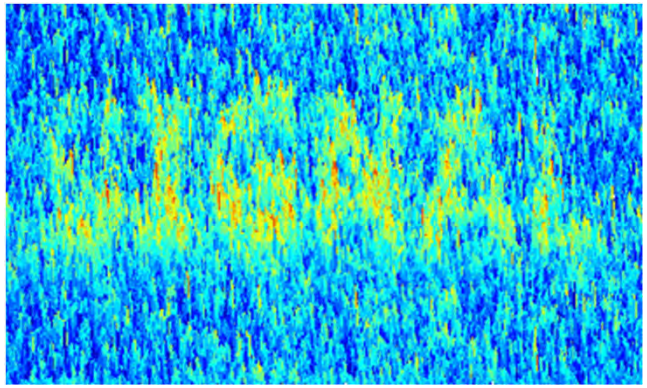
*624/729 ToxPrints "hit" ≥ 1 chemical*



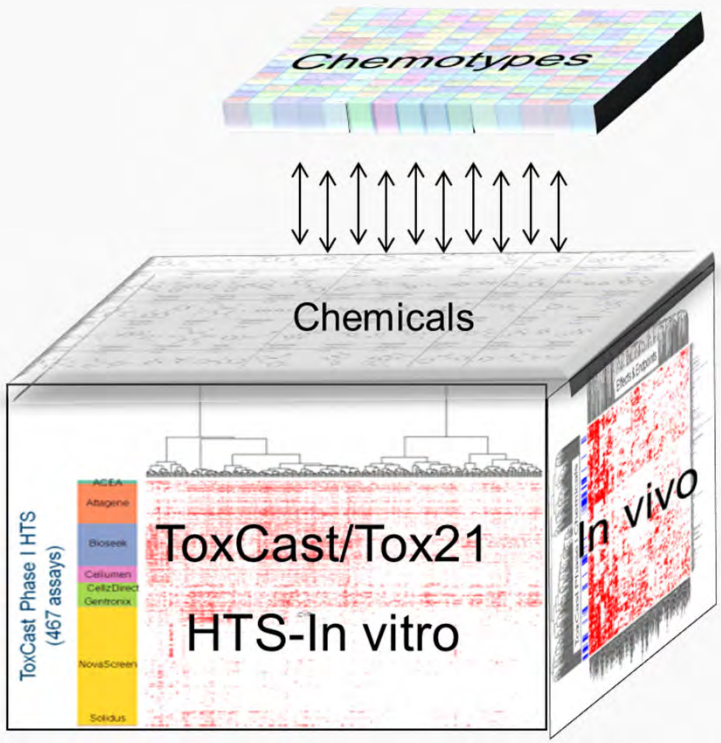



# Tox21 Library Profiling:

## *ToxPrint chemotype (CT) enrichments*



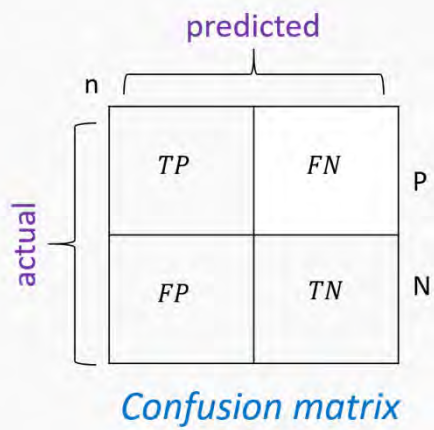
# Let's view the Tox21 chemical-assay space thru a "chemotype lens"



