Advancing Non-Targeted Analysis of Xenobiotics in Environmental & Biological Media

EPA United States Environmental Protection Agency

EPA's DSSTox Chemical Database: *A Resource for the Non-Targeted Testing Community*

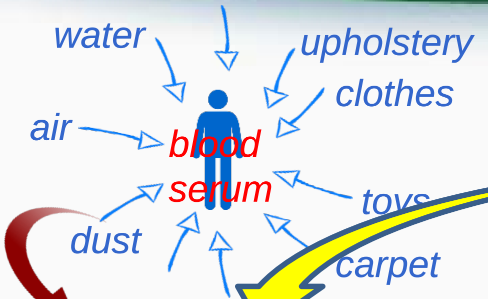
Ann Richard
National Center for Computational Toxicology
Office of Research & Development, US EPA

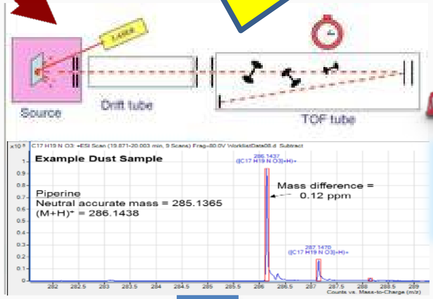
August 18-19, 2015
Research Triangle Park, NC

Outline

- ☐ Cheminformatics view of problem
- ☐ DSSTox chemical database
- ☐ ToxCast chemical library
- ☐ Tox21 analytical QC
- ☐ Challenges

Cheminformatics view of non-targeted testing problem





Thousands of mass ion peaks & abundances

What's in the sample?
&
Should I be worried?

Chemical universe

Exposure?

Toxic?

Suspect testing, physical standards

{mono-isotopic mass}

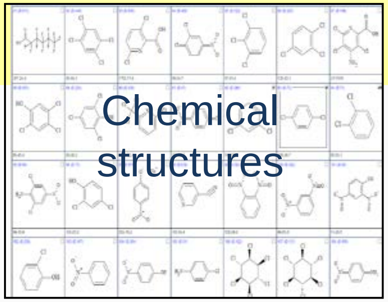
MI mass

1:many

{formulas}

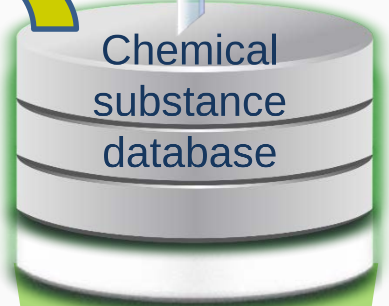
1:many

{parent structures}



Chemical structures

structure



Chemical substance database

Inventory/Data

{CAS-name}

1:1

{structure}

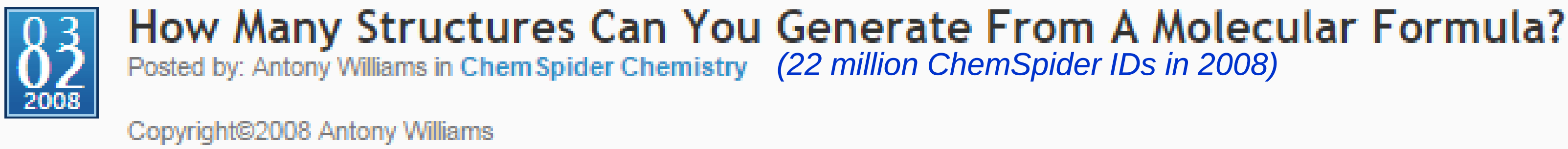
CURATION

CURATION

CURATION

How big is the problem?

http://www.chemspider.com/blog/



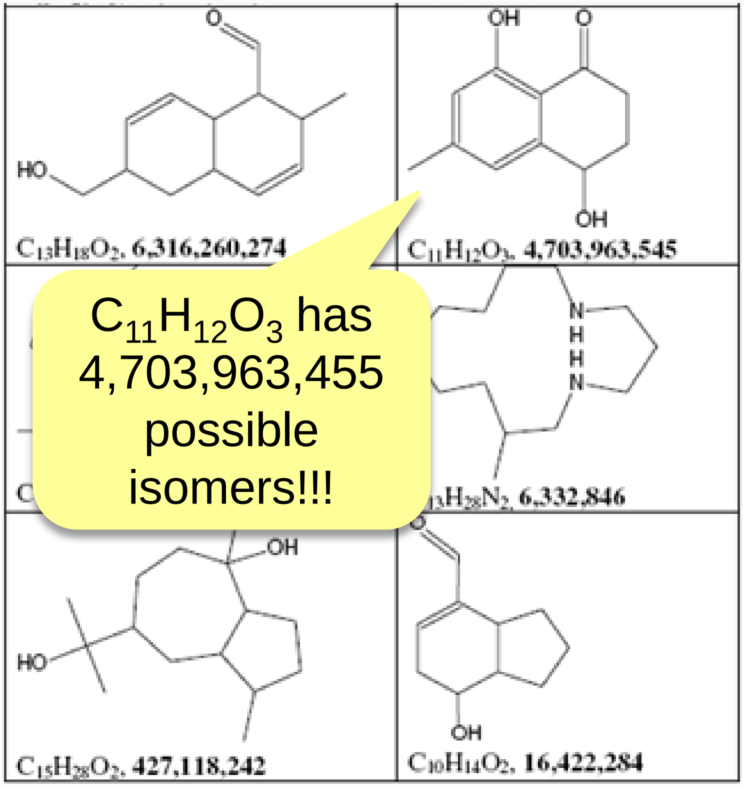
03 02 2008

How Many Structures Can You Generate From A Molecular Formula?

Posted by: Antony Williams in ChemSpider Chemistry

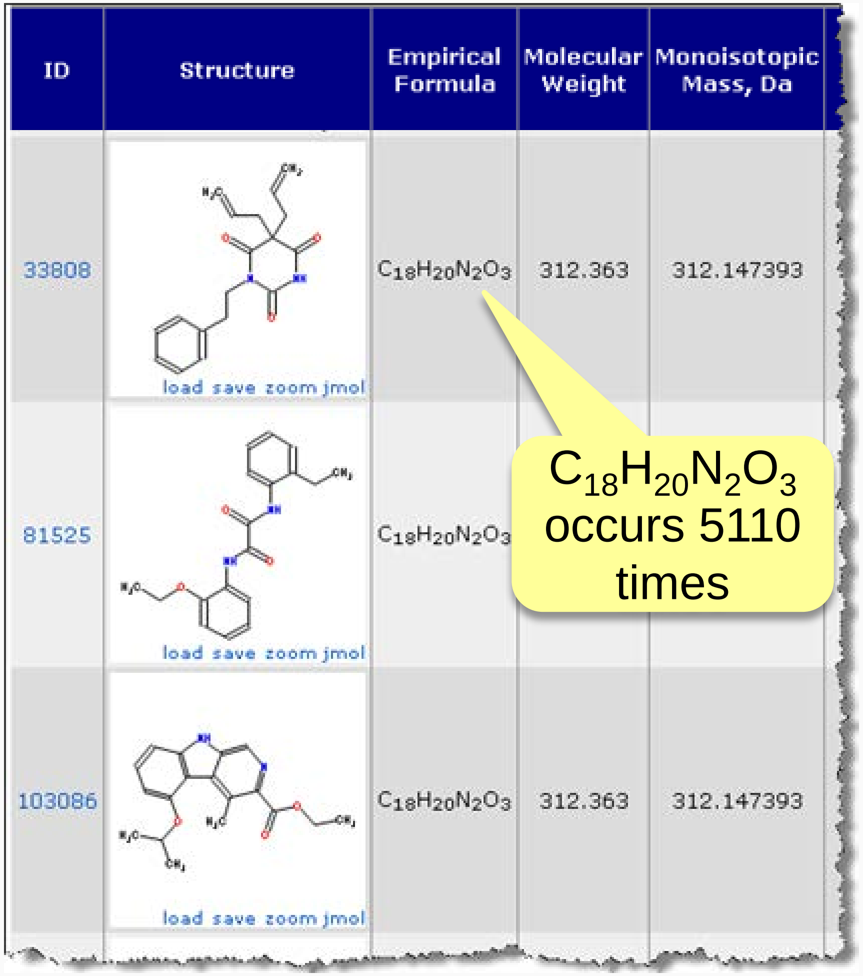
(22 million ChemSpider IDs in 2008)

Theoretically…


O
OH
O
HO
OH
$C_{13}H_{18}O_2$, 6,316,260,274
$C_{11}H_{12}O_3$, 4,703,963,545
N
H
H
N
$C_{13}H_{28}N_2$, 6,332,846
OH
HO
O
OH
$C_{15}H_{28}O_2$, 427,118,242
$C_{10}H_{14}O_2$, 16,422,284

$C_{11}H_{12}O_3$ has 4,703,963,455 possible isomers!!!

Highest frequency formula ChemSpider?



ID	Structure	Empirical Formula	Molecular Weight	Monoisotopic Mass, Da
33808	load save zoom jmol	$C_{18}H_{20}N_2O_3$	312.363	312.147393
81525	load save zoom jmol	$C_{18}H_{20}N_2O_3$	[illegible]	[illegible]
103086	load save zoom jmol	$C_{18}H_{20}N_2O_3$	312.363	312.147393

$C_{18}H_{20}N_2O_3$ occurs 5110 times

How big is the problem?

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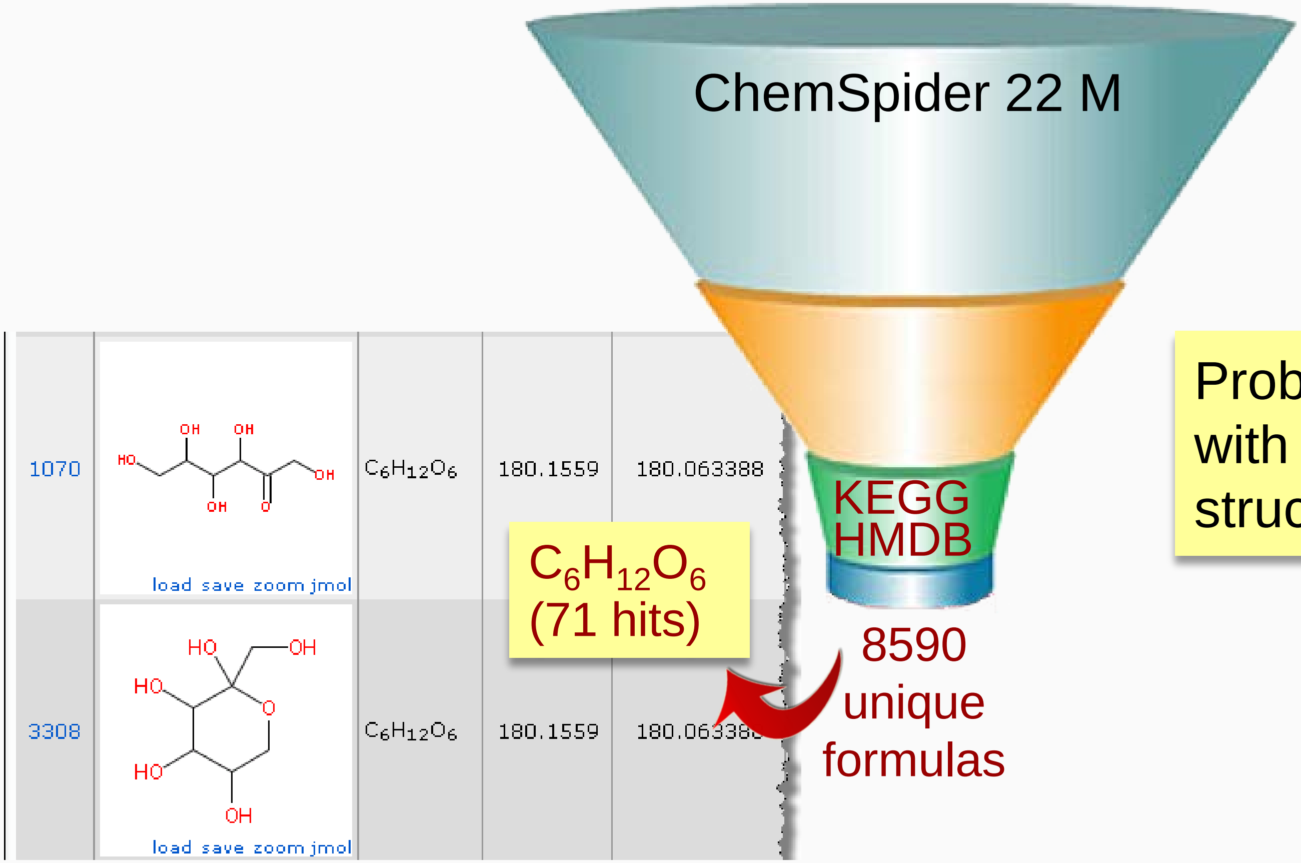


