

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

The Tox21 10K Compound Library: Collaborative Chemistry Advancing Toxicology

Ann M. Richard,* Ruili Huang, Suramyia 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

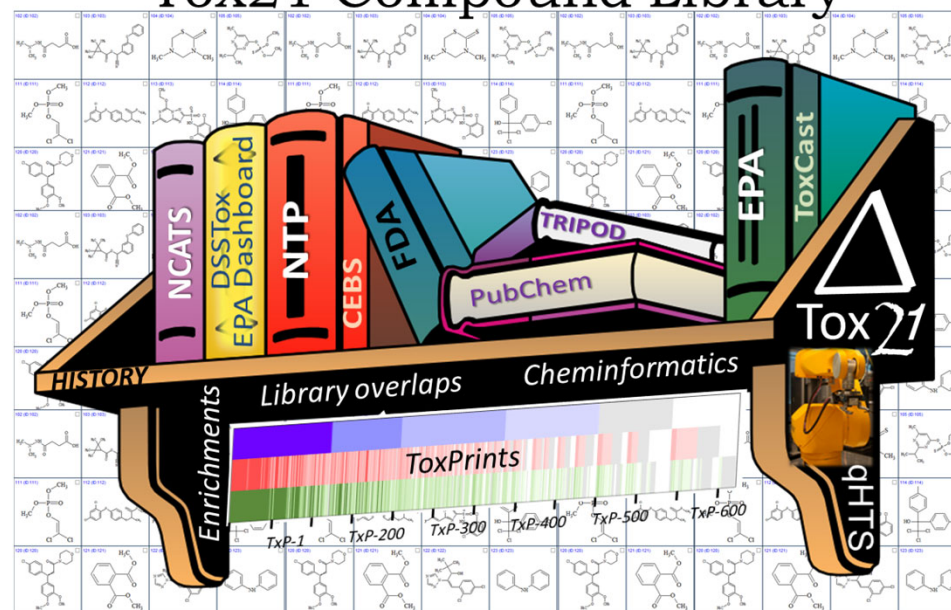
Altmetric

3

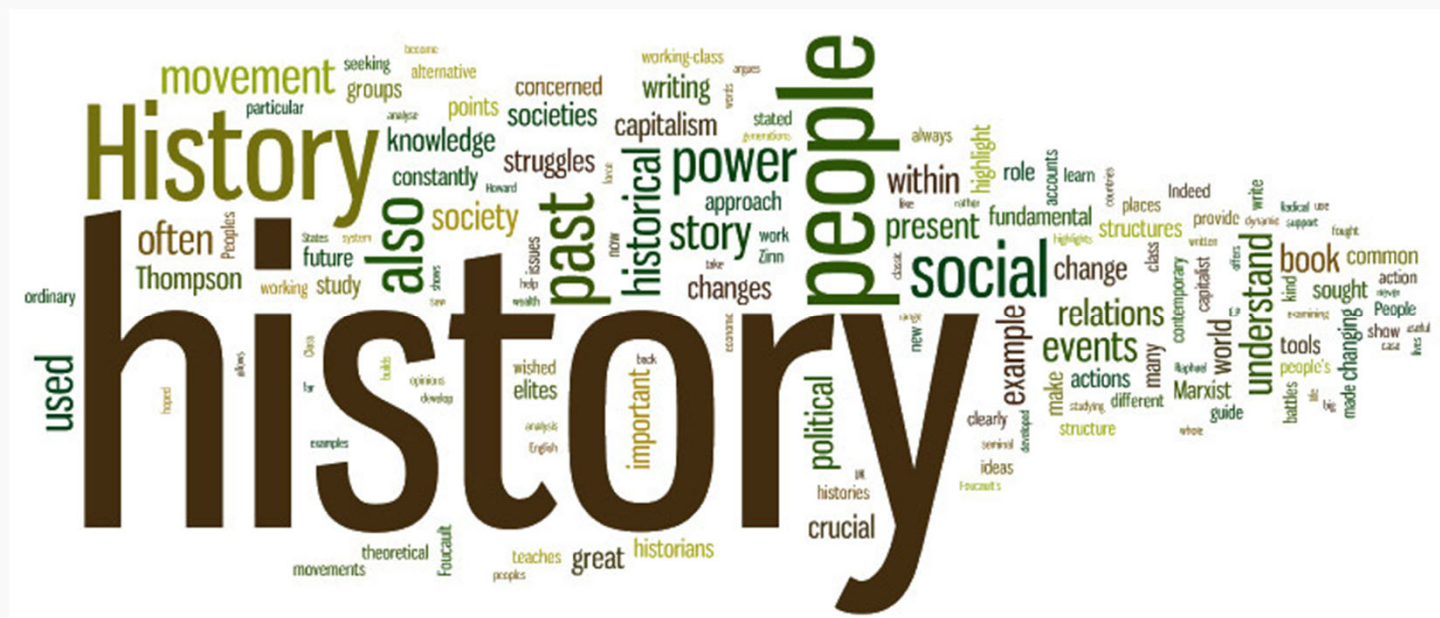
Citations

1

Tox21 Compound Library



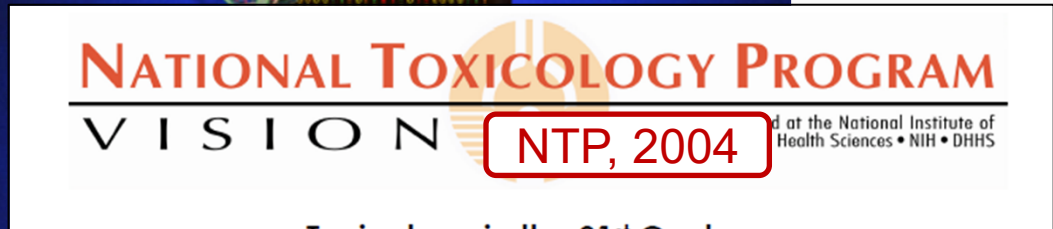
First, a bit of ...



Toxicity Testing in the 21st Century



EPA, 2003



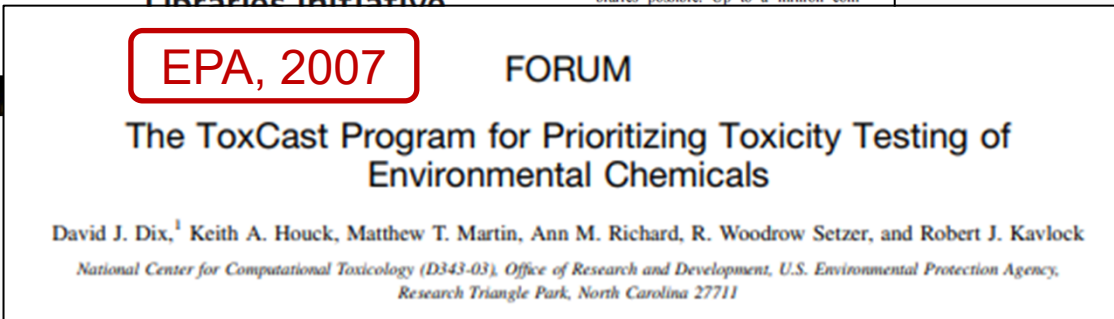
NTP, 2004

at the National Institute of Health Sciences • NIH • DHHS



NIH, 2004

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



Science, 2008

EPA, 2003

NATIONAL TOXICOLOGY PROGRAM VISION

POLICYFORUM

TOXICOLOGY

Transforming Environmental Health Protection

Francis S. Collins,^{1*} George M. Gray,^{2*} John R. Bucher^{2*}

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.

In 2005, the U.S. Environmental Protection Agency initiated a program of high-throughput screening (HTS) and other automation, usually between 2 and 10 μM, and toler-

POLICY FORUM

MOLECULAR BIOLOGY

NIH Molecular Libraries Initiative

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

NAS, 2007

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

REPORT IN BRIEF

ACCAM

Toxicity Testing in the 21st Century



EPA, 2003

Science, 2008

NATIONAL TOXICOLOGY PROGRAM
VISION

NTP, 2004

POLICYFORUM

TOXICOLOGY

Transforming
Health

PERSPECTIVE

PHARMACOLOGY

2011

Francis S. Collins, M.D.
In 2005, the U.S. E

The NCGC Pharmaceutical Collection:
A Comprehensive Resource of Clinically

POLICY FORUM

NIH

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>.

NIH Molecular
Libraries Initiative

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. Bucher¹

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

EPA, 2007

FORUM

NAS, 2007

REPORT

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

IN BRIEF

ACCAI

Toxicity Testing in the 21st Century



EPA, 2003

Science, 2008

NATIONAL TOXICOLOGY PR
VISION

NTP, 2004

POLICYFORUM

TOXICOLOGY

Transform
Health F

PERSPECTIVE

PHARMACOLOGY

2011

Francis S. Collins, M.D.
In 2005, the U.S. E

The NCGC Pharmaceutical Collection:
A Comprehensive Resource of Clinically

POLICY FORUM
MOLECULAR BIOLOGY

NIH

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

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

FDA U.S. FOOD & DRUG
ADMINISTRATION

2017

EPA, 2007

FORUM

The ToxCast Program for Prioritizing Toxicity Testin

FDA'S PREDICTIVE
TOXICOLOGY ROADMAP

NAS,

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

2018

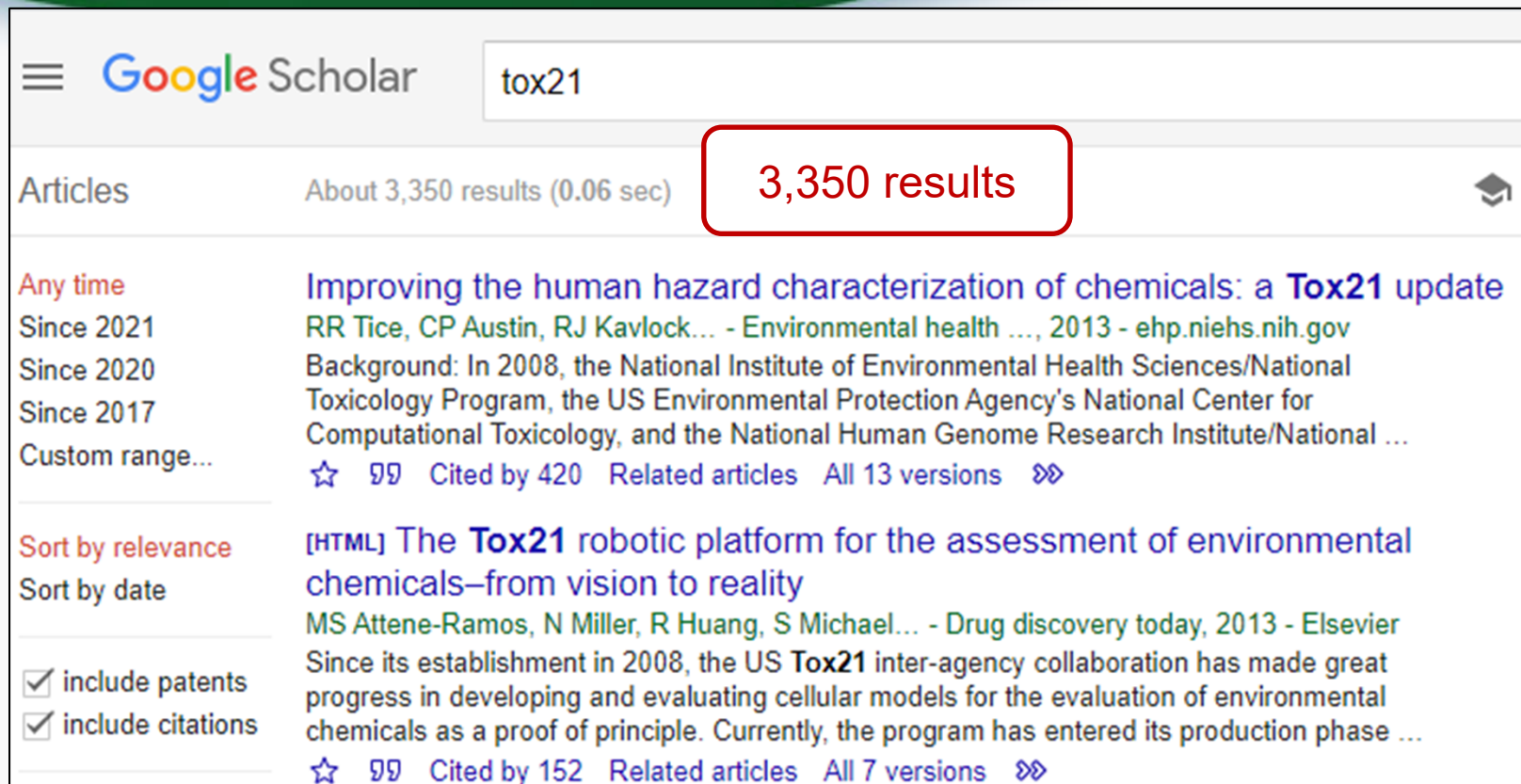
Toxicity Testing in the 21st
A Vision and a Strate

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

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

Russell S. Thomas¹, Richard S. Paules², Anton Simeonov³, Suzanne C. Fitzpatrick⁴, Kevin
M. Crofton¹, Warren M. Casey⁵, Donna L. Mendrick⁶

Tox21 Publications



Google Scholar search results for "tox21". The search bar shows "tox21" and the results count is "3,350 results". The first result is "Improving the human hazard characterization of chemicals: a Tox21 update" by RR Tice, CP Austin, RJ Kavlock... - Environmental health ..., 2013 - ehp.niehs.nih.gov. The second result is "[HTML] The Tox21 robotic platform for the assessment of environmental chemicals—from vision to reality" by MS Attene-Ramos, N Miller, R Huang, S Michael... - Drug discovery today, 2013 - Elsevier. The search filters on the left include "Any time", "Sort by relevance", and checkboxes for "include patents" and "include citations".