# Computing CT-Assay "Enrichments"

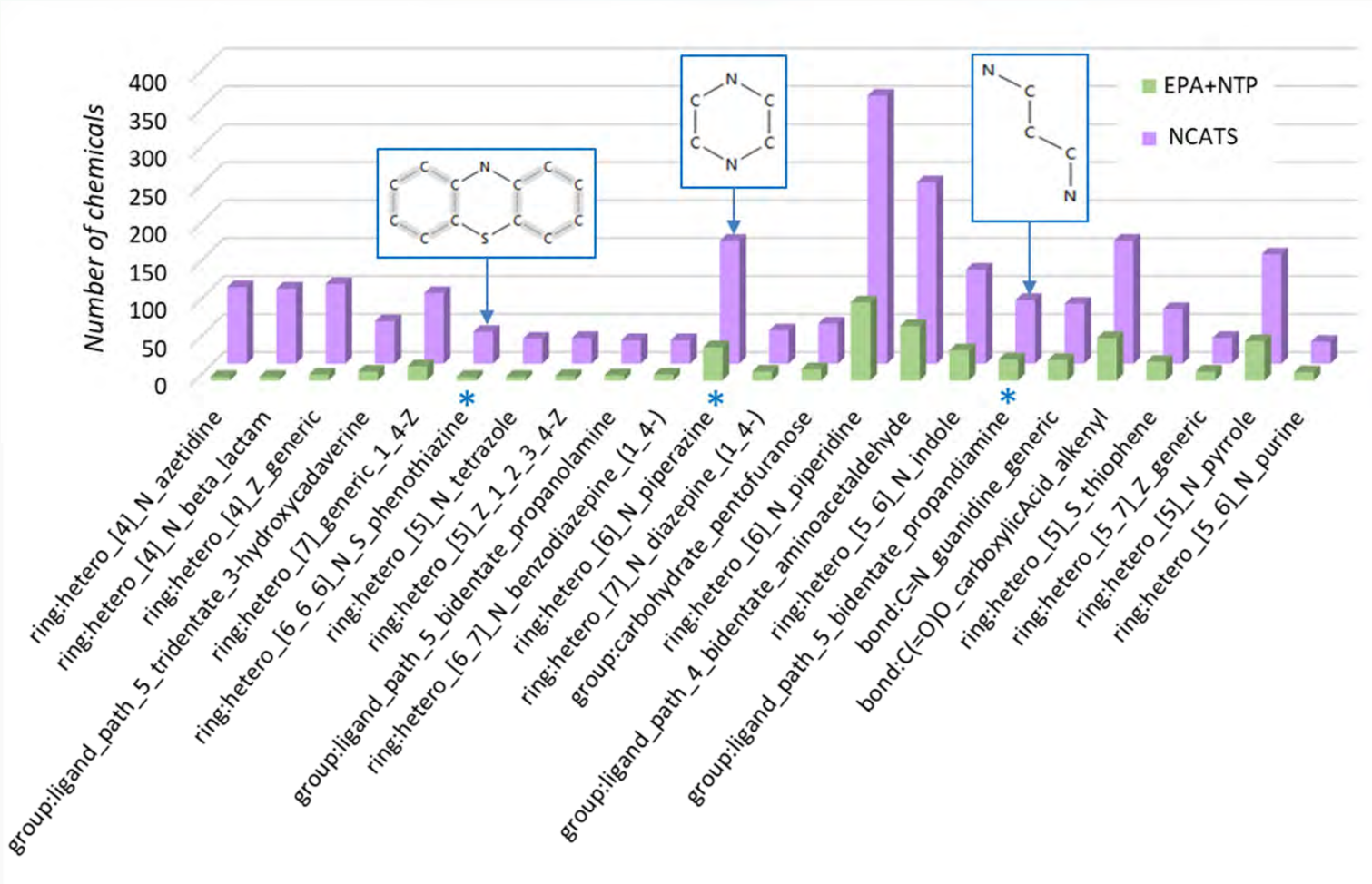
*Simple statistical thresholds & filters of significance:*

| TP_ID | ToxPrint_CT_name[2] | $CT_{Tot}$ | $T_{pos}$ | $F_{pos}$ | $F_{neg}$ | $T_{neg}$ | Odd's Ratio | Fischer's pval |
|---|---|---|---|---|---|---|---|---|
| 423 | chain:alkaneBranch_t-butyl_C4 | 41 | 24 | 17 | 294 | 693 | **3.3** | **2.0E-04** |
| 479 | chain:aromaticAlkane_Ph-C1-Ph | 39 | 27 | 12 | 291 | 698 | **5.4** | **6.5E-07** |
| 303 | bond:X[any_!C]_halide_inorganic | 28 | 17 | 11 | 301 | 699 | **3.6** | **9.0E-04** |