ChemSpider 22 M

KEGG
HMDB

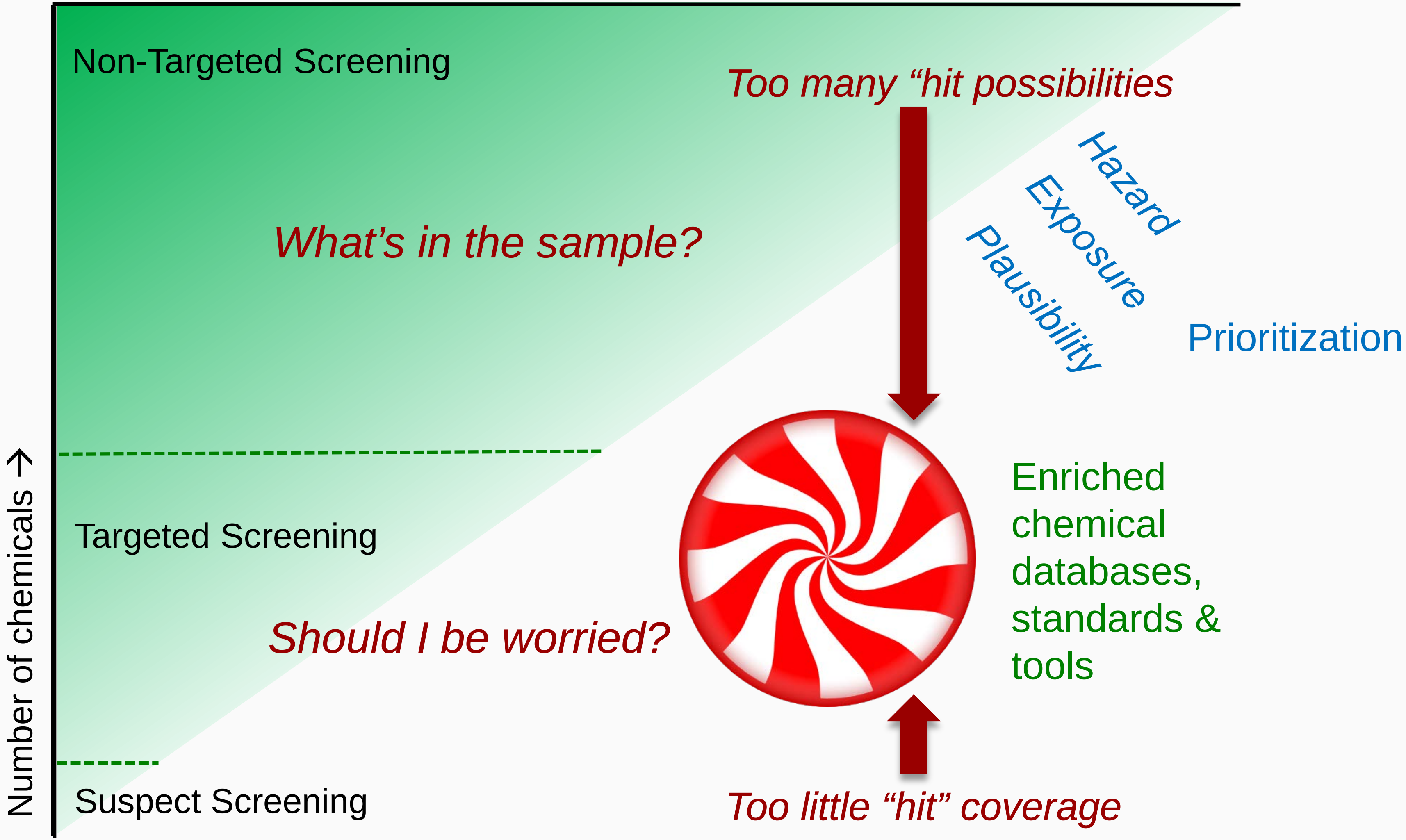
8590 unique formulas

$C_6H_{12}O_6$ (71 hits)

1070	load save zoom jmol	$C_6H_{12}O_6$	180.1559	180.063388
3308	load save zoom jmol	$C_6H_{12}O_6$	180.1559	180.06338

Problem too big to solve with formula matching & structure enumeration

Cheminformatics view of non-targeted testing problem



Non-Targeted Screening

What’s in the sample?

Targeted Screening

Should I be worried?

Suspect Screening

Number of chemicals →

Too many “hit possibilities

Hazard

Exposure

Plausibility

Prioritization

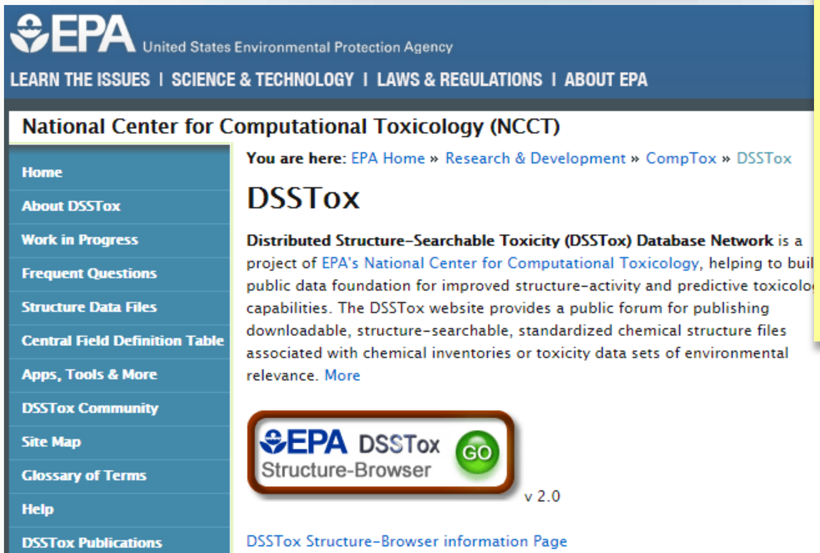
Enriched chemical databases, standards & tools

Too little “hit” coverage

DSSTox_v1 (thru 3/2014)

http://www.epa.gov/ncct/dsstox/

- Original target audience: Structure-Activity Relationship (SAR) toxicity modeling community
- Focus on EPA, HPV, environmental toxicity datasets
- Emphasis on accurate CAS-name-structure annotations at substance level
- Public resource for high-quality structure-data files



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National Center for Computational Toxicology (NCCT)

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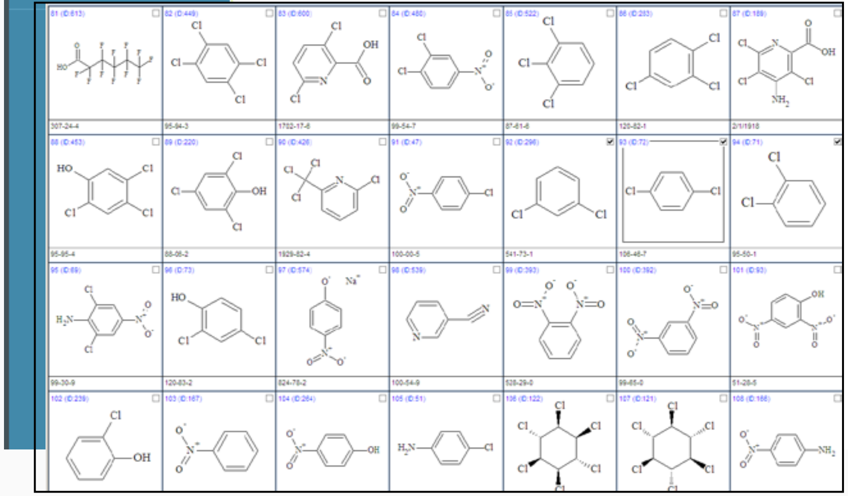
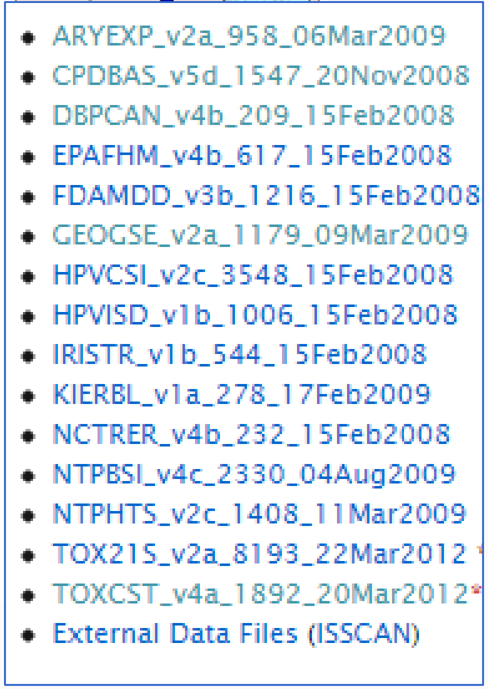
DSSTox

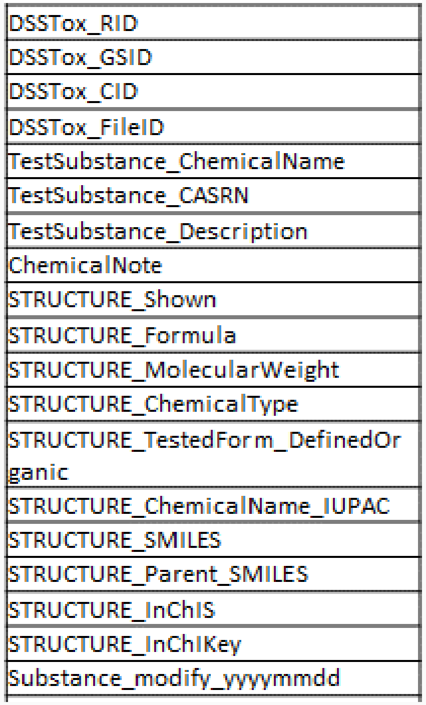
Distributed Structure-Searchable Toxicity (DSSTox) Database Network is a project of EPA's National Center for Computational Toxicology, helping to buil public data foundation for improved structure-activity and predictive toxicolo capabilities. The DSSTox website provides a public forum for publishing downloadable, structure-searchable, standardized chemical structure files associated with chemical inventories or toxicity data sets of environmental relevance. More

DSSTox Structure-Browser information Page





- ARYEXP_v2a_958_06Mar2009
- CPDBAS_v5d_1547_20Nov2008
- DBPCAN_v4b_209_15Feb2008
- EPAFHM_v4b_617_15Feb2008
- FDAMDD_v3b_1216_15Feb2008
- GEOGSE_v2a_1179_09Mar2009
- HPVCSI_v2c_3548_15Feb2008
- HPVISD_v1b_1006_15Feb2008
- IRISTR_v1b_544_15Feb2008
- KIERBL_v1a_278_17Feb2009
- NCTRER_v4b_232_15Feb2008
- NTPBSI_v4c_2330_04Aug2009
- NTPHTS_v2c_1408_11Mar2009
- TOX21S_v2a_8193_22Mar2012
- TOXCST_v4a_1892_20Mar2012*
- External Data Files (ISSCAN)

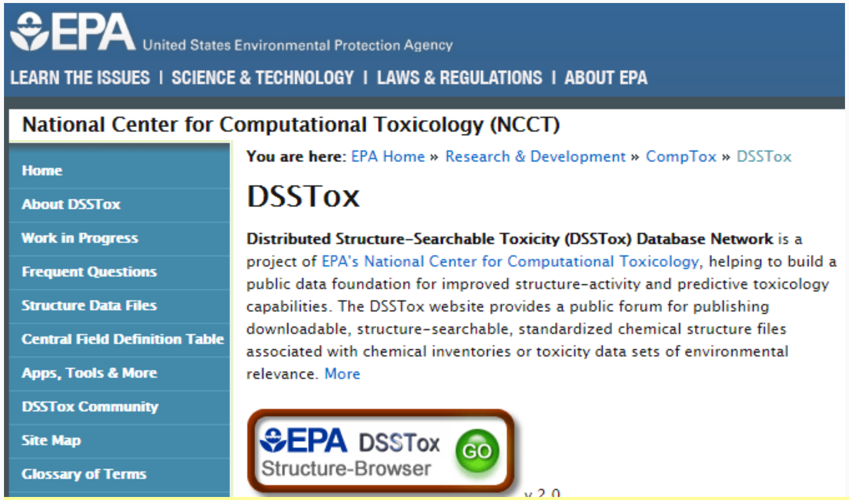


DSSTox_RID
DSSTox_GSID
DSSTox_CID
DSSTox_FileID
TestSubstance_ChemicalName
TestSubstance_CASRN
TestSubstance_Description
ChemicalNote
STRUCTURE_Shown
STRUCTURE_Formula
STRUCTURE_MolecularWeight
STRUCTURE_ChemicalType
STRUCTURE_TestedForm_DefinedOrganic
STRUCTURE_ChemicalName_IUPAC
STRUCTURE_SMILES
STRUCTURE_Parent_SMILES
STRUCTURE_InChIS
STRUCTURE_InChIKey
Substance_modify_yyyymmdd

Approx. 25K CAS-substances, 16K structures

DSSTox Update

DSSTox_v1



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DSSTox

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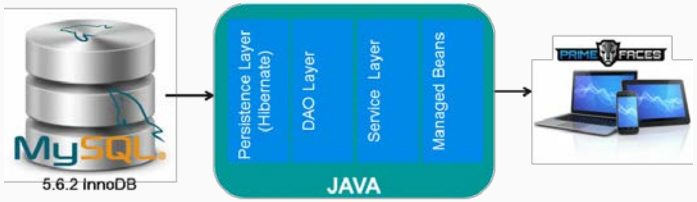
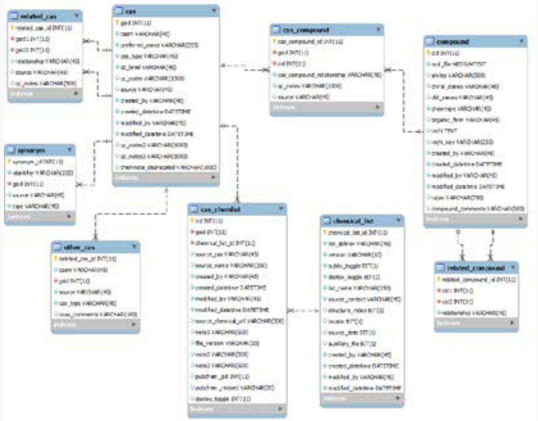
- Website to be retired 9/30/2015
- DSSTox_v1 files & documentation will remain available on EPA ftp site
- Original 25K substance records stored in MS ACCESS and Excel tables serve as the initial Level 1,2 input to DSSTox_v2