Articles About 3,350 results (0.06 sec) **3,350 results**

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

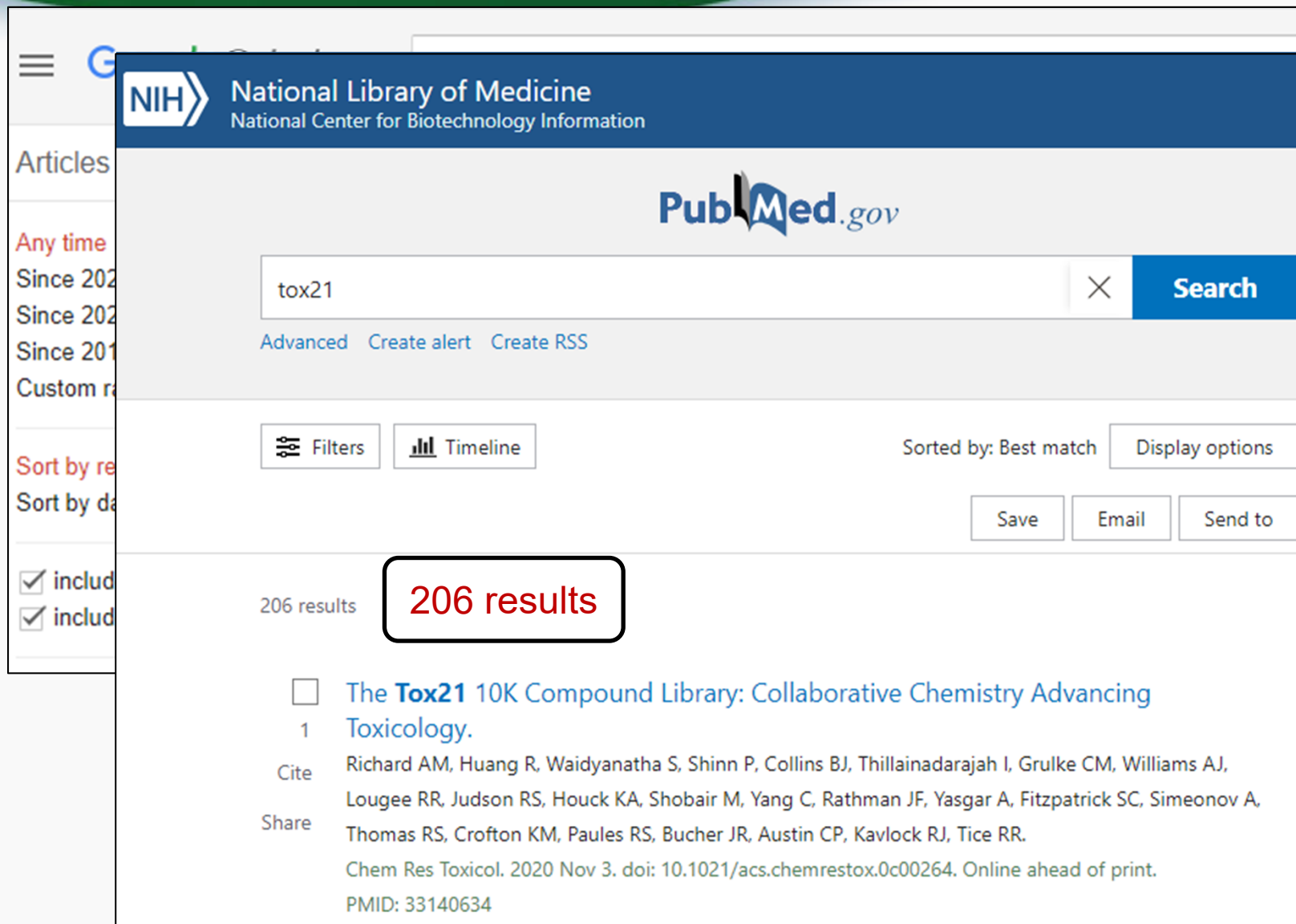
Sort by relevance
Sort by date

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 ...
☆ 99 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 ...
☆ 99 Cited by 152 Related articles All 7 versions »

Tox21 Publications



NIH National Library of Medicine
National Center for Biotechnology Information

PubMed.gov

tox21

Advanced Create alert Create RSS

Filters Timeline Sorted by: Best match Display options

Save Email Send to

206 results **206 results**

The **Tox21** 10K Compound Library: Collaborative Chemistry Advancing Toxicology.
1
Cite Richard AM, Huang R, Waidyanatha S, Shinn P, Collins BJ, Thillainadarajah I, Grulke CM, Williams AJ, Lougee RR, Judson RS, Houck KA, Shobair M, Yang C, Rathman JF, Yasgar A, Fitzpatrick SC, Simeonov A, Thomas RS, Crofton KM, Paules RS, Bucher JR, Austin CP, Kavlock RJ, Tice RR.
Share Chem Res Toxicol. 2020 Nov 3. doi: 10.1021/acs.chemrestox.0c00264. Online ahead of print.
PMID: 33140634

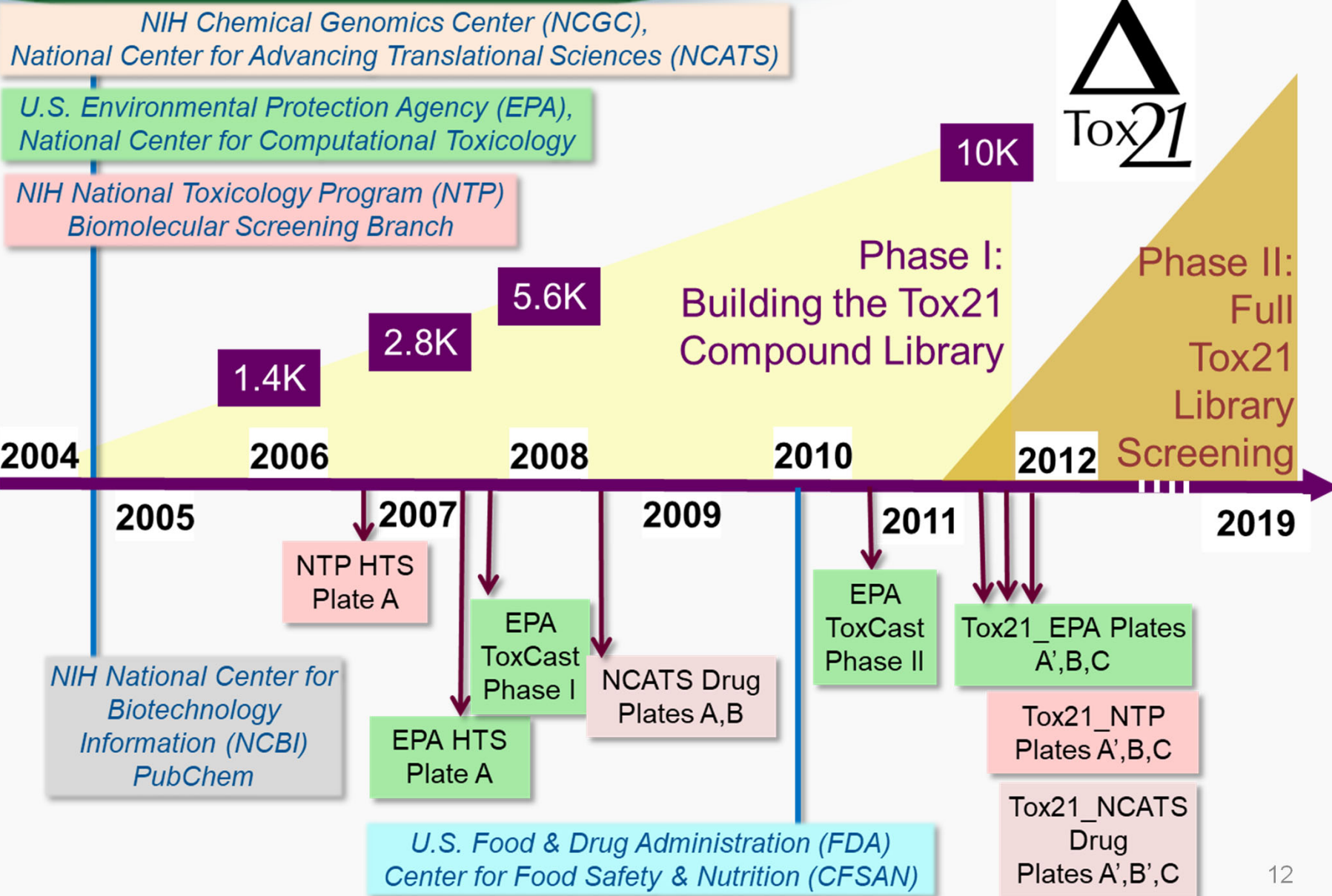
Tox21 Publications



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)

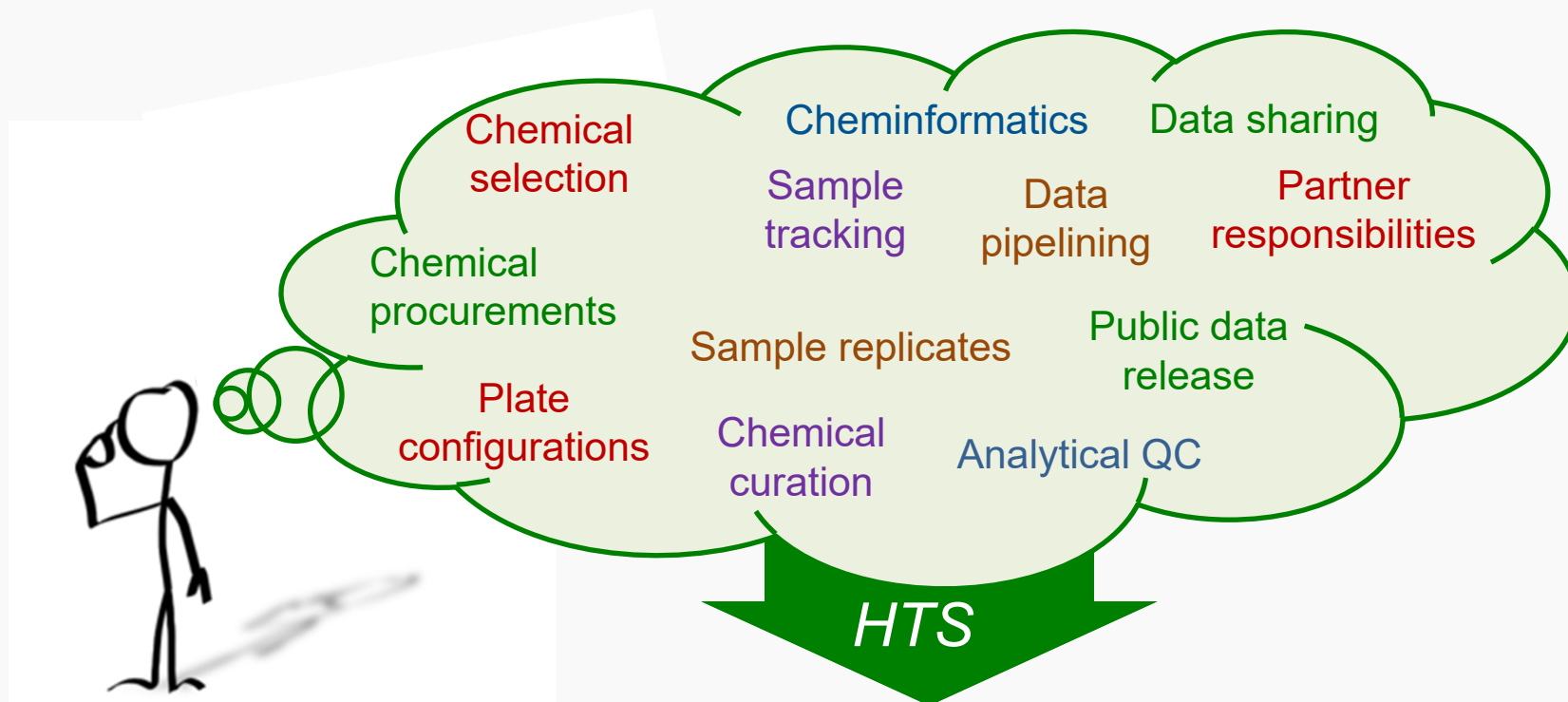
EPA's ToxCast library

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

EPA
(4078 total)

