United States Environmental Protection Agency

EPA Project Updates:
DSSTox and ToxCast™ generating new data and data linkages for use in predictive modeling

June 8-12, 2008
QSARs in Environmental Sciences , Syracuse, NY

Ann Richard
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Office of Research and Development
National Center for Computational Toxicology

Part I

Data & Data Linkages

U.S. ENVIRONMENTAL PROTECTION AGENCY

Distributed Structure-Searchable Toxicity (DSSTox) Public Database Network

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- Central Field Definition Table
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- Glossary of Terms
- Help

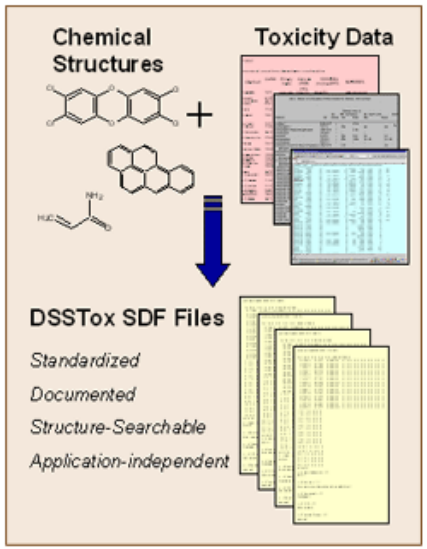
DSSTox

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

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

EPA DSSTox Structure-Browser GO

DSSTox Structure-Browser information Page



- DSSTox Graphic Flowchart
- DSSTox Project Goals
- DSSTox Publications

29 April 2008

- Minor QA revisions to TOXCST and CPDBAS.

24 April 2008

- NTPBSI: National Toxicology Program Bioassay On-line Database Structure-Index Locator File ** *Updated to v3a*

- All current DSSTox Data File substance inventories are now available in PubChem, with

ng below).

nd retrieving

est. May

InChIKey

ons in field

PUBCHEM_ACTIVITY_OUTCOME (active/inactive/inconclusive):

ActivityOutcome_CPDBAS_Rat
ActivityOutcome_CPDBAS_Mouse
ActivityOutcome_CPDBAS_Hamster
ActivityOutcome_CPDBAS_Dog_Primates
ActivityOutcome_CPDBAS_Mutagenicity
ActivityOutcome_CPDBAS_SingleCellCall
ActivityOutcome_CPDBAS_MultiCellCall
ActivityOutcome_DBPCAN
ActivityOutcome_EPAFHM
ActivityOutcome_NCTRER

PUBCHEM_ACTIVITY_SCORE [log(1/ activity) mapped onto INTEGER[0-100] range):

DSSTox Data Files: Details>

CPDBAS_v5c_1547_29Apr2008 *revise
DBPCAN_v4b_209_15Feb2008
EPAFHM_v4b_617_15Feb2008
FDAMDD_v3b_1216_15Feb2008
HPVCSI_v2c_3548_15Feb2008
HPVISD_v1b_1006_15Feb2008
IRISTR_v1b_544_15Feb2008
NCTRER_v4b_232_15Feb2008
NTPBSI_v3a_2303_24Apr2008 *update
NTPHTS_v1b_1408_15Jul2008
TOXCST_v2c_320_29Apr2008 *revise

>Other (non-DSSTox) Data Files

NAMEID	version #records date	Expanded DSSTox Data File Title & Description
CPDBAS	v5b 1547 10Feb2008	**Carcinogenic Potency Database Summary Tables - All Species:** Tumor target site incidence, TD50 potencies, summary activity calls for rat, mouse, hamster, dog, and/or non-human primate; data reviewed and compiled from literature and NTP studies.
DBPCAN	v4b 209 15Feb2008	**EPA Water Disinfection By-Products with Carcinogenicity Estimates Database:** Carcinogenicity estimates (high, moderate, low concern) by EPA experts using a mechanism-based analog SAR approach on a set of 209 water disinfection by-products, mostly small halogenated organics.
EPAFHM	v4b 617 15Feb2008	**EPA Fathead Minnow Acute Toxicity Database:** Acute toxicities of 617 chemicals tested in common assay, with mode-of-action assessments and confirmatory measures.
FDAMDD	v3b 1216 15Feb2008	**FDA Center for Drug Evaluation & Research - Maximum (Recommended) Daily Dose Database:** Maximum (recommended) daily dose (MRDD) values for 1216 pharmaceuticals in mg/kg-body weight (bw)/day, converted to mmol and normalized to dataset; MRDD values extracted from public literature sources.
HPVCSI	v2c 3548 15Feb2008	**EPA High Production Volume Challenge Program** Structure-Index File: Compiled structures for three chemical lists provided on EPA HPV Challenge Program website; each record includes reference index to dated list.
HPVISD	v1b 1006 15Feb2008	**EPA High Production Volume Information System (HPV-IS) Data** Structure-Index Locator File: Compiled structures for the chemical inventory of the on-line EPA HPV-IS with chemical-specific URLs linking to HPV-IS data pages containing chemical properties, fate properties and toxicity data.
IRISTR	v1b 544 15Feb2008	**EPA Integrated Risk Information System (IRIS) Toxicity Review Data File:** Compiled structures for EPA IRIS website with chemical-specific URLs linking to risk assessment summary data pages for 544 chemical substances.
NCTRER	v4b 232 15Feb2008	**FDA National Center for Toxicological Research (NCTR) - Estrogen Receptor Binding Database:** Estrogen receptor relative binding affinities tested in a common in vitro assay for 232 chemicals, listed with chemical class-based structure-activity features.
NTPBSI	v2b 2293 15Feb2008	**National Toxicology Program (NTP) On-line Chemical Bioassay Database** Structure-Index Locator File: Compiled structures for the NTP On-line Database with chemical-specific URLs linking to NTP study summary pages; file includes fields for each of 4 main bioassay study areas with indicator values specifying presence or absence of study data for the chemical substance record.
NTPHTS	v2b 1408 15Feb2008	**National Toxicology Program (NTP) High-Throughput Screening Project** Structure-Index File: Compiled structures for set of 1408 NTP chemical substances provided to the NIH Chemical Genomics Center for HTS bioassay testing and to PubChem (PubChem_CIDs and PubChem_SIDs included in NTPHTS_v2a file); NCGC HTS bioassay data are being deposited into PubChem and can be retrieved with these PubChem chemical CID and SID record listings.
TOXCST	v2b 320 08Feb2008	**Research Chemical Inventory for EPA's ToxCast™ Program** Structure-Index File: Compiled structures for 320 chemical substances that are candidates for Phase I High-Throughput screening (HTS) within the EPA ToxCast™ program. File will be updated with links to PubChem CIDs and SIDs for retrieving assay data, and with updates to chemical inventory as Program moves to Phase II and beyond.

NCBI

PubChem Substance

Search PubChem Substance for dsstox Go Clear Save Search

Limits | Preview/Index | History | Clipboard | Details

Display Summary Show 20 Sort by Send to

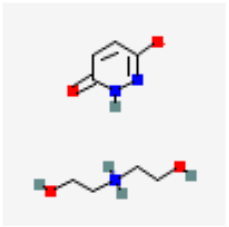
Tools: Links: Related Structures, BioAssays, Literature, Other Links

All: 12940 | BioAssay: 3821 | Protein3D: 0 | Rule of 5: 7987

12940 DSSTox Substances

Items 1 - 20 of 12940

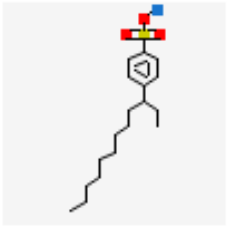
1: SID: 48423627 Related Structures



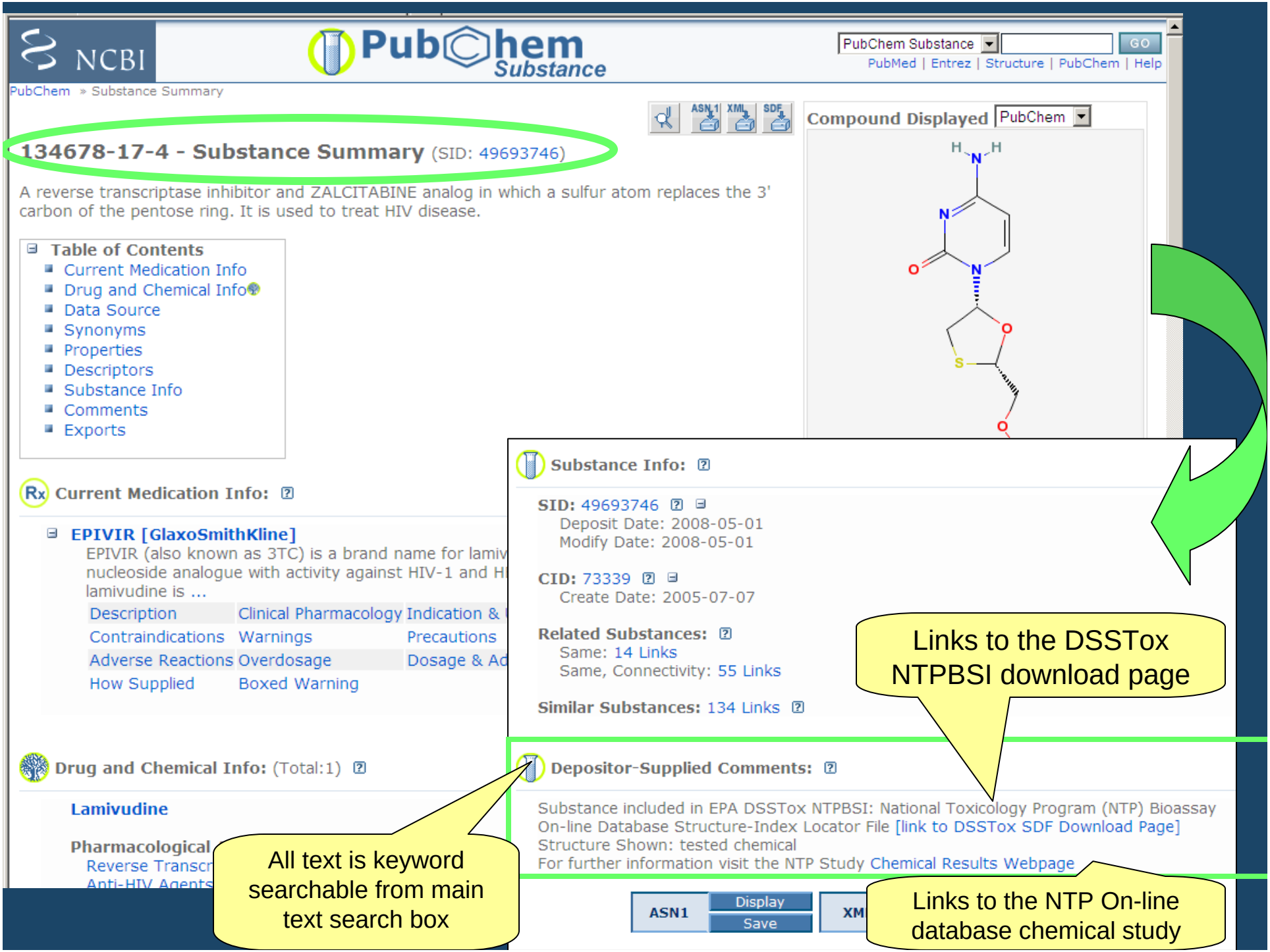
MALEIC HYDRAZIDE DIETHANOLAMINE; 2-hydroxy-N-(2-hydroxyethyl)ethanaminium 6-oxo-1,2,3,6-tetrahydropyridazin-3-olate; 5716-15-4
Compound ID: 24180705
Source: EPA DSSTox (31555)
IUPAC: bis(2-hydroxyethyl)azanium; 6-oxo-1H-py
MW: 217.222400 g/mol | **MF**: C8H15N3O4

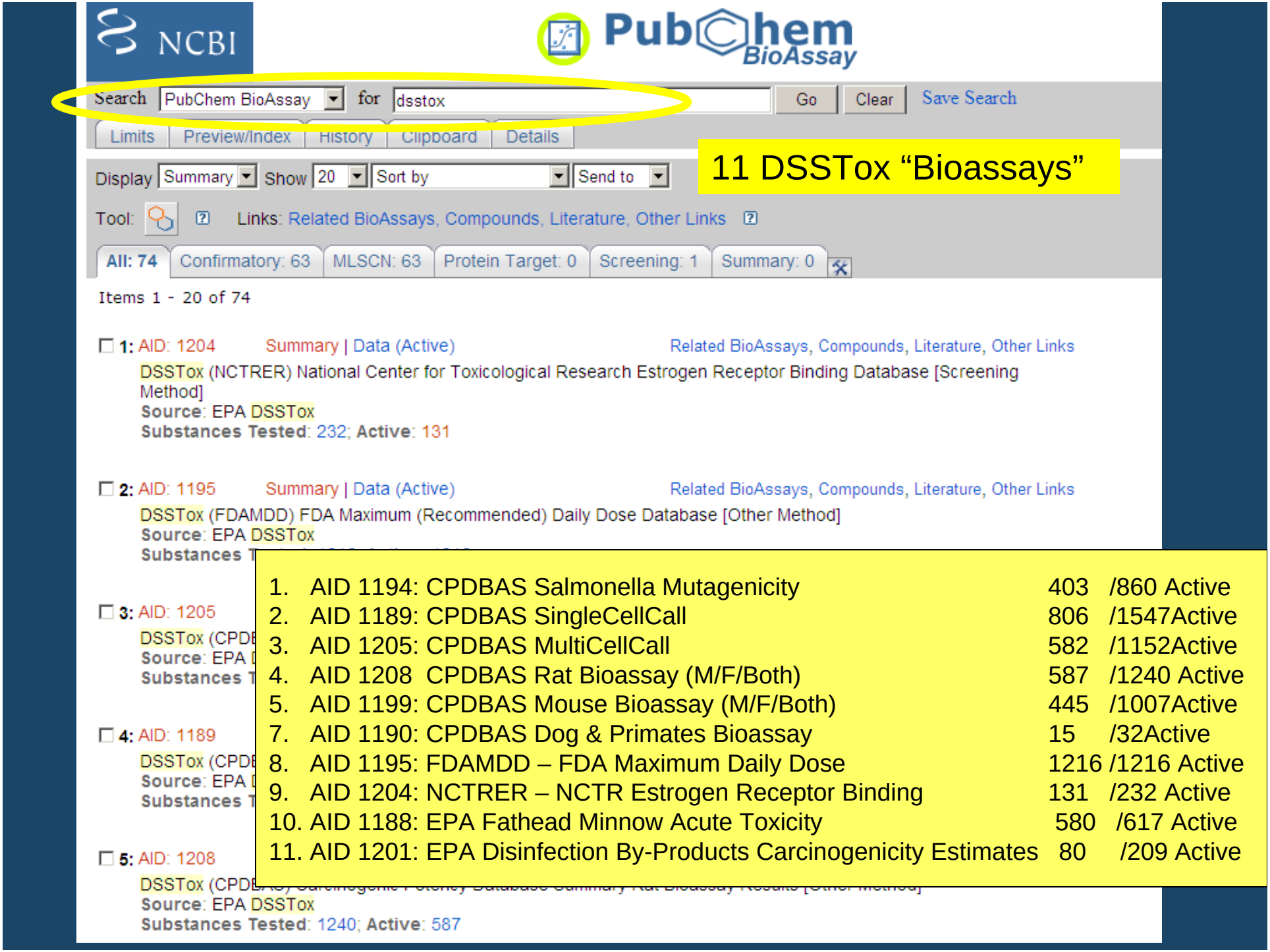
Links to DSSTox Download Page & Source data page

2: SID: 48423362 Related Structures, Literature



Dodecylbenzenesulfonic acid, sodium salt; 25155-30-0
Compound ID: 23707968
Source: EPA DSSTox (31261)
IUPAC: sodium 4-dodecan-3-ylbenzenesulfonate
MW: 348.475830 g/mol | **MF**: C18H29NaO3S


NCBI
PubChem Substance
PubChem Substance
GO
PubMed | Entrez | Structure | PubChem | Help
PubChem » Substance Summary
ASN.1
XML
SDF
Compound Displayed
PubChem
134678-17-4 - Substance Summary (SID: 49693746)
A reverse transcriptase inhibitor and ZALCITABINE analog in which a sulfur atom replaces the 3' carbon of the pentose ring. It is used to treat HIV disease.
Table of Contents
Current Medication Info
Drug and Chemical Info
Data Source
Synonyms
Properties
Descriptors
Substance Info
Comments
Exports
Current Medication Info:
EPIVIR [GlaxoSmithKline]
EPIVIR (also known as 3TC) is a brand name for lamiv
nucleoside analogue with activity against HIV-1 and H
lamivudine is ...
Description
Clinical Pharmacology
Indication &
Contraindications
Warnings
Precautions
Adverse Reactions
Overdosage
Dosage & Ac
How Supplied
Boxed Warning
Drug and Chemical Info: (Total:1)
Lamivudine
Pharmacological
Reverse Transcr
Anti-HIV Agents
Substance Info:
SID: 49693746
Deposit Date: 2008-05-01
Modify Date: 2008-05-01
CID: 73339
Create Date: 2005-07-07
Related Substances:
Same: 14 Links
Same, Connectivity: 55 Links
Similar Substances: 134 Links
Depositor-Supplied Comments:
Substance included in EPA DSSTox NTPBSI: National Toxicology Program (NTP) Bioassay On-line Database Structure-Index Locator File [link to DSSTox SDF Download Page]
Structure Shown: tested chemical
For further information visit the NTP Study Chemical Results Webpage
ASN1
Display
Save
XM
Links to the DSSTox NTPBSI download page
All text is keyword searchable from main text search box
Links to the NTP On-line database chemical study


NCBI
PubChem BioAssay
Search PubChem BioAssay for dsstox Go Clear Save Search
Limits Preview/Index History Clipboard Details
11 DSSTox "Bioassays"
Display Summary Show 20 Sort by Send to
Tool: Links: Related BioAssays, Compounds, Literature, Other Links
All: 74 Confirmatory: 63 MLSCN: 63 Protein Target: 0 Screening: 1 Summary: 0
Items 1 - 20 of 74
1: AID: 1204 Summary | Data (Active) Related BioAssays, Compounds, Literature, Other Links
DSSTox (NCTRER) National Center for Toxicological Research Estrogen Receptor Binding Database [Screening Method]
Source: EPA DSSTox
Substances Tested: 232; Active: 131
2: AID: 1195 Summary | Data (Active) Related BioAssays, Compounds, Literature, Other Links
DSSTox (FDAMDD) FDA Maximum (Recommended) Daily Dose Database [Other Method]
Source: EPA DSSTox
3: AID: 1205
4: AID: 1189
5: AID: 1208
Source: EPA DSSTox
Substances Tested: 1240; Active: 587
1. AID 1194: CPDBAS Salmonella Mutagenicity 403 /860 Active
2. AID 1189: CPDBAS SingleCellCall 806 /1547Active
3. AID 1205: CPDBAS MultiCellCall 582 /1152Active
4. AID 1208 CPDBAS Rat Bioassay (M/F/Both) 587 /1240 Active
5. AID 1199: CPDBAS Mouse Bioassay (M/F/Both) 445 /1007Active
7. AID 1190: CPDBAS Dog & Primates Bioassay 15 /32Active
8. AID 1195: FDAMDD – FDA Maximum Daily Dose 1216 /1216 Active
9. AID 1204: NCTRER – NCTR Estrogen Receptor Binding 131 /232 Active
10. AID 1188: EPA Fathead Minnow Acute Toxicity 580 /617 Active
11. AID 1201: EPA Disinfection By-Products Carcinogenicity Estimates 80 /209 Active

Related BioAssays by Activity Overlap

AID: 1205

Name: DSSTox (CPDBAS) Carcinogenic Potency Database Summary MultiCellCall Results
Data Source: EPA DSSTox

BioActivity Analysis: Structure-Activity

Activity Overlap for CPDBAS MultiCellCall Results

334 **Related BioAssays by Activity Overlap of AID** 1205

Total Pages: 17 **Display:** 20 Go To Page 1

#		Activity Similarity	Active in Both	BioAssay Name
1	☐	72.6%	572	AID: 1189, DSSTox (CPDBAS) Carcinogenic Potency Database Summary SingleCellCall Results
2	☐	62.3%	441	AID: 1208, DSSTox (CPDBAS) Carcinogenic Potency Database Summary Rat Bioassay Results
3	☐	56%	362	AID: 1199, DSSTox (CPDBAS) Carcinogenic Potency Database Summary Mouse Bioassay Results
4	☐	32.8%	239	AID: 1194, DSSTox (CPDBAS) Carcinogenic Potency Database Salmonella Mutagenicity
5	☐	6.9%	40	AID: 1191, DSSTox (CPDBAS) Carcinogenic Potency Database Summary Hamster Bioassay Results
6	☐	4.3%	29	AID: 426, Cell Viability - Jurkat
7	☐	4.2%	29	AID: 544, Cell Viability - SH-SY5Y
8	☐	3.8%	42	AID: 1188, DSSTox (EPAFHM) EPA Fathead Minnow Acute Toxicity
9	☐	3.6%	24	AID: 540, Cell Viability - N2a
10	☐	3.3%	22	AID: 543, Cell Viability - H-4-II-E
11	☐	3.3%	22	AID: 981, Cell Viability - LYMP2-010
12	☐	3.2%	20	AID: 427, Cell Viability - Hek293
13	☐	3.2%	55	AID: 1195, DSSTox (FDAMDD) FDA Maximum (Recommended) Daily Dose Database

U.S. ENVIRONMENTAL PROTECTION AGENCY

Distributed Structure-Searchable Toxicity (DSSTox) Public Database Network

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DSSTox

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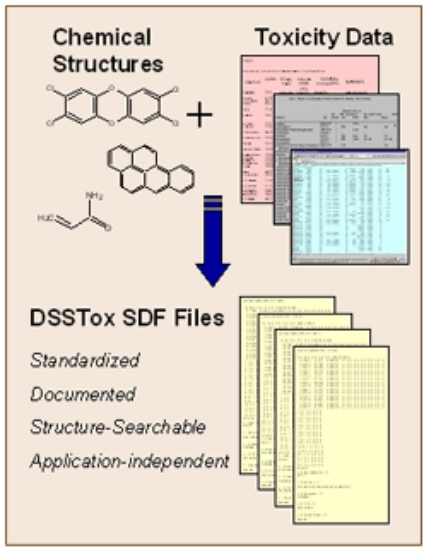
EPA DSSTox Structure-Browser GO

DSSTox Structure-Browser information Page



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- DSSTox Project Goals
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29 April 2008

- Minor QA revisions to TOXCST and CPDBAS.