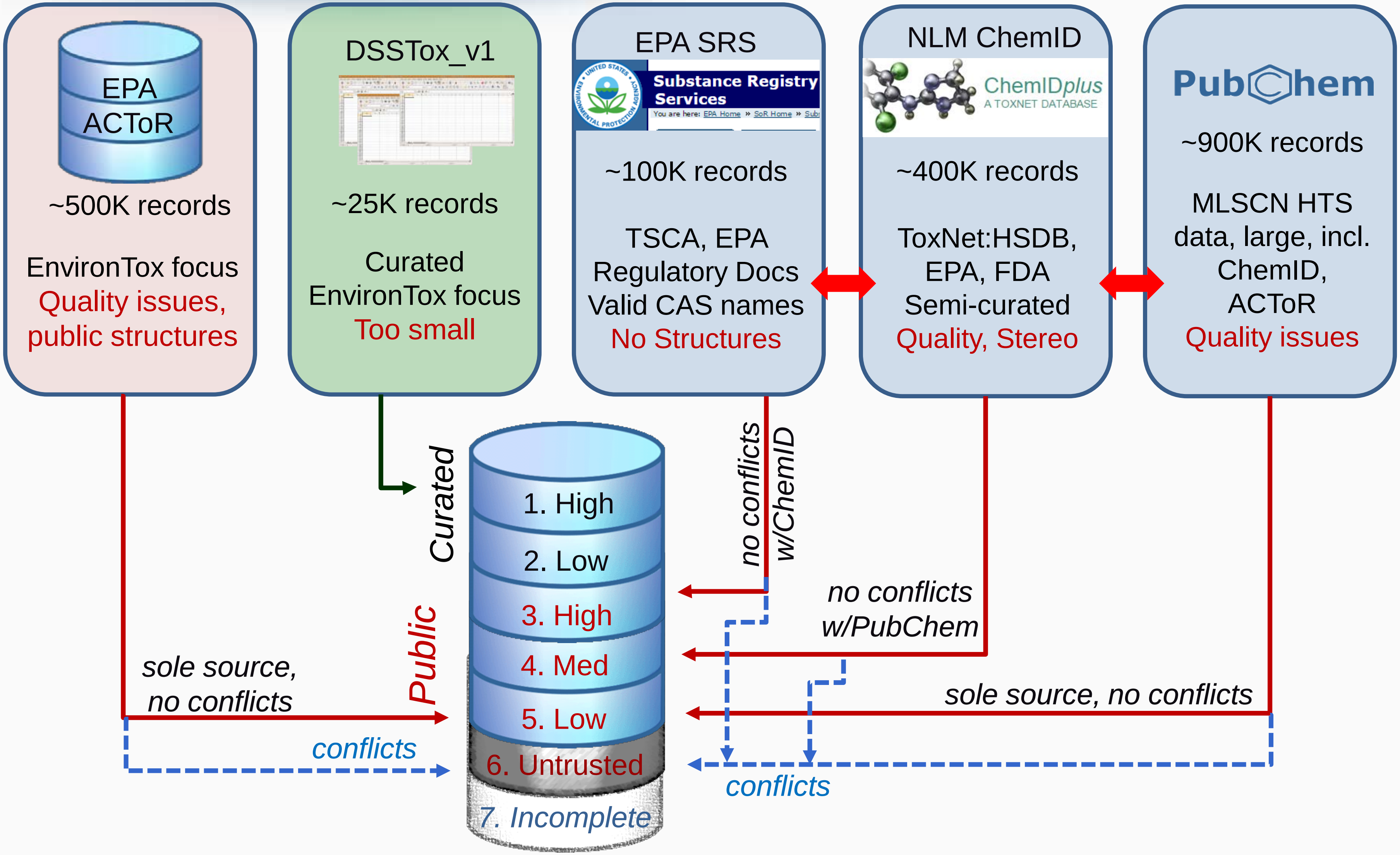
DSSTox_v2

- Convert DSSTox tables to MySQL
- Develop curation interface
- Implement cheminformatics workflow
- Expand chemical content
- Register ACToR data inventories
- Web-services & Dashboard access





DSSTox_v2 CAS-Structure Sources: QC levels


Substance Registry Services
You are here: EPA Home » SoR Home » Sub
ChemIDplus
A TOXNET DATABASE
PubChem

EPA ACToR

~500K records

EnvironTox focus

Quality issues, public structures

DSSTox_v1

~25K records

Curated EnvironTox focus

Too small

EPA SRS

~100K records

TSCA, EPA Regulatory Docs

Valid CAS names

No Structures

NLM ChemID

~400K records

ToxNet:HSDB, EPA, FDA

Semi-curated

Quality, Stereo

PubChem

~900K records

MLSCN HTS data, large, incl. ChemID, ACToR

Quality issues

Curated

Public

1. High
2. Low
3. High
4. Med
5. Low
6. Untrusted
7. *Incomplete*

no conflicts w/ChemID

no conflicts w/PubChem

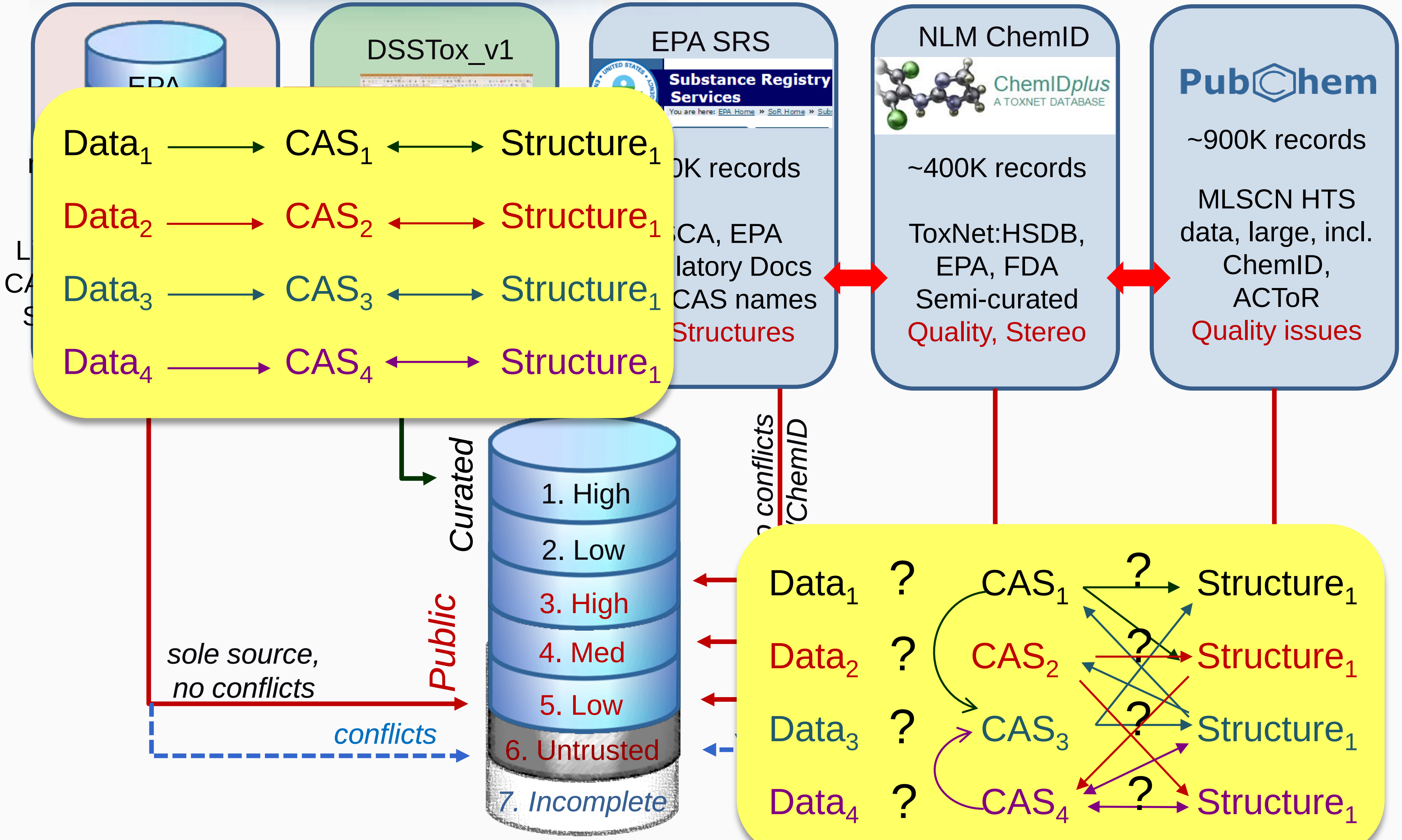
sole source, no conflicts

sole source, no conflicts

conflicts

conflicts

DSSTox_v2 CAS-Structure Sources: QC levels



EPA

r

L
CA
S

DSSTox_v1

EPA SRS

Substance Registry Services

You are here: EPA Home » SoR Home » Sub

0K records

CA, EPA
latory Docs
CAS names
Structures

NLM ChemID

ChemIDplus
A TOXNET DATABASE

~400K records

ToxNet:HSDB,
EPA, FDA
Semi-curated
Quality, Stereo

PubChem

~900K records

MLSCN HTS
data, large, incl.
ChemID,
ACToR
Quality issues

$Data_1$ → CAS_1 ↔ $Structure_1$

$Data_2$ → CAS_2 ↔ $Structure_1$

$Data_3$ → CAS_3 ↔ $Structure_1$

$Data_4$ → CAS_4 ↔ $Structure_1$

Curated

1. High
2. Low
3. High
4. Med
5. Low
6. Untrusted
7. *Incomplete*

Public

sole source,
no conflicts

conflicts

o conflicts
/ChemID

$Data_1$? CAS_1 ? $Structure_1$

$Data_2$? CAS_2 ? $Structure_1$

$Data_3$? CAS_3 ? $Structure_1$

$Data_4$? CAS_4 ? $Structure_1$

DSSTox_v2 Construction

Data source load order:

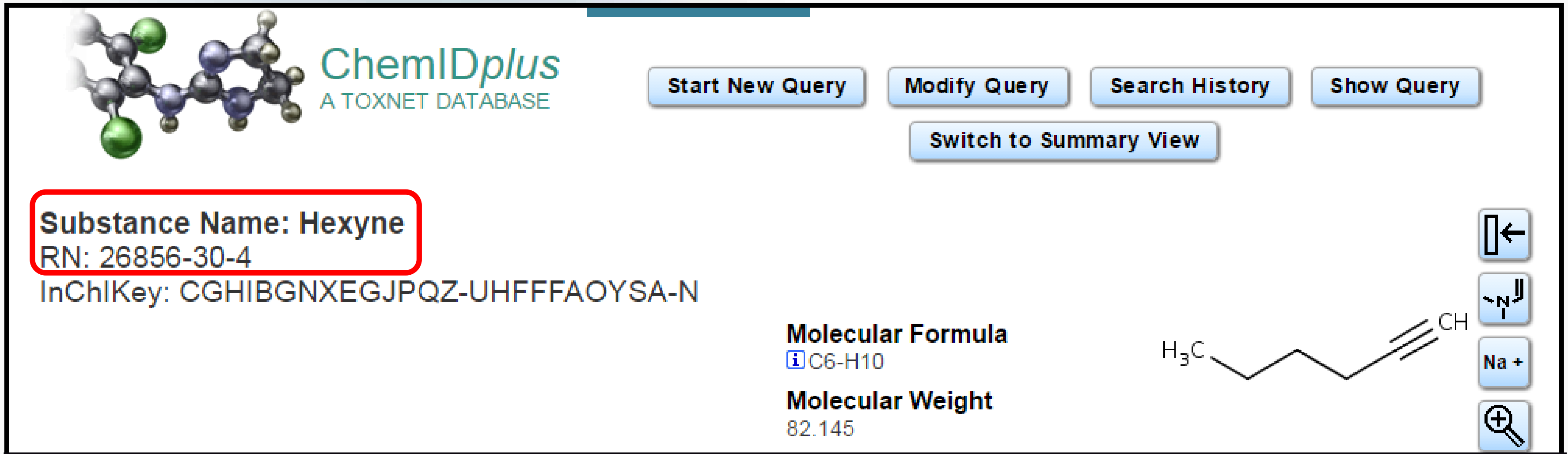
1) DSSTox_v1 (~22K)
   - ✓ 1:1 CAS-structure mappings
   - ✓ Assign NOCAS_GSID
   - ✓ Related CAS & structure mappings (e.g., NOCAS, mixtures)

2) EPA SRS (~77K)
   - ✓ *systematic name → structure conversion*
   - ✓ *internal CAS-structure conflicts (12.5%)*
   - ✓ *ChemID conflicts (24% of 30K overlaps)*
   - ✓ *DSSTox conflicts (8% of 6200 overlaps) → queue for curation*

3) ChemID (~77K)
   - ✓ *internal CAS-structure conflicts (4.5%)*
   - ✓ *PubChem conflicts (45% of 225K overlaps) … OUCH!!*
   - ✓ *DSSTox conflicts (11% of 2300 overlaps) → queue for curation*