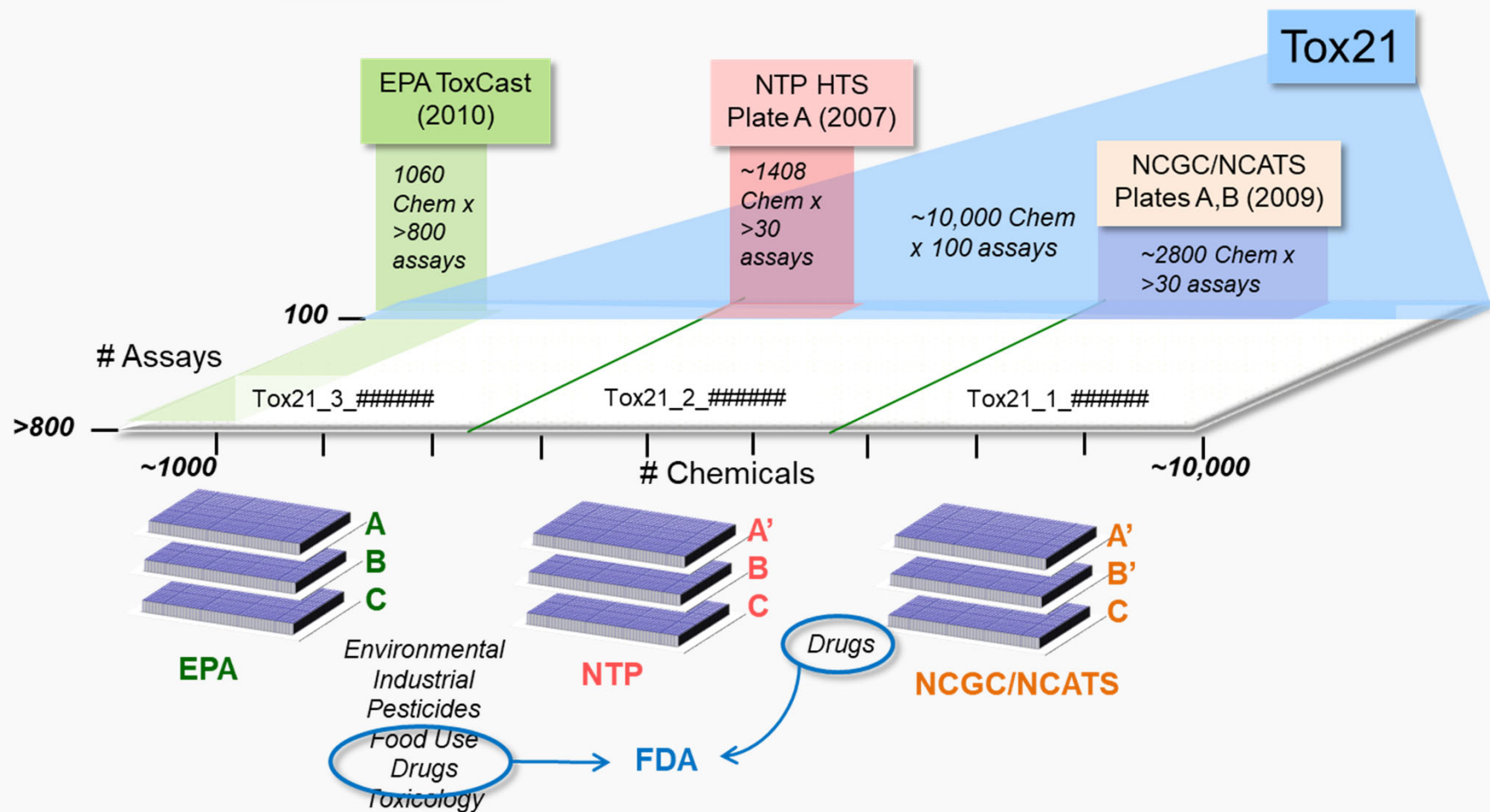
Planning ahead

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

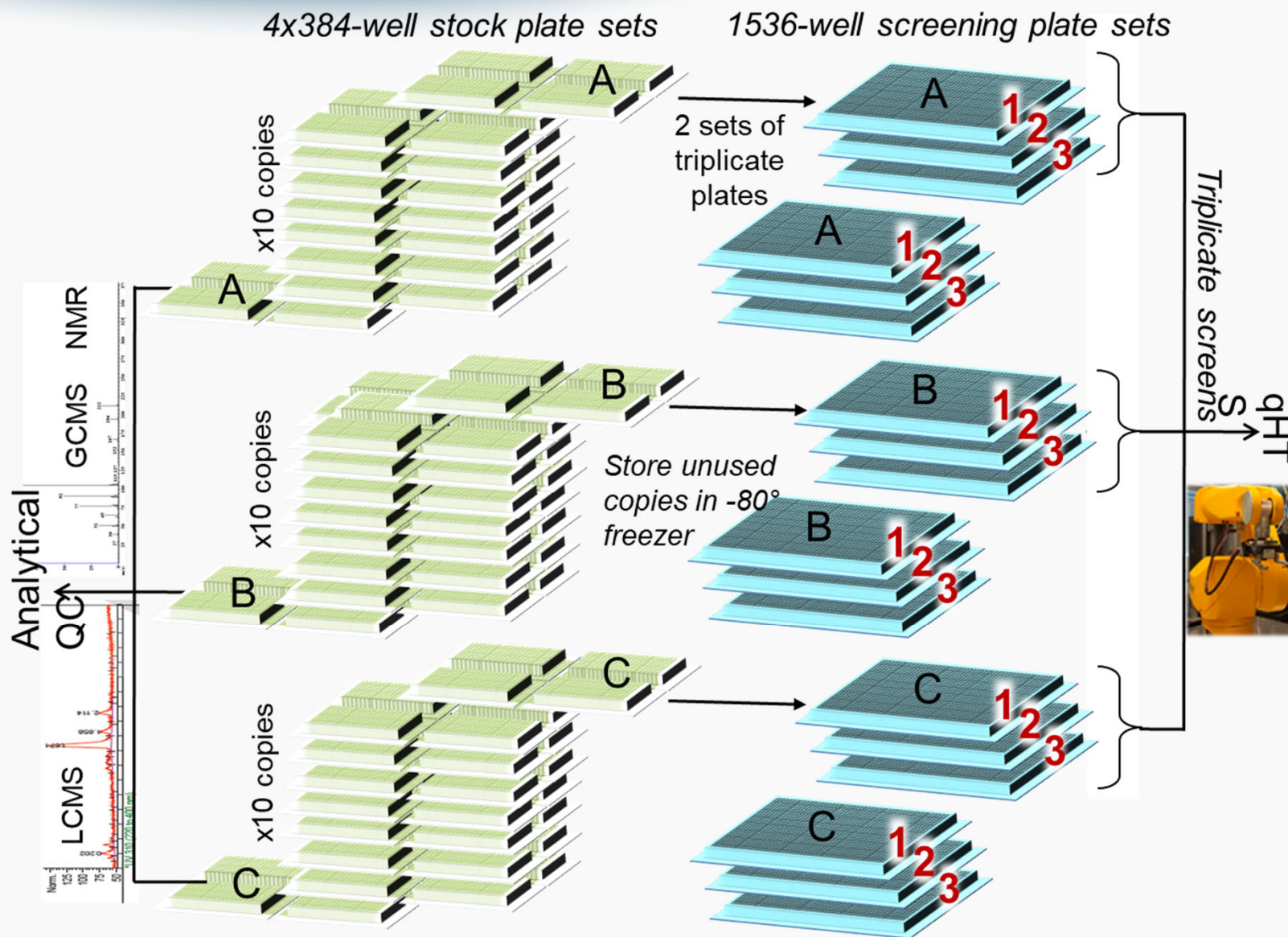


*Modeling, analyses, publications,
scientific breakthroughs!*

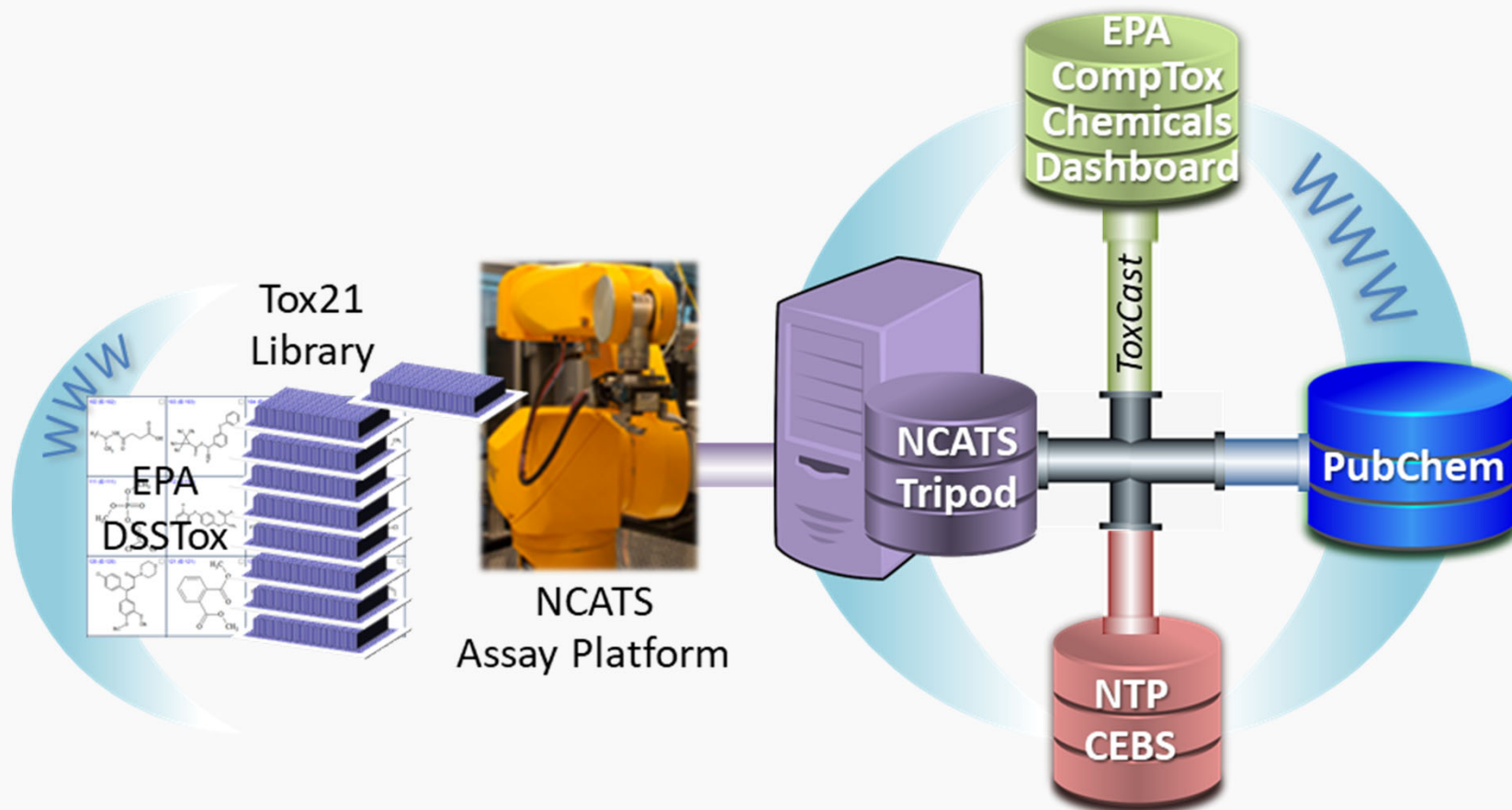
Building the Tox21 library



Processing each partner library



Tox21 Public Data Release



Tox21:EPA Public Data Release



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 further in-depth investigation. [Learn more about NCATS role in the Tox21 collaboration.](#)



Tox21:EPA Public Data Release



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




Environment

Related Topics

Toxicology (Tox)

Toxicology in... among EPA, N... Translational... National Instit... and Drug Adm... toxicity assess... whether certa... disrupt proces... health effects... chemical scre... [Learn more ab...](#) Using a high-t... NCATS, resear... (called the Tox... researchers p...



United States Environmental Protection Agency

Home Advanced Search Batch Search Lists Predictions Downloads

Share Search all data

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>

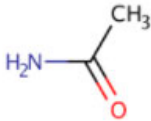
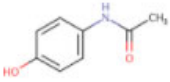
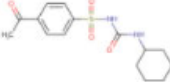

Update (Nov 20, 2018):

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: Filter by Name or CASRN

 <p>Acetamide DTXSID:DTXSID7020005 CASRN:60-35-5 TOXCAST:17/864</p>	 <p>Acetaminophen DTXSID:DTXSID2020006 CASRN:103-90-2 TOXCAST:5/849</p>	 <p>Acetohexamide DTXSID:DTXSID7020007 CASRN:968-81-0 TOXCAST:7/403</p>	 <p>Acetonitrile DTXSID:DTXSID7020009 CASRN:75-05-8 TOXCAST:0/235</p>
--	--	--	--

Tox21:EPA Public Data Release



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

The screenshot displays the EPA CompTox Chemicals Dashboard. At the top, the EPA logo and the text "United States Environmental Protection Agency" are visible. The main heading is "CompTox Chemicals Dashboard" with a sub-heading "883 Thousand Chemicals". Below this, there are three tabs: "Chemicals", "Product/Use Categories", and "Assay/Gene", with "Assay/Gene" selected. A search bar contains the text "tox21". The search results list several assays, each with a brief description of the data component analyzed. The assays listed are:

- ASSAY: TOX21_AhR_LUC_Agonist
Data from the assay component TOX21_AhR_LUC_Agonist was analyzed into ...
- ASSAY: TOX21_AhR_LUC_Agonist_viability
TOX21_AhR_LUC_Agonist_viability used a type of growth reporter where L...
- ASSAY: TOX21_AP1_BLA_Agonist_ch1
Data from the assay component TOX21_AP1_BLA_Agonist_ch1 was analyzed i...
- ASSAY: TOX21_AP1_BLA_Agonist_ch2
Data from the assay component TOX21_AP1_BLA_Agonist_ch2 was analyzed i...
- ASSAY: TOX21_AP1_BLA_Agonist_ratio
Data from the assay component TOX21_AP1_BLA_Agonist_ratio was analyzed...
- ASSAY: TOX21_AP1_BLA_Agonist_viability
TOX21_AP1_BLA_Agonist_viability used a type of growth reporter where L...
- ASSAY: TOX21_AR_BLA_Agonist_ch1
Data from the assay component TOX21_AR_BLA_Agonist_ch1 was analyzed in...
- ASSAY: TOX21_AR_BLA_Agonist_ch2
Data from the assay component TOX21_AR_BLA_Agonist_ch2 was analyzed in...
- ASSAY: TOX21_AR_BLA_Agonist_ratio
Data from the assay component TOX21_AR_BLA_Agonist_ratio was analyzed ...
- ASSAY: TOX21_AR_BLA_Antagonist_ch1
Data from the assay component TOX21_AR_BLA_Antagonist_ch1 was analyzed...
- ASSAY: TOX21_AR_BLA_Antagonist_ch2
Data from the assay component TOX21_AR_BLA_Antagonist_ch2 was analyzed...
- ASSAY: TOX21_AR_BLA_Antagonist_ratio
Data from the assay component TOX21_AR_BLA_Antagonist_ratio was analyz...

On the left side of the dashboard, there is a sidebar with the EPA logo, the word "Environment", and a "Related Topics" section. The "Toxicology (Toxicology)" link is highlighted. Below this, there is a brief description of the Tox21 program and a "Learn more about Tox21" link. At the bottom of the sidebar, there is a "Using a high-throughput screening approach..." section.

Tox21:EPA Public Data Release



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

Perfluorooctanoic acid
335-67-1 | DTXSID8031865
Searched by DSSTox Substance Id.

ToxCast/Tox21

QC Data ID	Grade	Description
Tox21_300688	Not determined	Analysis in progress

Assay Selection 1 Selected
 Active Inactive All

tox21

Tox21/NCGC (1 of 235 selected)

- TOX21_AR_BLA_Agonist_ch1
- TOX21_AR_BLA_Agonist_ch2
- TOX21_AR_BLA_Agonist_AR
- TOX21_AR_BLA_AntagonistAR
- TOX21_AR_BLA_Antagonist_I
- TOX21_AR_LUC_MDAKB;AR
- TOX21_AR_LUC_MDAKB;AR
- TOX21_AR_LUC_MDAKB2_A
- TOX21_Aromatase_CYP19A1
- TOX21_Aromatase_Inhibition_
- TOX21_AutoFluor_HEK293_C
- TOX21_AutoFluor_HEK293_C
- TOX21_AutoFluor_HEK293_C
- TOX21_AutoFluor_HEK293_M

Percentage Activity

Log Concentration (uM)

IC50 (0.000) Cytotoxic limit (1000.00)

Submit Comment Save Chart Save Data

Constant Model Gain-Loss Model Hill Model

Environment

Related Topics

Toxicology (Tox)

Toxicology in... among EPA, N... Translational... National Instit... and Drug Adm... toxicity assess... whether certa... disrupt proces... health effects... chemical scre... [Learn more at](#)

Using a high-t... NCATS, resear... (called the To... researchers p...