24 April 2008

- NTPBSI: National Toxicology Program Bioassay On-line Database Structure-Index Locator File ** *Updated to v3a*

- All current DSSTox Data File substance inventories are now available in PubChem, with explicit DSSTox bioassay summary data provided for main data files (see listing below).

Note: Updated instructions and PubChem_SID txt files for use in searching and retrieving PubChem data for DSSTox substances will soon be posted on this website (*est. May 2008*).

25 February 2008

***File Updates and Enhancements:

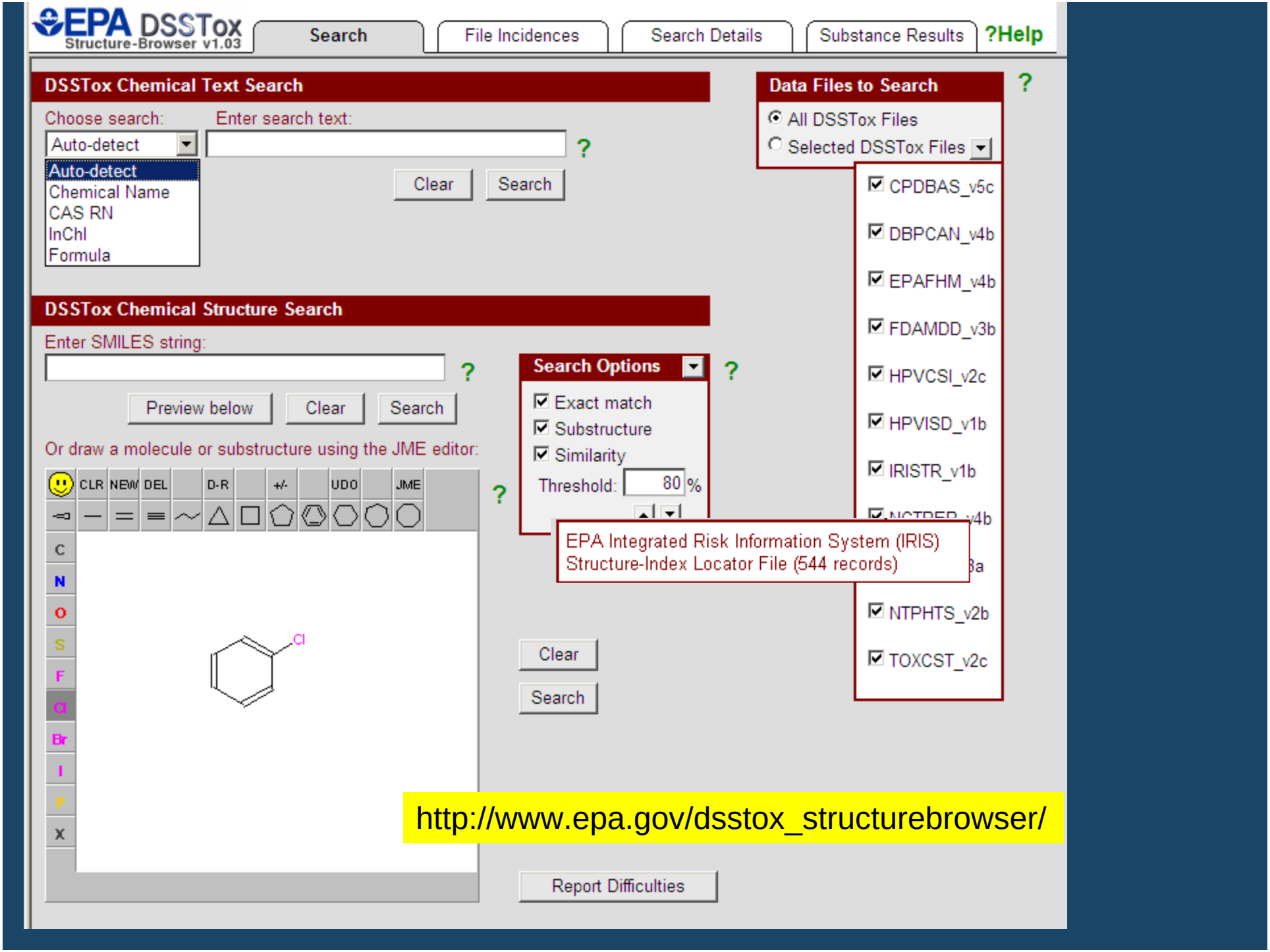
- Addition of new DSSTox Standard Chemical Field to all files: STRUCTURE_InChIKey

- Additional QA review, structure/CAS modifications, elimination of abbreviations in field entries, etc.

DSSTox Data Files: Details>

CPDBAS_v5c_1547_29Apr2008 *revise
DBPCAN_v4b_209_15Feb2008
EPAFHM_v4b_617_15Feb2008
FDAMDD_v3b_1216_15Feb2008
HPVCSI_v2c_3548_15Feb2008
HPVISD_v1b_1006_15Feb2008
IRISTR_v1b_544_15Feb2008
NCTRER_v4b_232_15Feb2008
NTPBSI_v3a_2303_24Apr2008 *update
NTPHTS_v1b_1408_15Jul2008
TOXCST_v2c_320_29Apr2008 *revise

>Other (non-DSSTox) Data Files


EPA DSSTox
Structure-Browser v1.03
Search
File Incidences
Search Details
Substance Results
?Help
DSSTox Chemical Text Search
Choose search:
Enter search text:
Auto-detect
Auto-detect
Chemical Name
CAS RN
InChI
Formula
Clear
Search
Data Files to Search
All DSSTox Files
Selected DSSTox Files
CPDBAS_v5c
DBPCAN_v4b
EPAFHM_v4b
FDAMDD_v3b
HPVCSI_v2c
HPVISD_v1b
IRISTR_v1b
NTPHTS_v2b
TOXCST_v2c
DSSTox Chemical Structure Search
Enter SMILES string:
Preview below
Clear
Search
Or draw a molecule or substructure using the JME editor:
CLR
NEW
DEL
D-R
+/-
UDO
JME
Search Options
Exact match
Substructure
Similarity
Threshold:
80
%
EPA Integrated Risk Information System (IRIS)
Structure-Index Locator File (544 records)
Clear
Search
Report Difficulties
http://www.epa.gov/dsstox_structurebrowser/

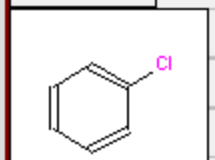
EPA DSSTox Structure-Browser v1.03

Search | File Incidences | Search Details | Substance Results | ?Help

EPA DSSTox Structure-Browser v1.03

Search | File Incidences | ?Help

Search Results Summary for DSSTox Substances - File Breakdown Incidences

Query	Results Type	Hits	Display
Structure: 	Exact matches	1	Details
	Substructures	518	Details
	Similarity > 80%	6	Details

?

DSSTox File ?	Total#Records	Exact matches	Substructures	Similarity > 80%
CPDBAS_v5c	1547	1	112	3
DBPCAN_v4b	209	-	2	-
EPAFHM_v4b	617	1	62	3
FDAMDD_v3b	1216	-	136	-
HPVCSI_v2c	3548	1	68	5
HPVISD_v1b	1006	1	22	4
IRISTR_v1b	544	1	73	4
NCTRER_v4b	232	-	24	-
NTPBSI_v3a	2303	1	188	6
NTPHTS_v2b	1408	1	134	5
TOXCST_v2c	320	-	78	-
Total Unique Substance Hits		**1**	**518**	**6**
Total Substance Hits - All Files		**7**	**899**	**30**

?

Report Difficulties

EPA DSSTox Structure-Browser v1.03

Search | File Incidences | Search Details | Substance Results | ?Help

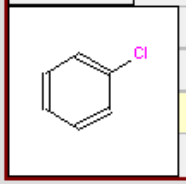
EPA DSSTox Structure-Browser v1.03

Search | File Incidences | ?Help

EPA DSSTox Structure-Browser v1.03

Search | File Incidences | Search Details | ?Help

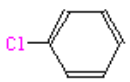
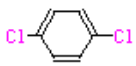
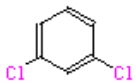
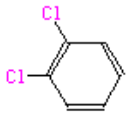
Details

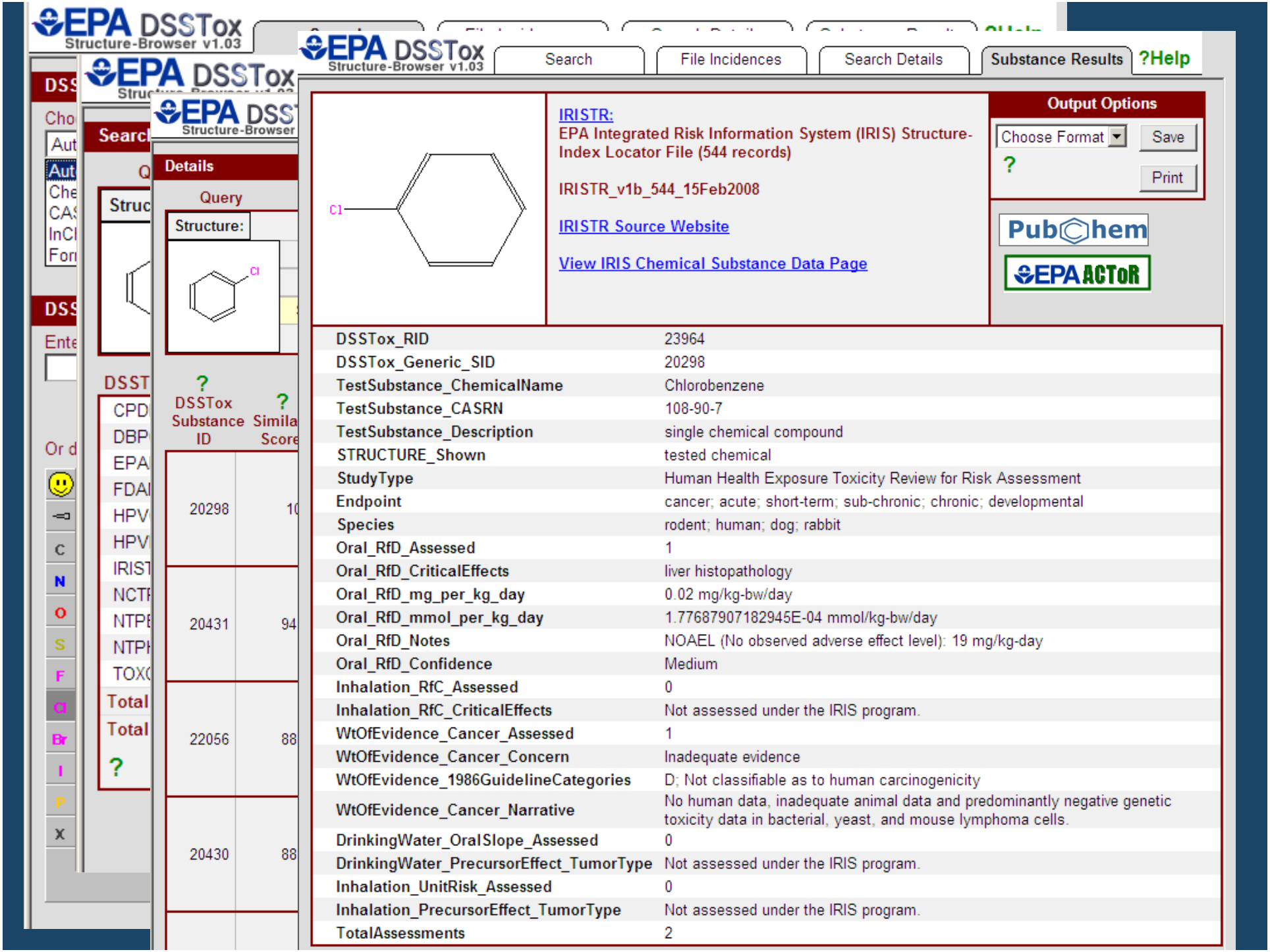
Query	Results Type	Hits	Display
Structure: 	Exact matches	1	Details
	Substructures	518	Details
	Similarity > 80%	6	Details

?

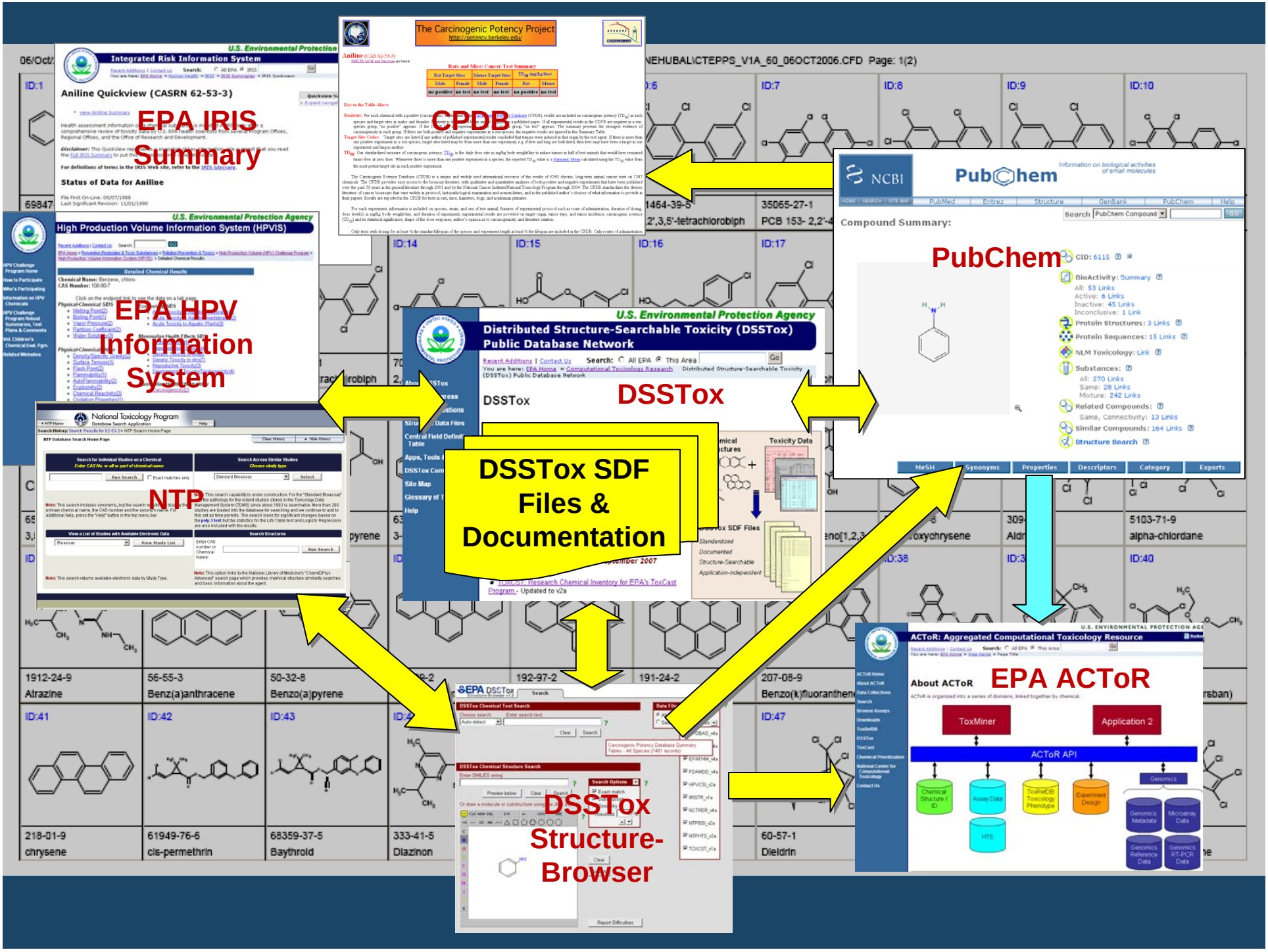
Output Options

Choose Format | Save | Print | ?

? DSSTox Substance ID	? Similarity Score%	Structure Match	Substance Name	CASRN	Substance Description	Details (Data Files)
20298	100		Chlorobenzene	108-90-7	single chemical compound	CPDBAS EPAFHM HPVCSI HPVISD IRISTR NTPBSI NTPHTS
20431	94.1		1,4-Dichlorobenzene	106-46-7	single chemical compound	CPDBAS HPVCSI IRISTR NTPBSI
22056	88.8		1,3-Dichlorobenzene	541-73-1	single chemical compound	EPAFHM HPVCSI HPVISD IRISTR NTPBSI NTPHTS
20430	88.8		1,2-Dichlorobenzene	95-50-1	single chemical compound	CPDBAS EPAFHM HPVCSI HPVISD IRISTR NTPBSI NTPHTS
						

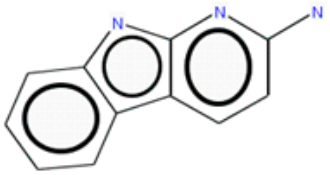


DSSTox_RID	23964
DSSTox_Generic_SID	20298
TestSubstance_ChemicalName	Chlorobenzene
TestSubstance_CASRN	108-90-7
TestSubstance_Description	single chemical compound
STRUCTURE_Shown	tested chemical
StudyType	Human Health Exposure Toxicity Review for Risk Assessment
Endpoint	cancer; acute; short-term; sub-chronic; chronic; developmental
Species	rodent; human; dog; rabbit
Oral_RfD_Assessed	1
Oral_RfD_CriticalEffects	liver histopathology
Oral_RfD_mg_per_kg_day	0.02 mg/kg-bw/day
Oral_RfD_mmol_per_kg_day	1.77687907182945E-04 mmol/kg-bw/day
Oral_RfD_Notes	NOAEL (No observed adverse effect level): 19 mg/kg-day
Oral_RfD_Confidence	Medium
Inhalation_RfC_Assessed	0
Inhalation_RfC_CriticalEffects	Not assessed under the IRIS program.
WtOfEvidence_Cancer_Assessed	1
WtOfEvidence_Cancer_Concern	Inadequate evidence
WtOfEvidence_1986GuidelineCategories	D; Not classifiable as to human carcinogenicity
WtOfEvidence_Cancer_Narrative	No human data, inadequate animal data and predominantly negative genetic toxicity data in bacterial, yeast, and mouse lymphoma cells.
DrinkingWater_OralSlope_Assessed	0
DrinkingWater_PrecursorEffect_TumorType	Not assessed under the IRIS program.
Inhalation_UnitRisk_Assessed	0
Inhalation_PrecursorEffect_TumorType	Not assessed under the IRIS program.
TotalAssessments	2


EPA IRIS Summary
CPDB
EPA HPV Information System
DSSTox
PubChem
NTP
DSSTox SDF Files & Documentation
DSSTox Structure-Browser
EPA ACToR
Integrated Risk Information System
Aniline Quickview (CASRN 62-53-3)
The Carcinogenic Potency Project
High Production Volume Information System (HPVIS)
Distributed Structure-Searchable Toxicity (DSSTox) Public Database Network
National Toxicology Program
PubChem
Compound Summary:
ACToR: Aggregated Computational Toxicology Resource
About ACToR
ToxMiner
Application 2
ACToR API
1912-24-9
Atrazine
56-55-3
Benz(a)anthracene
50-32-8
Benzo(a)pyrene
207-08-9
Benzo(k)fluoranthene
5103-71-9
alpha-chlordane
218-01-9
chrysene
61949-76-6
cis-permethrin
68359-37-5
Baythroid
333-41-5
Diazinon
60-57-1
Dieldrin

Generic Chemical

Preferences: Refresh | Visibility | Table Size | Select Skin



GCID: 1
CASRN: 26148-68-5
CID: 11869
CCID: 11869
Formula: C11H9N3
MW: 183.212
SMILES: NC1C=CC2=C(N=1)NC3=CC=CC=C23
INCHI: InChI=1/C11H9N3/c12-10-6-5-8-7-3-1-2-4-9(7)13-11(8)
QC Status: QUEUED

Substances

Chemical Id	Data Collection	Name
1	CPDBAS_DSSTOX	A-alpha-C
18819	CalEPA	A-alpha-C (2-Amino-9H-pyrido[2,3-b]indole)
35633	INCHEM_IARC	A-alpha-C (2-Amino-9H-Pyrido[2,3-b]Indole)
78935	Scorecard	2-AMINO-9H-PYRIDO (2,3-B) INDOLE (A-ALPHA-C)
95724	SRS_CAS-9CI	2-Amino-9H-pyrido[2,3-b]indole
168920	SRS_ChemIDStd	2-Amino-9H-pyrido[2,3-b]indole
514465	ChemIDplus	1H-Pyrido(2,3-b)indol-2-amine
919306	EPA	26148-68-5
1413536	EPA_SRS_NTS	1H-Pyrido[2,3-b]indol-2-amine

Notes

Chemical Id	Data Collection	Note
1	CPDBAS_DSSTOX	blank
1413536	EPA_SRS_NTS	ACD/Name-to-Structure Batch v. 8.05

Synonyms

Name
.
1H-Pyrido(2,3-b)indol-2-amine
1H-Pyrido[2,3-b]indol-2-amine
2-AMINO-9H-PYRIDO (2,3-B) INDOLE (A-ALPHA-C)
2-AMINO-9H-PYRIDO(2,3-B)INDOLE
2-Amino-9H-pyrido[2,3-b]indole
2-Amino-alpha-carboline
26148-68-5
9H-Pyrido(2,3-b)indole, 2-amino-
9H-pyrido[2,3-b]indol-2-amine

Previous 1-10 of 17 Next 7

MSDS

MSDS Id

No rows yet.