4) And so on …

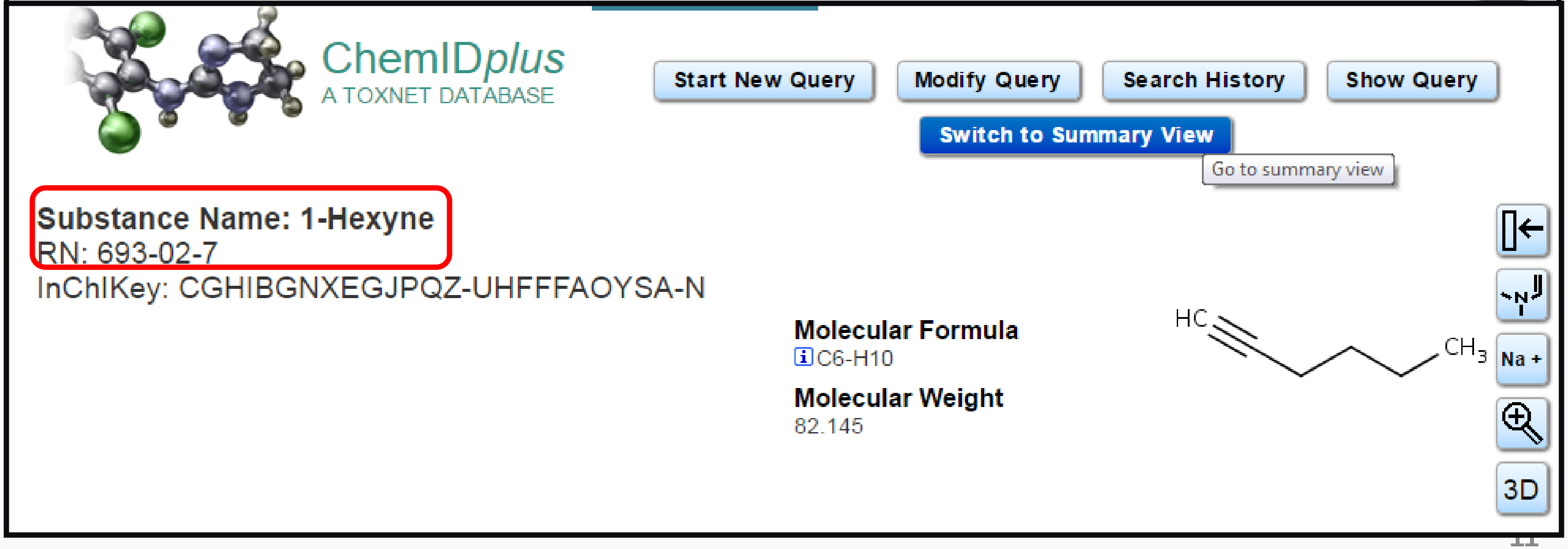
Example problem



Substance Name: Hexyne
RN: 26856-30-4
InChIKey: CGHIBGNXEGJPQZ-UHFFFAOYSA-N

Molecular Formula
C6-H10

Molecular Weight
82.145

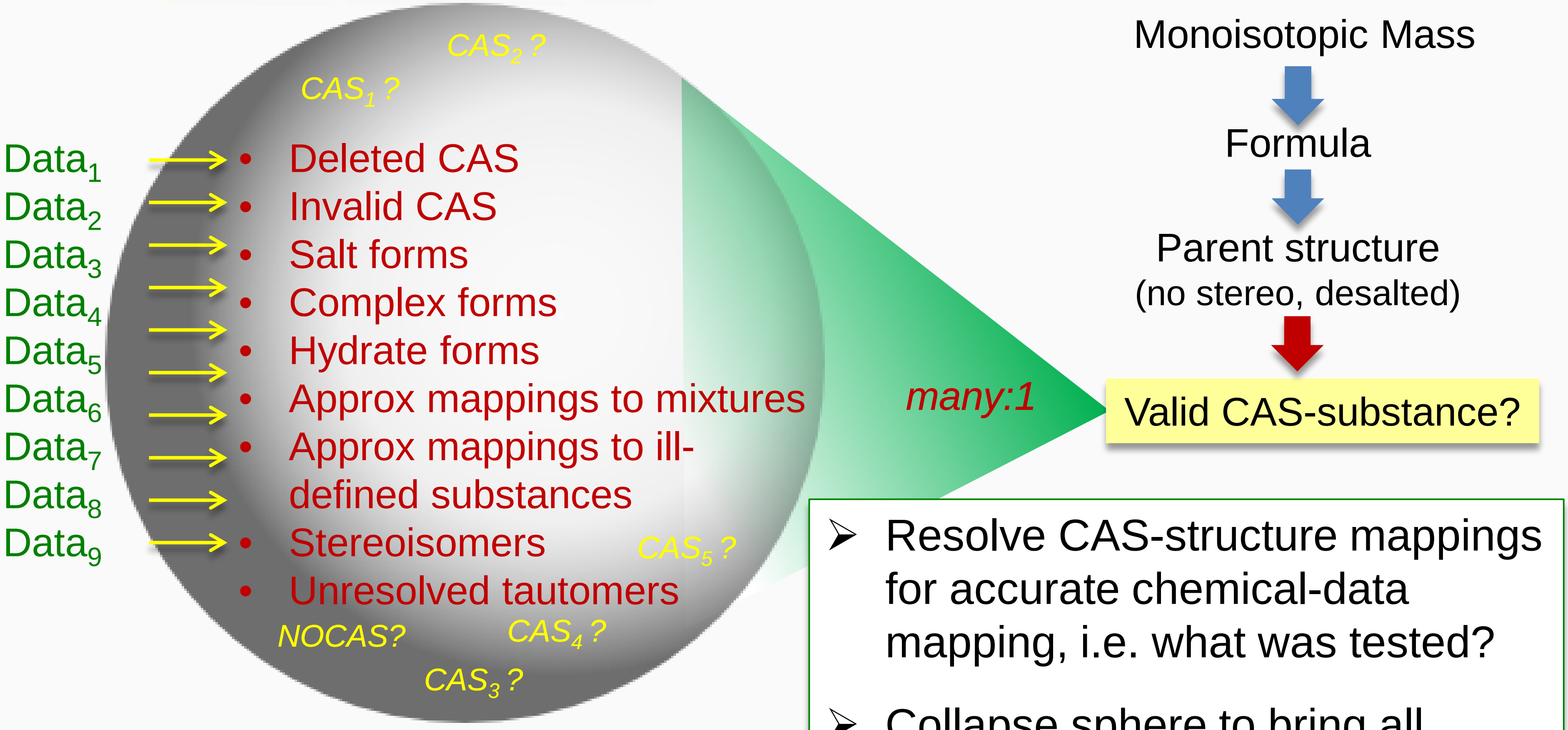


Substance Name: 1-Hexyne
RN: 693-02-7
InChIKey: CGHIBGNXEGJPQZ-UHFFFAOYSA-N

Molecular Formula
C6-H10

Molecular Weight
82.145

CAS-Structure
“Sphere of Confusion”



Data$_1$

Data$_2$

Data$_3$

Data$_4$

Data$_5$

Data$_6$

Data$_7$

Data$_8$

Data$_9$

- Deleted CAS
- Invalid CAS
- Salt forms
- Complex forms
- Hydrate forms
- Approx mappings to mixtures
- Approx mappings to ill-defined substances
- Stereoisomers
- Unresolved tautomers

many:1

Monoisotopic Mass

Formula

Parent structure
(no stereo, desalted)

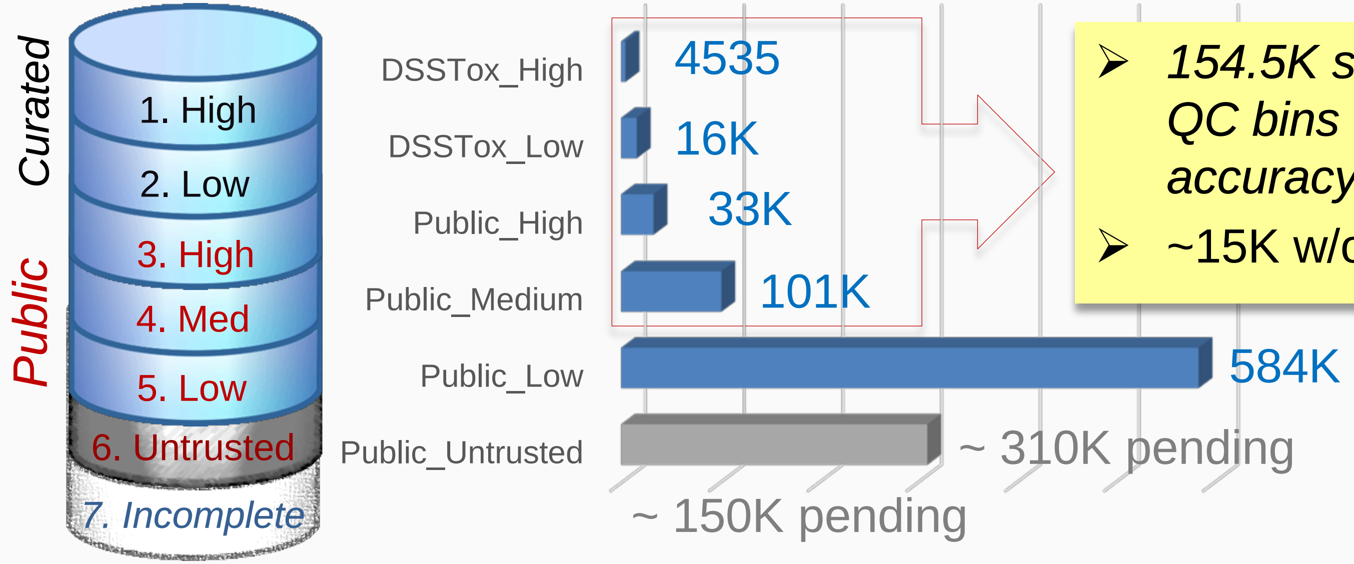
Valid CAS-substance?

- ➢ Resolve CAS-structure mappings for accurate chemical-data mapping, i.e. what was tested?
- ➢ Collapse sphere to bring all related data to NTS parent structure-formula level

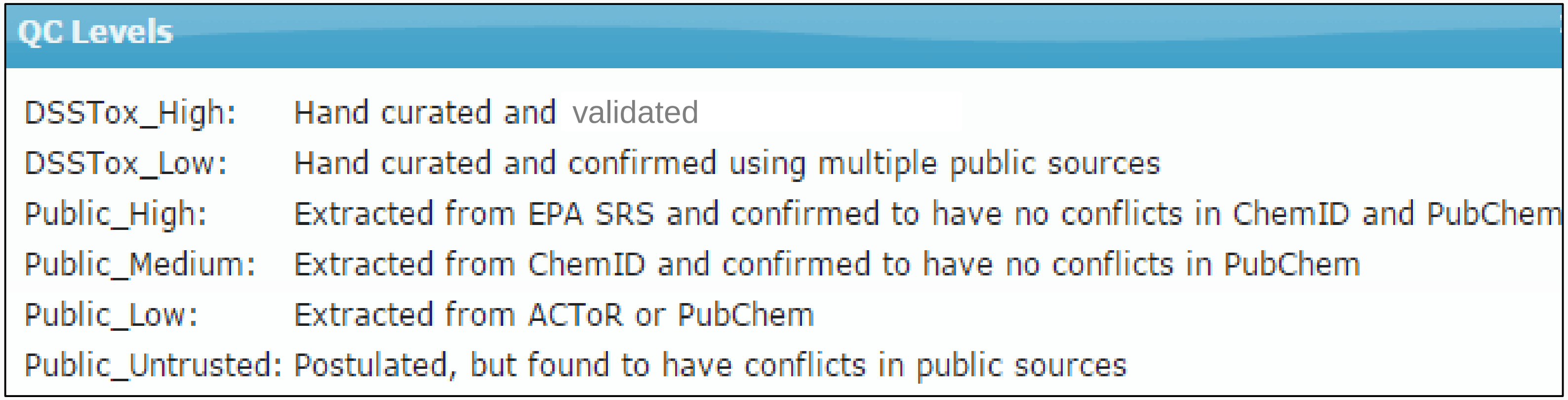
DSSTox_v2 Database
& Cheminformatics Layer

DSSTox_v2 Totals

QC Level Totals (12Jun2015)



- *154.5K substances in top 4 QC bins exceed public accuracy standards*
- ~15K w/o structures



QC Levels

DSSTox_High:	Hand curated and validated
DSSTox_Low:	Hand curated and confirmed using multiple public sources
Public_High:	Extracted from EPA SRS and confirmed to have no conflicts in ChemID and PubChem
Public_Medium:	Extracted from ChemID and confirmed to have no conflicts in PubChem
Public_Low:	Extracted from ACToR or PubChem
Public_Untrusted:	Postulated, but found to have conflicts in public sources

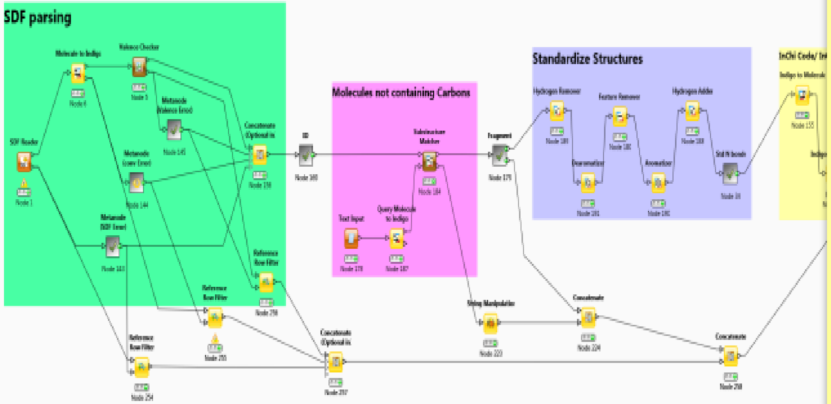
KNIME structure-“cleaning” workflow

EPA
United States
Environmental Protection
Agency

https://www.knime.org/knime

Objectives:

- Combine community approaches to structure processing
- Develop a flexible workflow to be used by EPA and shared publicly
- Process DSSTox files to create “QSAR-ready” structures



- ✓ Parse SDF, remove fragments
- ✓ Explicit hydrogen removed
- ✓ Dearomatization
- ✓ Removal of chirality info, isotopes and pseudo-atoms
- ✓ Aromatization + add explicit hydrogen atoms
- ✓ Standardize Nitro groups
- ✓ Other tautomerize/mesomerization
- ✓ Neutralize (when possible)

Publicly available cheminformatics toolkits in KNIME:

Indigo

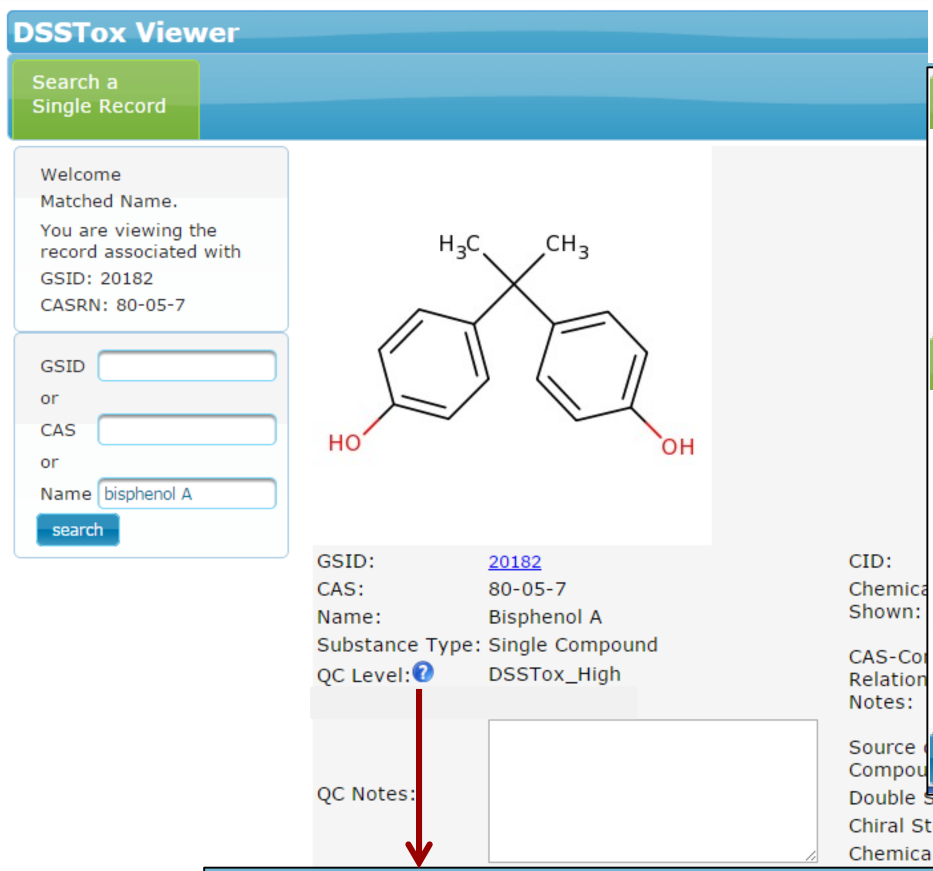
RDKit
Open-Source Cheminformatics and Machine Learning

Pharmaceutical Data Exploration Laboratory

Slide courtesy of K. Mansouri

DSSTox Viewer (EPA Intranet)

http://rtpavaki1.epa.gov:8080/DSSToxViewer/

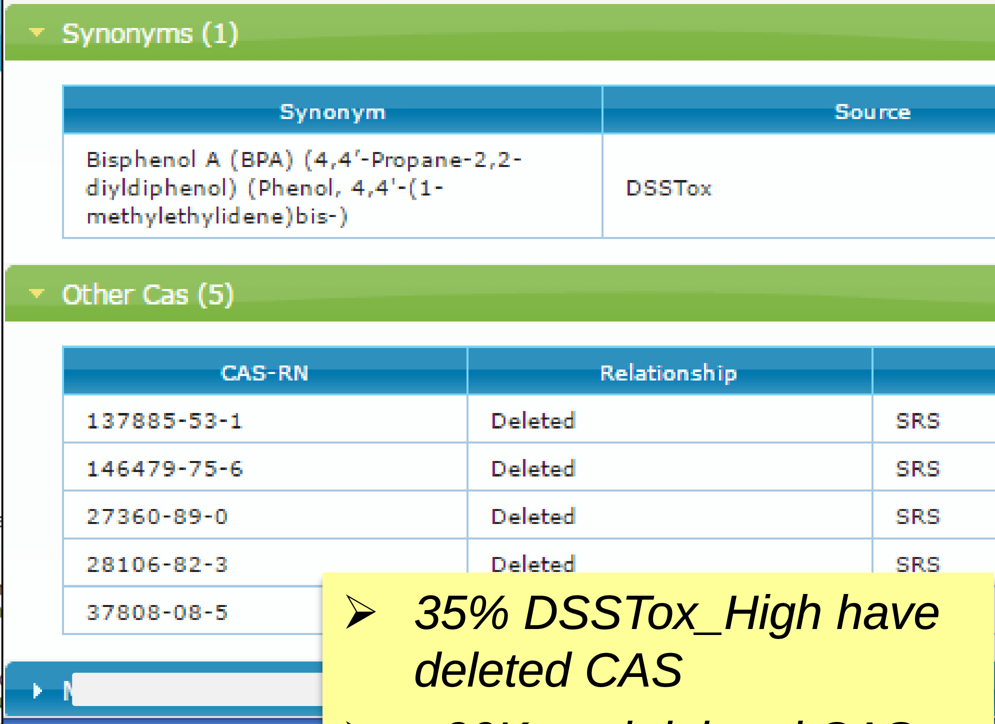


Welcome
Matched Name.
You are viewing the record associated with
GSID: 20182
CASRN: 80-05-7

GSID
or
CAS
or
Name bisphenol A

GSID: 20182
CAS: 80-05-7
Name: Bisphenol A
Substance Type: Single Compound
QC Level: DSSTox_High
QC Notes:

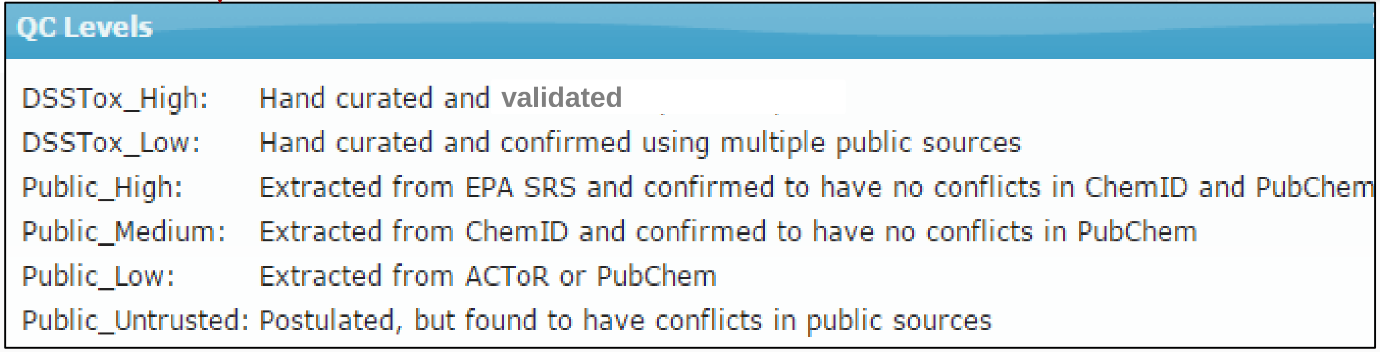
CID:
Chemica
Shown:
CAS-Co
Relation
Notes:
Source
Compou
Double Stereo:
Chiral Stereo:
Chemical Form: Organic



Synonym	Source
Bisphenol A (BPA) (4,4'-Propane-2,2-diyldiphenol) (Phenol, 4,4'-(1-methylethylidene)bis-)	DSSTox

CAS-RN	Relationship	
137885-53-1	Deleted	SRS
146479-75-6	Deleted	SRS
27360-89-0	Deleted	SRS
28106-82-3	Deleted	SRS
37808-08-5		

- *35% DSSTox_High have deleted CAS*
- *>20K total deleted CAS*



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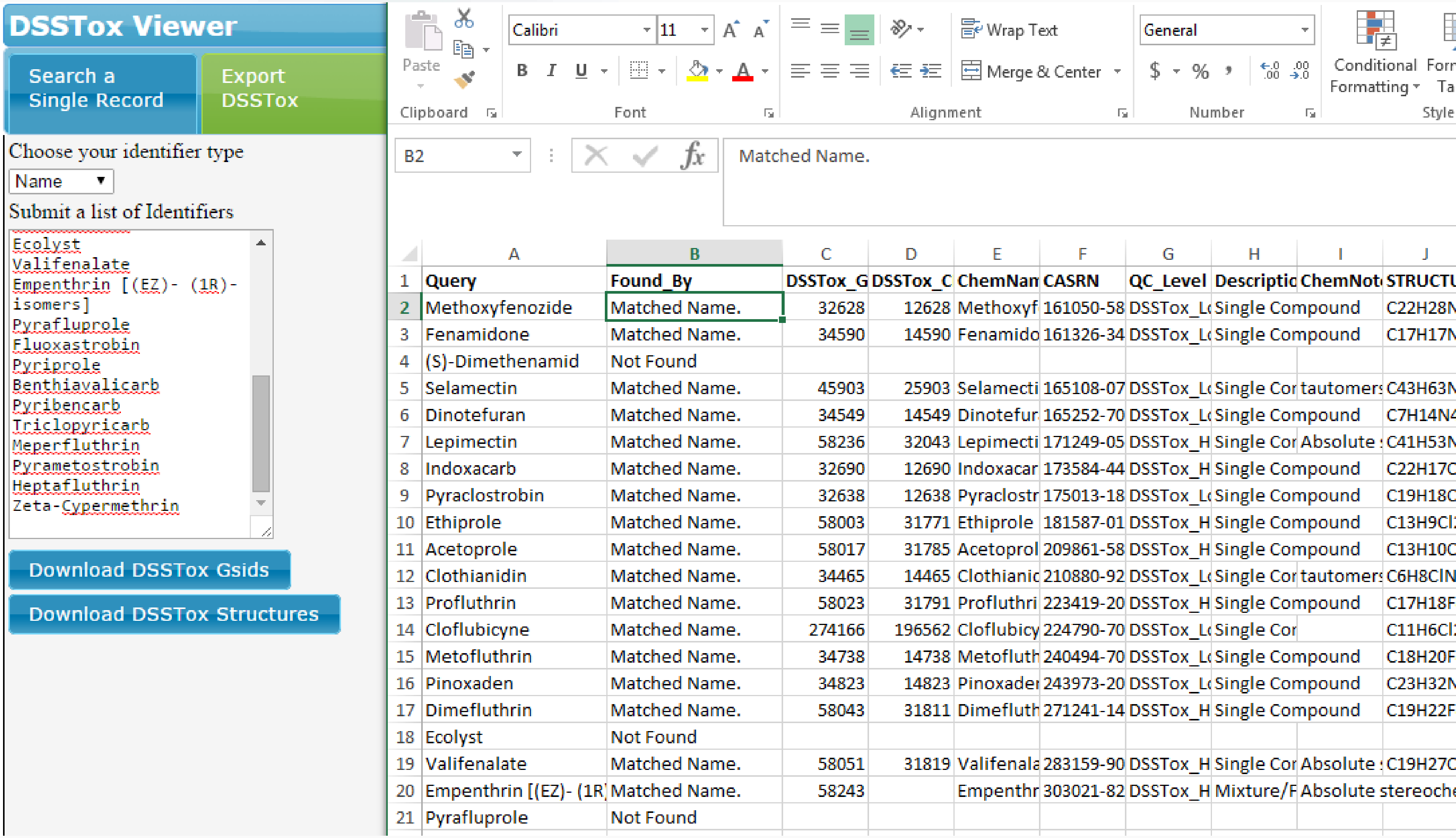
Public_Untrusted:	Postulated, but found to have conflicts in public sources

DSSTox Batch Tool (EPA Intranet)

http://rtpavaki1.epa.gov:8080/DSSToxViewer/



Choose your identifier type

Name

Submit a list of Identifiers

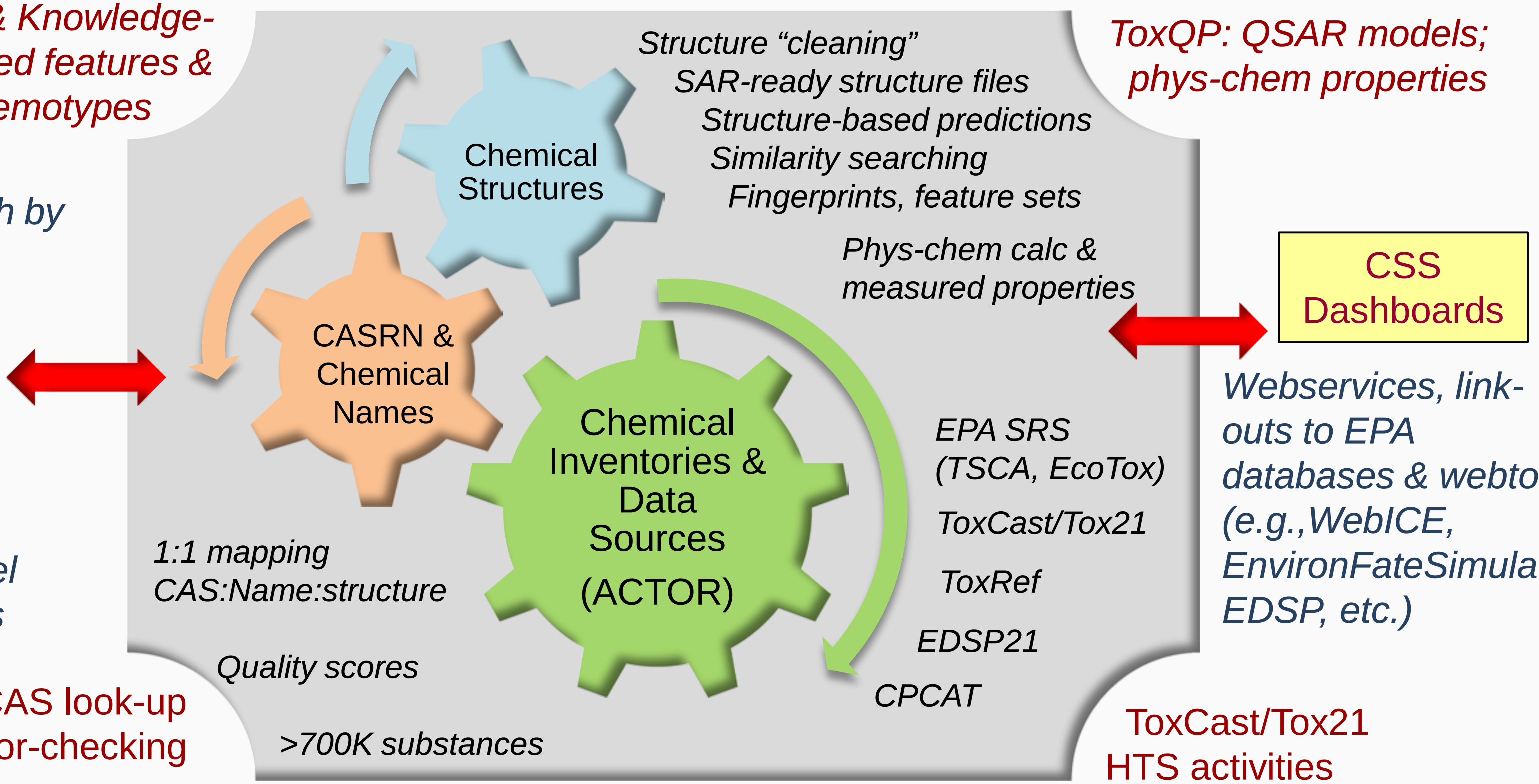
Ecolyst
Valifenalate
Empenthrin [(EZ)- (1R)-isomers]
Pyrafluprole
Fluoxastrobin
Pyriprole
Benthiavalicarb
Pyribencarb
Triclopyricarb
Meperfluthrin
Pyrametostrobin
Heptafluthrin
Zeta-Cypermethrin

B2 = Matched Name.