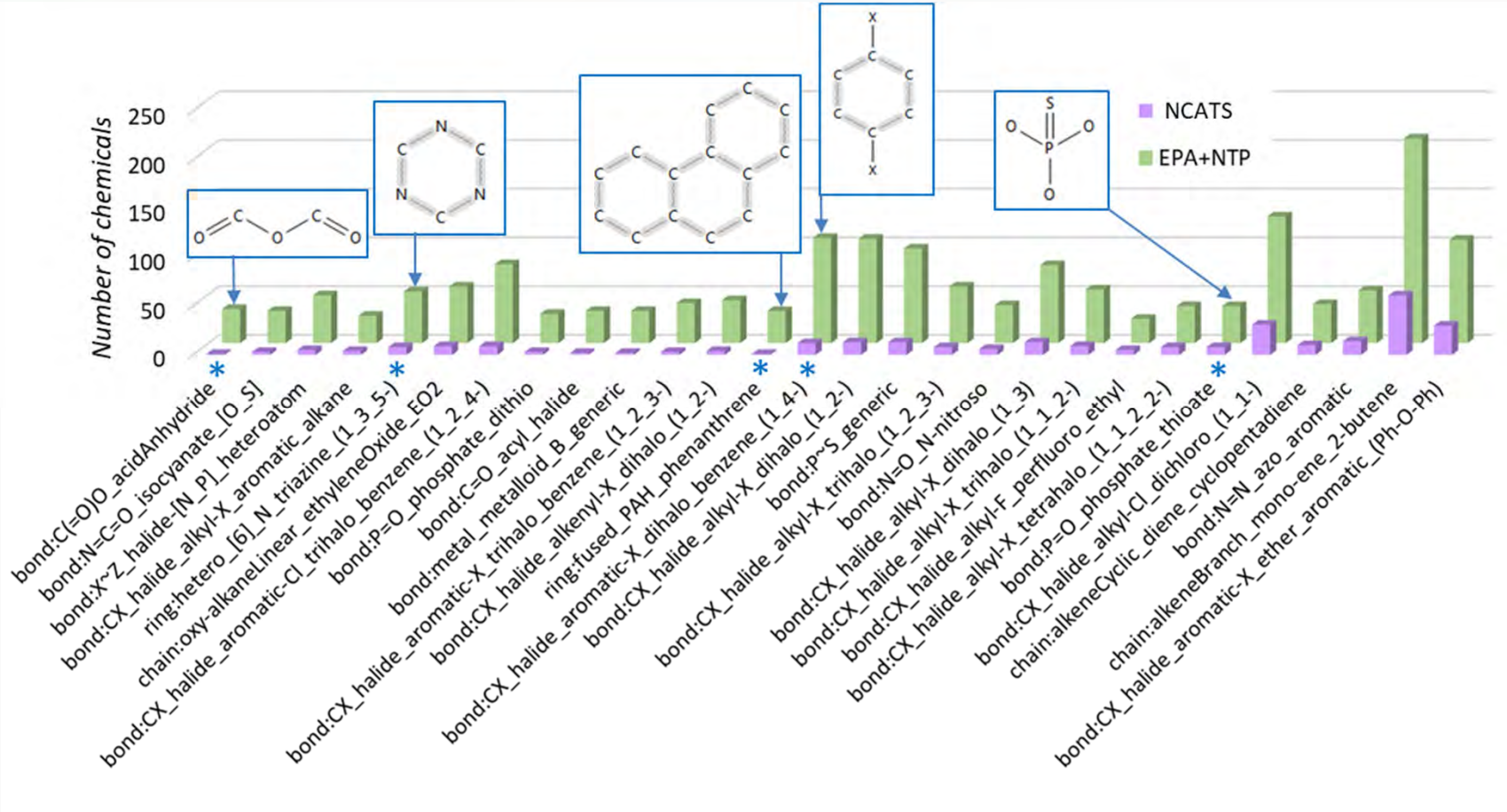



- Odds Ratio $\geq 3$, *conveys simple fractional enrichment*
- Fischer's exact p value $\leq 0.05$, *compensates for size of dataset*
- $T_{pos}$ (TP) $\geq 3$, *require at least 3 chemicals with CT in Positives*