Mesh

Mesh Name

PubMed via MeSH: 2-amino-9H

External Search

External Search

TOXNET CCRIS
TOXNET DART ETIC
TOXNET EMIC
TOXNET GENETOX
TOXNET HazMap
TOXNET Houshold Products
TOXNET HSDB
TOXNET MESH Headings
TOXNET TOXLINE
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ACToR: Aggregated Computational Toxicology Resource

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Data Collection

Name: IRISTR_DSSTOX

Description: EPA Integrated Risk Information System http://www.epa.gov/iris/. A structure index file with links to webpage for
Source Type: DSSTox Collection
Number of Substances: 544
Number of Generic Chemicals: 536
Compilation Date: 9/27/2007
Compilation Instructions: Download SD and excel files from DSSTox site. Preprocess according to ToxCast SOP 004

Fetch Size: 100 Offset: 0 Fetch

Generic Chemical	CASRN	Structure	Substance	Source SID	Name	Structure	PhysicoChemical	Biochemical	In vivo toxicology (tabular primary)	In vivo toxicology (study listing primary)	In vivo toxicology (tabular secondary)	In vivo toxicology (summary calls)	In vivo toxicology (summary report via URL)	Regulation	Chemical Use Level	Carcinogenicity	GeneTox	DevTox	ReproTox	EcoTox	FoodSafe
Details	83-32-9		Details	DSSTOX_1774	Acenaphthylene, 1,2-dihydro-	1687	10	7	1	1	4	3	5	5		5	6	3	3	1	
Details	208-96-8		Details	DSSTOX_3845	Acenaphthylene	5129					1	1	3	2		4	3	3	2	1	
				DSSTOX_3846	Acephate	5130	9			6	1	10	5	1		9	4	6	5	3	
				DSSTOX_2	Acetaldehyde	2	9	40	3	1	4	16	8	9		14	9	5	3	2	1

Where are the data??

Part II

Toxicity Profiling

National Academy of Sciences Report (2007)
Toxicity Testing in the Twenty-first Century: A Vision and a Strategy

NAS PANEL SEEKS MAJOR SHIFT IN HOW EPA ASSESSES CHEMICALS' TOXICITY

Date: June 22, 2007 -

Inside EPA
Online access provided by InsideEPA.com

A National Academy of Sciences (NAS) panel is calling for a major shift in how EPA assesses chemicals' toxicity, recommending that the agency base its toxicological research and regulatory processes on how substances affect biological pathways -- which send information within and between cells -- rather than so-called health endpoints, such as cancer.

POLICYFORUM

Science: Feb 15, 2008

TOXICOLOGY

Transforming Environmental Health Protection

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

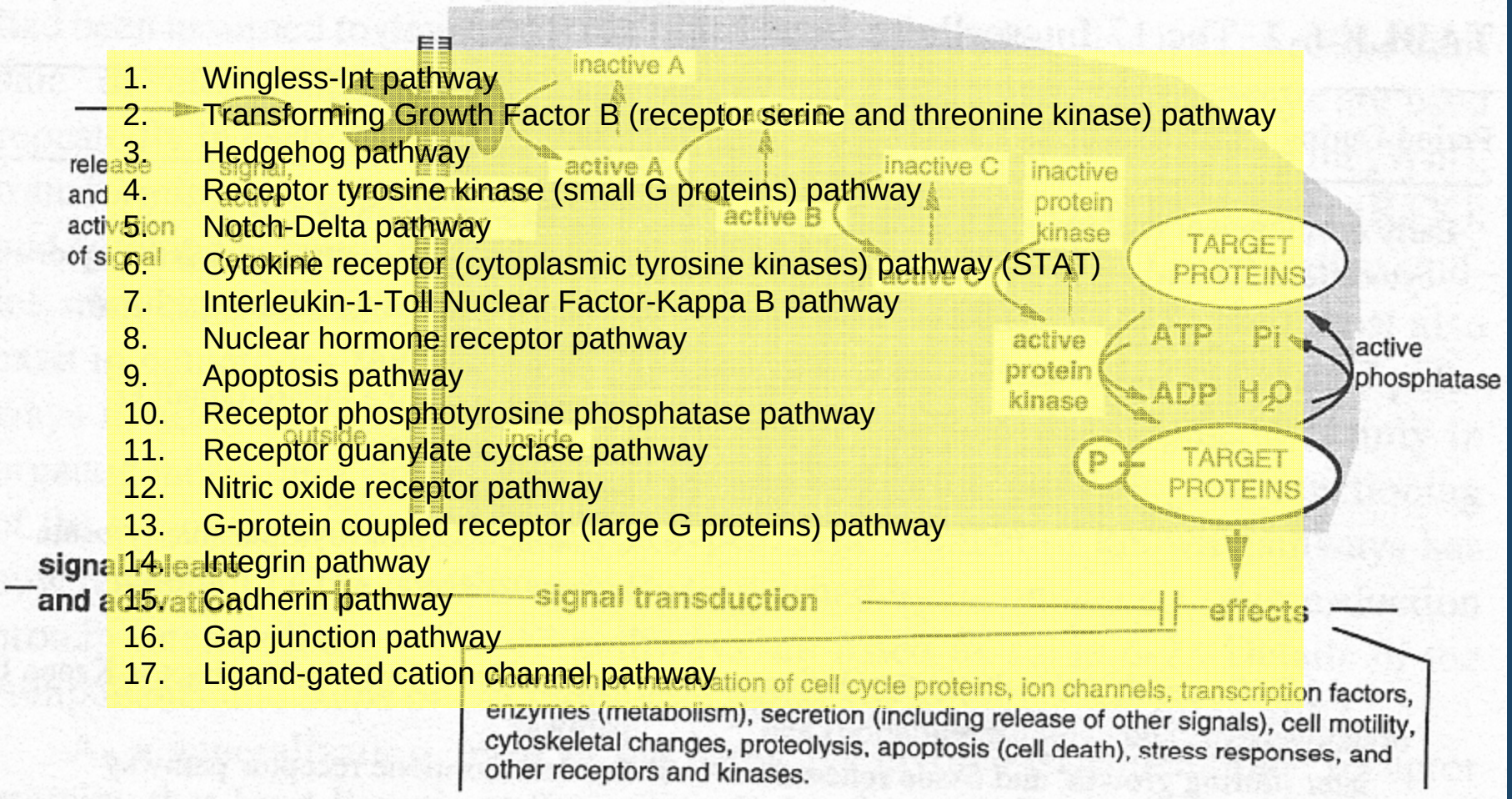
We propose a shift from primarily in vivo animal studies to in vitro assays, in vivo assays with lower organisms, and computational modeling for toxicity assessments.

In 2005, the U.S. Environmental Protection Agency (EPA), with support from the U.S. throughput screening (HTS) and other automated screening assays into its testing tion, usually between 2 and 10 μM, and tolerate high false-negative rates. In contrast, in

Scientific Frontiers in Developmental Toxicology & Risk Assessment -

National Academy of Sciences, 2000

1. Wingless-Int pathway
2. Transforming Growth Factor B (receptor serine and threonine kinase) pathway
3. Hedgehog pathway
4. Receptor tyrosine kinase (small G proteins) pathway
5. Notch-Delta pathway
6. Cytokine receptor (cytoplasmic tyrosine kinases) pathway (STAT)
7. Interleukin-1-Toll Nuclear Factor-Kappa B pathway
8. Nuclear hormone receptor pathway
9. Apoptosis pathway
10. Receptor phosphotyrosine phosphatase pathway
11. Receptor guanylate cyclase pathway
12. Nitric oxide receptor pathway
13. G-protein coupled receptor (large G proteins) pathway
14. Integrin pathway
15. Cadherin pathway
16. Gap junction pathway
17. Ligand-gated cation channel pathway



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National Center for Computational Toxicology

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

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- Publications
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- Jobs and Opportunities
- Related Information

ToxCast™ Program

Predicting Hazard, Characterizing Toxicity Pathways, and Prioritizing the Toxicity Testing of Environmental Chemicals

ToxCast™ Navigation

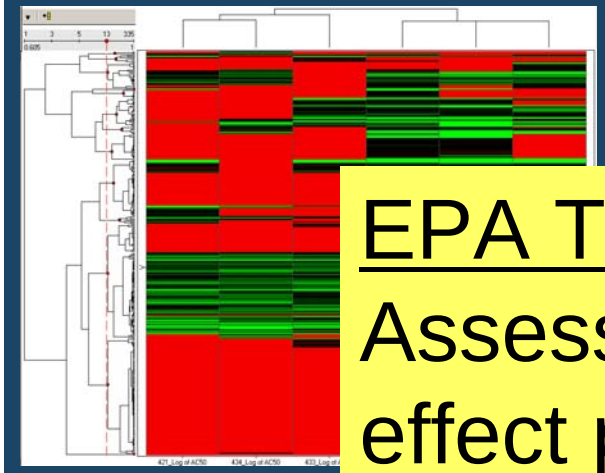
- Introduction
- ToxCast™ Chemicals
- ToxCast™ Assays
- ToxCast™ Information Management
- ToxCast™ Partnerships
- ToxCast™ Contractors
- ToxCast™ Presentations
- ToxCast™ Publications
- ToxCast™ News

Introduction

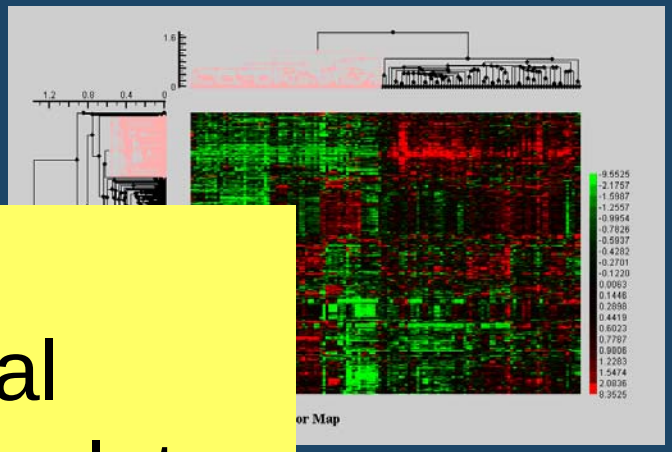
In 2007, EPA launched ToxCast™ in order to develop a cost-effective approach for prioritizing the toxicity testing of large numbers of chemicals in a short period of time. Using data from state-of-the-art high throughput screening (HTS) bioassays developed in the pharmaceutical industry, ToxCast™ is building computational models to forecast the potential human toxicity of chemicals. These hazard predictions will provide EPA regulatory programs with science-based information helpful in prioritizing chemicals for more detailed toxicological evaluations, and lead to more efficient use of animal testing.

In its first phase, ToxCast™ is profiling over 300 well-characterized chemicals (primarily pesticides) in over 400 HTS endpoints. These endpoints include biochemical assays of protein function, cell-based transcriptional reporter assays, multi-cell interaction assays, transcriptomics on primary cell cultures, and developmental assays in zebrafish embryos. Almost all of the compounds being examined in Phase 1 of ToxCast™ have been tested in traditional toxicology tests, including developmental toxicity, multi-generation studies, and sub-chronic and chronic rodent bioassays. ToxRefDB, a relational database being created to house this information, will contain nearly $1B worth of toxicity studies in animals when completed. ToxRefDB is integrated into a more comprehensive data management system developed by NCCT called ACToR (Aggregated Computational Toxicology Resource), that manages the large-

Correlating Domain Outputs

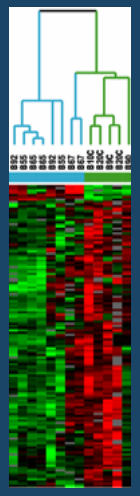


CellularA

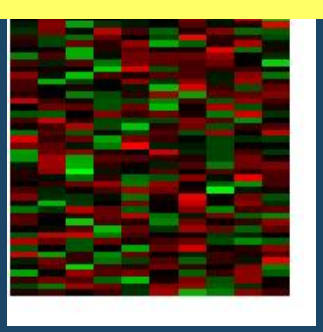


emical properties

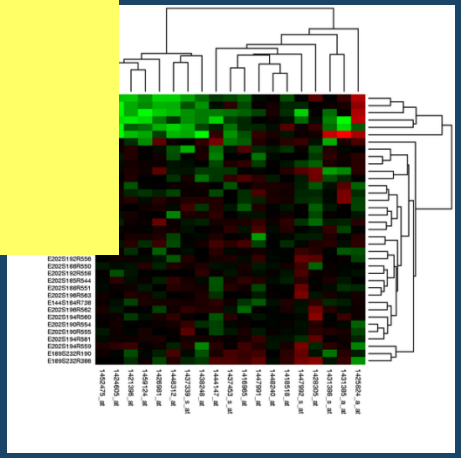
EPA ToxCast Goal:
Assess broad biological effect patterns and correlate with the patterns of known toxicants for forecasting potential for hazard