	A	B	C	D	E	F	G	H	I	J
1	**Query**	**Found_By**	**DSSTox_G**	**DSSTox_C**	**ChemNan**	**CASRN**	**QC_Level**	**Descriptic**	**ChemNot**	**STRUCTU**
2	Methoxyfenozide	Matched Name.	32628	12628	Methoxyf	161050-58	DSSTox_L	Single Compound		C22H28N
3	Fenamidone	Matched Name.	34590	14590	Fenamido	161326-34	DSSTox_L	Single Compound		C17H17N
4	(S)-Dimethenamid	Not Found								
5	Selamectin	Matched Name.	45903	25903	Selamecti	165108-07	DSSTox_L	Single Cor	tautomers	C43H63N
6	Dinotefuran	Matched Name.	34549	14549	Dinotefur	165252-70	DSSTox_L	Single Compound		C7H14N4
7	Lepimectin	Matched Name.	58236	32043	Lepimecti	171249-05	DSSTox_H	Single Cor	Absolute s	C41H53N
8	Indoxacarb	Matched Name.	32690	12690	Indoxacar	173584-44	DSSTox_H	Single Compound		C22H17C
9	Pyraclostrobin	Matched Name.	32638	12638	Pyraclostr	175013-18	DSSTox_L	Single Compound		C19H18C
10	Ethiprole	Matched Name.	58003	31771	Ethiprole	181587-01	DSSTox_H	Single Compound		C13H9Cl
11	Acetoprole	Matched Name.	58017	31785	Acetoprol	209861-58	DSSTox_H	Single Compound		C13H10C
12	Clothianidin	Matched Name.	34465	14465	Clothianic	210880-92	DSSTox_L	Single Cor	tautomers	C6H8ClN
13	Profluthrin	Matched Name.	58023	31791	Profluthri	223419-20	DSSTox_H	Single Compound		C17H18F
14	Cloflubicyne	Matched Name.	274166	196562	Cloflubicy	224790-70	DSSTox_L	Single Cor		C11H6Cl
15	Metofluthrin	Matched Name.	34738	14738	Metofluth	240494-70	DSSTox_L	Single Compound		C18H20F
16	Pinoxaden	Matched Name.	34823	14823	Pinoxader	243973-20	DSSTox_L	Single Compound		C23H32N
17	Dimefluthrin	Matched Name.	58043	31811	Dimefluth	271241-14	DSSTox_H	Single Compound		C19H22F
18	Ecolyst	Not Found								
19	Valifenalate	Matched Name.	58051	31819	Valifenala	283159-90	DSSTox_H	Single Cor	Absolute s	C19H27C
20	Empenthrin [(EZ)- (1R)	Matched Name.	58243		Empenthr	303021-82	DSSTox_H	Mixture/F	Absolute stereoche	
21	Pyrafluprole	Not Found								

CSS Chemical Explorer Dashboard

(powered by DSSTox & ACToR)



MOA & Knowledge-informed features & chemotypes

Chemical search by
CAS-names
SMILES
Structures

Structure file downloads

PK/ADME model inputs & outputs

CAS look-up
New list error-checking

Structure "cleaning"
SAR-ready structure files
Structure-based predictions
Similarity searching
Fingerprints, feature sets

Phys-chem calc & measured properties

1:1 mapping
CAS:Name:structure

Quality scores

>700K substances

EPA SRS (TSCA, EcoTox)

ToxCast/Tox21

ToxRef

EDSP21

CPCAT

ToxQP: QSAR models; phys-chem properties

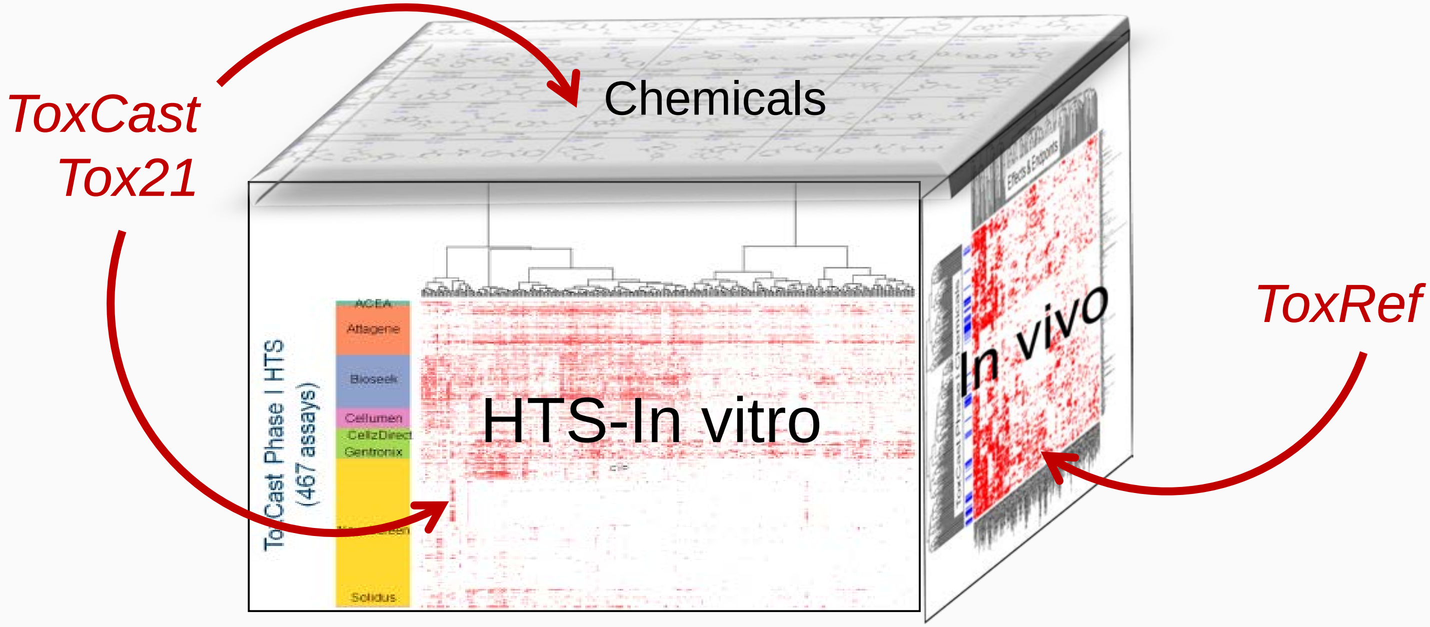
CSS Dashboards

Webservices, link-outs to EPA databases & webtools (e.g.,WebICE, EnvironFateSimulator, EDSP, etc.)

ToxCast/Tox21
HTS activities

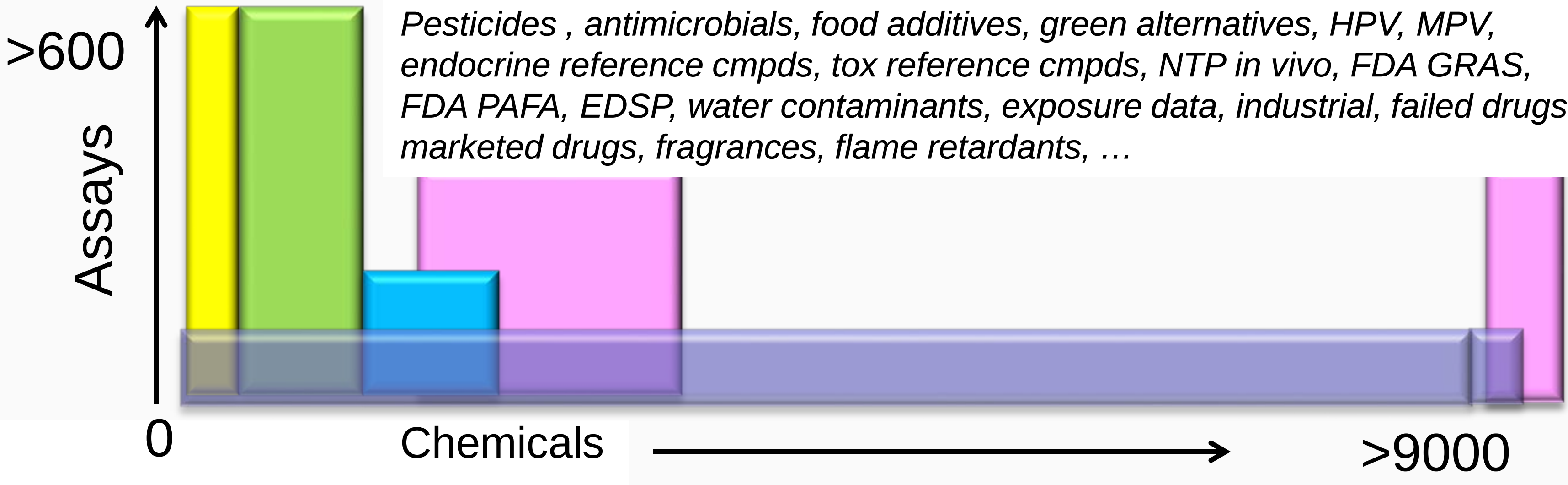
EPA's ToxCast/Tox21 Projects

- Build a diverse, highly prioritized chemical library of interest to EPA regulatory programs (e.g., EDSP) and of relevance to environmental toxicology
- Use high-throughput screening (HTS) to generate bioassay profiles and fill data gaps for thousands of chemicals
- Use all of these data to improve ability to model adverse outcomes



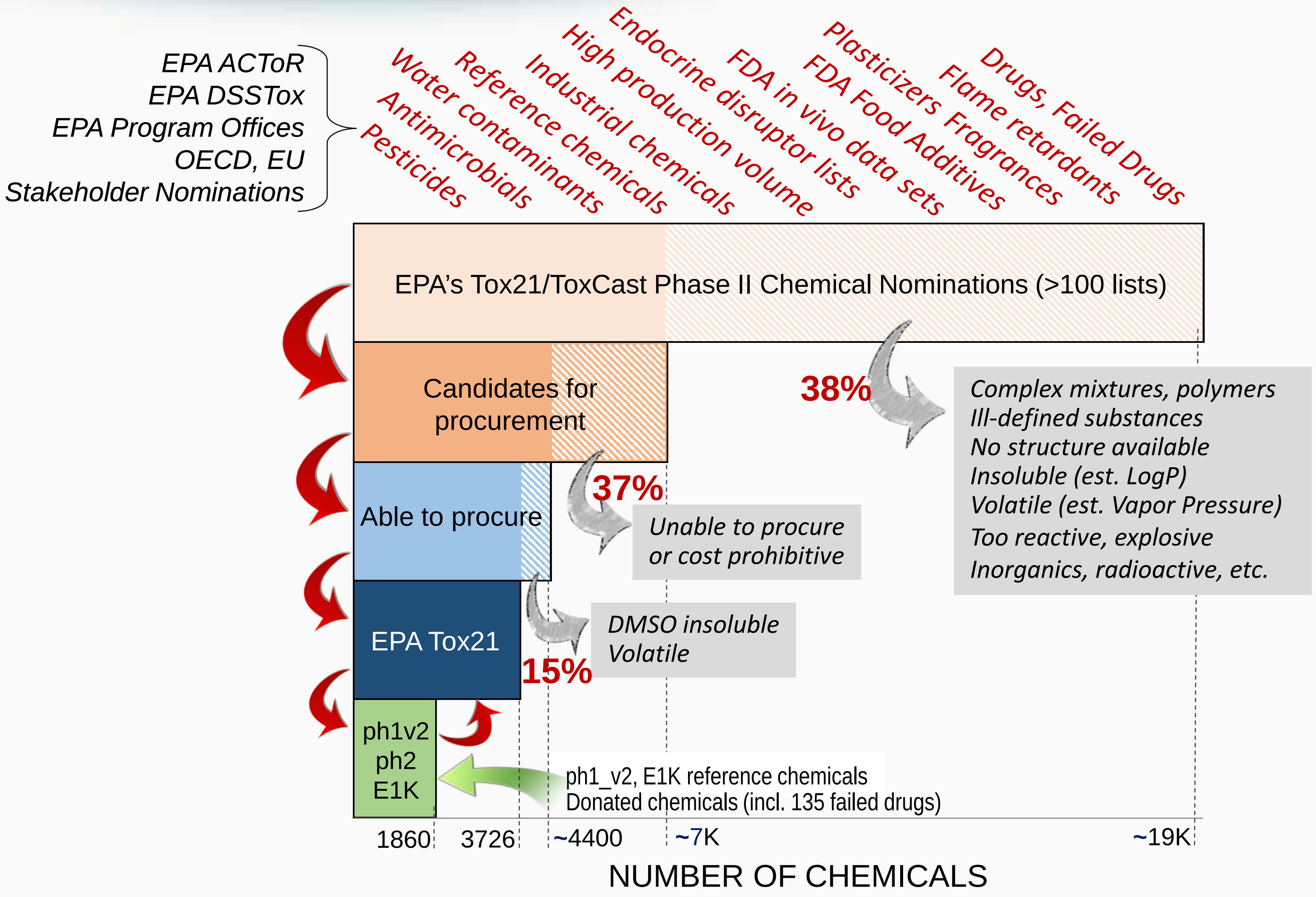
ToxCast & Tox21 Inventories

Set	Chemicals	Assays	Endpoints	Completion	Available
ToxCast Phase I	🟨 293	~600	~700	2011	Now
ToxCast Phase II	🟩 767	~600	~700	03/2013	Now
ToxCast E1K	🟦 800	~50	~120	03/2013	Now
Tox21	🟥 ~8900	~80	~150	Ongoing	Ongoing
ToxCast Phase III	🟪 ~2000	~300	~300	In process	2014-2015