Tox21:NCATS Public Data Release



<https://ncats.nih.gov/tox21>



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

Target Category

Category	Count
NR	38
SR	8
G...	4
G...	5
C...	6
C...	3
D...	4
5...	3

Species / Tissue Type

Species / Tissue Type	Count
28	28
9	9
7	7
5	5
2	2
5	5
2	2
4	4
4	4
4	4

☆ 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/>

National Center

NIH National Center for Advancing Translational Sciences

TOX21 PUBLIC DATA

SEARCH

REPLICATE AGGREGATED UPDATE

DOWNLOAD SUBSCRIBE

Target Categories

Structure Search Search...

Home / Tox21 Samples / Tox21_202992

Bisphenol A

QC Grade

T0	A	MW Confirmed, Purity > 90%
T4	A	MW Confirmed, Purity > 90%

Identifiers

Tox21	Tox21_202992
NCATS	NCGC00260537-01
CAS	80-05-7
PubChem	144210190

☆ Used in

Protocol M

tox21-ahr

tox21-ap1

tox21-ar-b

Tox21:NCATS Public Data Release



<https://ncats.nih.gov/tox21>

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

National Center
for Advancing
Translational Sciences

TOX21 PUBLIC DATA

REPLICATE AGGREGATED UPDATE

SEARCH DOWNLOAD SUBSCRIBE

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 Category

D...

5...

C...

4...

C...

8...

G...

7...

G...

5...

SR

1...

Home / Tox21

Bisphenol A

HO

Chromatograms showing ELSD, CLND, UV 310, +MS, -MS, +EIC, and -EIC traces for Bisphenol A. The +EIC trace shows a peak at 2.27 min with a chemical structure of Bisphenol A.

RT	Found	ELS%	UV %	ELS [mg/mL]	Adj [ELS]	[N mM]	Adj [CLN]	#N
1.71		0.0	0.0					0.0
1.84		0.0	0.0					0.0
2.09		0.0	0.0					0.0
2.27	Yes	100.0	100.0	1.76	7.73 mM			0.0

Comment: Passed

PubChem MW Confirmed, Purity > 90%

OpAns Process.MAC Version A.01.10 - Dec 9, 2010

Tox21:NCATS Public Data Release



<https://ncats.nih.gov/tox21>

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

The screenshot displays the Tox21 public data release interface. At the top, the National Center for Advancing Translational Sciences (NCATS) logo is visible. Below it, the National Library of Medicine (NLM) logo and the text "National Center for Biotechnology Information" are present. A search bar contains the text "tox21". To the right of the search bar, there are buttons for "REPLICATE", "AGGREGATED", "DOWNLOAD", and "SUBSCRIBE". Below the search bar, a table lists data sources with the following counts:

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

Below the table, there is a note: "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...](#)"

At the bottom of the interface, there are buttons for "11,267 results", "Filters", "SORT BY", "Relevance", and "Download".

Tox21:NTP Public Data Release



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

Search the NTP Website

- 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

Toxicology in the 21st Century (Tox21)

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:

Robotic arm used for Tox21 testing



SHARE THIS:



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

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/>



Search the NTP Website **SEARCH**

What We Study ▾

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

Home » What We Study »

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

What We Study

Health Effects Assessment

Highlighted Research Topics

NICEATM: Alternative Methods

NTP Laboratory Research

Testing Program

Tox21

History of Tox21

High-Throughput Transcriptomics and the S1500+ Gene Set Strategy

Research Phases

Selected Publications

Tox21

History of Tox21

High-Throughput Transcriptomics & the S1500+ Gene Set Strategy

Research Phases

Selected Publications

Tox21 Toolbox

Tox21 Toolbox

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.

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

SHARE THIS:



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

On This Page

- [NIEHS/NTP Tools](#)
- [External Tools](#)

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*

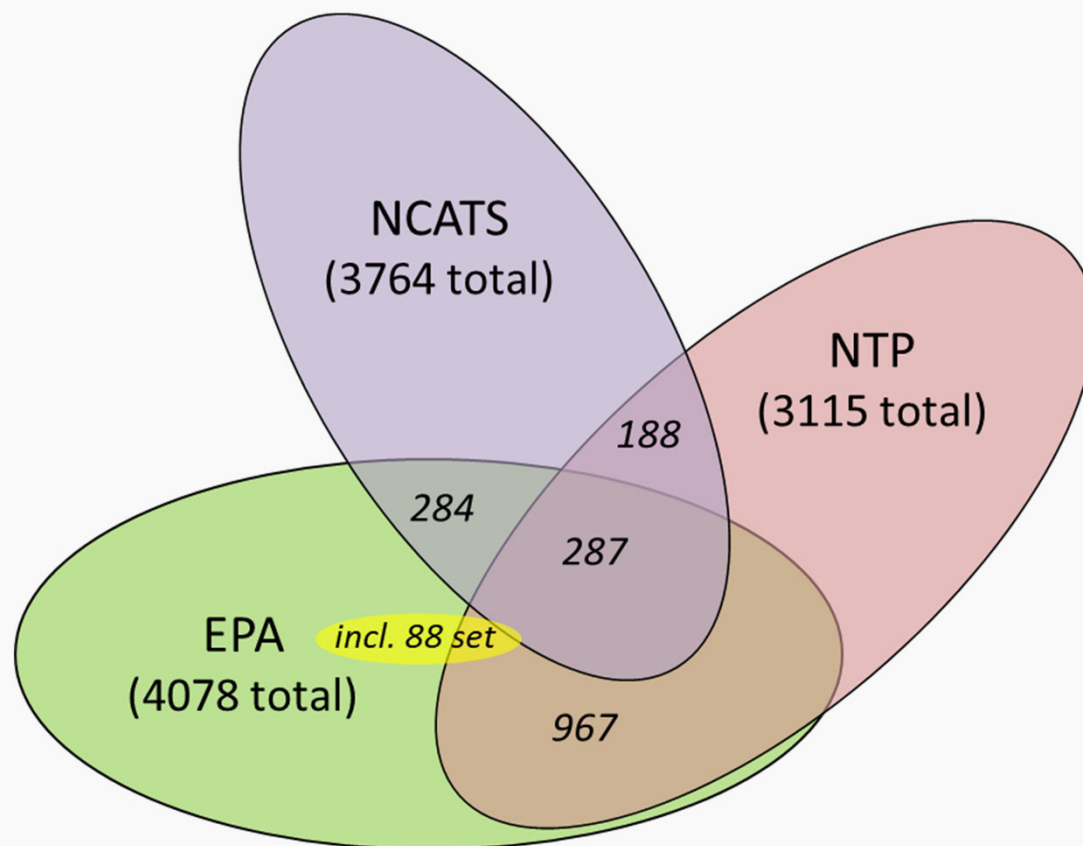
NTP
(3115 total)

EPA's ToxCast library

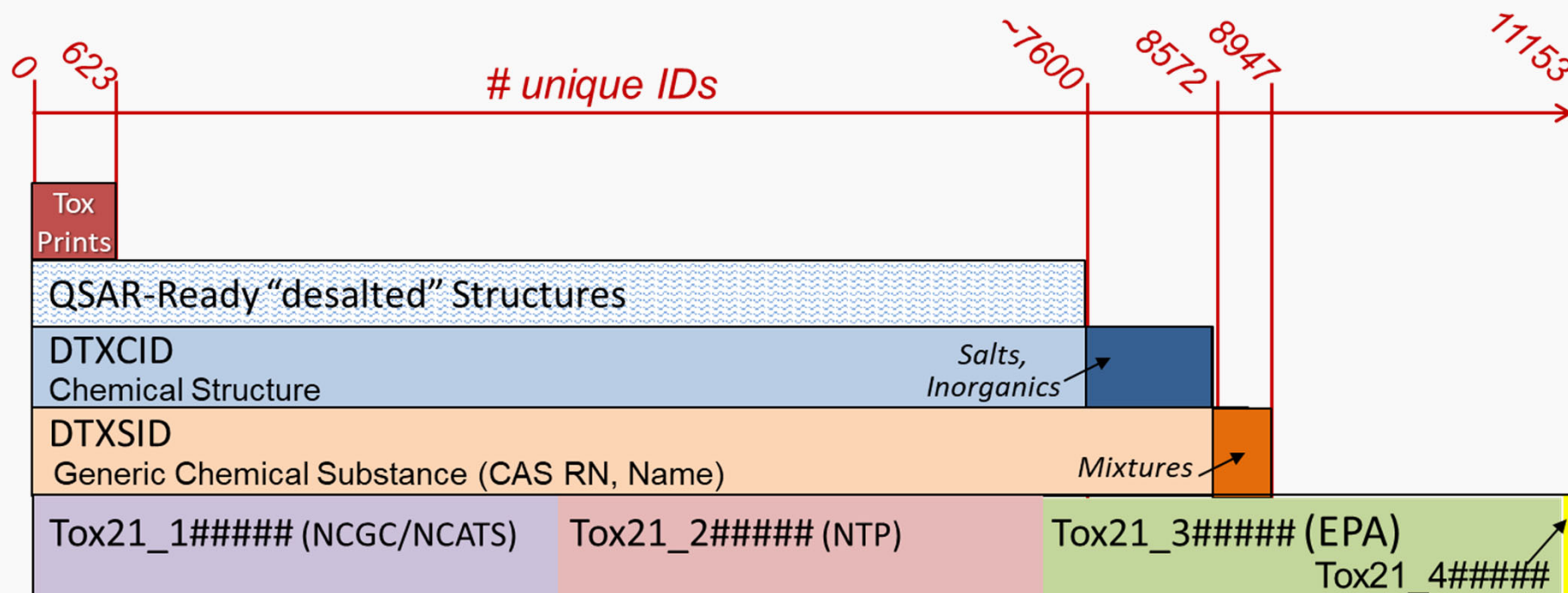
- *environmental/industrial*
- *pesticides*
- *pharmaceutical*
- *known toxicants*

EPA
(4078 total)