Biochemical Assays

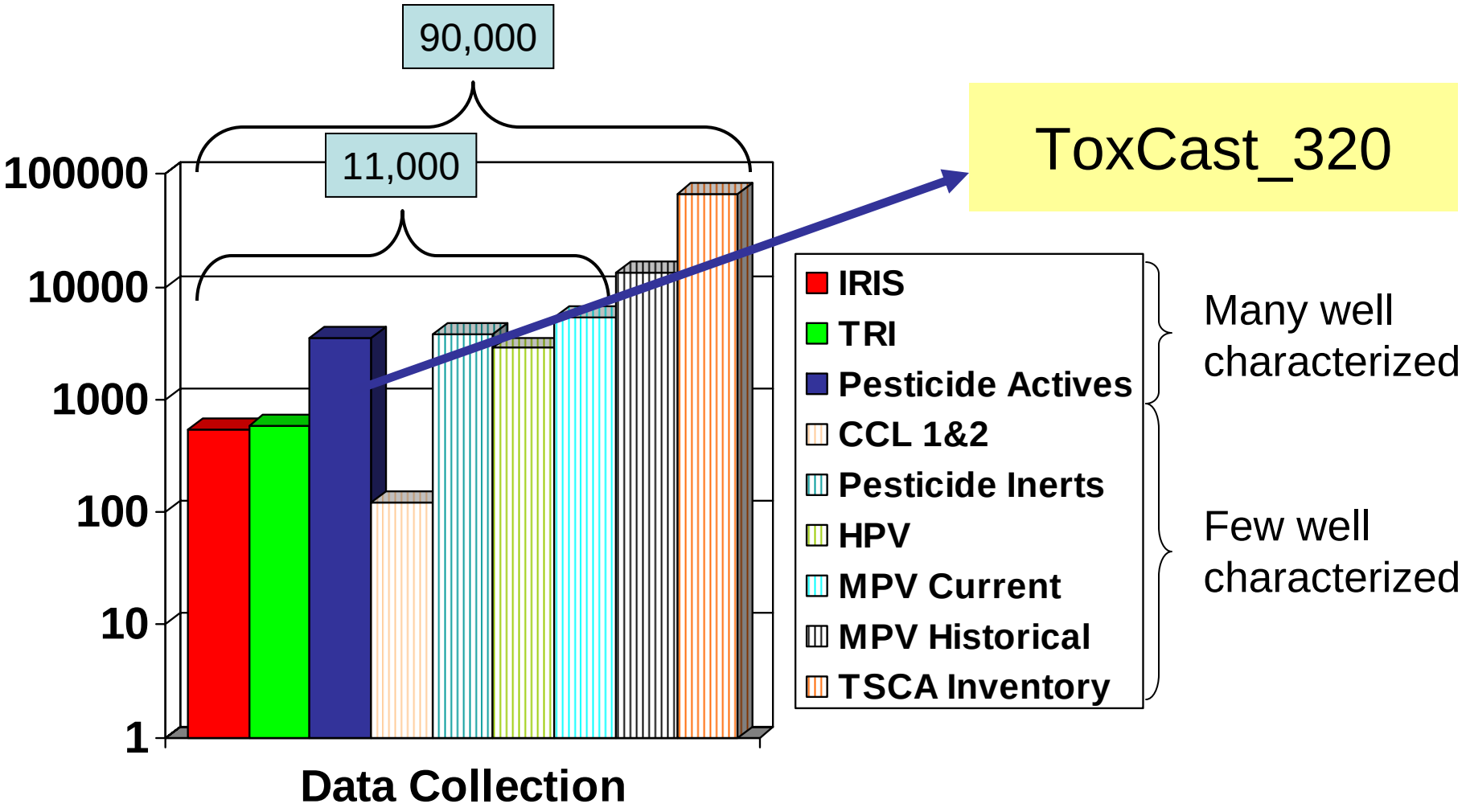


Genomic Signatures



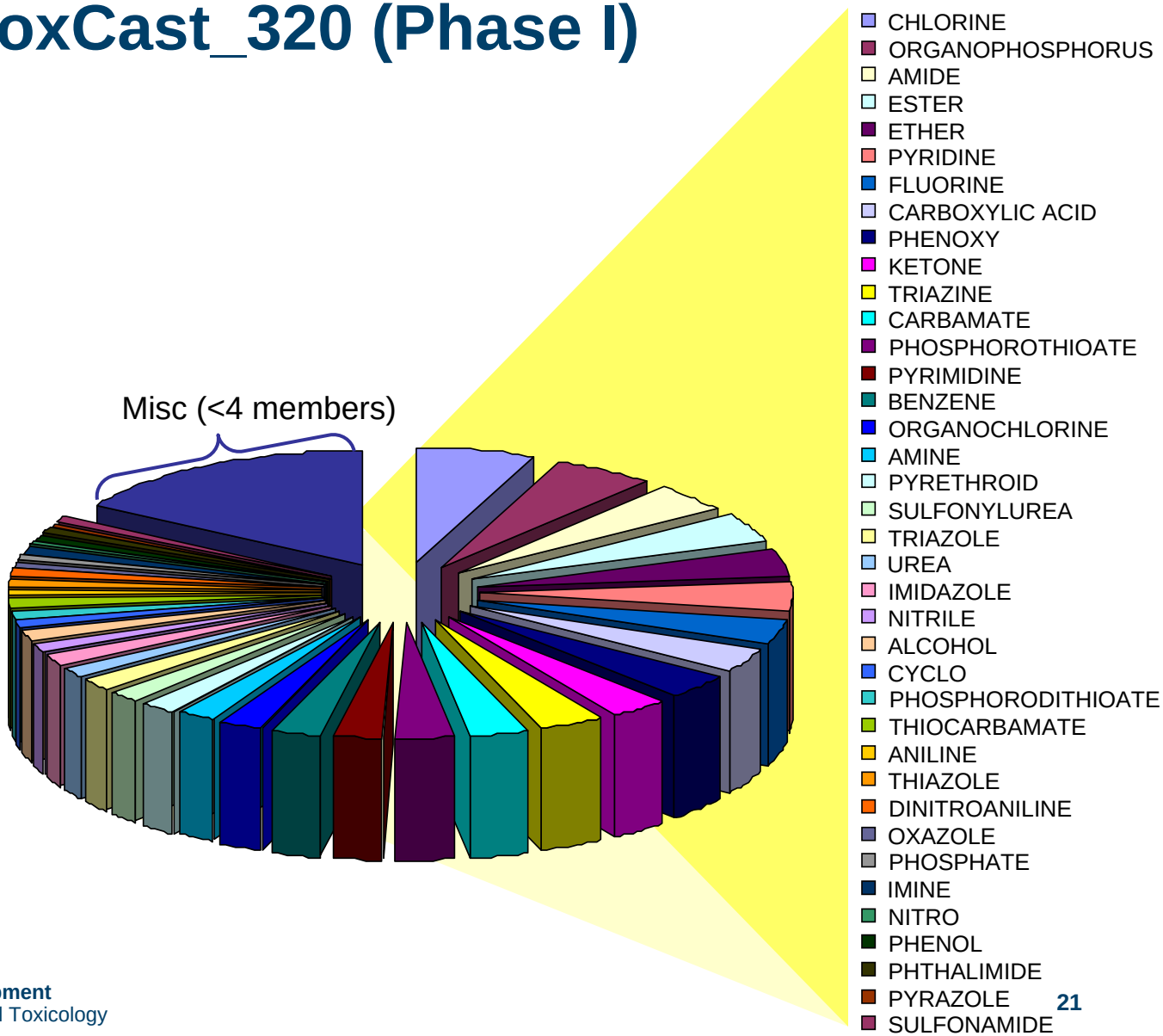
Toxicology Endpoints

ToxCast Phase I Chemicals

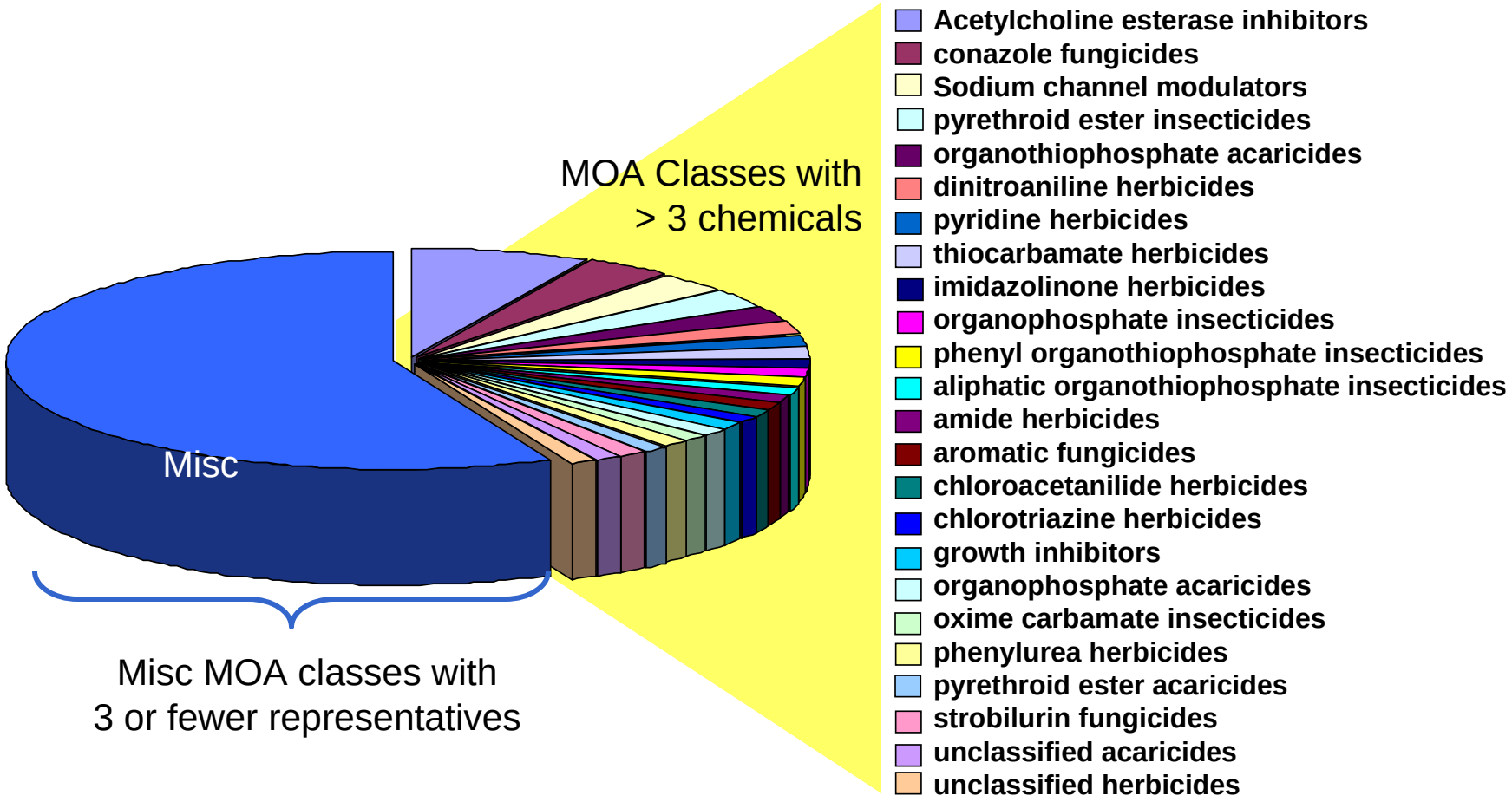


Chemical Classes in ToxCast_320 (Phase I)

- 309 Unique Structures
- Replicates for QC
- 291 Pesticide Actives
- 9 Industrial Chemicals
- 8 Metabolites
- 56/73 Proposed Tier 1 EDSP
- 14 HPV
- 11 HPV Challenge



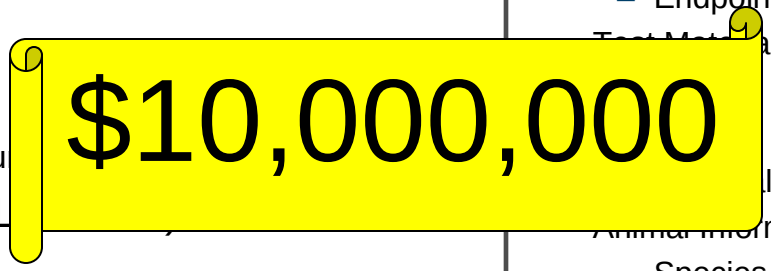
Mode-of-Action Classes in ToxCast_320 (Phase I)



Classification based on OPPIN

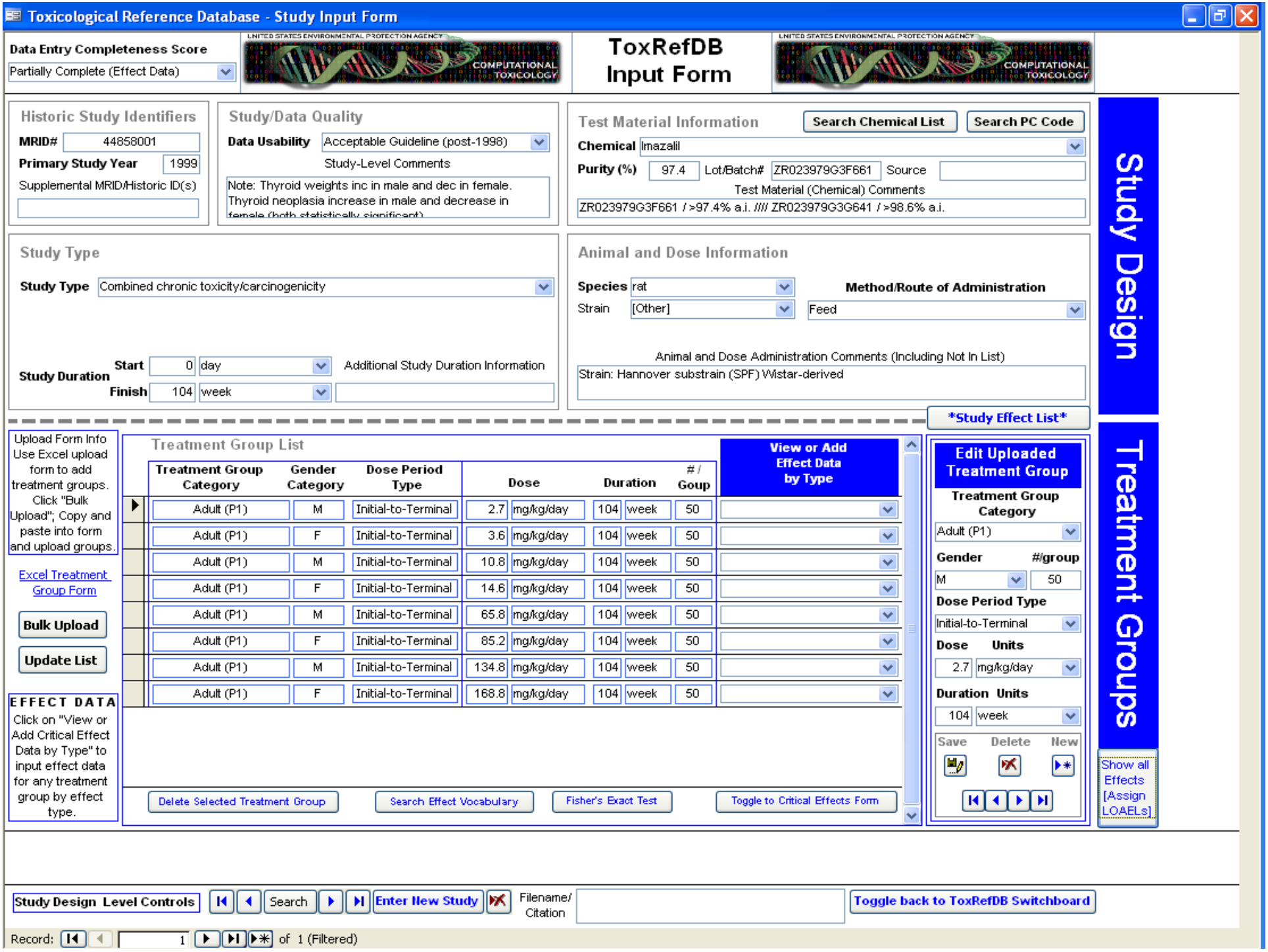
EPA Pesticide Programs: Data Evaluation Records (DERs)

- Used for hazard identification and characterization
- Study Types
  - Chronic
  - Cancer
  - Subchronic
  - Multigeneration
  - Developmental
  - Others: DNT, Neurotox, Immu
- Derive Endpoints (NOAEL
  - Systemic
  - Parental
  - Offspring
  - Reproductive
  - Maternal
  - Developmental
- Critical Effects for Endpoints



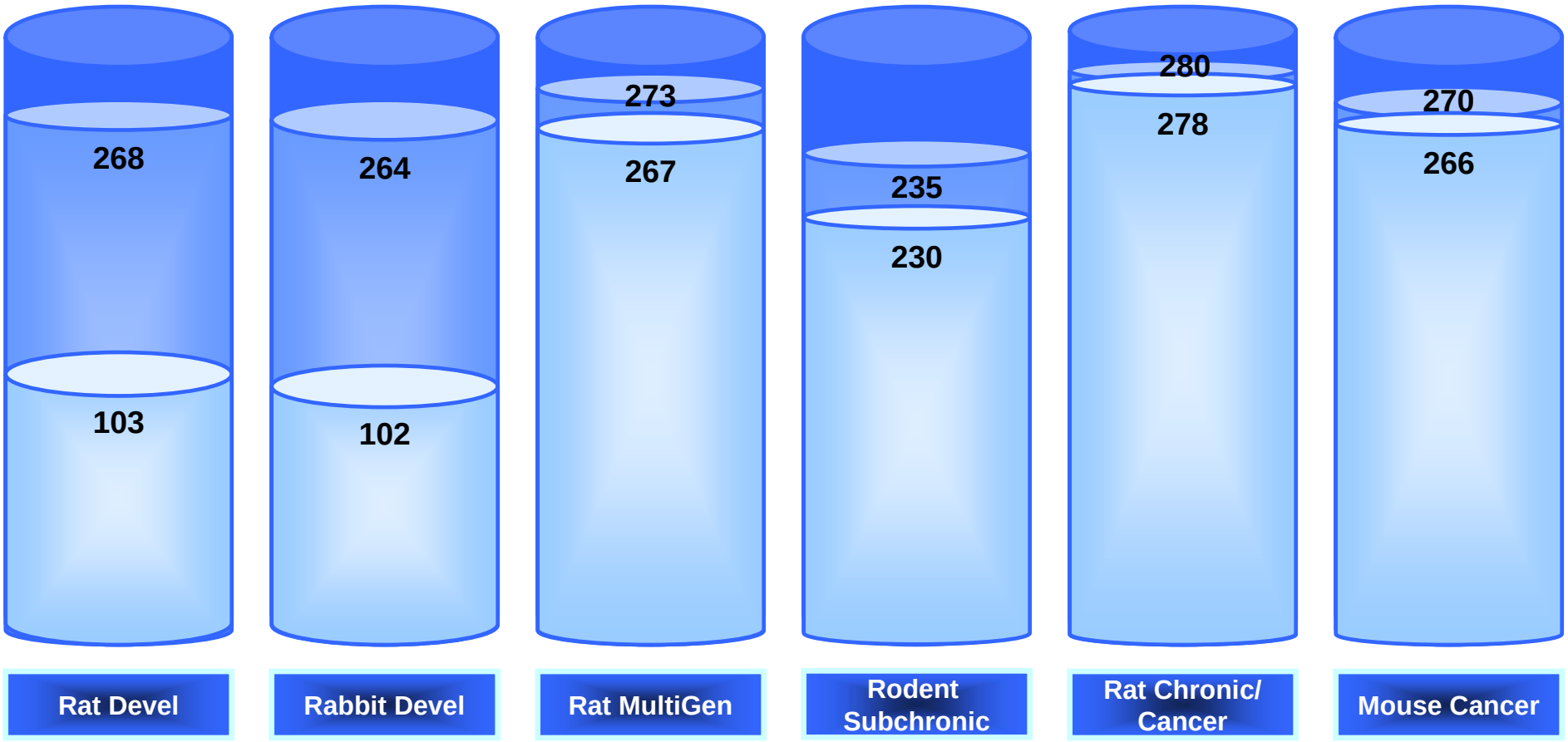
DER Format

- Study Identifiers
  - Tested Chemical Information
    - IDs
    - Name
    - Purity
  - Study Type IDs
  - Reviewer Information
- Citation(s)
- Executive Summary
  - Summary Study Design
  - Summary Effects
  - Endpoints (NOAEL/LOAEL)
  - Test Material
  - l/Chemical Properties
  - Animal Information
  - Species
  - Strain
  - Husbandry
- Results (full dose-response)
  - Clinical signs
  - Body weight
  - Clinical Chemistry/ Hematology
  - Gross Pathology
  - Non-neoplastic Pathology
  - Neoplastic Pathology
  - Parental vs. Offspring
  - Maternal vs. Fetal


Toxicological Reference Database - Study Input Form
Data Entry Completeness Score
Partially Complete (Effect Data)
ToxRefDB Input Form
Historic Study Identifiers
MRID# 44858001
Primary Study Year 1999
Supplemental MRID/Historic ID(s)
Study/Data Quality
Data Usability Acceptable Guideline (post-1998)
Study-Level Comments
Note: Thyroid weights inc in male and dec in female. Thyroid neoplasia increase in male and decrease in female (both statistically significant)
Test Material Information
Search Chemical List
Search PC Code
Chemical Imazalil
Purity (%) 97.4
Lot/Batch# ZR023979G3F661
Source
Test Material (Chemical) Comments
ZR023979G3F661 / >97.4% a.i. /// ZR023979G3G641 / >98.6% a.i.
Study Type
Study Type Combined chronic toxicity/carcinogenicity
Study Duration Start 0 day
Finish 104 week
Additional Study Duration Information
Animal and Dose Information
Species rat
Strain [Other]
Method/Route of Administration
Feed
Animal and Dose Administration Comments (Including Not In List)
Strain: Hannover substrain (SPF) Wistar-derived
Study Effect List
Study Design
Treatment Groups
Upload Form Info
Use Excel upload form to add treatment groups. Click "Bulk Upload"; Copy and paste into form and upload groups.
Excel Treatment Group Form
Bulk Upload
Update List
EFFECT DATA
Click on "View or Add Critical Effect Data by Type" to input effect data for any treatment group by effect type.
Treatment Group List
Treatment Group Category | Gender Category | Dose Period Type | Dose | Duration | # / Goup | View or Add Effect Data by Type
Adult (P1) | M | Initial-to-Terminal | 2.7 mg/kg/day | 104 week | 50
Adult (P1) | F | Initial-to-Terminal | 3.6 mg/kg/day | 104 week | 50
Adult (P1) | M | Initial-to-Terminal | 10.8 mg/kg/day | 104 week | 50
Adult (P1) | F | Initial-to-Terminal | 14.6 mg/kg/day | 104 week | 50
Adult (P1) | M | Initial-to-Terminal | 65.8 mg/kg/day | 104 week | 50
Adult (P1) | F | Initial-to-Terminal | 85.2 mg/kg/day | 104 week | 50
Adult (P1) | M | Initial-to-Terminal | 134.8 mg/kg/day | 104 week | 50
Adult (P1) | F | Initial-to-Terminal | 168.8 mg/kg/day | 104 week | 50
Delete Selected Treatment Group
Search Effect Vocabulary
Fisher's Exact Test
Toggle to Critical Effects Form
Edit Uploaded Treatment Group
Treatment Group Category
Adult (P1)
Gender
M
#/group
50
Dose Period Type
Initial-to-Terminal
Dose
2.7
Units
mg/kg/day
Duration
104
Units
week
Save
Delete
New
Show all Effects [Assign LOAELs]
Study Design Level Controls
Search
Enter New Study
Filename/ Citation
Toggle back to ToxRefDB Switchboard
Record: 1 of 1 (Filtered)