# CT Profile & Assay "Enrichments"

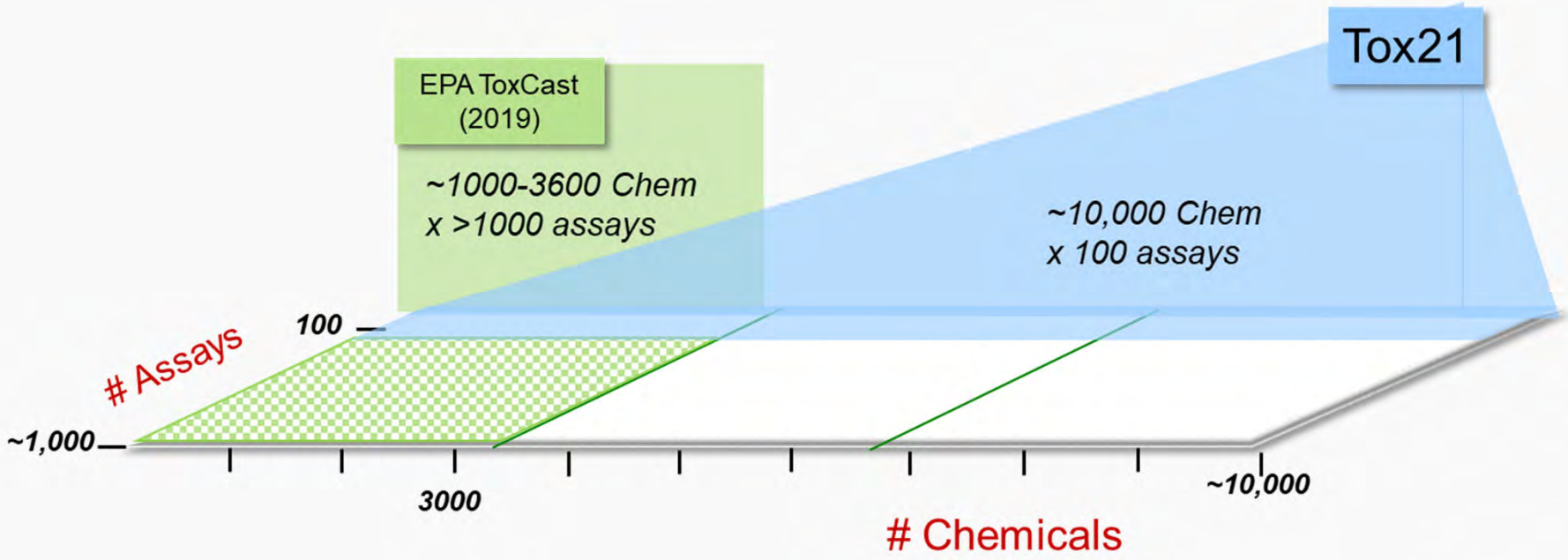


# CT Profile & Assay "Enrichments"

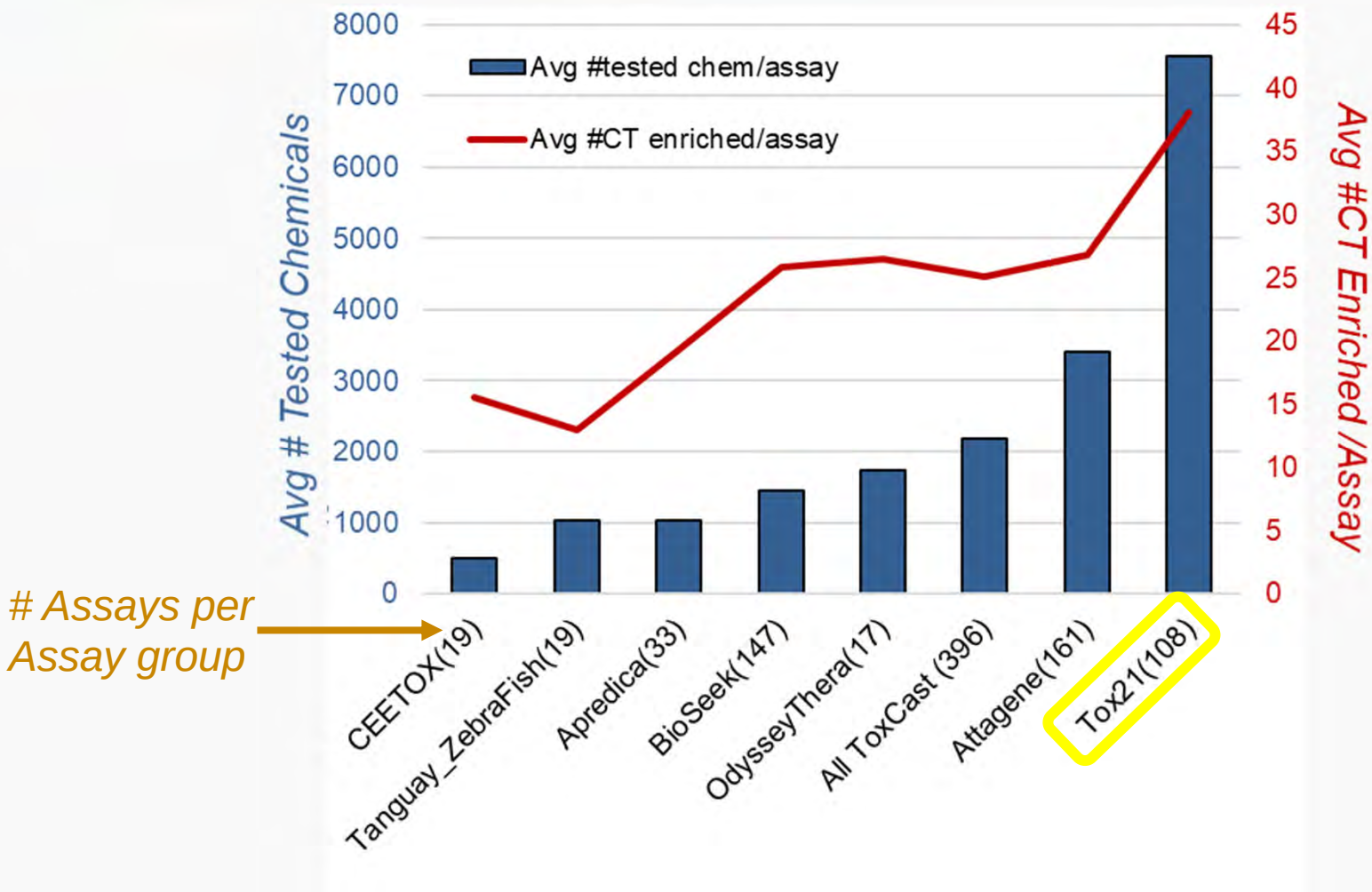