Tox21 Partner Library Overlaps



Tox21 Cheminformatics

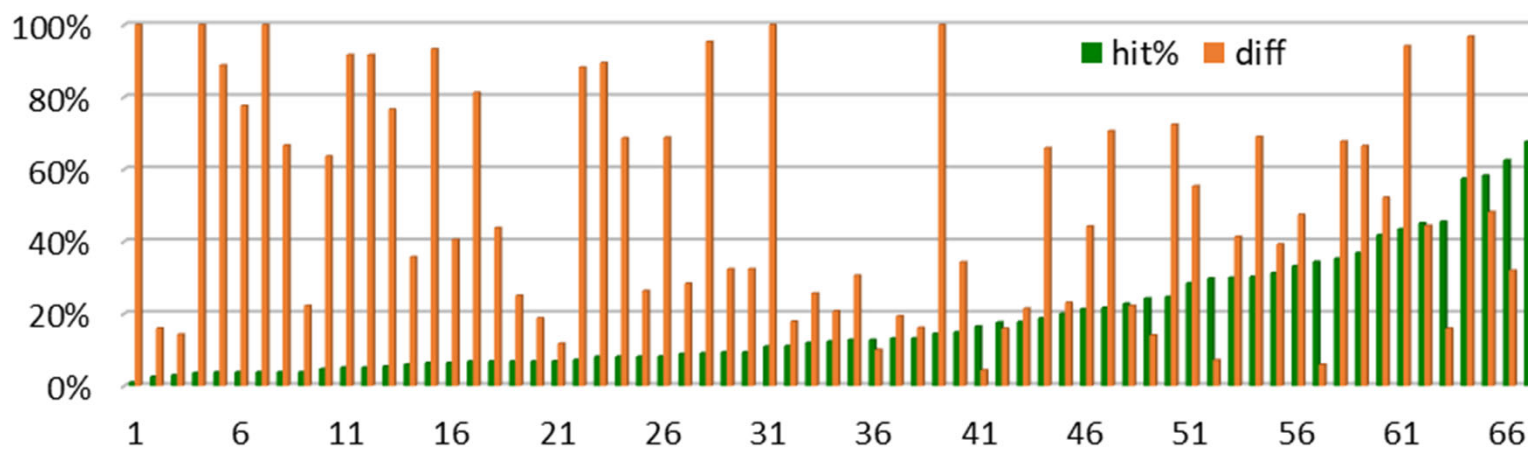


DSSTox
Cheminformatics



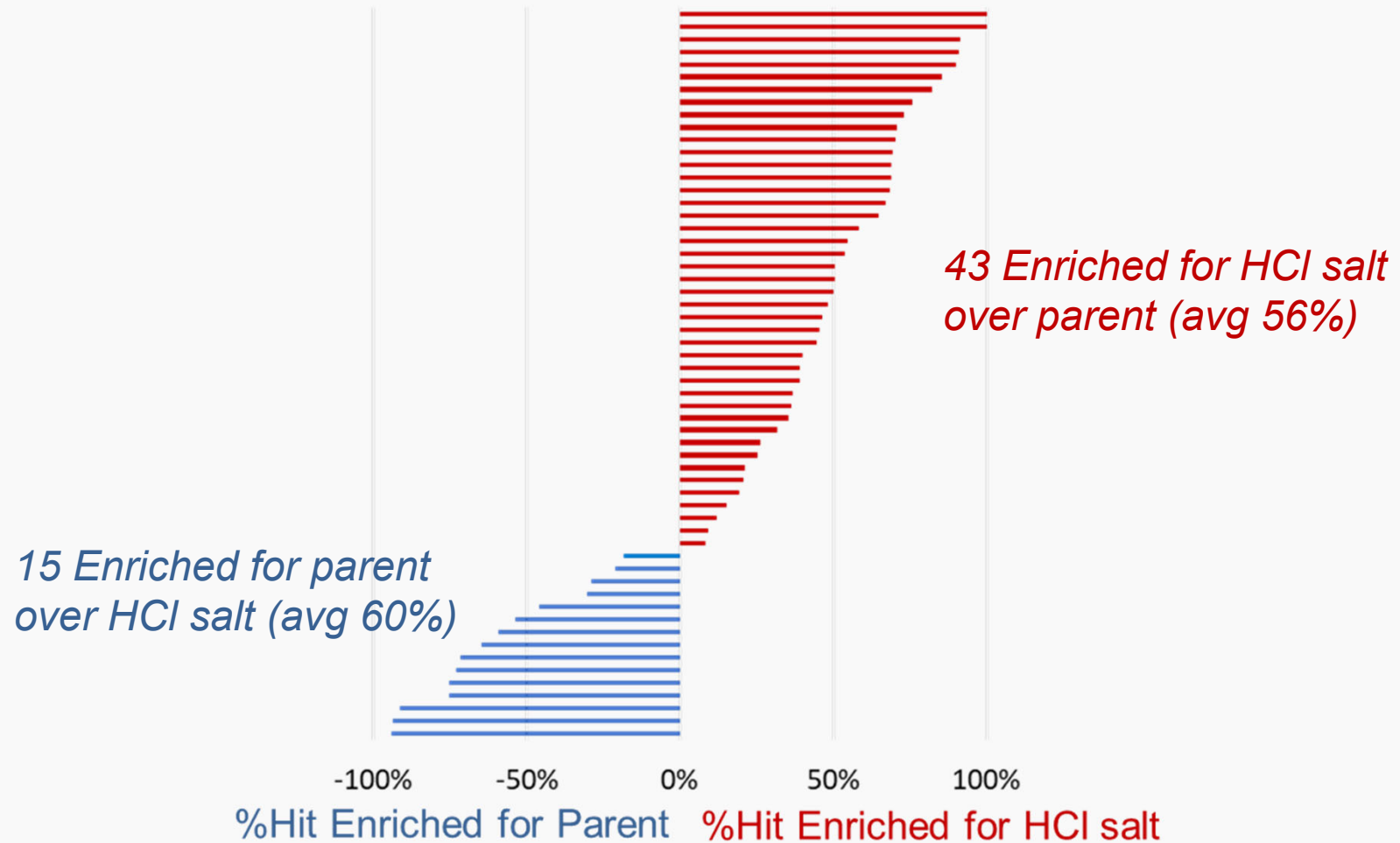
What sorts of questions can
we ask of the Tox21
chemical-assay landscape?

Does stereochemistry matter?

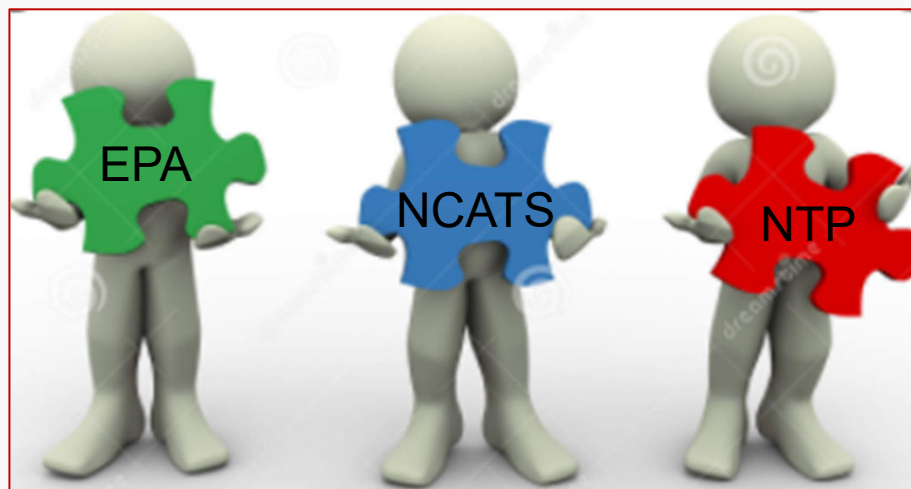


67 Stereo isomer pairs with %hit >3%

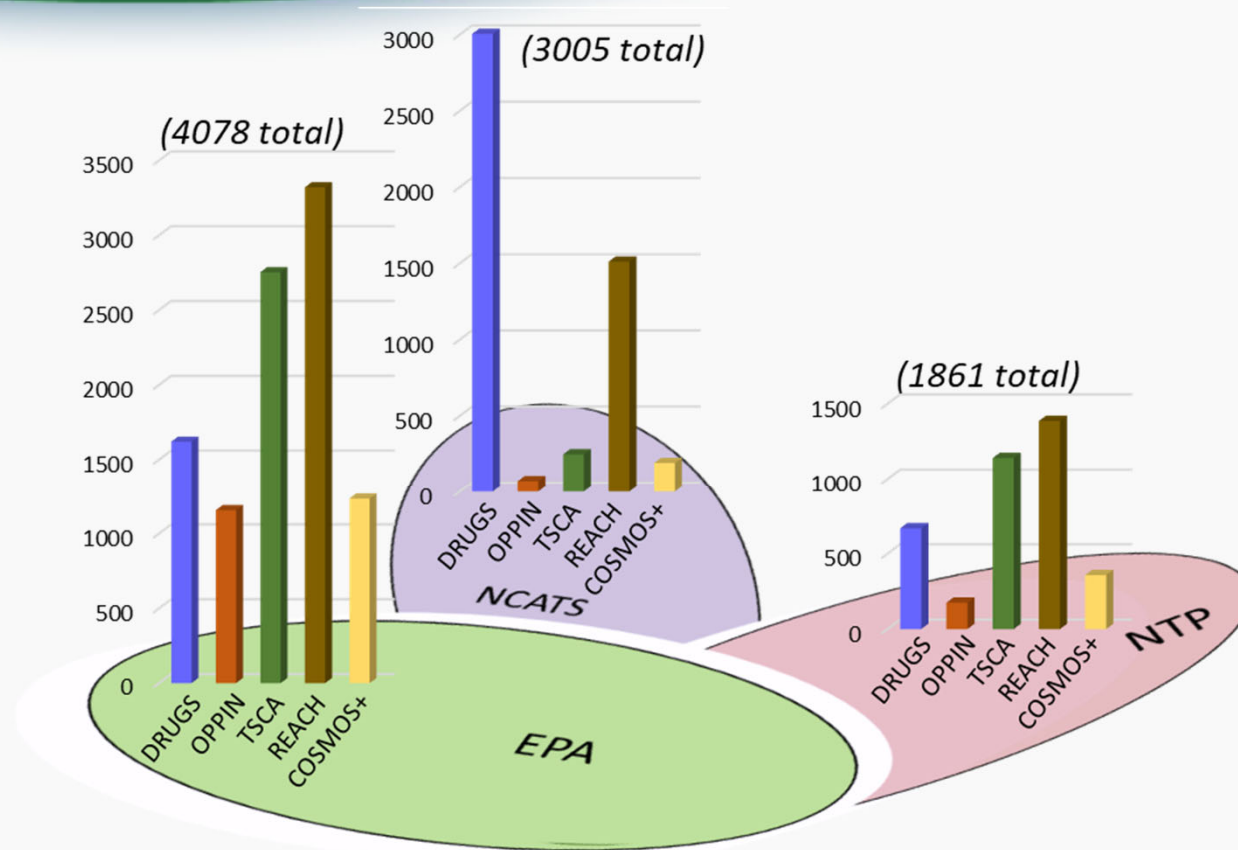
Does salt form matter?