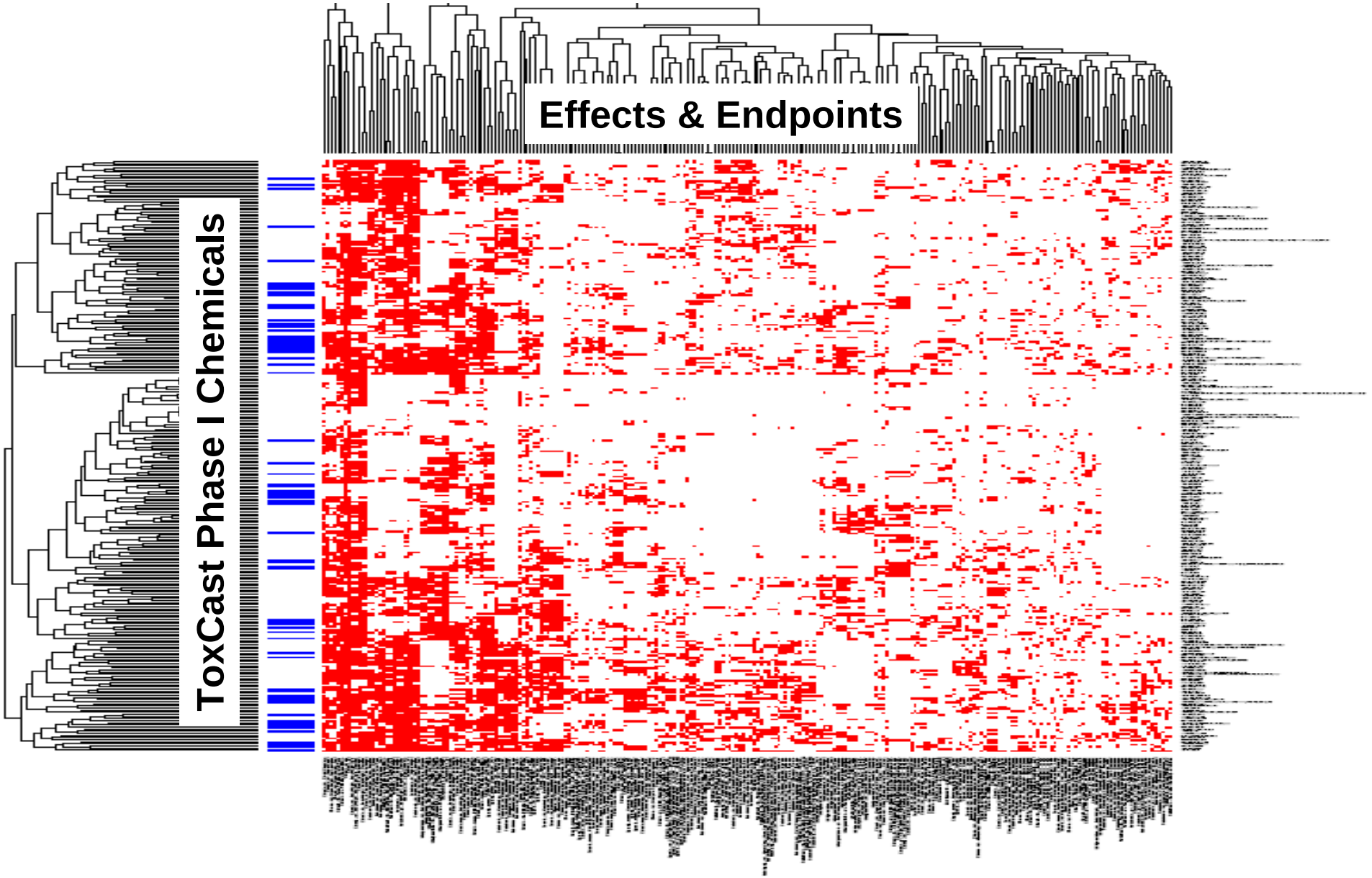
ToxRefDB Data Entry Status

ToxCast Phase I Chemicals Only
Total: 291 Pesticides

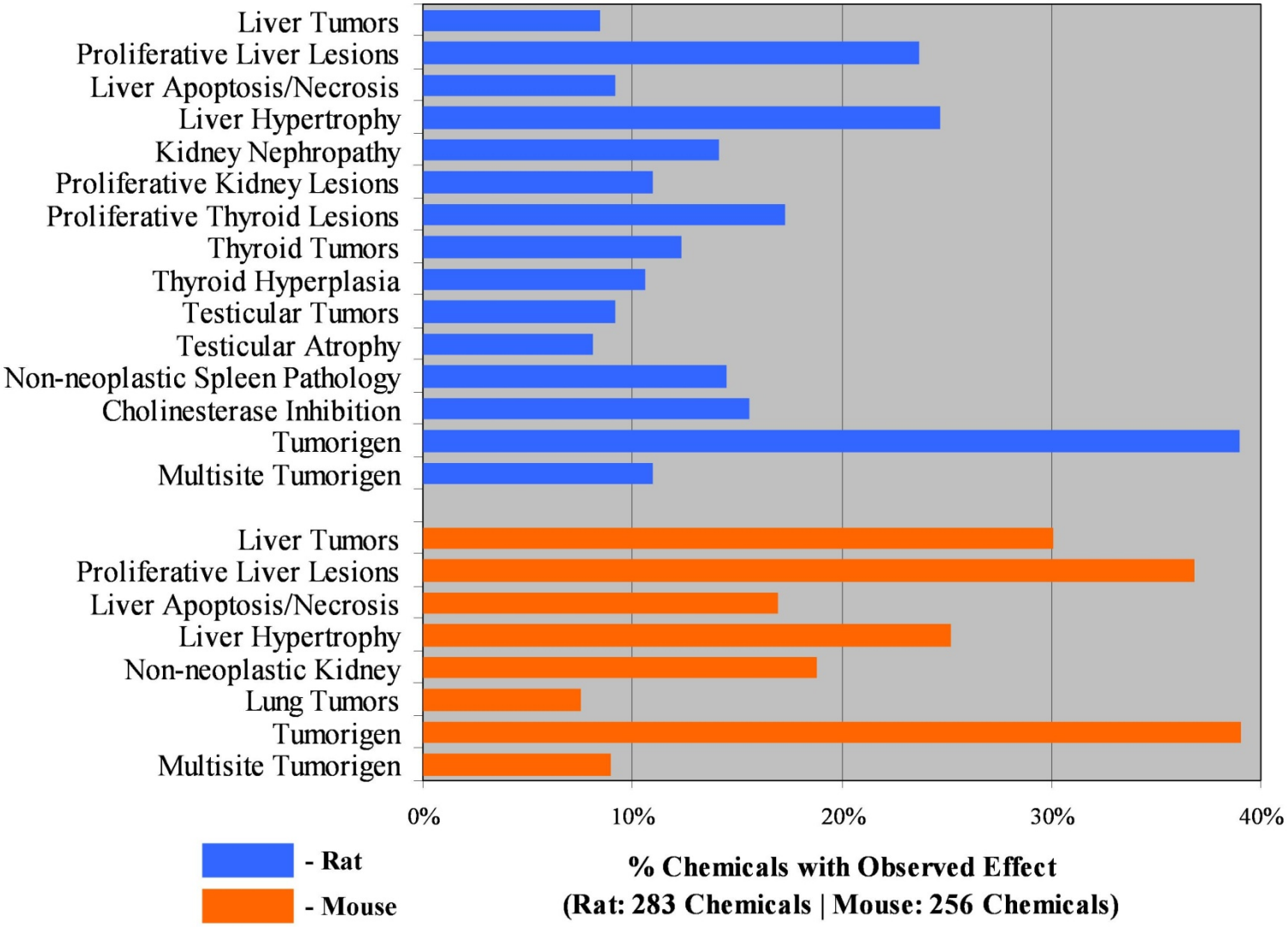


$400 Million Dollars Worth of *In Vivo* Chronic/Cancer Bioassay Effects and Endpoints

EPA United States Environmental Protection Agency



Common Phenotypes in Chronic Rodent Studies



ToxCast Contracts for Generating HTS and Genomics Data

Receptors, Enzymes

Cell Signaling

Compound Focus, Inc.

BioFocus DPI
A Galápagos Company

BioSeek

NovaScreen
company

Transcription Factors

Metabolic Transformation

attagene
The Home of TFomics™

CELLUMEN

Cell Function

ACEA Biosciences, Inc.

EXPRESSION ANALYSIS

PHYLONIX
Zebrafish Assays for Drug Screening

Nine contracts p… …ocurement; hundreds …
…ochemical, cell… …d genomic assays; mo…
…anisms; and the capacity to screen up to 10,000 ch…

In vitro Genomics

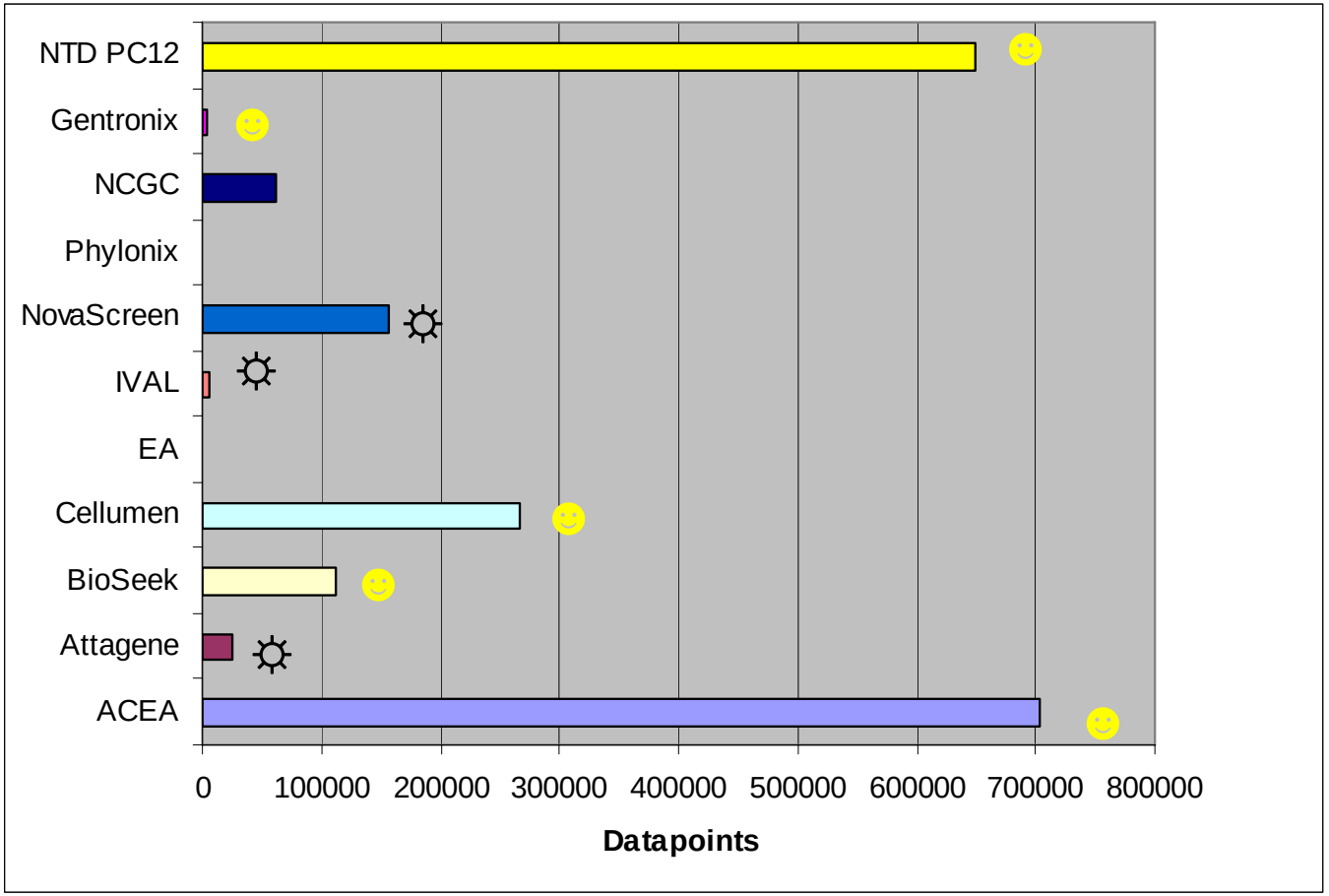
Cell Function

Alternative Species

Assay Type	# Assays	# Endpoints	Assay Source	Comment	Source	ToxCast_320 Status 04dec2007
HTS	**240**	**240**	**Human, rat, other**	**Enzyme inhibition, receptor binding**	**NovaScreen**	Single concentration data delivered; multiple concentration to follow
uHTS	**10+**	**10+**	**Human and rodent**	**Nuclear receptor reporter gene assays**	**NIH Chemical Genomics Center**	Multiple concentration (11) data from 2 of 10 assays delivered
Reporter Gene Assays	**2**	**67**	**HepG2 cells (human liver)**	**Nuclear receptor, transcription factor**	**Attagene**	Single concentration data delivered; multiple concentration to follow
Genomics	**1**	**22,000**	**Hepatocyte-Kupffer co-culture**	**PCR, microarrays**	**IVAL and Expression Analysis**	Multiple concentration (5) in rat system underway
Kinetic Cell Growth	**1**	**Kinetic**	**A549 cells (human lung)**	**Real time electrical impedance**	**ACEA Biosciences**	Multiple concentration (8) data delivered
Cell Co-Culture	**1**	**6**	**Human liver, lung, kidney cells**	**Cytotoxicity, shared metabolism**	**IVAL**	Multiple concentration (8) data underway
Complex Cell Culture	**8**	**87**	**Primary human cells**	**Cell signaling pathways**	**Bioseek**	Multiple concentration (4) data delivered
HCS	**1**	**11**	**HepG2 cells (human liver)**	**Imaging cytotoxicity**	**Cellumen**	Multiple concentration (10) data delivered
Tissue Slice Culture	**1**	**1**	**Rat liver, lung, kidney**	**Precision-cut Tissue slices**	**Hamner Institutes**	Multiple concentration (5) data underway
Zebrafish	**1**	**11**	**Danio rerio**	**Teratogenesis**	**Phylonix**	Multiple concentration (3) data underway for 20 chemicals
TOTAL	**265**	**22,433**				

United States Environmental Protection Agency

The Deluge of Data has Started……..



☺ Data acquisition completed; ☼ Concentration response follow up underway

U.S. ENVIRONMENTAL PROTECTION AGE

ACToR: Aggregated Computational Toxicology Resource

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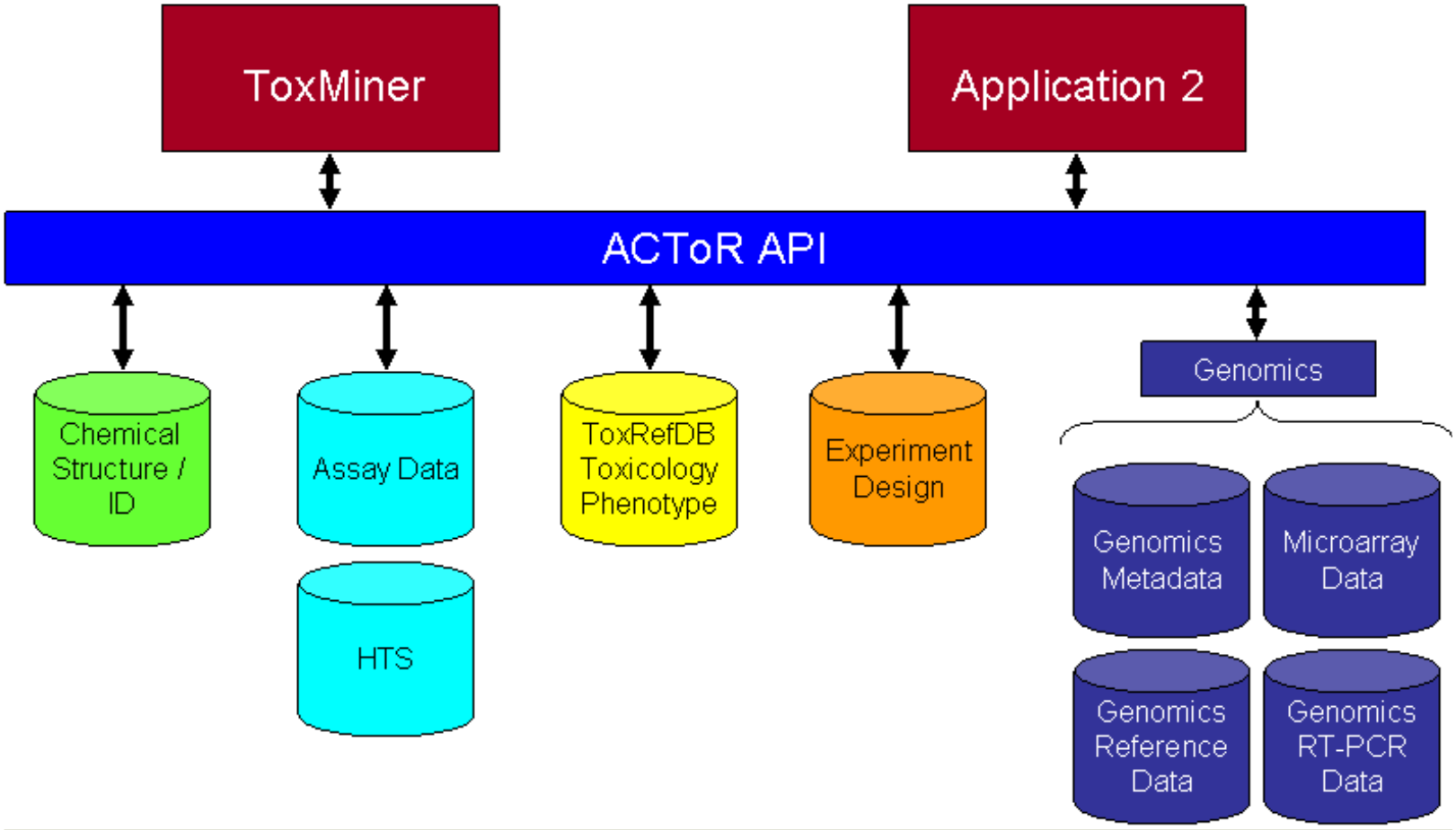
About ACToR

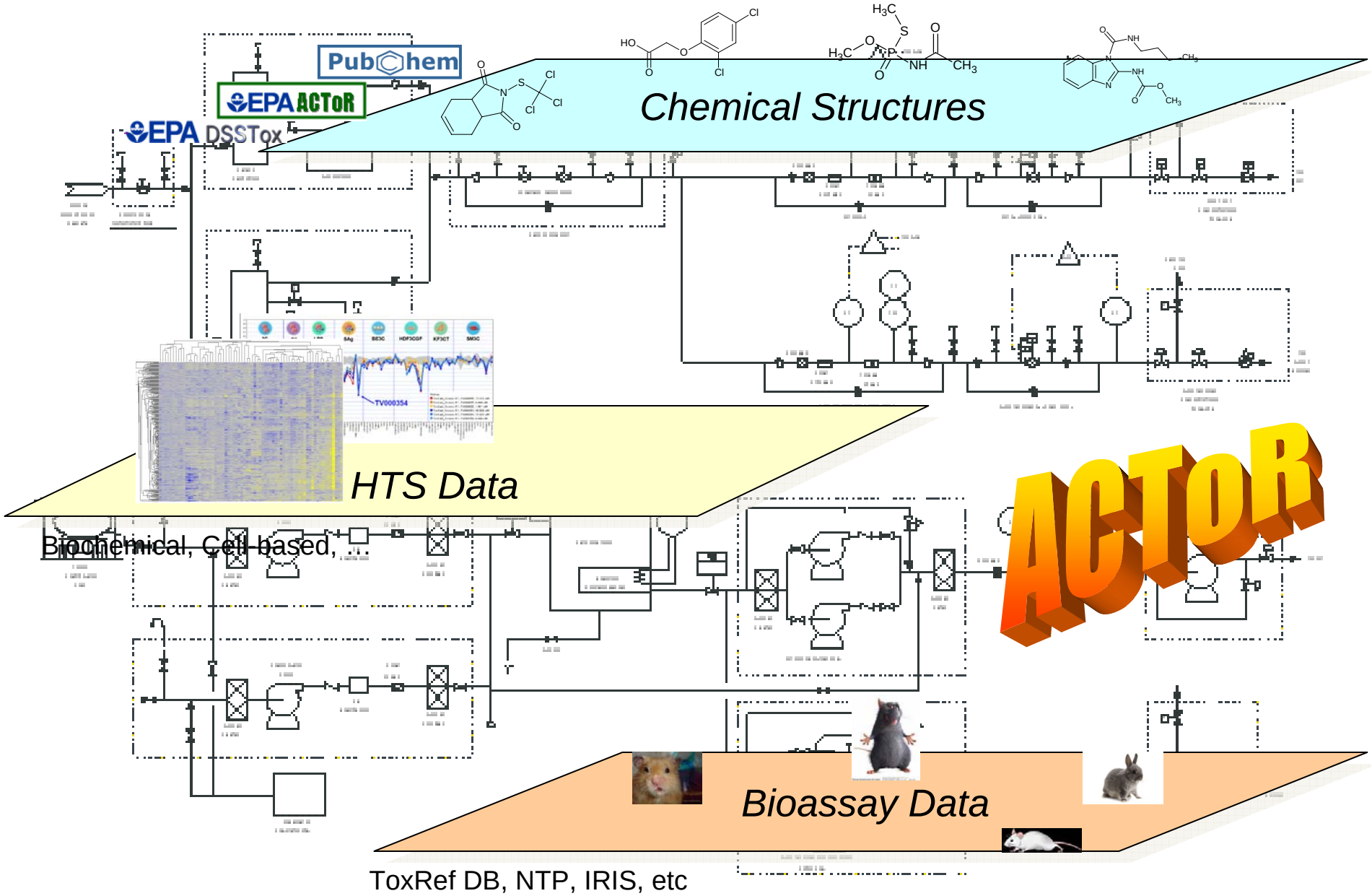
ACToR is organized into a series of domains, linked together by chemical.