BONUS

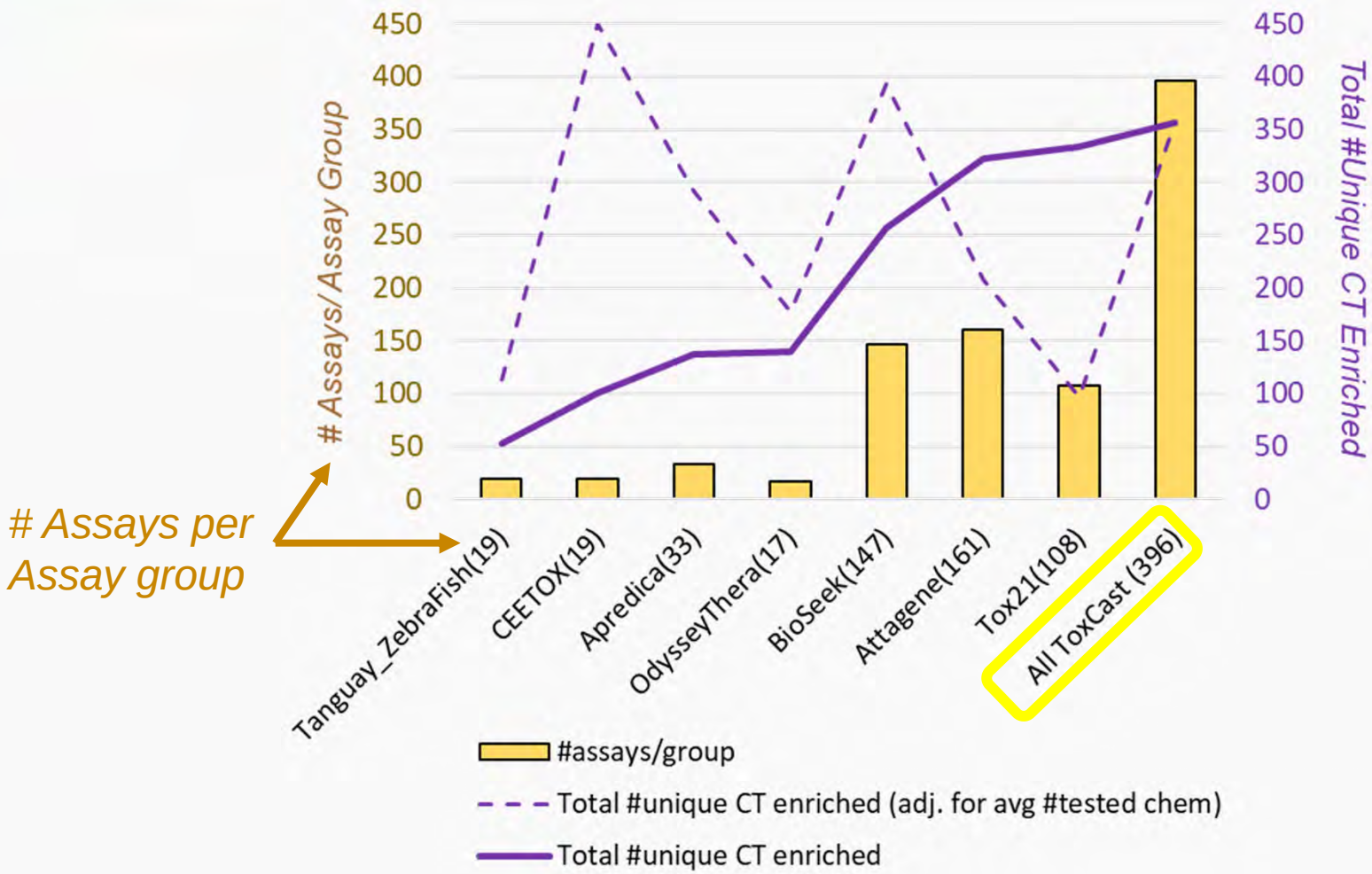
# Let's not forget that we also have ToxCast HTS data for a significant fraction of EPA's Tox21 library