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



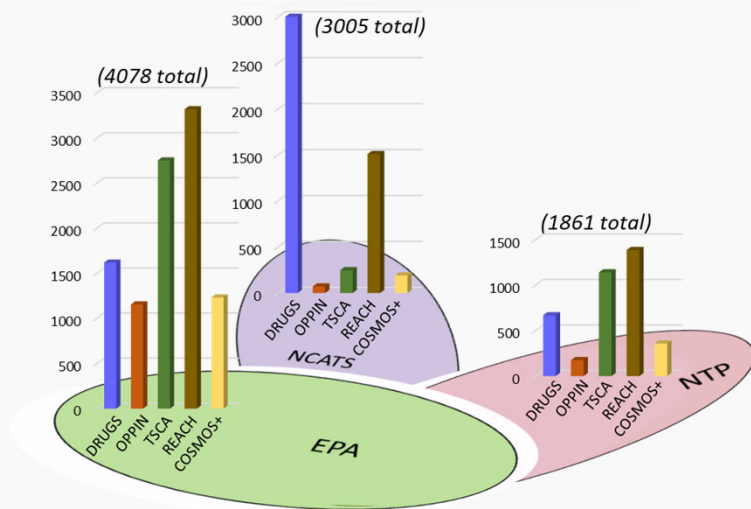
Regulatory Use-List Coverage



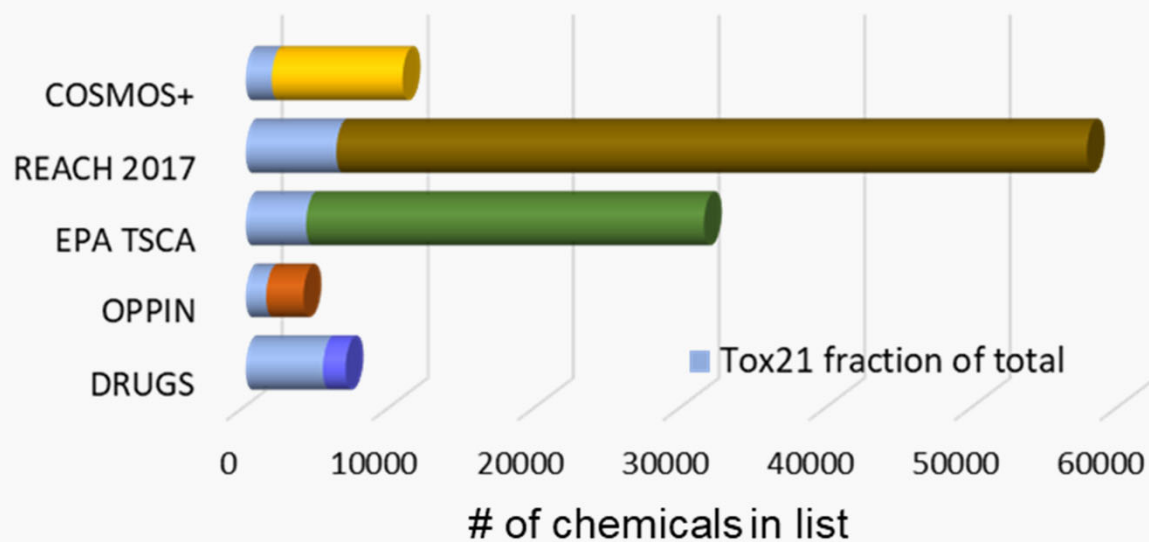
Drugs
OPPIN
TSCA
REACH
COSMOS+

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

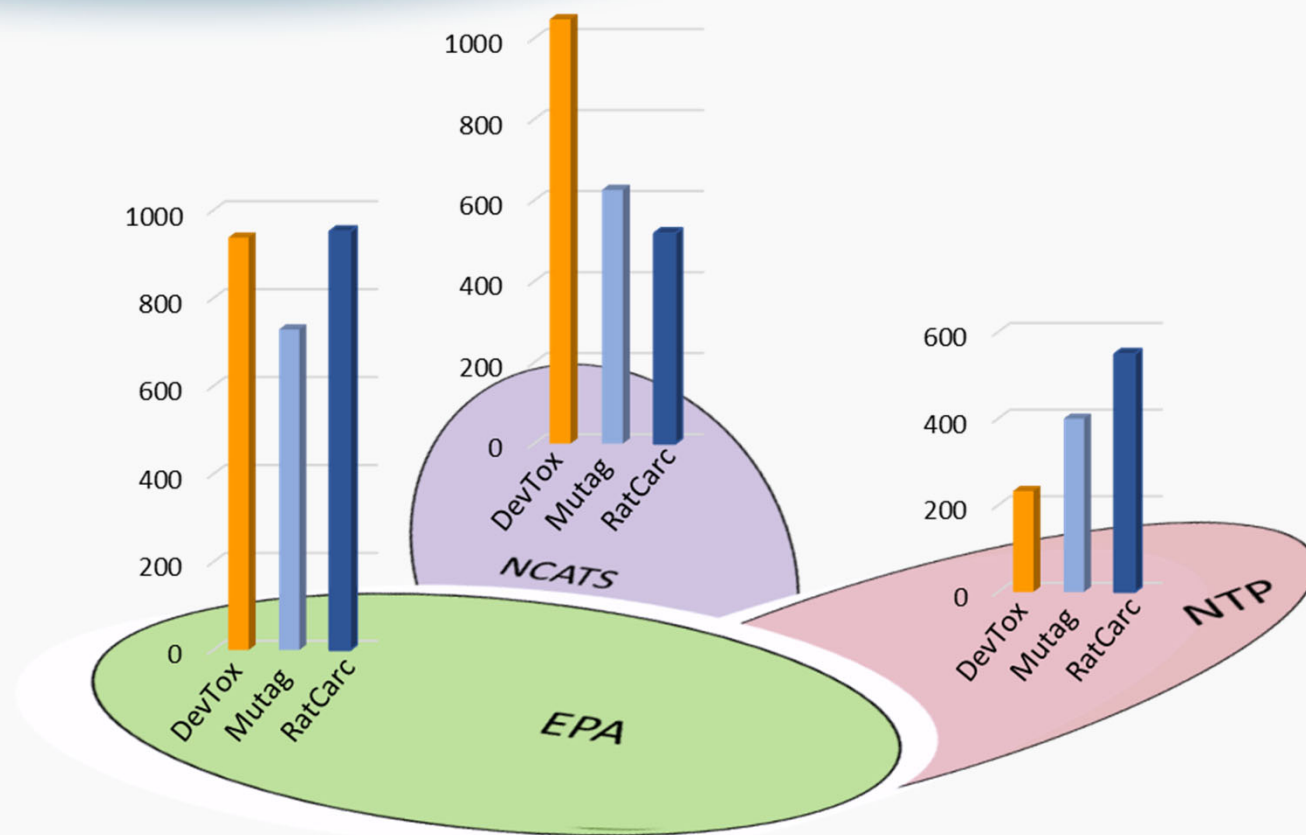
Regulatory Use-List Coverage



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

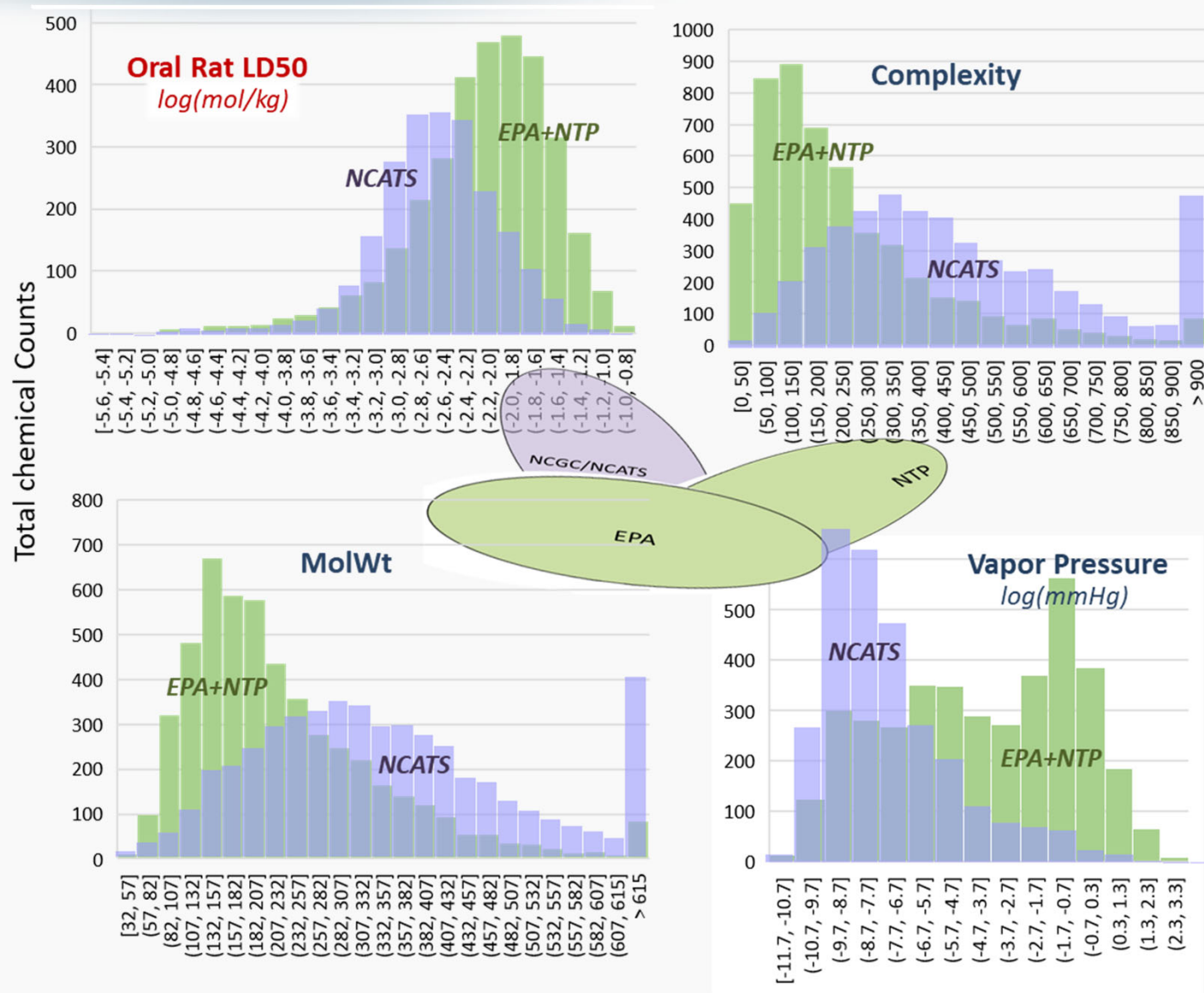


DevTox
Mutag
RatCarc

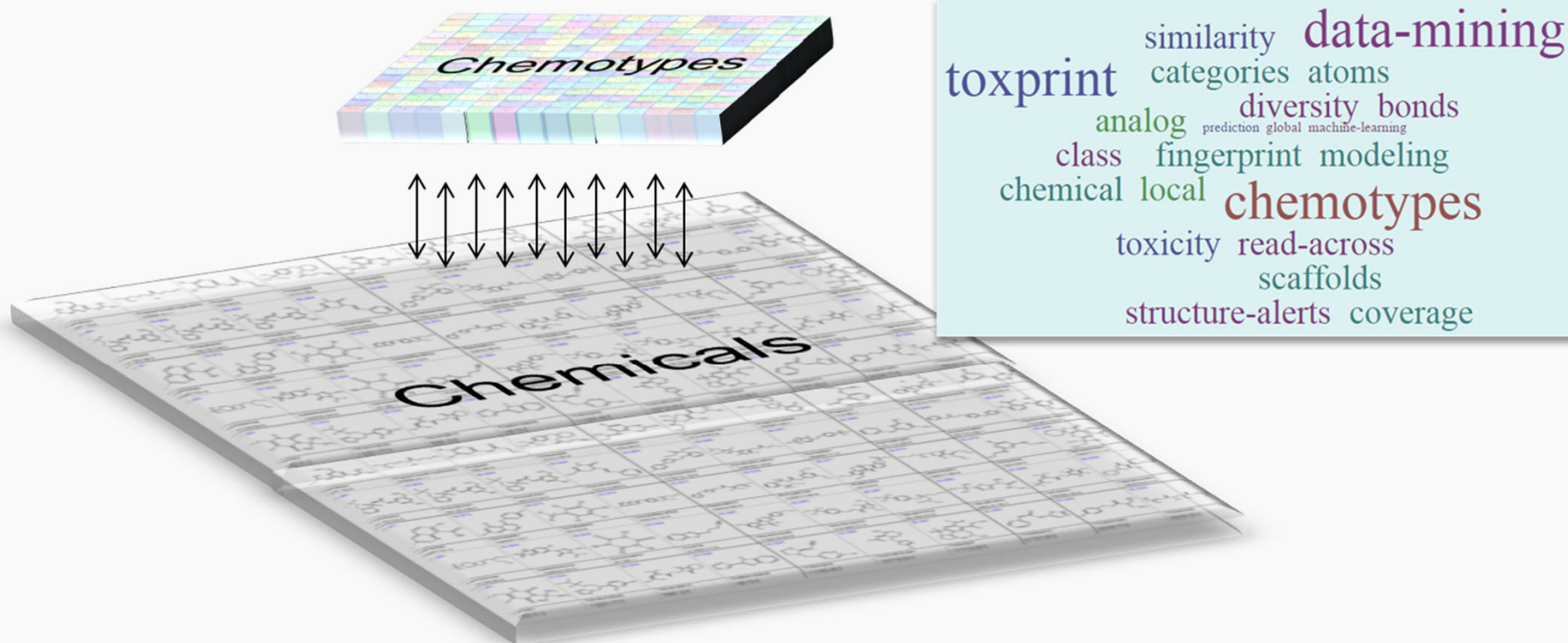
Developmental Toxicity (predicted from EPA T.E.S.T. model*)
Mutagenicity (predicted from EPA T.E.S.T. model*)
Rodent Carcinogenicity (predicted from LHASA Derek Nexus)

* 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"



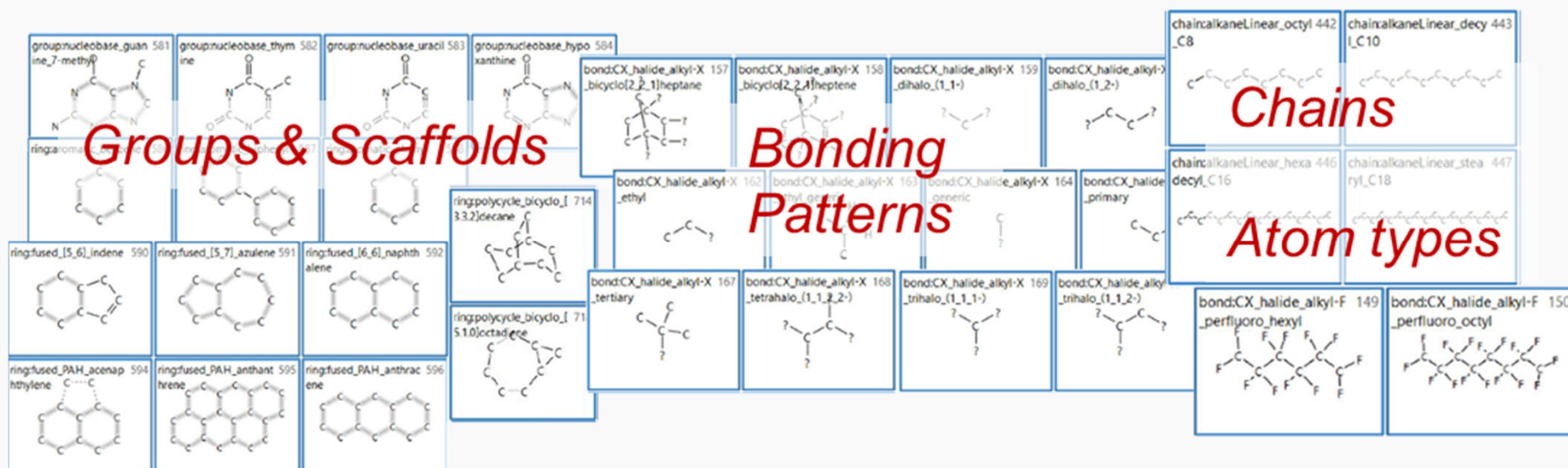
“Chemotype” (CT) profiling of the Tox21 library



ToxPrints: A public set of chemotypes

<http://www.toxprint.org>

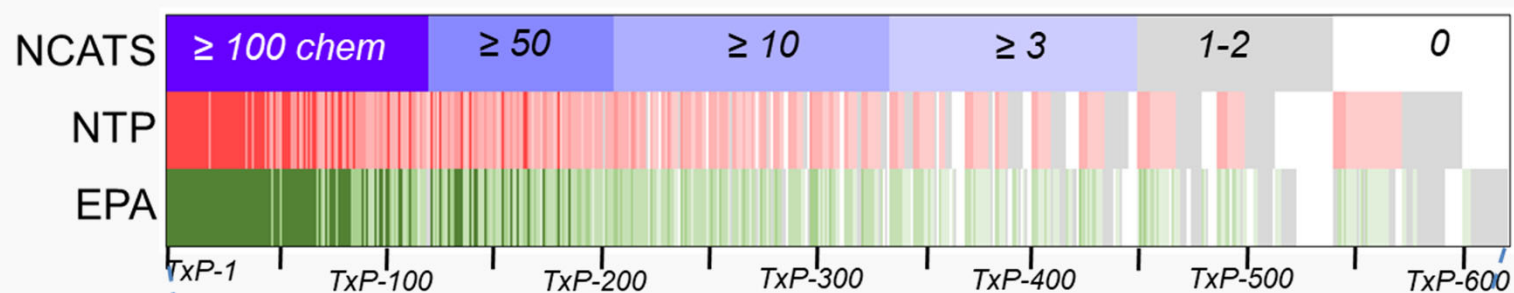
729 structural features important to EPA & FDA's "chemical exposure" landscape and safety assessment workflow



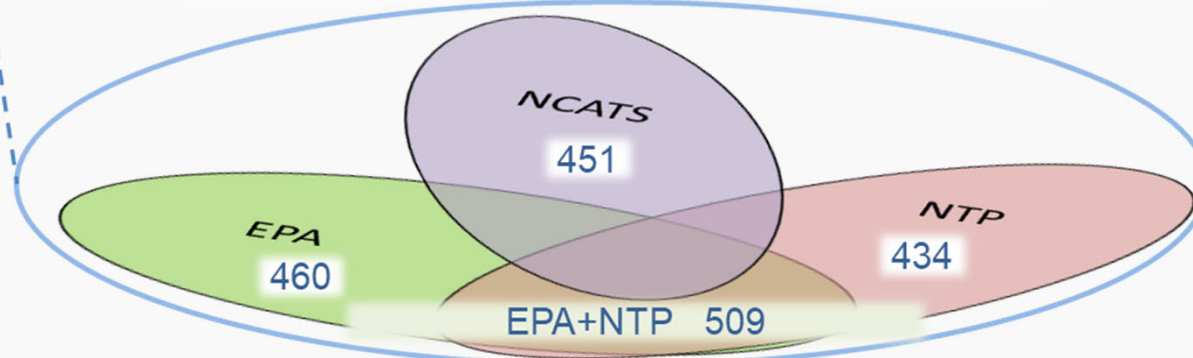
Yang et al. (2015). New publicly available chemical query language, CSRML, to support chemotype representations for application to data mining and modeling. *Journal of chemical information and modeling*, 55(3), 510-528.