Part III

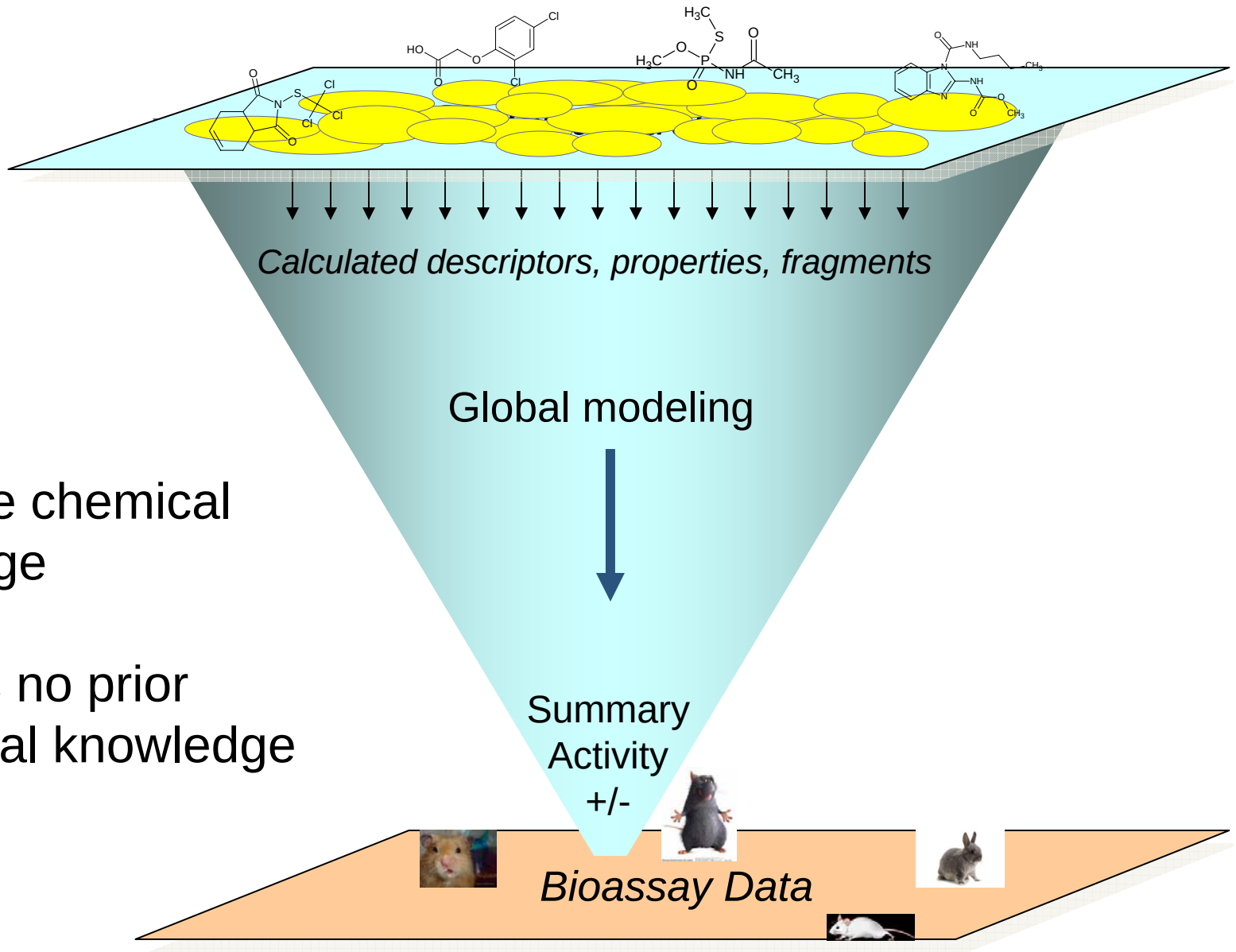
Incorporating SAR Concepts into ToxCast

ToxCast: Multidimensional Data



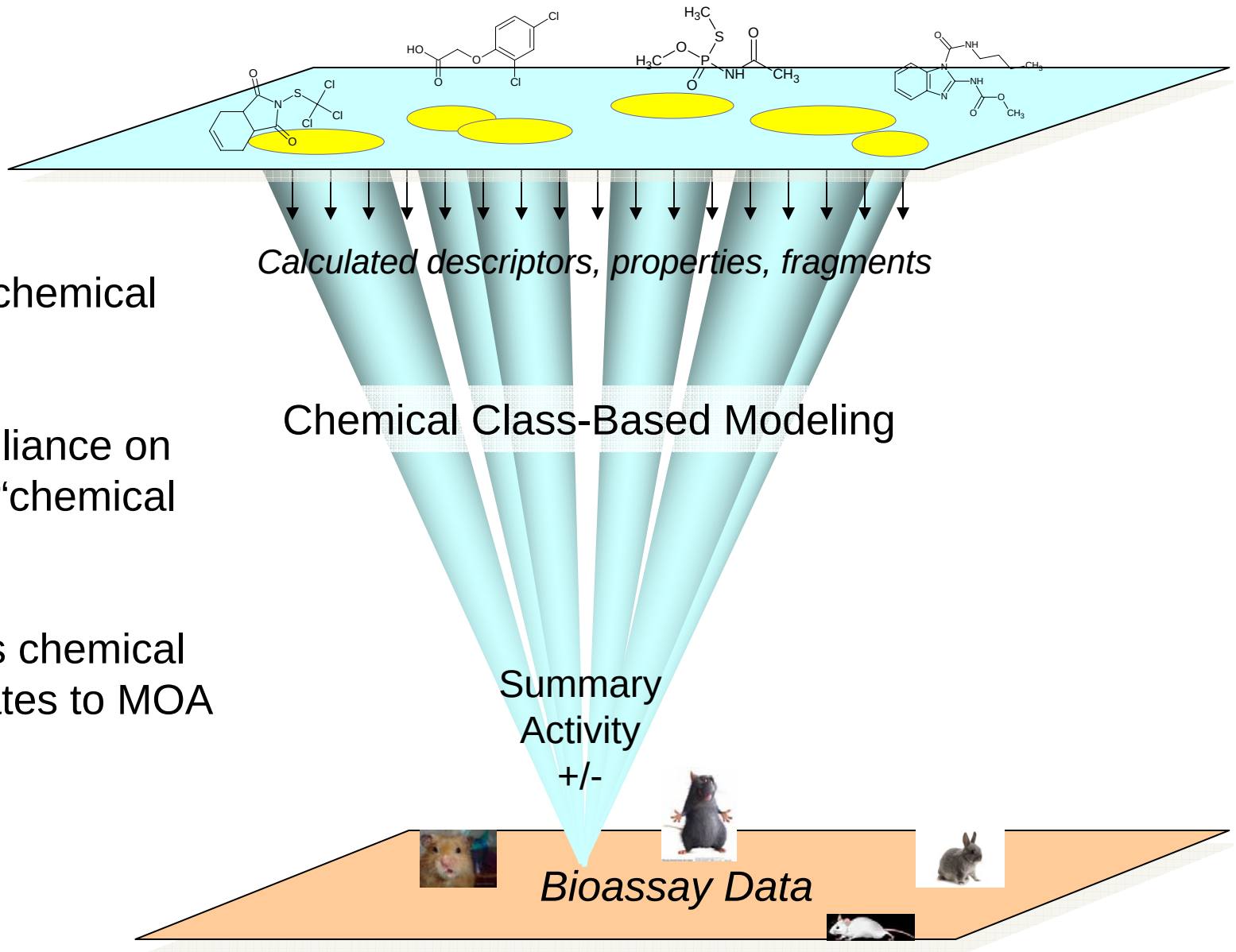
Structure-Activity Approaches to Toxicity Prediction

- Large chemical coverage
- Uses no prior chemical knowledge

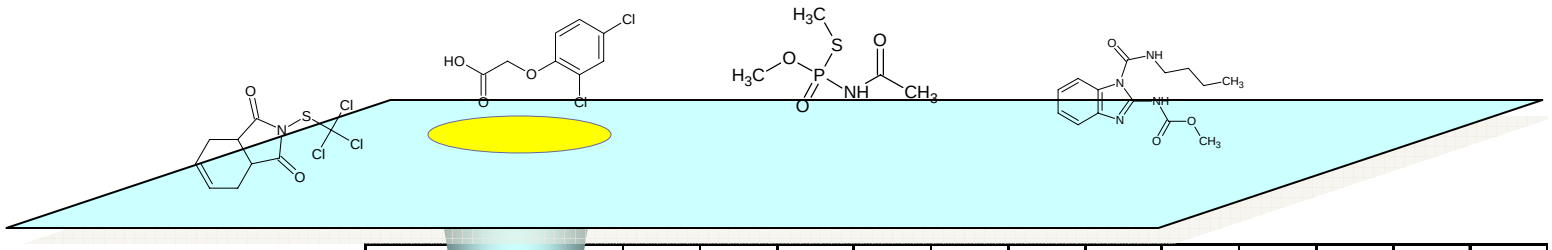


Structure-Activity Approaches to Toxicity Prediction

- Limited chemical coverage
- Heavy reliance on perceived “chemical similarity”
- Assumes chemical class equates to MOA

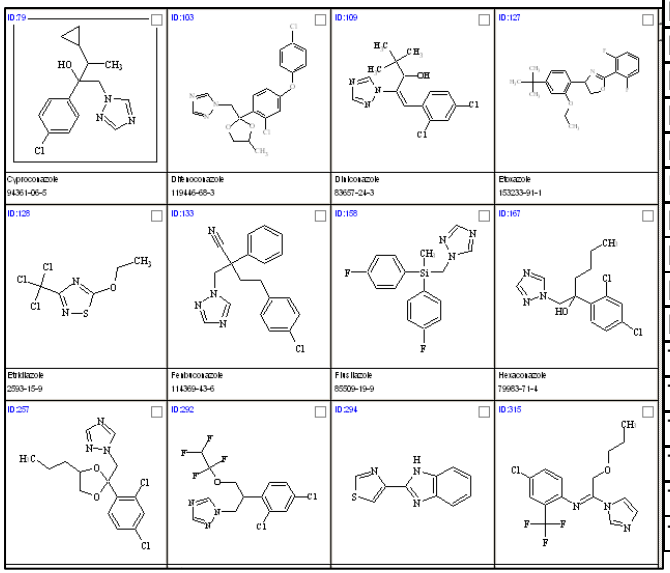


Bioactivity Profile of Structure Class



Sample HTS Results for Conazoles

- Patterns can inform SAR
- Chemical structures can suggest basis for activity differences



NAME	CYP2C19	CYP2C9	CYP3A1	Dopamine Transporter (Human)	CYP2D2	Androgen Receptor	Dopamine Transporter (Rat)	CYP2B6	CYP2D1	CYP3A4	Progesterone Receptor	Benzodiazepine Receptor
Cyproconazole	1	1	1	1	1	0	1	0	0	1	0	0
Difenoconazole	1	1	1	1	1	0	0	1	1	0	0	0
Diniconazole	1	1	1	0	1	0	0	0	1	1	1	0
Fenbuconazole	1	1	0	0	0	0	0	0	0	1	0	0
Flusilazole	1	1	1	0	1	1	0	1	1	NA	1	1
Hexaconazole	1	1	1	1	1	0	1	1	1	NA	1	0
Imazalil	1	1	1	1	1	1	1	1	1	1	1	1
Myclobutanil	1	1	1	1	0	0	0	0	0	NA	0	0
Paclobutrazol	1	0	1	1	0	1	1	0	1	1	0	0
Prochloraz	1	1	1	1	1	1	1	1	1	NA	1	1
Propiconazole	1	1	1	0	0	0	0	1	0	NA	0	1
Tetraconazole	1	1	1	0	1	1	0	1	0	1	1	0
Triadimefon	1	1	0	1	1	1	1	0	0	1	0	1
Triadimenol	1	0	0	1	0	1	1	0	0	0	0	0
Triflumizole	1	1	1	1	1	1	0	1	1	1	1	1
Triticonazole	1	1	1	1	0	1	1	0	0	NA	0	0
Totals	**16**	**14**	**13**	**11**	**10**	**9**	**8**	**8**	**8**	**8**	**7**	**6**

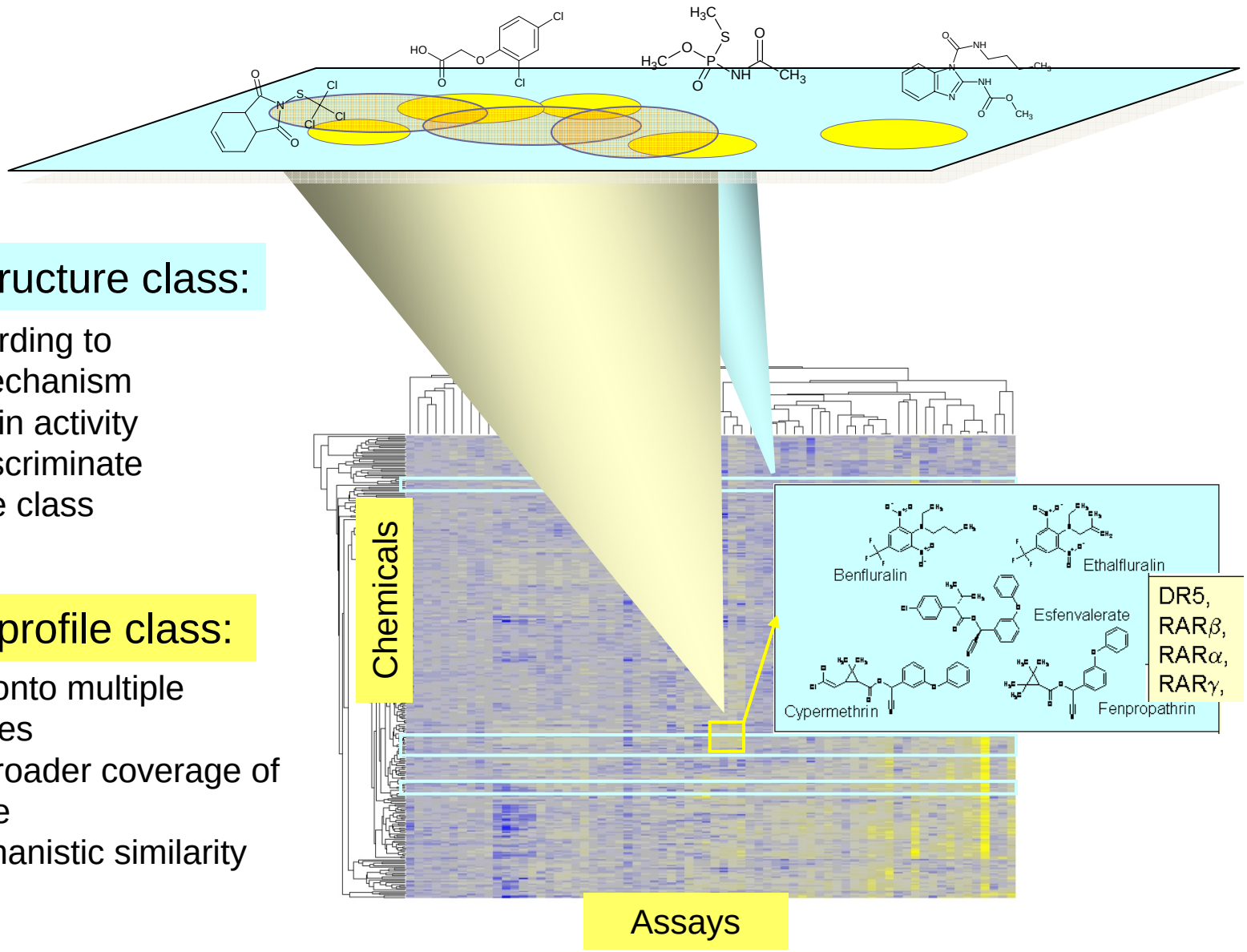
Structure Class vs Bioactivity Class

Chemical structure class:

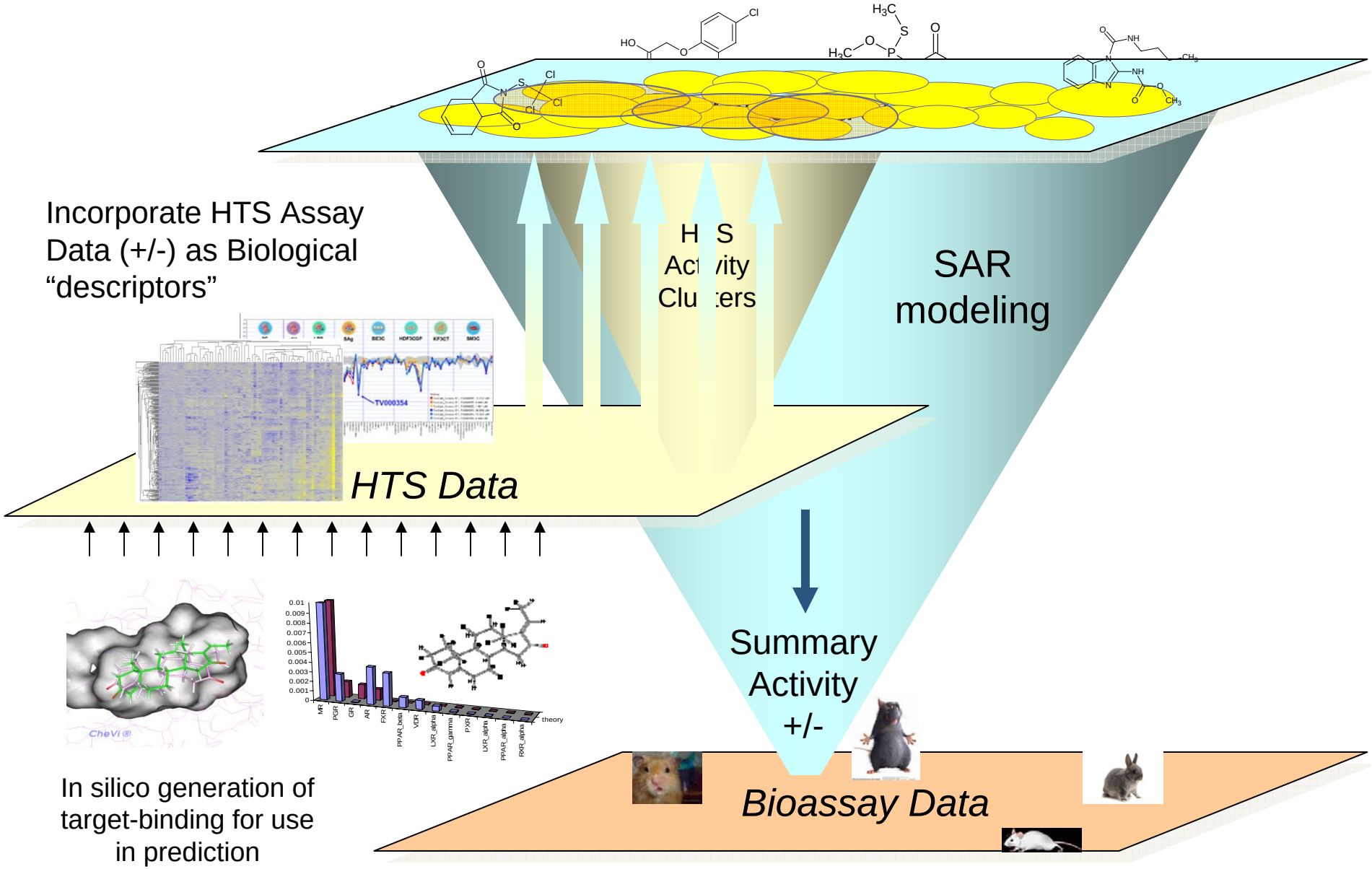
- Cluster according to activity and mechanism
- Differences in activity profiles can discriminate within structure class

Bioactivity profile class:

- Can project onto multiple chemical classes
- Potentially broader coverage of chemical space
- Implies mechanistic similarity