# Test Set Size Matters!



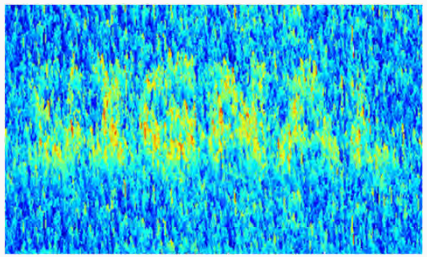
# CT Profile & Assay "Enrichments"



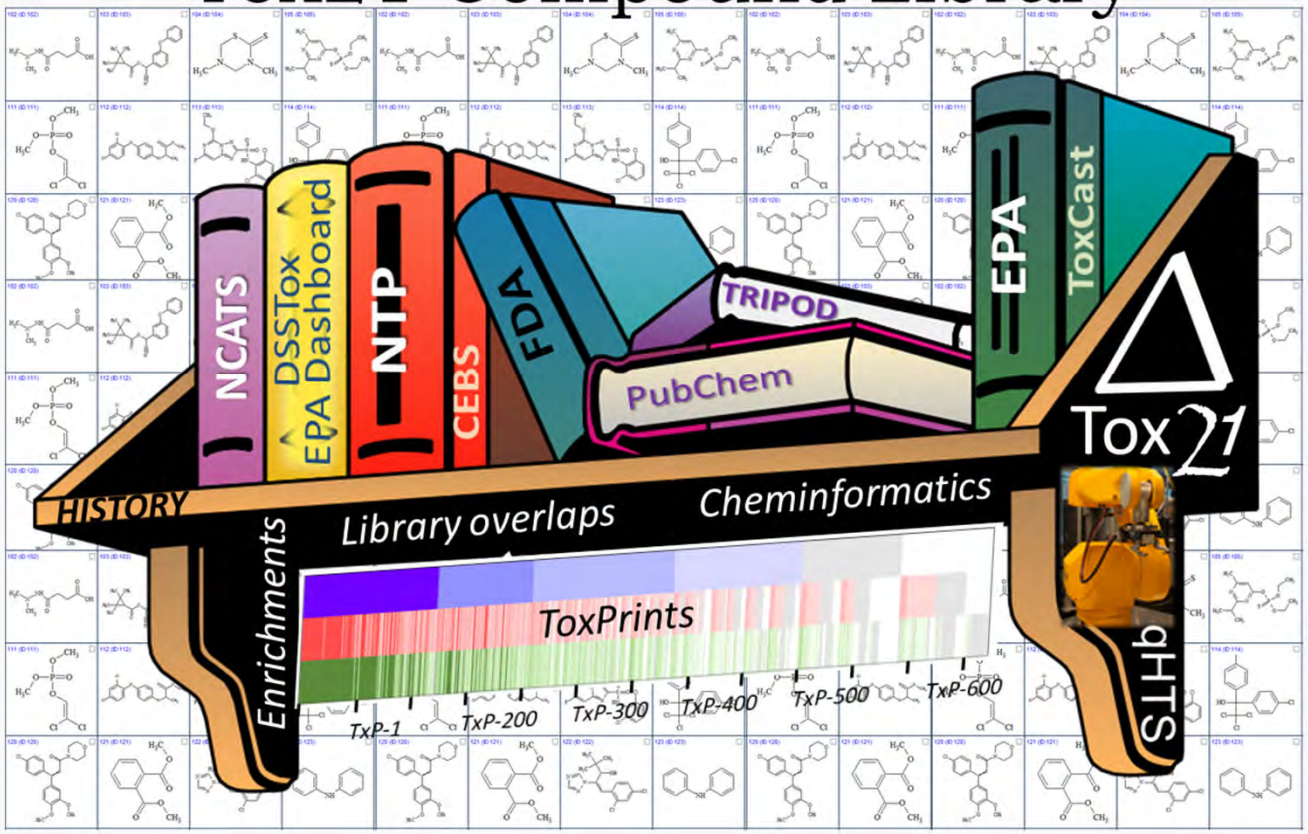
# Tox21 Data Analysis Challenge

ToxPrints & CT = enrichments

for detecting



# Tox21 Compound Library



# The Tox21 10K Compound Library: Collaborative Chemistry Advancing Toxicology

Ann M. Richard*, Ruili Huang, Suramya Waidyanatha, Paul Shinn, Bradley J. Collins, Inthirany Thillainadarajah, Christopher M. Grulke, Antony J. Williams, Ryan R. Lougee, Richard S. Judson, Keith A. Houck, Mahmoud Shobair, Chihae Yang, James F. Rathman, Adam Yasgar, Suzanne C. Fitzpatrick, Anton Simeonov, Russell S. Thomas, Kevin M. Crofton, Richard S. Paules, John R. Bucher, Christopher P. Austin, Robert J. Kavlock, and Raymond R. Tice

Cite this: *Chem. Res. Toxicol.* 2020, XXXX, XXX, XXX-XXX
Publication Date: November 3, 2020
https://doi.org/10.1021/acs.chemrestox.0c00264
Copyright © 2020 American Chemical Society
RIGHTS & PERMISSIONS
ACS Editors' Choice

Article Views 5170
Altmetric 3
Citations 1
LEARN ABOUT THESE METRICS
Share Add to Export
RIS

EPA Tox21: Leadership & Chemical Library Team

NCGC/NCATS Tox21: Leadership & Chemical LibraryTeam

NTP Tox21: Leadership & Chemical Library Team

FDA Tox21: Leadership