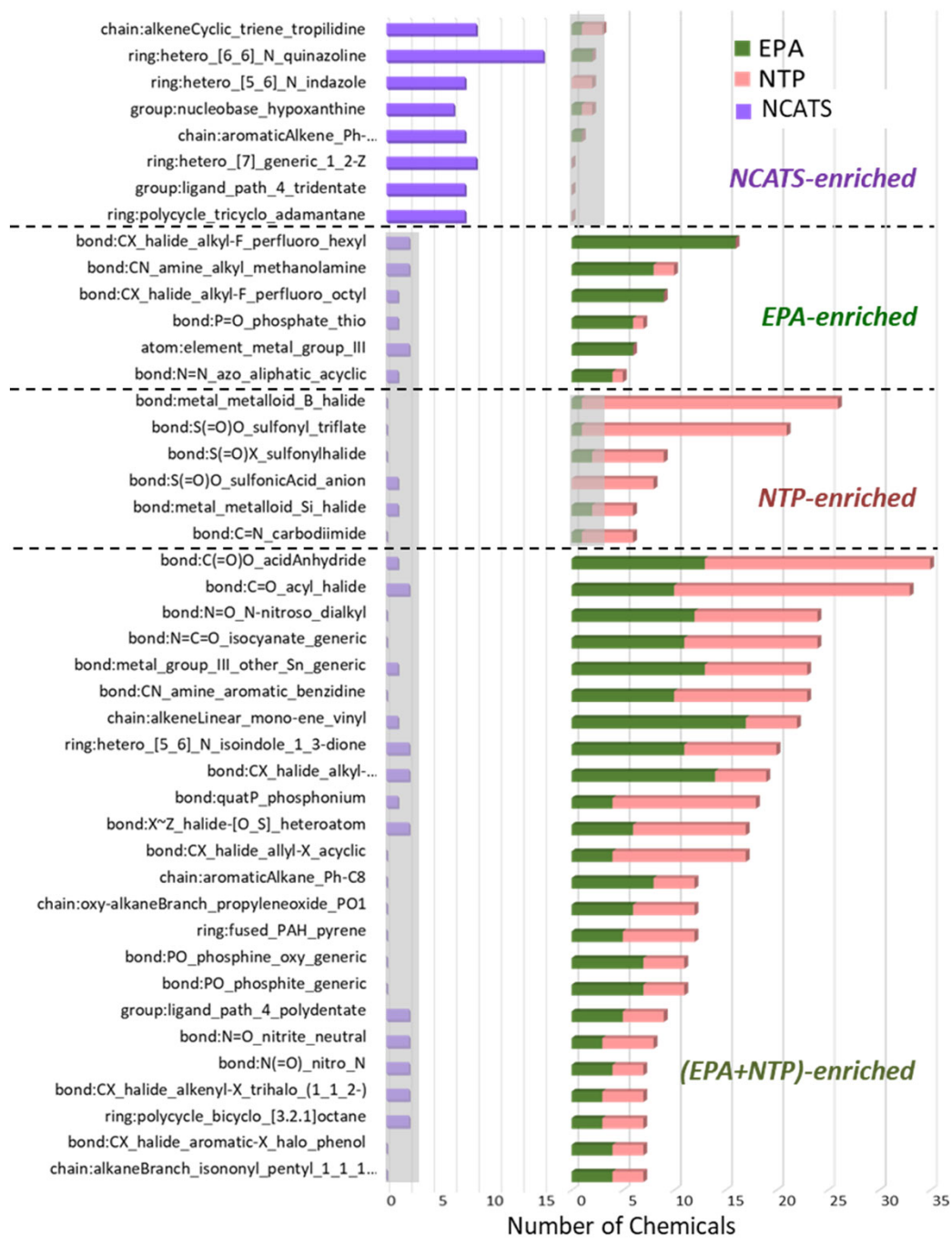
Tox21 Library Profiling: *Structural Diversity & Coverage*

624/729 ToxPrints "hit" ≥ 1 chemical

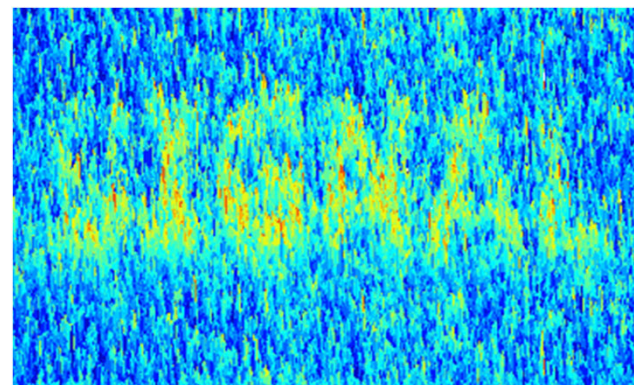


550 unique ToxPrints hit ≥ 3 chemicals



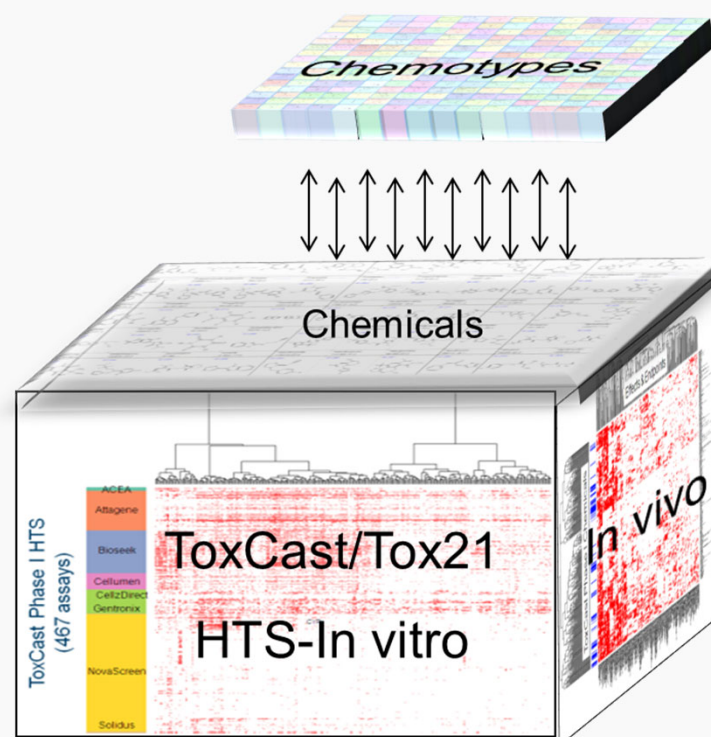


Tox21 Library Profiling: ToxPrint chemotype (CT) enrichments





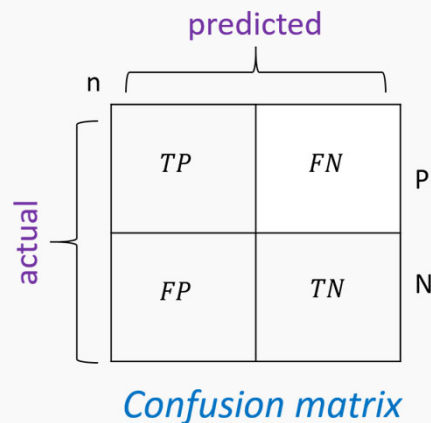
Let's view the Tox21 chemical-assay space
thru a "chemotype lens"



Computing CT-Assay “Enrichments”

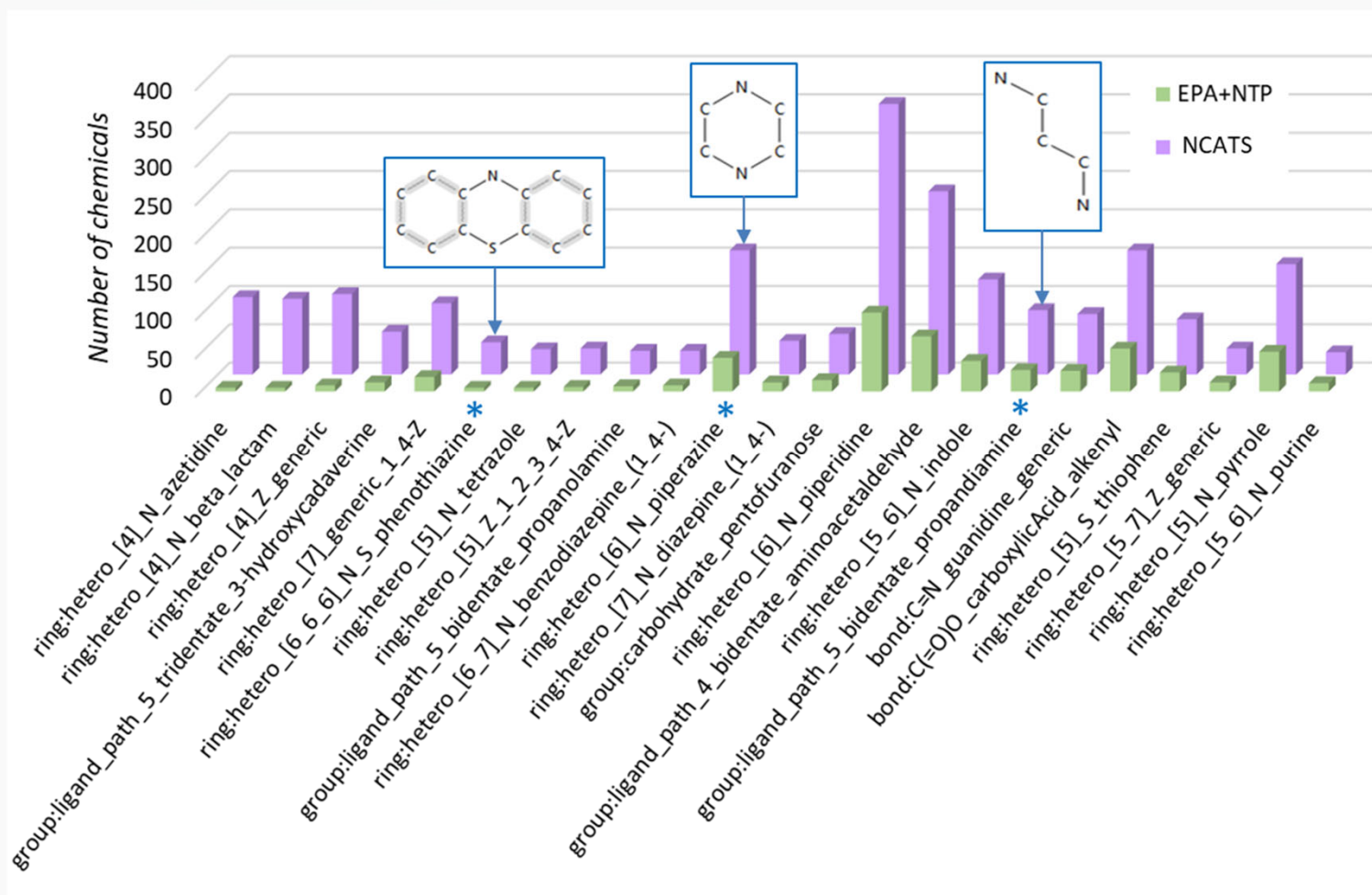
Simple statistical thresholds & filters of significance:

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

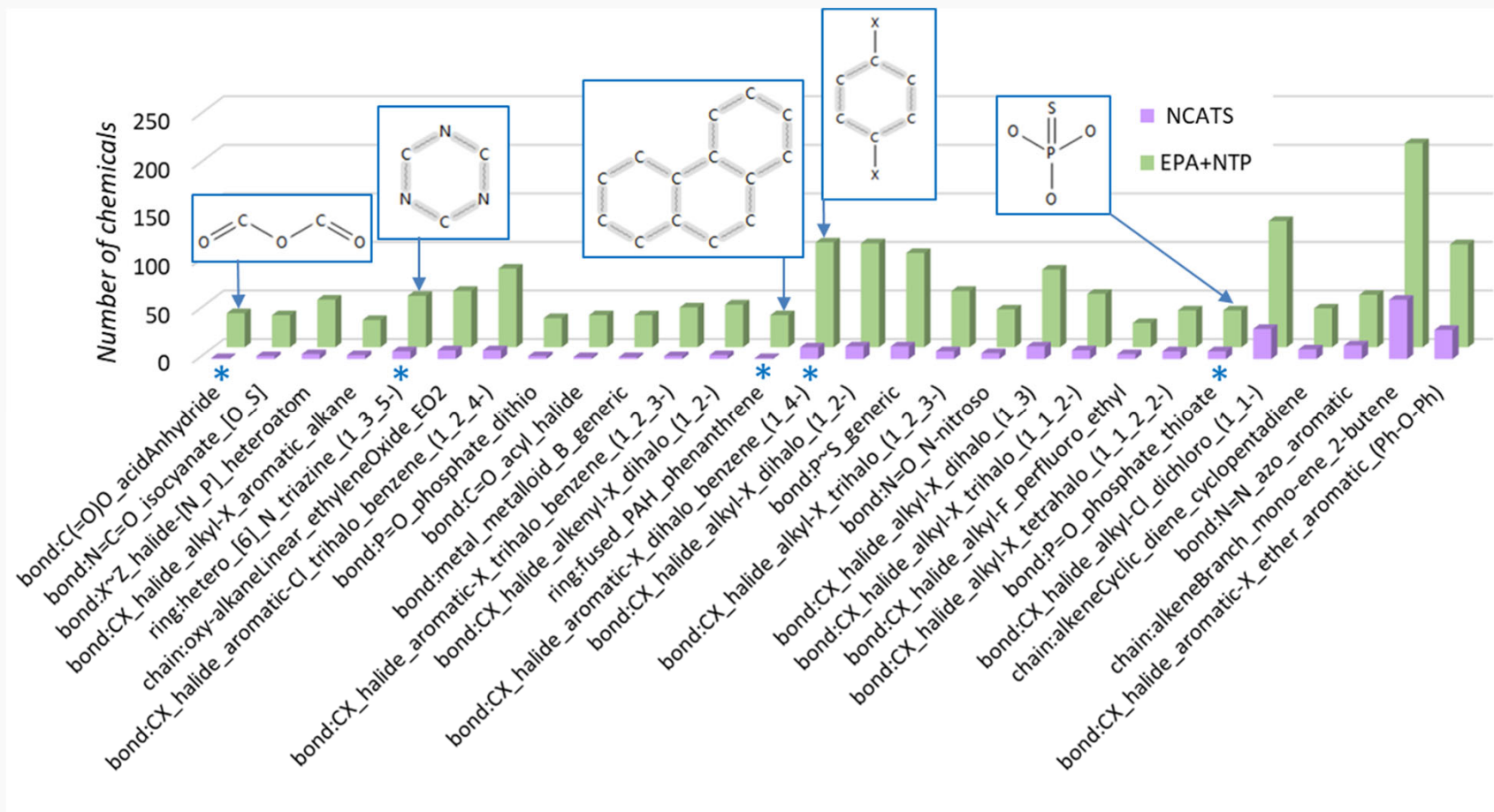


- Odds Ratio ≥ 3 , *conveys simple fractional enrichment*
- Fischer's exact p value ≤ 0.05 , *compensates for size of dataset*
- T_{pos} (TP) ≥ 3 , *require at least 3 chemicals with CT in Positives*

CT Profile & Assay “Enrichments”