Pesticides , antimicrobials, food additives, green alternatives, HPV, MPV, endocrine reference cmpds, tox reference cmpds, NTP in vivo, FDA GRAS, FDA PAFA, EDSP, water contaminants, exposure data, industrial, failed drugs, marketed drugs, fragrances, flame retardants, …

Construction of EPA’s Tox21/ToxCast Inventories



EPA ACToR
EPA DSSTox
EPA Program Offices
OECD, EU
Stakeholder Nominations

Pesticides
Antimicrobials
Water contaminants
Reference chemicals
Industrial chemicals
High production volume
Endocrine disruptor lists
FDA in vivo data sets
FDA Food Additives
Plasticizers Fragrances
Flame retardants
Drugs, Failed Drugs

EPA’s Tox21/ToxCast Phase II Chemical Nominations (>100 lists)

Candidates for procurement

Able to procure

EPA Tox21

ph1v2
ph2
E1K

38%

Complex mixtures, polymers
Ill-defined substances
No structure available
Insoluble (est. LogP)
Volatile (est. Vapor Pressure)
Too reactive, explosive
Inorganics, radioactive, etc.

37%

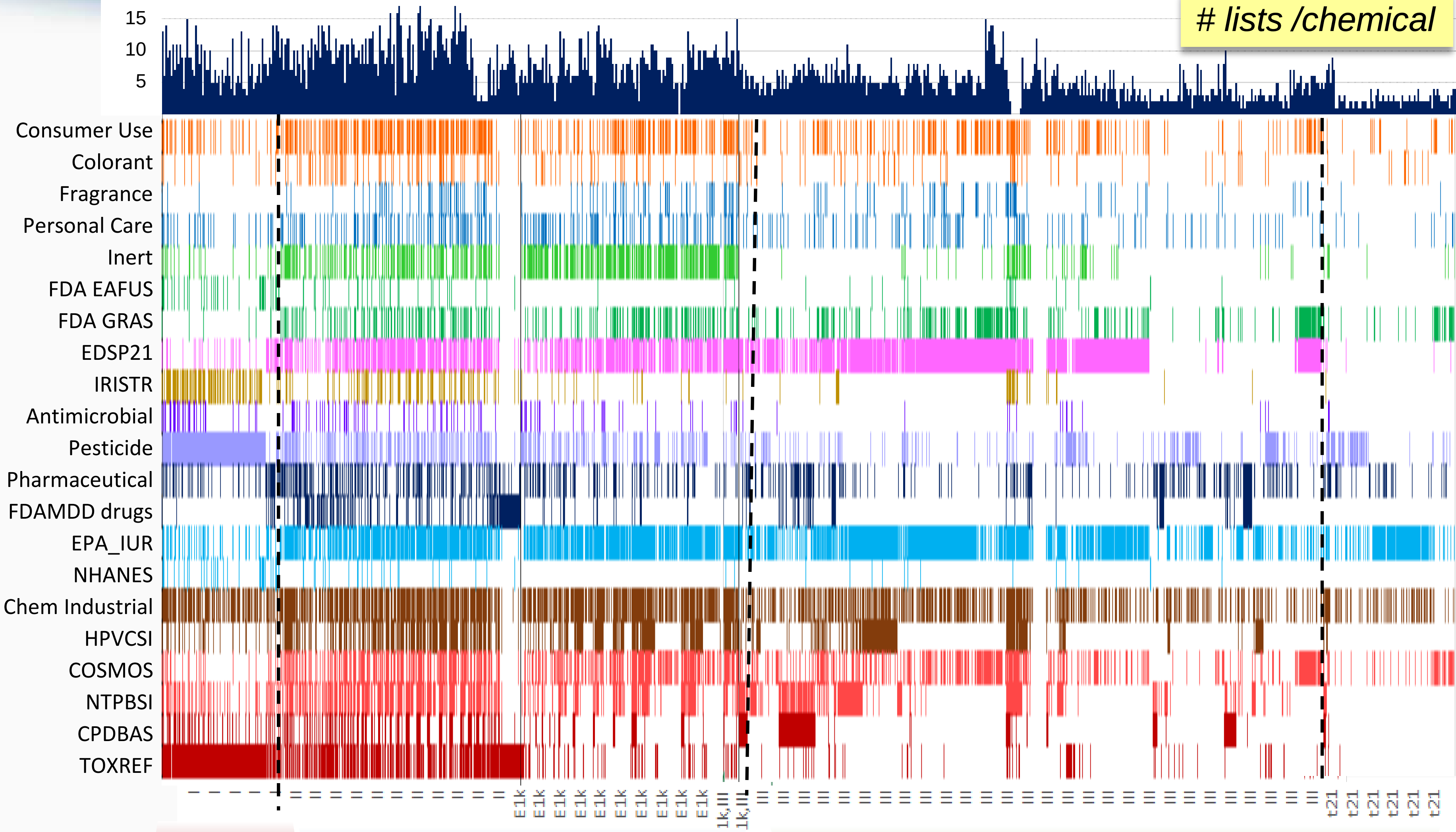
Unable to procure
or cost prohibitive

DMSO insoluble
Volatile

15%

ph1_v2, E1K reference chemicals
Donated chemicals (incl. 135 failed drugs)

ToxCast Chemical Coverage: Use, Exposure, Toxicity



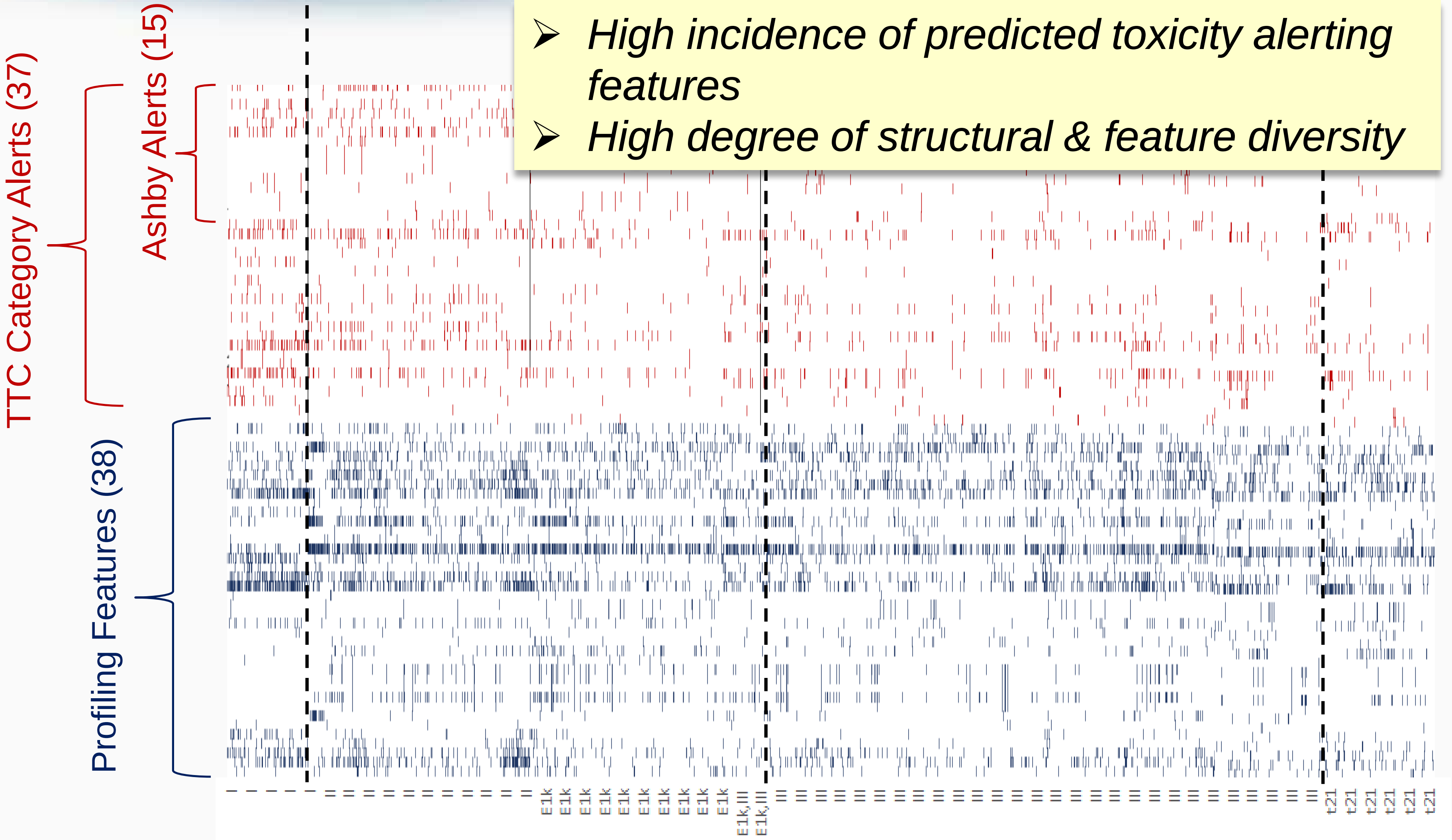
# lists /chemical

Phase I:
Pesticides
In vivo-rich

Phase II (ph2,E1K):
In vivo-rich; donated failed drugs; EDSP21; high diversity, coverage of toxicity space

Phase III (ph3):
Toxicity reference chemicals; EDSP21; extend coverage of industrial chemicals

ToxCast: Toxicity Structure-Alerts & Generic Feature Coverage



- ➢ *High incidence of predicted toxicity alerting features*
- ➢ *High degree of structural & feature diversity*

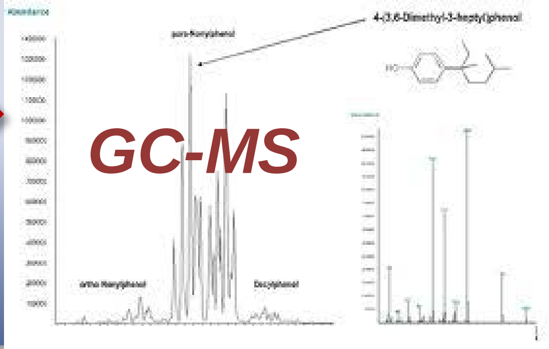
ToxCast Chemicals (4214) ordered by Testing Phase

Tox21 Analytical QC

A copy of each parent Tox21 384 well plate is subjected to analytical QC for assessing purity, identity, concentration, stability

Confirm parent ion peak and >90% purity

Fail, inconclusive or analytical method inappropriate



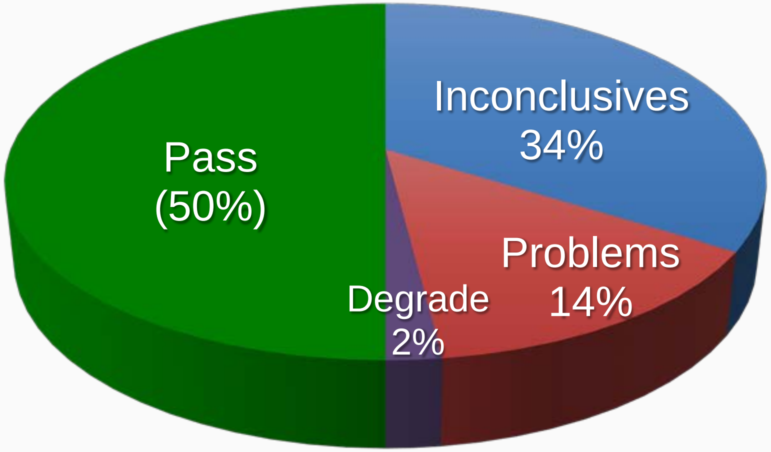
Retest at 4 mo. time point under assay conditions for stability

Publish QC summary results in association with assay data

Work performed under NIH Contract with OpAns, Durham, NC

Tox21 and ToxCast Chemical Library Analytical QC Results (8/2015)

Tox21_QC_Sum-GSID (8593 total)