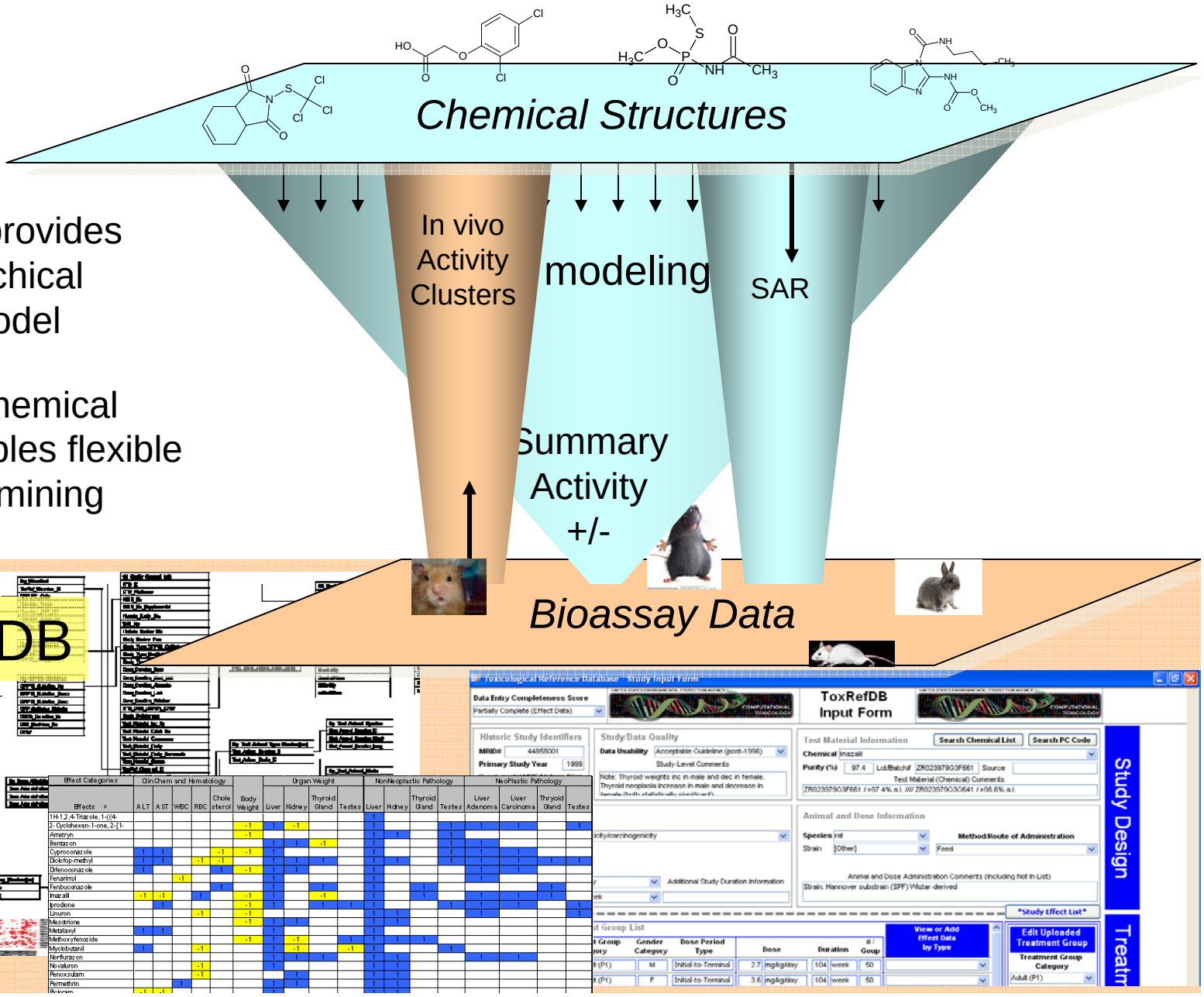


Structure-Activity Approaches to Toxicity Prediction



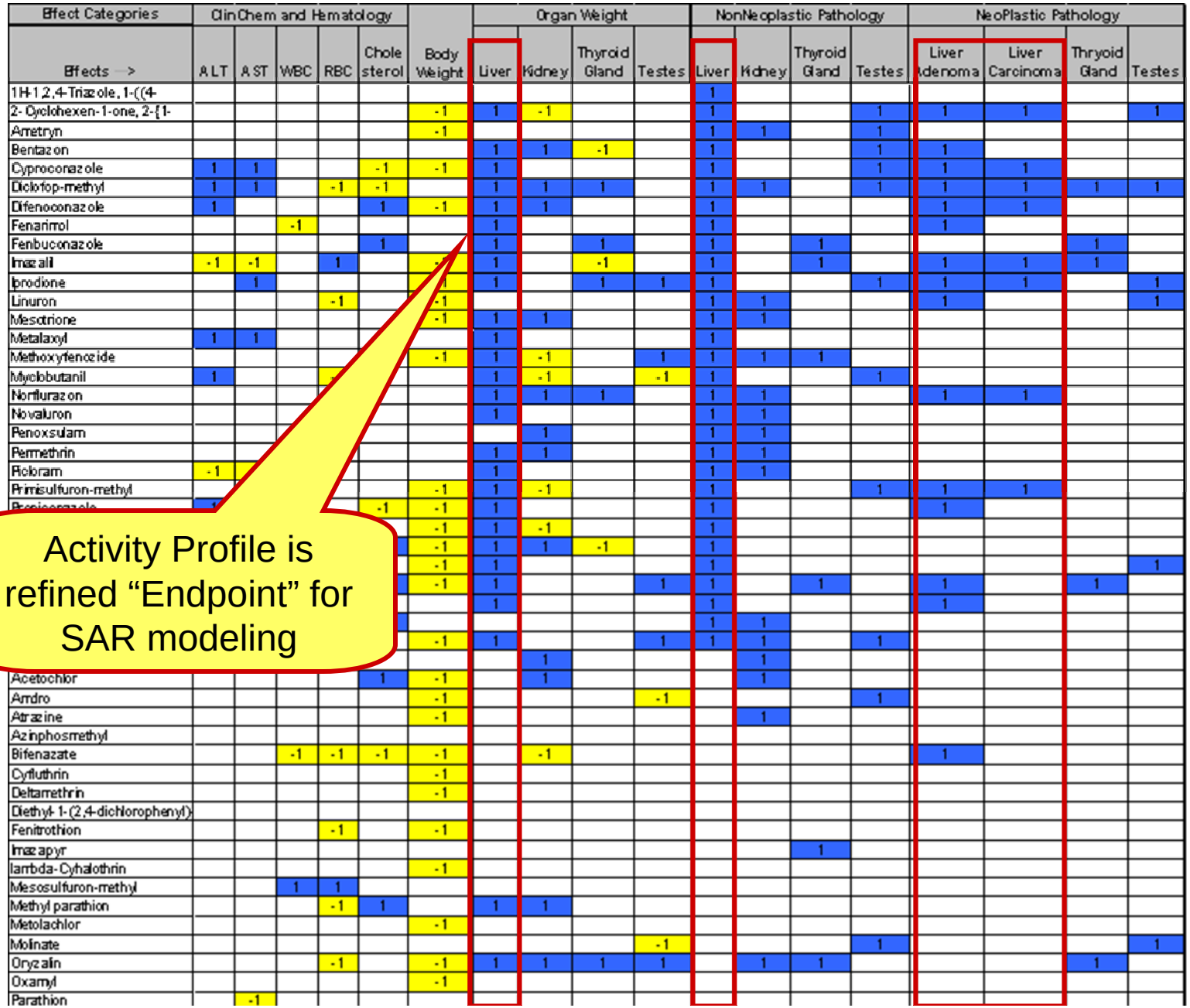
Use of Bioassay Activity Categories in SAR

- ToxRef DB provides detailed hierarchical toxicity data model
- Linkage to chemical structures enables flexible SAR and data mining

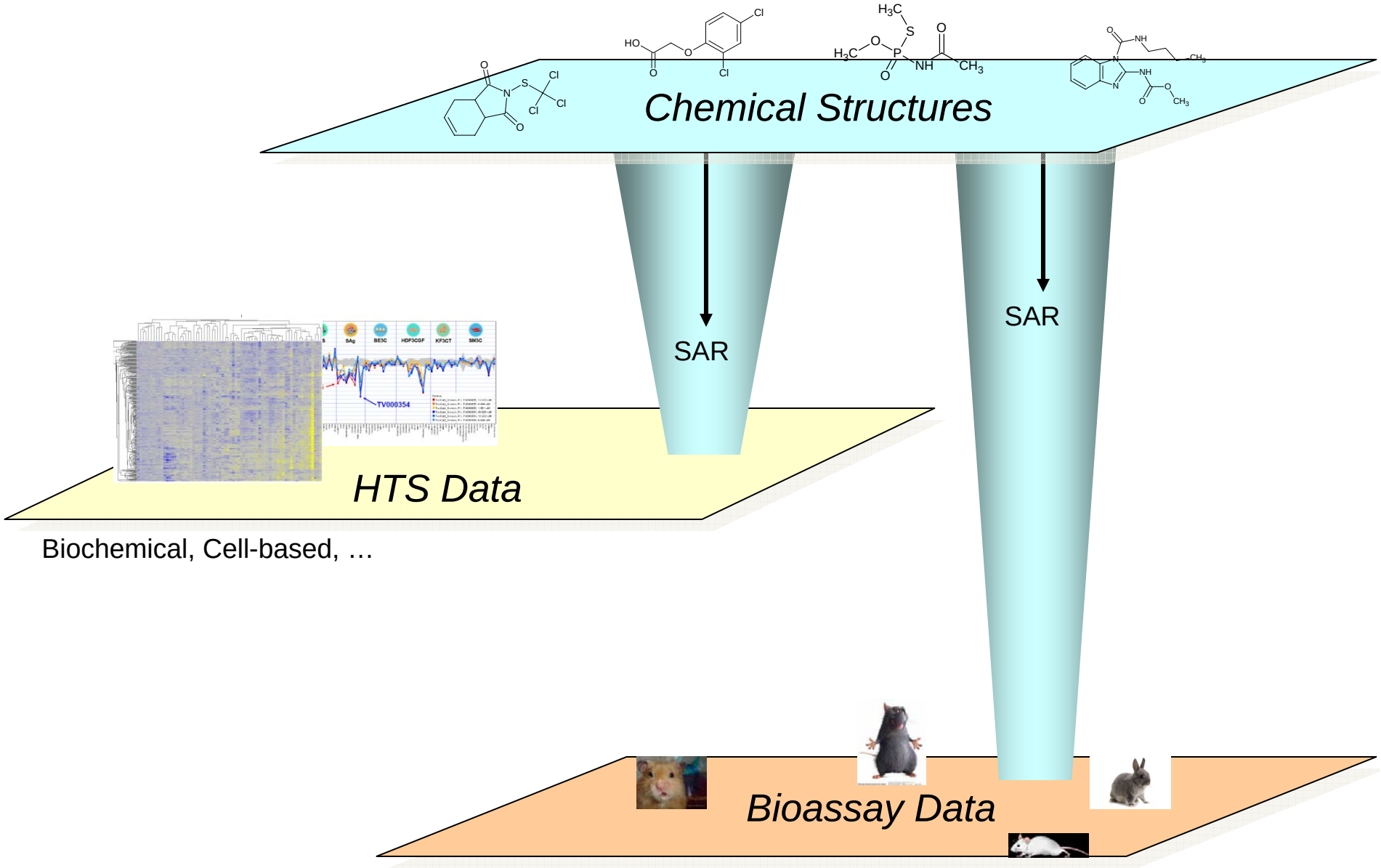


ToxRefDB Profiling of Liver Effects for Pesticides

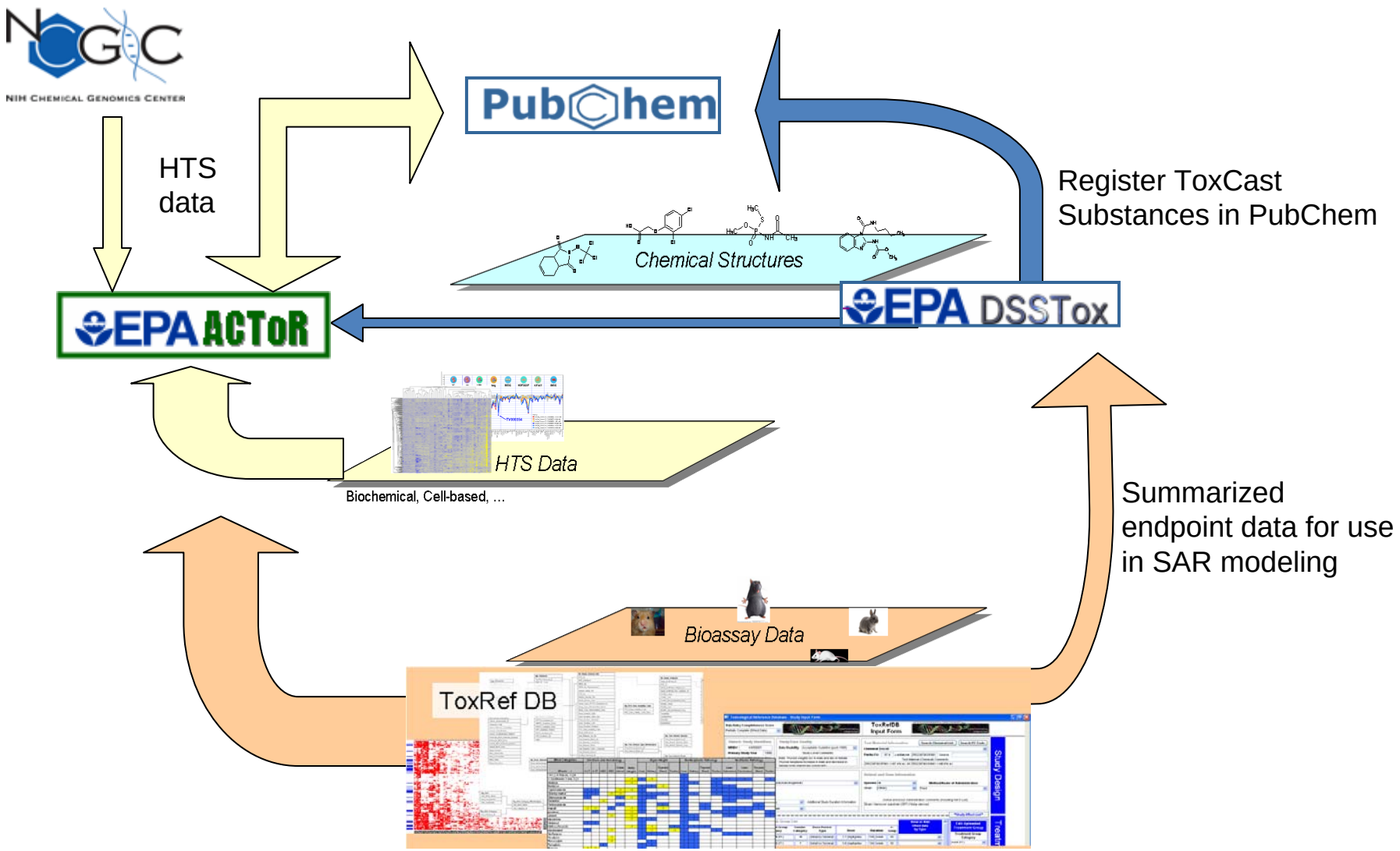
Liver non-neoplastic histopathology and increased organ weight are often associated with tumors and cancer



Structure-Analog Approaches



ToxCast: Data Publication & Exploration

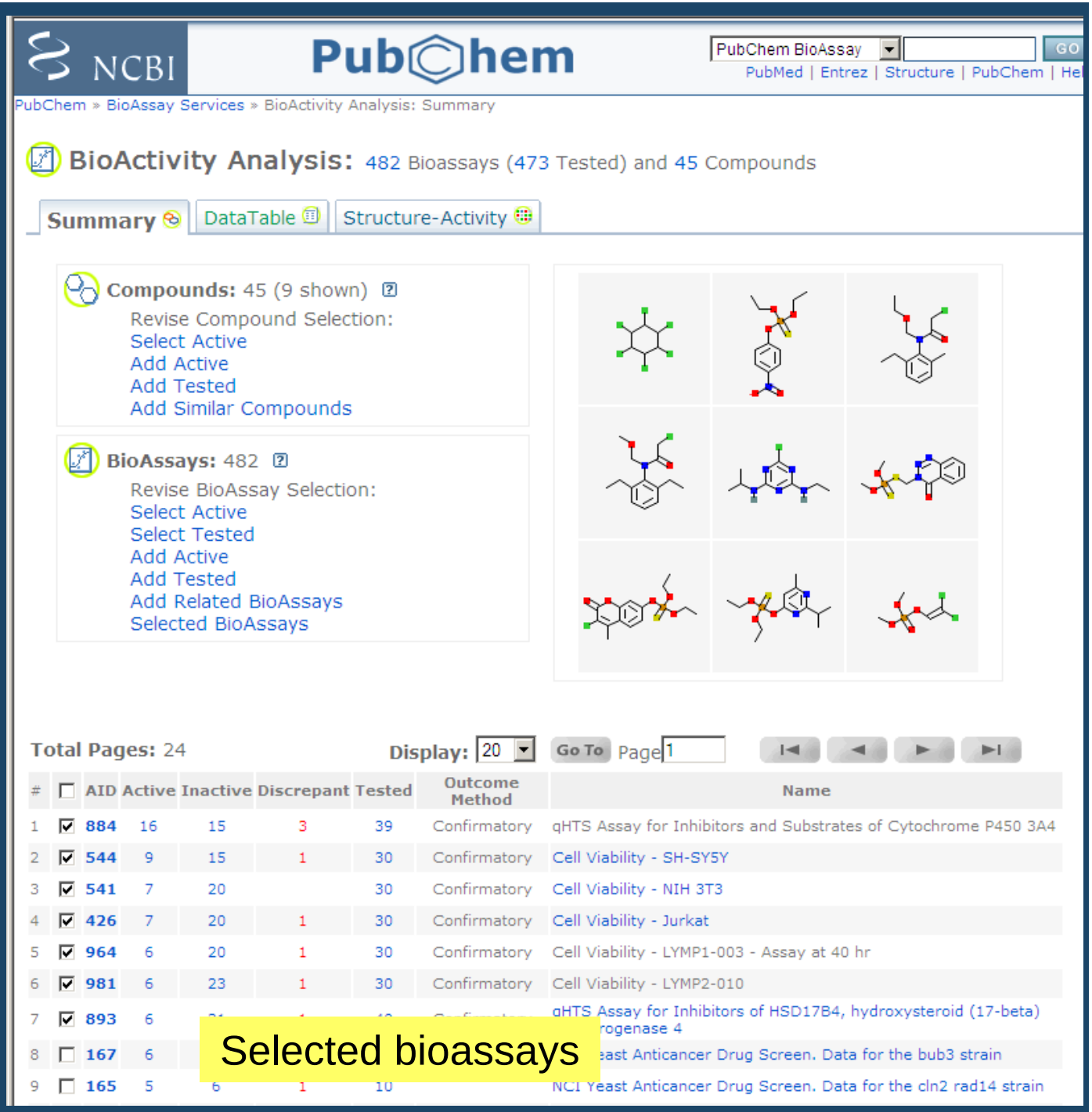


ToxCast_320

Bioactivity Analysis:

Retrieve all bioassay data in PubChem for ToxCast_320

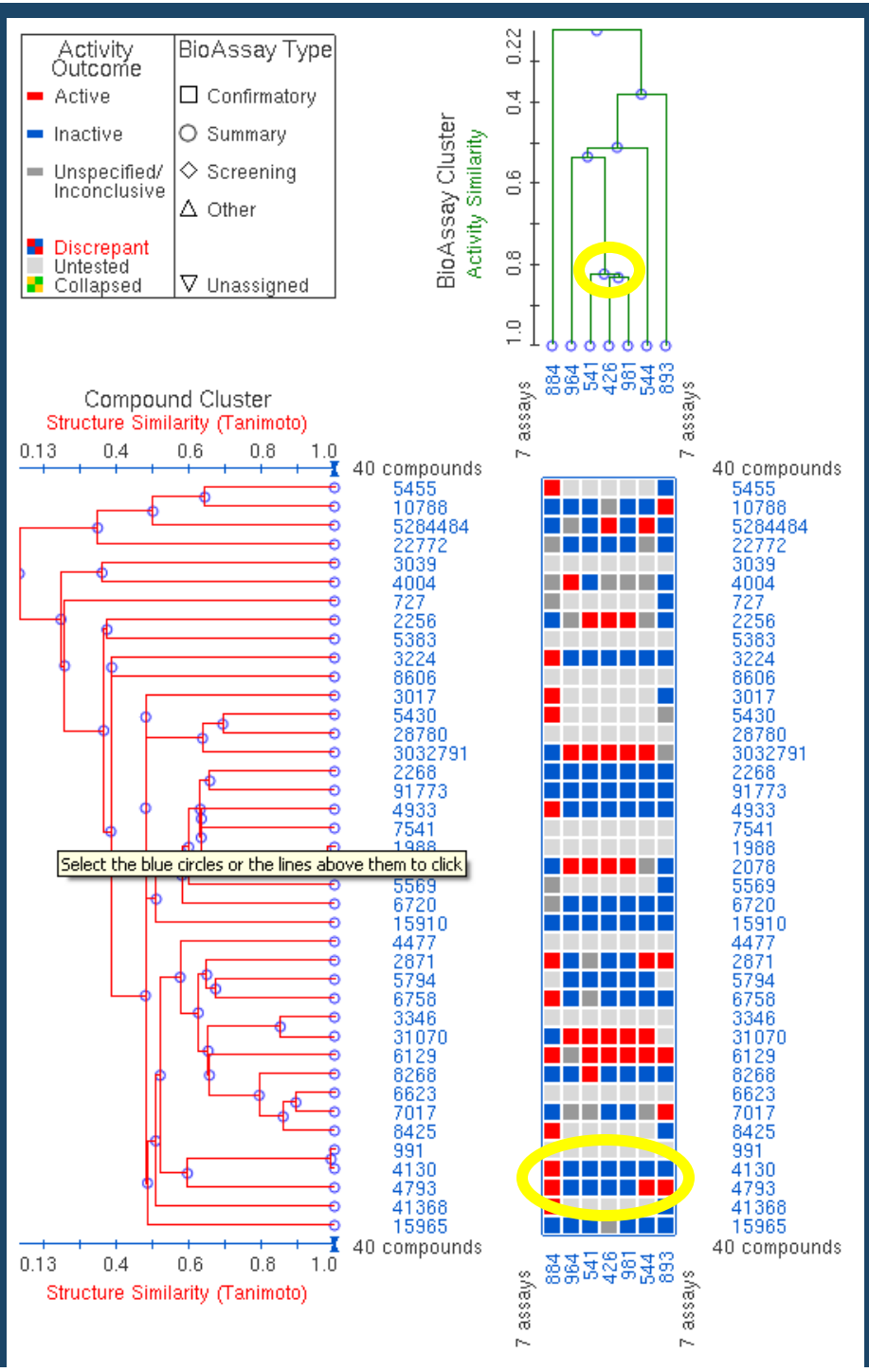
482 Bioassays
45 Compounds



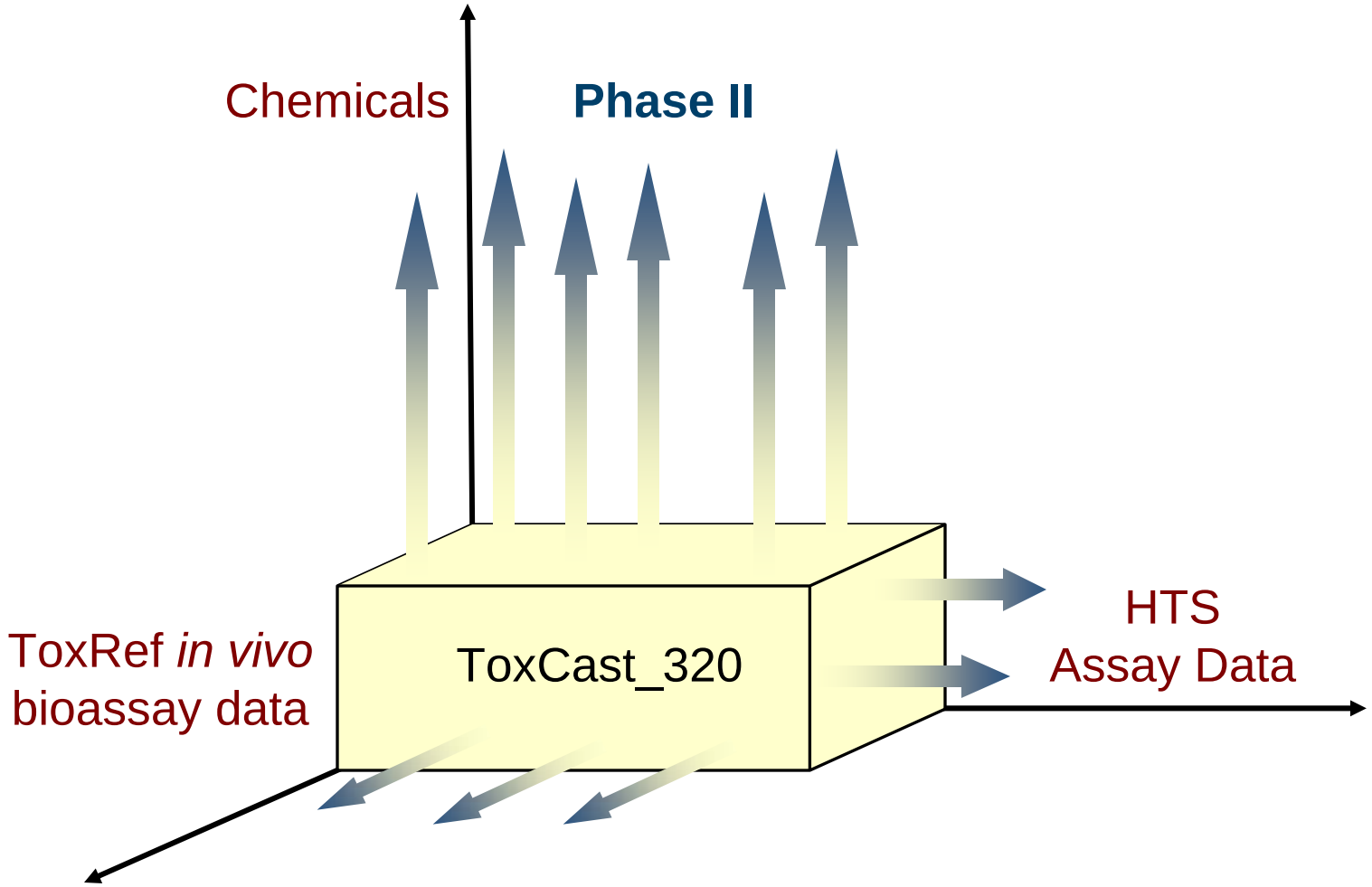
Structure-Activity *Bioactivity Analysis:*

7 bioassays, 45 Actives

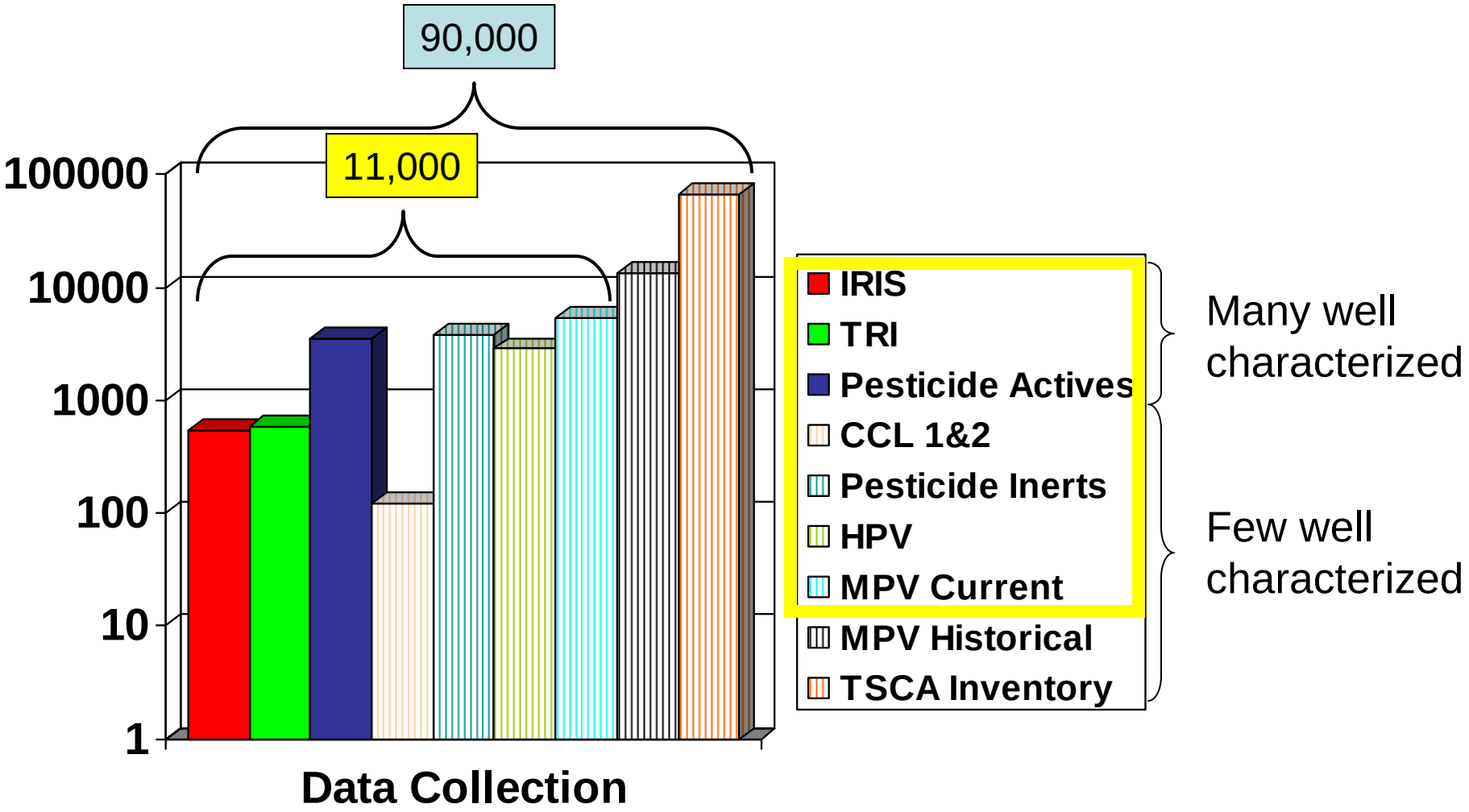
View Bioassay Profile by Structure Similarity Cluster



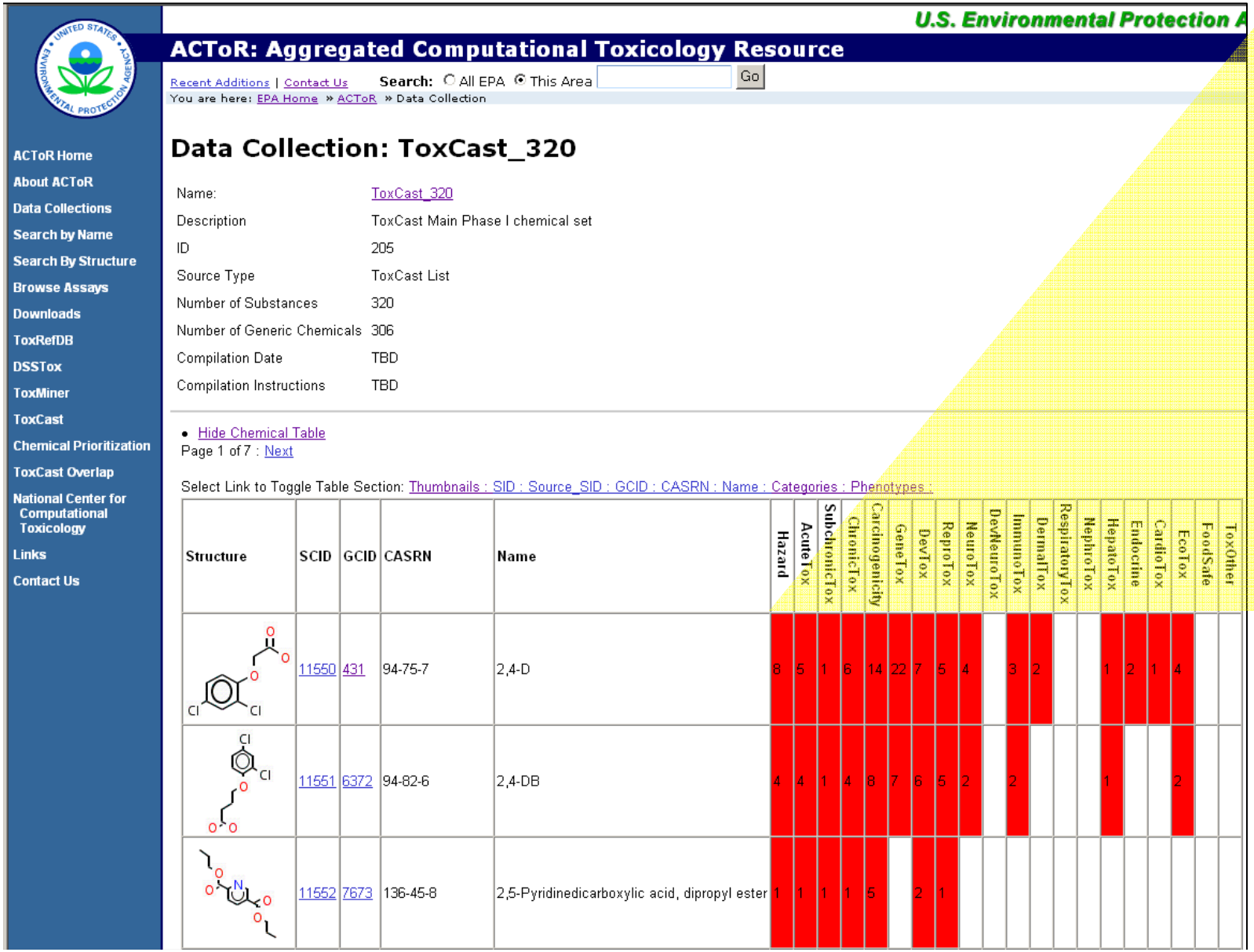
ToxCast Phase I: Proof of Concept



ToxCast Phase II Chemicals



ACToR Incidence Table:
Data Collections & Assays



U.S. Environmental Protection A

ACToR: Aggregated Computational Toxicology Resource

Recent Additions | Contact Us Search: All EPA This Area Go

You are here: EPA Home » ACToR » Data Collection

Data Collection: ToxCast_320

Name:	ToxCast_320
Description	ToxCast Main Phase I chemical set
ID	205
Source Type	ToxCast List
Number of Substances	320
Number of Generic Chemicals	306
Compilation Date	TBD
Compilation Instructions	TBD

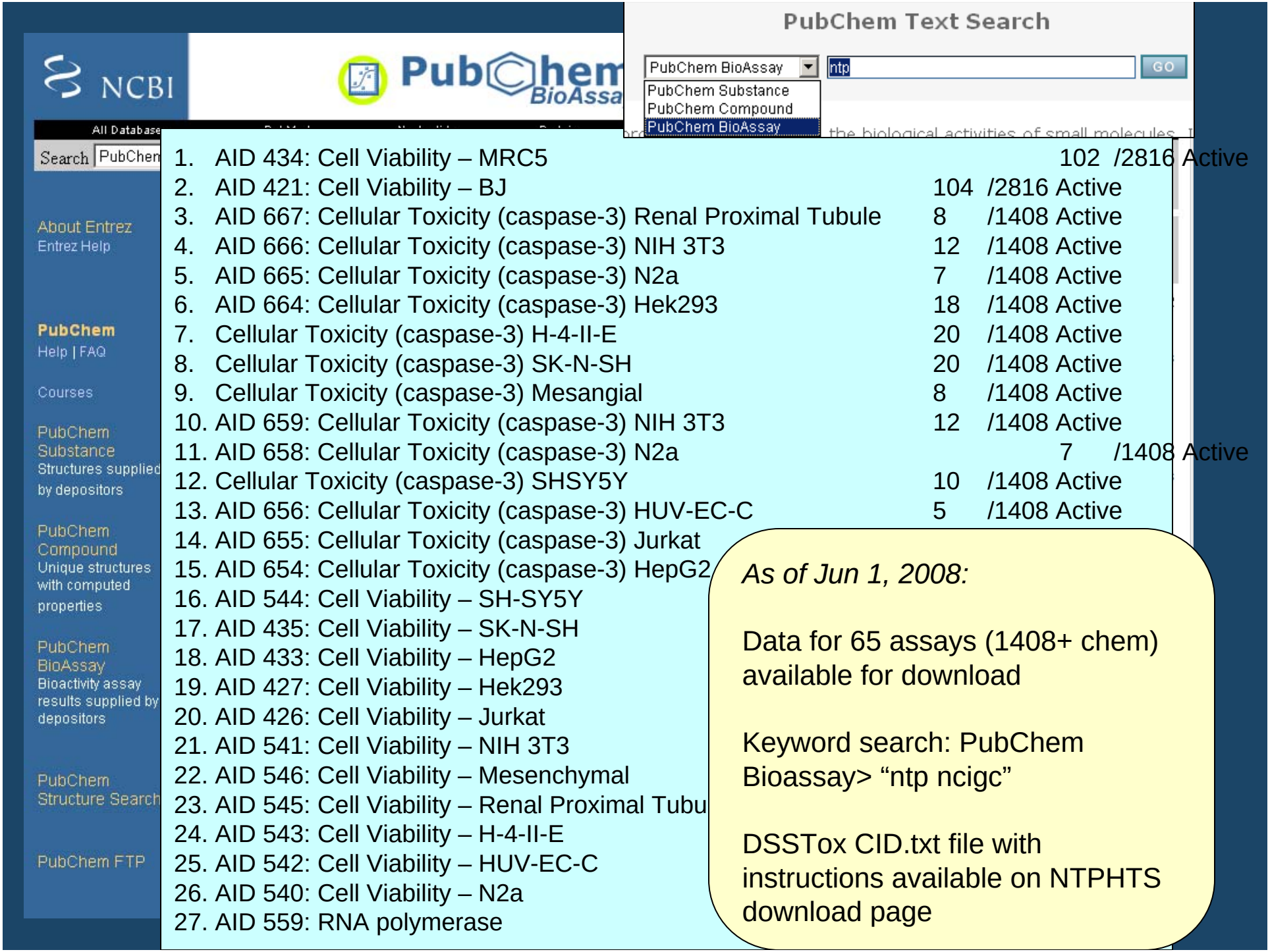
- Hide Chemical Table

Page 1 of 7 : Next

Select Link to Toggle Table Section: Thumbnails : SID : Source_SID : GCID : CASRN : Name : Categories : Phenotypes :

Structure	SCID	GCID	CASRN	Name	Hazard	AcuteTox	SubchronicTox	ChronicTox	Carcinogenicity	GeneTox	DevTox	ReproTox	NeuroTox	DevNeuroTox	ImmunoTox	DermalTox	RespiratoryTox	NephroTox	HepatoTox	Endocrine	CardioTox	EcoTox	FoodSafe	ToxOther
	11550	431	94-75-7	2,4-D	8	5	1	6	14	22	7	5	4		3	2			1	2	1	4		
	11551	6372	94-82-6	2,4-DB	4	4	1	4	8	7	6	5	2		2				1			2		
	11552	7673	136-45-8	2,5-Pyridinedicarboxylic acid, dipropyl ester	1	1	1	1	5		2	1												

Data Source
CPDBAS_DSSTOX
HPVCSI_DSSTOX
IRISTR_DSSTOX
NCTRER_DSSTOX
NTPBSI_DSSTOX
NTPHTS_DSSTOX
ToxCast_320
CERCLA
EDC73
EPA_DWC
EXTOXNET
HPVChallenge
HPV
INCHEM_EHC
INCHEM_EHC
INCHEM_IARC
ITER_TERA
IUR_2002
IUR_86_02



1. AID 434: Cell Viability – MRC5 102 /2816 Active
2. AID 421: Cell Viability – BJ 104 /2816 Active
3. AID 667: Cellular Toxicity (caspase-3) Renal Proximal Tubule 8 /1408 Active
4. AID 666: Cellular Toxicity (caspase-3) NIH 3T3 12 /1408 Active
5. AID 665: Cellular Toxicity (caspase-3) N2a 7 /1408 Active
6. AID 664: Cellular Toxicity (caspase-3) Hek293 18 /1408 Active
7. Cellular Toxicity (caspase-3) H-4-II-E 20 /1408 Active
8. Cellular Toxicity (caspase-3) SK-N-SH 20 /1408 Active
9. Cellular Toxicity (caspase-3) Mesangial 8 /1408 Active
10. AID 659: Cellular Toxicity (caspase-3) NIH 3T3 12 /1408 Active
11. AID 658: Cellular Toxicity (caspase-3) N2a 7 /1408 Active
12. Cellular Toxicity (caspase-3) SHSY5Y 10 /1408 Active
13. AID 656: Cellular Toxicity (caspase-3) HUV-EC-C 5 /1408 Active
14. AID 655: Cellular Toxicity (caspase-3) Jurkat
15. AID 654: Cellular Toxicity (caspase-3) HepG2
16. AID 544: Cell Viability – SH-SY5Y
17. AID 435: Cell Viability – SK-N-SH
18. AID 433: Cell Viability – HepG2
19. AID 427: Cell Viability – Hek293
20. AID 426: Cell Viability – Jurkat
21. AID 541: Cell Viability – NIH 3T3
22. AID 546: Cell Viability – Mesenchymal
23. AID 545: Cell Viability – Renal Proximal Tubu
24. AID 543: Cell Viability – H-4-II-E
25. AID 542: Cell Viability – HUV-EC-C
26. AID 540: Cell Viability – N2a
27. AID 559: RNA polymerase

As of Jun 1, 2008:

Data for 65 assays (1408+ chem) available for download

Keyword search: PubChem Bioassay> “ntp ncigc”

DSSTox CID.txt file with instructions available on NTPHTS download page

Joint Screening Program: NIH/NCGC, NIEHS/NTP, EPA/NCCT

- Combined HTS plates (2x1408) high interest chemicals
- Joint assay development
- Use of NCGC HTS informatics capabilities

Science: Feb 15, 2008


POLICY FORUM

TOXICOLOGY

Transforming Environmental Health Protection

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

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  Matt Martin (ToxRefDB)
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