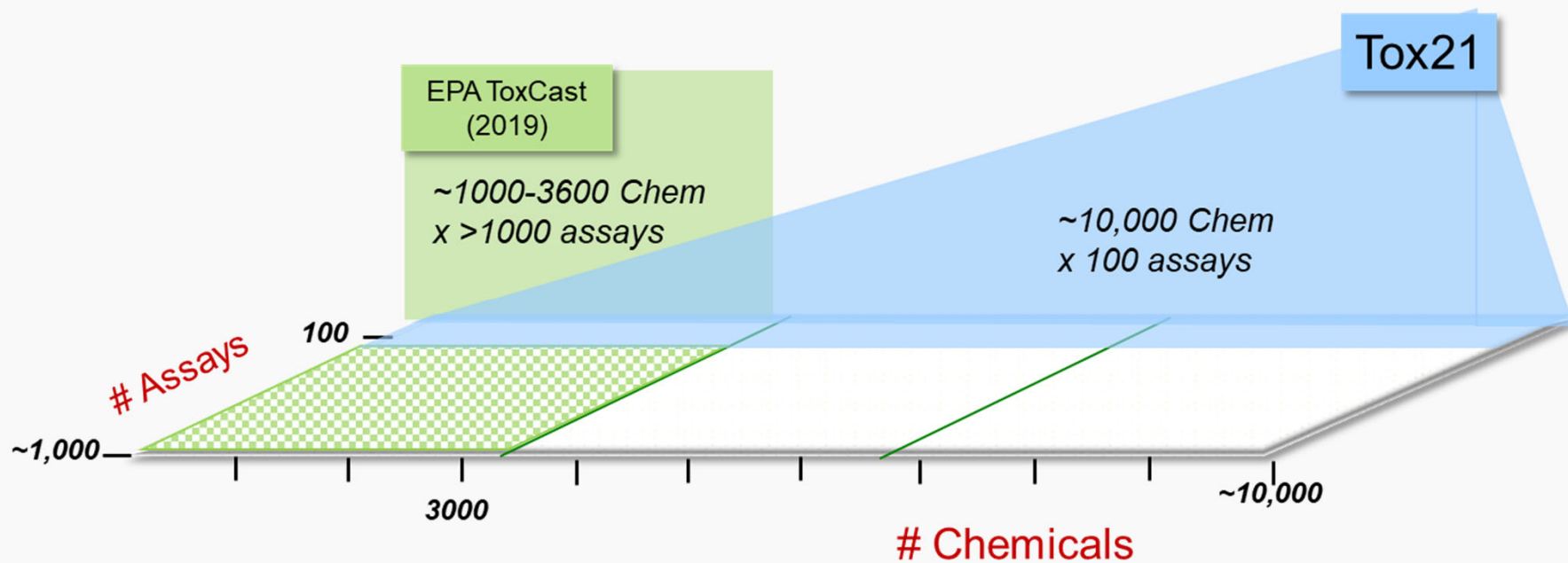


CT Profile & Assay “Enrichments”

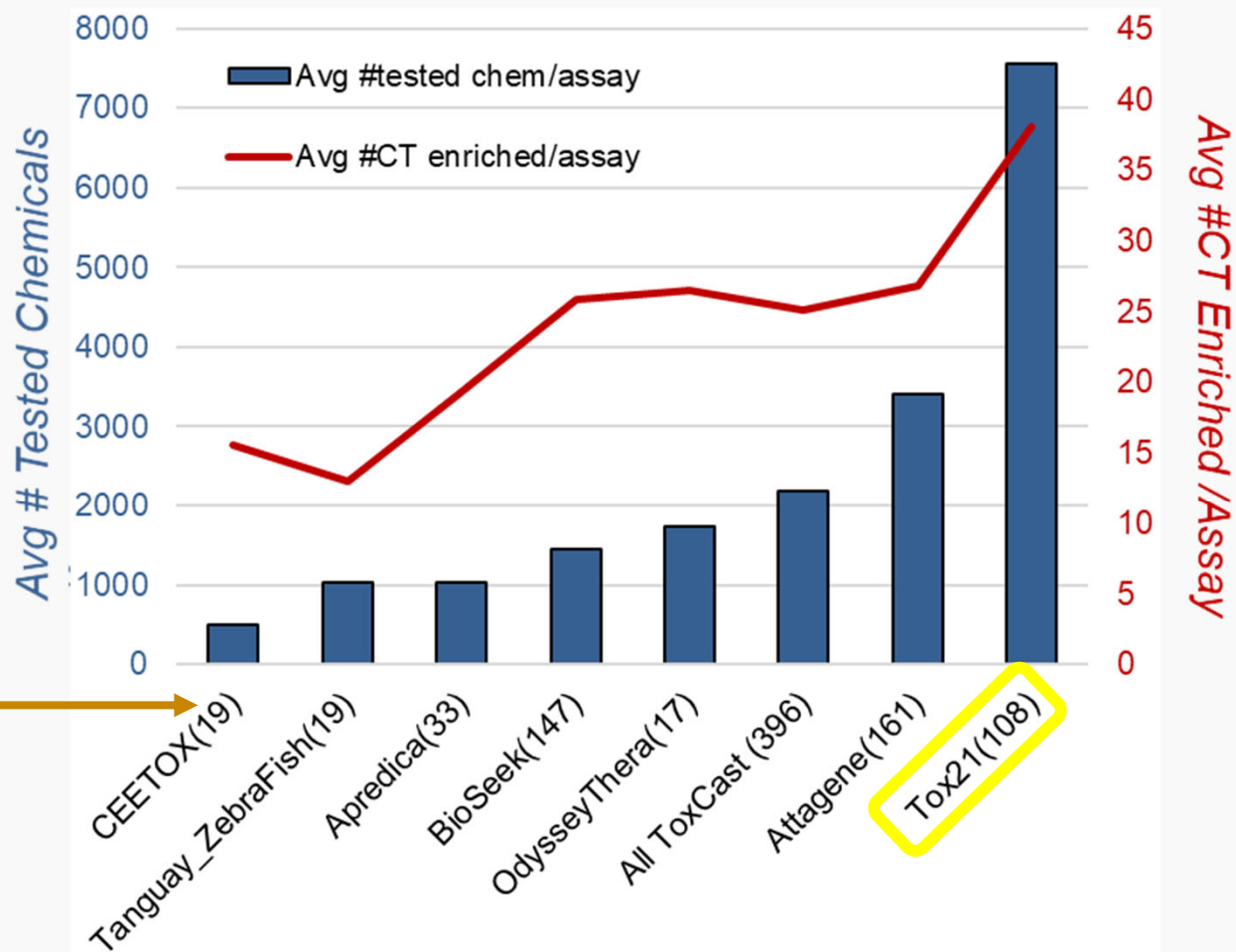


BONUS

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

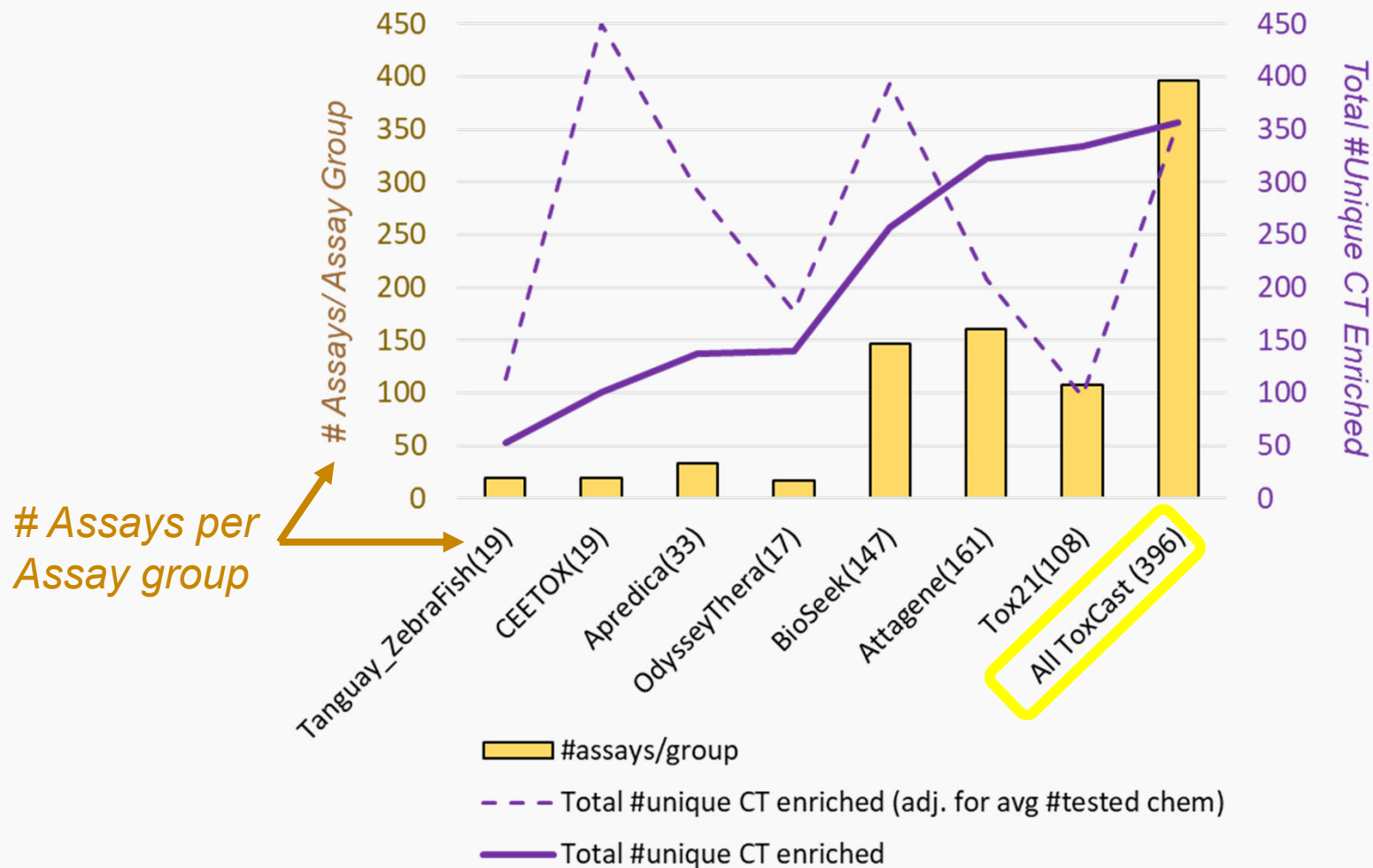


Test Set Size Matters!



Assays per Assay group

CT Profile & Assay “Enrichments”



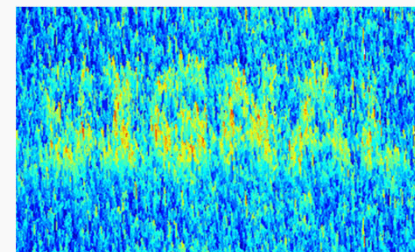
Tox21 Data Analysis Challenge



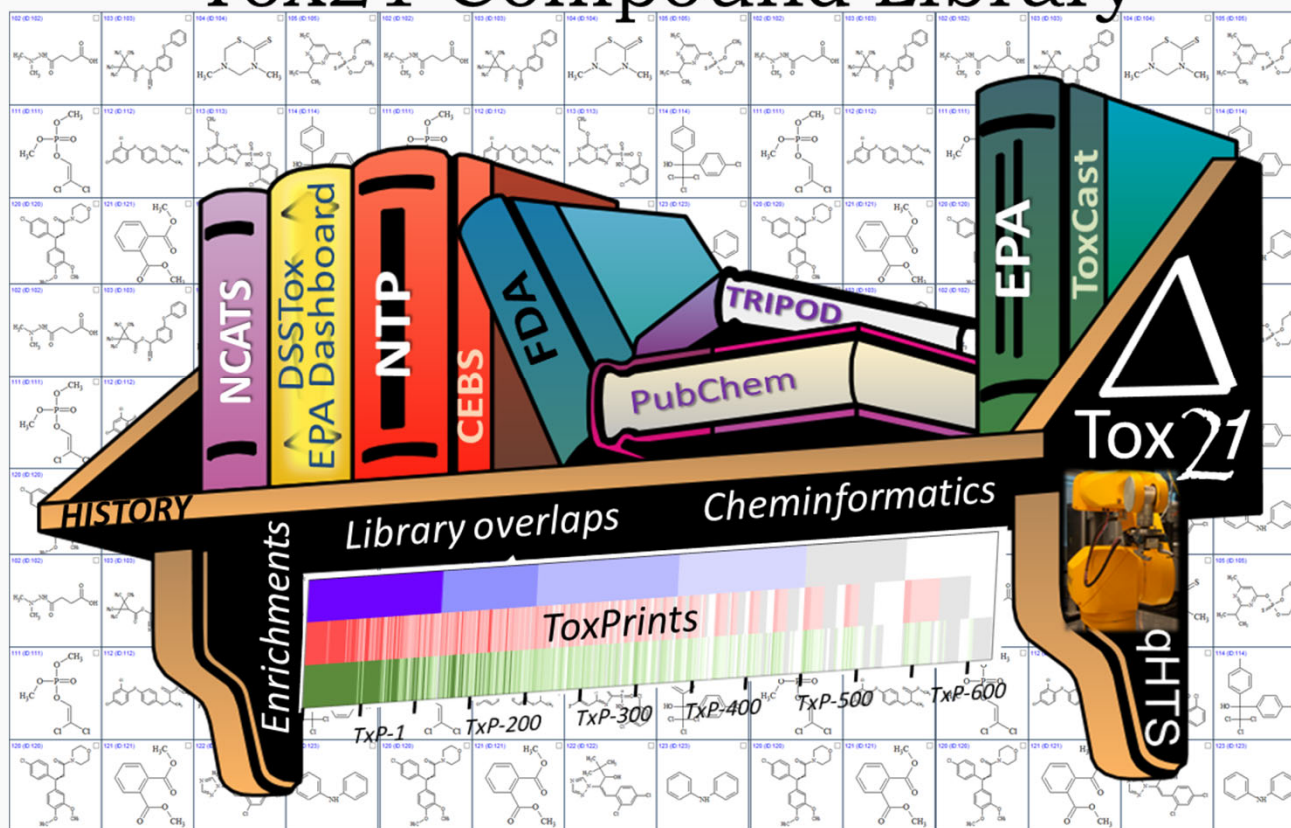
ToxPrints & CT =
enrichments



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



EPA Tox21: Leadership & Chemical Library Team

NCGC/NCATS Tox21: Leadership & Chemical Library Team

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.