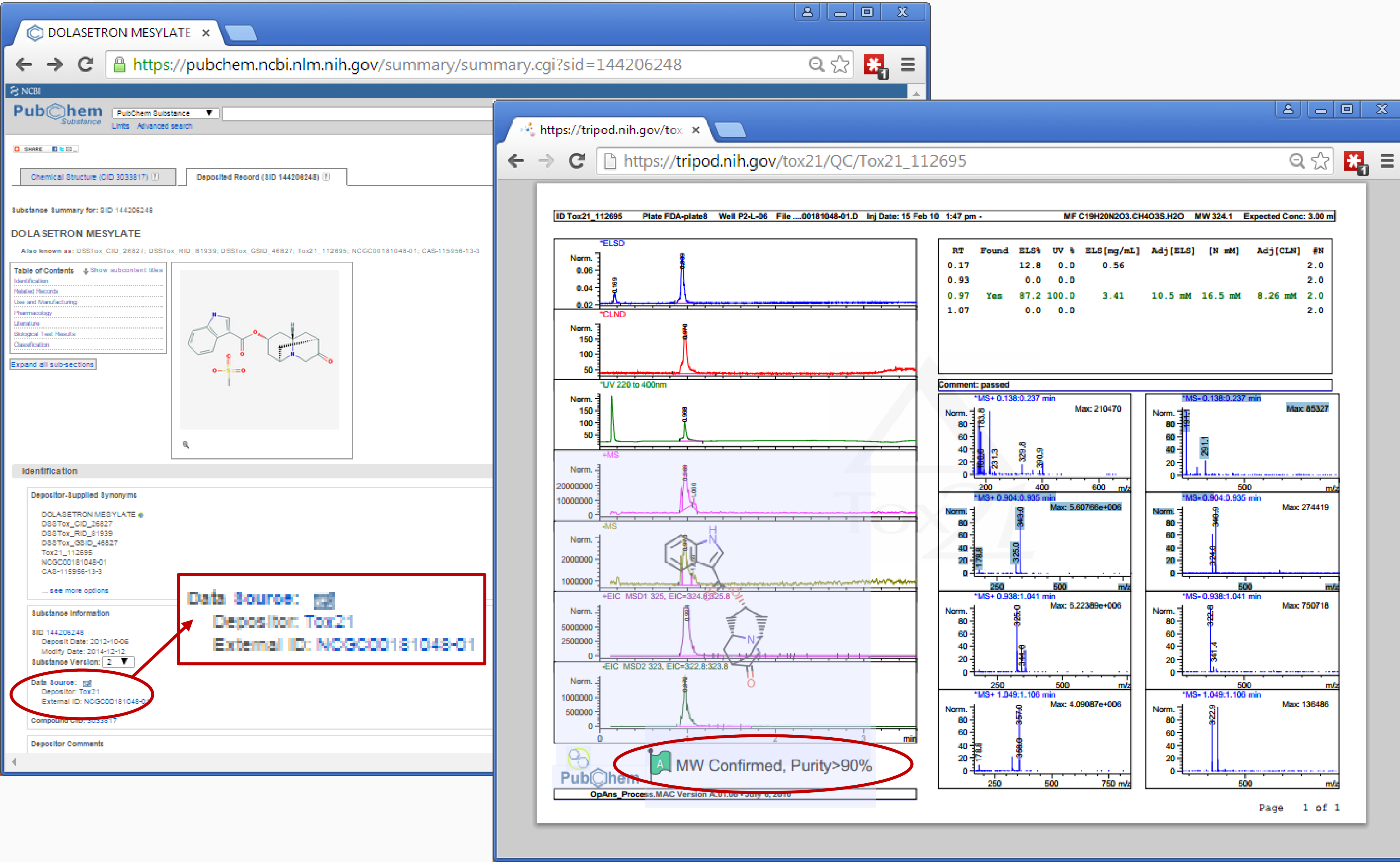


- 50% pass purity/ID/concentration checks
- A third(34%) of library pose analytical QC challenges (LC-MS and GC-MS)
- 2% degrade after 4 months under testing conditions
- 14% problems - purity (<75%), ID and/or low concentration (<30% of expected [C])

- ➢ *Which chemicals have QC issues? (e.g. SVOCs?)*
- ➢ *Which chemicals were not analyzed? (e.g., mixtures, inorganics, etc.)*
- ➢ *How are the HTS activity profiles linked to QC?*

Results as of 8/2015

Tox21 Analytical Chemical QC:
Publicly available in PubChem



Substance Summary for: SID 144206248

DOLASETRON MESYLATE

Also known as: DSSTox_CID_26827; DSSTox_RID_81939; DSSTox_GSID_46827; Tox21_112695; NCGC00181048-01; CAS-115956-13-3

Identification

Depositor-Supplied Synonyms

DOLASETRON MESYLATE
DSSTox_CID_26827
DSSTox_RID_81939
DSSTox_GSID_46827
Tox21_112695
NCGC00181048-01
CAS-115956-13-3

... see more options

Substance Information

SID 144206248
Deposit Date: 2012-10-06
Modify Date: 2014-12-12
Substance Version: 2

Data Source:
Depositor: Tox21
External ID: NCGC00181048-01

Compound CID: 3033817

Depositor Comments

Data Source:
Depositor: Tox21
External ID: NCGC00181048-01

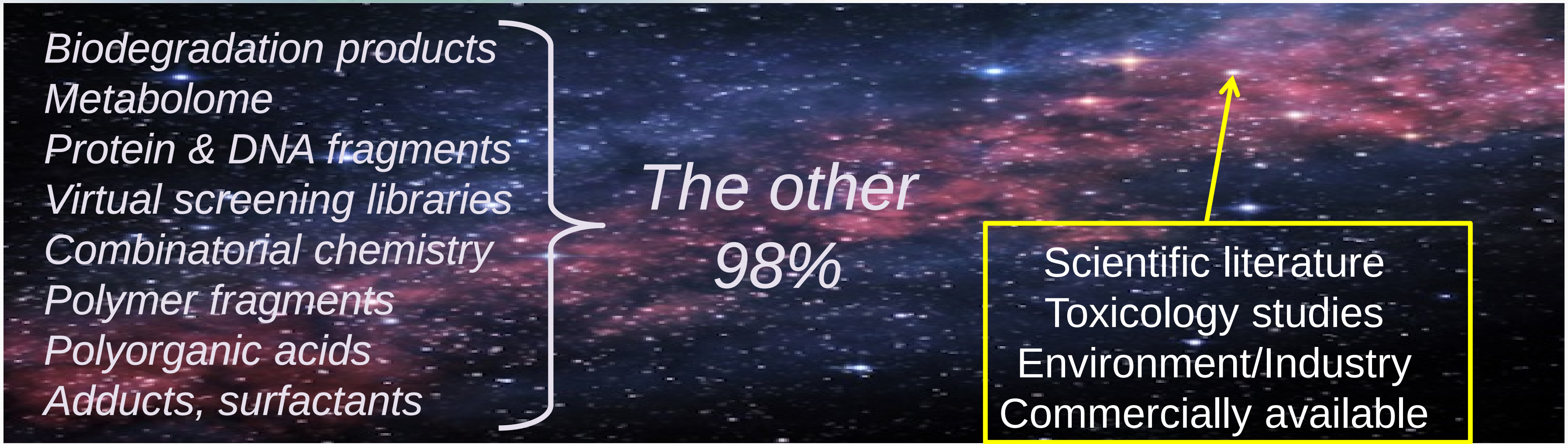
ID Tox21_112695 Plate FDA-plate8 Well P2-L-06 File ....00181048-01.D Inj Date: 15 Feb 10 1:47 pm • MF C19H20N2O3.CH4O3S.H2O MW 324.1 Expected Conc: 3.00 m

RT	Found	ELS%	UV %	ELS[mg/mL]	Adj[ELS]	[N mM]	Adj[CLN]	#N
0.17		12.8	0.0	0.56				2.0
0.93		0.0	0.0					2.0
0.97	Yes	87.2	100.0	3.41	10.5 mM	16.5 mM	8.26 mM	2.0
1.07		0.0	0.0					2.0

Comment: passed

MW Confirmed, Purity>90%

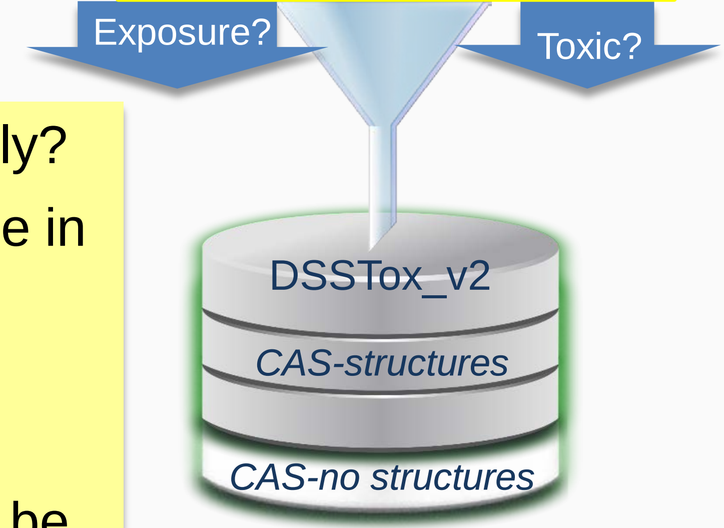
Chemical “Universe” problem



Biodegradation products
Metabolome
Protein & DNA fragments
Virtual screening libraries
Combinatorial chemistry
Polymer fragments
Polyorganic acids
Adducts, surfactants

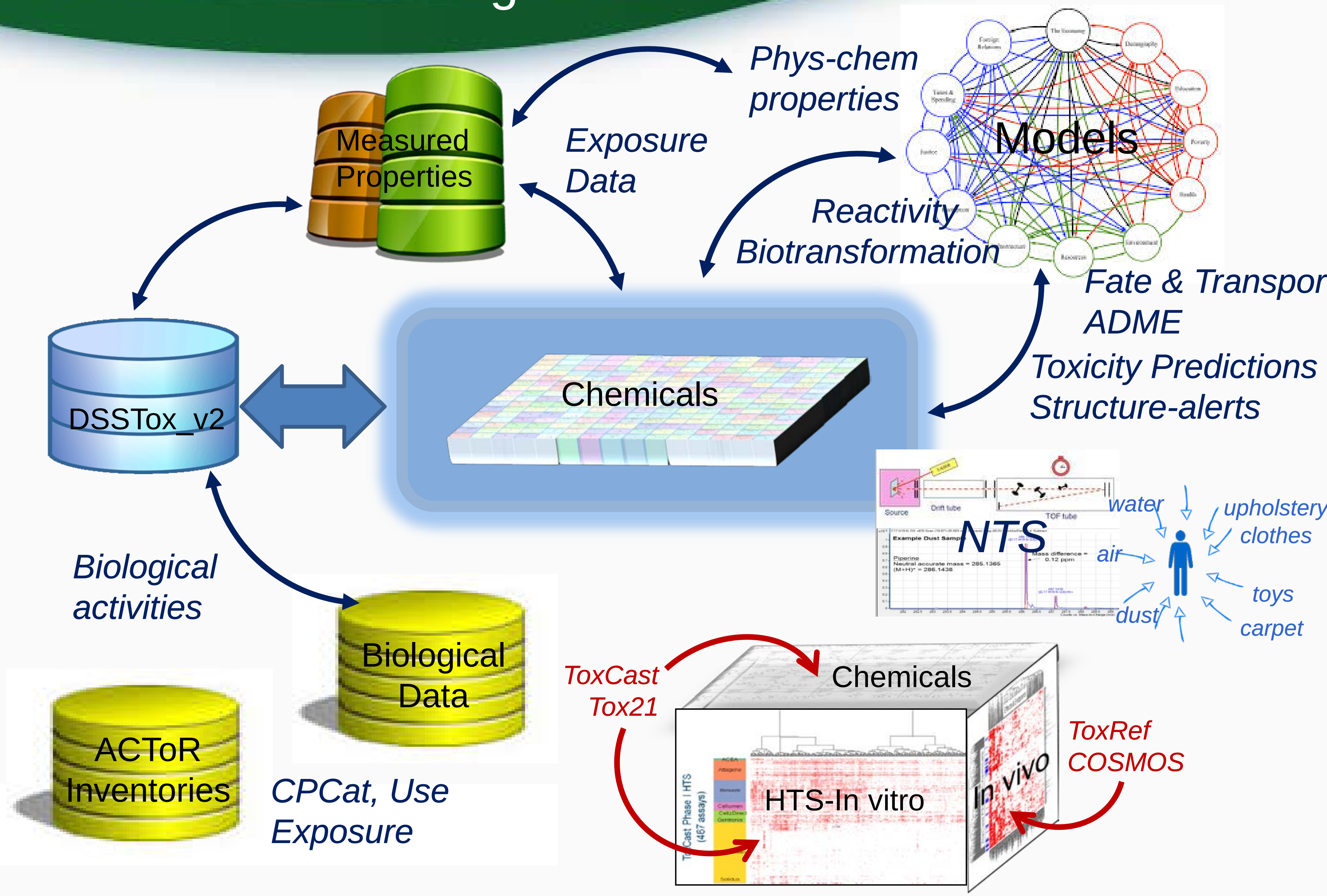
The other 98%

Scientific literature
Toxicology studies
Environment/Industry
Commercially available



- Where should DSSTox expand chemically?
- What part of the universe should we store in databases?
- How can the valuable ToxCast physical library be shared for greatest gain?
- What cheminformatics “plumbing” would be most useful to this community?

Building EPA's Chemical Informatics Infrastructure & Linkages



Measured Properties

Exposure Data

Phys-chem properties

Models

Reactivity
Biotransformation

Fate & Transpor
ADME

Toxicity Predictions
Structure-alerts

DSSTox_v2

Chemicals

NTS

water
upholstery
clothes
air
toys
dust
carpet

Biological activities

Biological Data

ACToR Inventories

CPCat, Use
Exposure

ToxCast
Tox21

Chemicals

HTS-In vitro

In vivo

ToxRef
COSMOS

Acknowledgements:

- Chris Grulke - Lockheed Martin Contractor to EPA
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  KNIME workflow
- Jayaram Kancherla - ORISE Pre-Doctoral Fellow
  Chemical dashboard, web-tools development
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  ACToR Project Lead
- Antony Williams - NCCT
  Cheminformatics Lead
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