MN-AM (Molecular Networks, Altamira): ToxPrints & Chemotyper

*We acknowledge the following past and present Tox21 leads and working group team members for: (1) leadership of the Tox21 program - past (David Dix and Reeder Sams) and present (Warren Casey, Monica Linnenbrink, and Donna Mendrick); (2) the compound library (Katherine Coutros, present manager of the EPA's chemical contract, and William Leister, who oversaw analytical QC analysis of the library); (3) generation and analysis of screening results (NCATS: Menghang Xia, Matias Attene-Ramos, and Noel Southall; NTP: Nicole Kleinstreuer, Nisha Sipes, Keith Shockley, Kristine Witt, Fred Parham, Scott Auerbach, and Alex Merrick; EPA: Katie Paul-Friedman, Thomas Knudsen, and Michael DeVito). The authors acknowledge the invaluable contributions of EPA's chemical contractor (Evotec (US), Branford, CT) and NTP's chemical contractor (MRIGlobal, Kansas City, MO) in helping to procure and manage their respective chemical libraries. Finally, the authors dedicate this manuscript to Cynthia Smith (1950−2017), who led NTP's Tox21 compound library efforts through to her retirement in 2012, and Maritja (Marty) Wolf (1946−2014), who established high standards for DSSTox curation and sample registration of both EPA's ToxCast and Tox21 libraries.*