United States Environmental Protection Agency

New Toxico-Cheminformatics & Computational Toxicology Initiatives at EPA

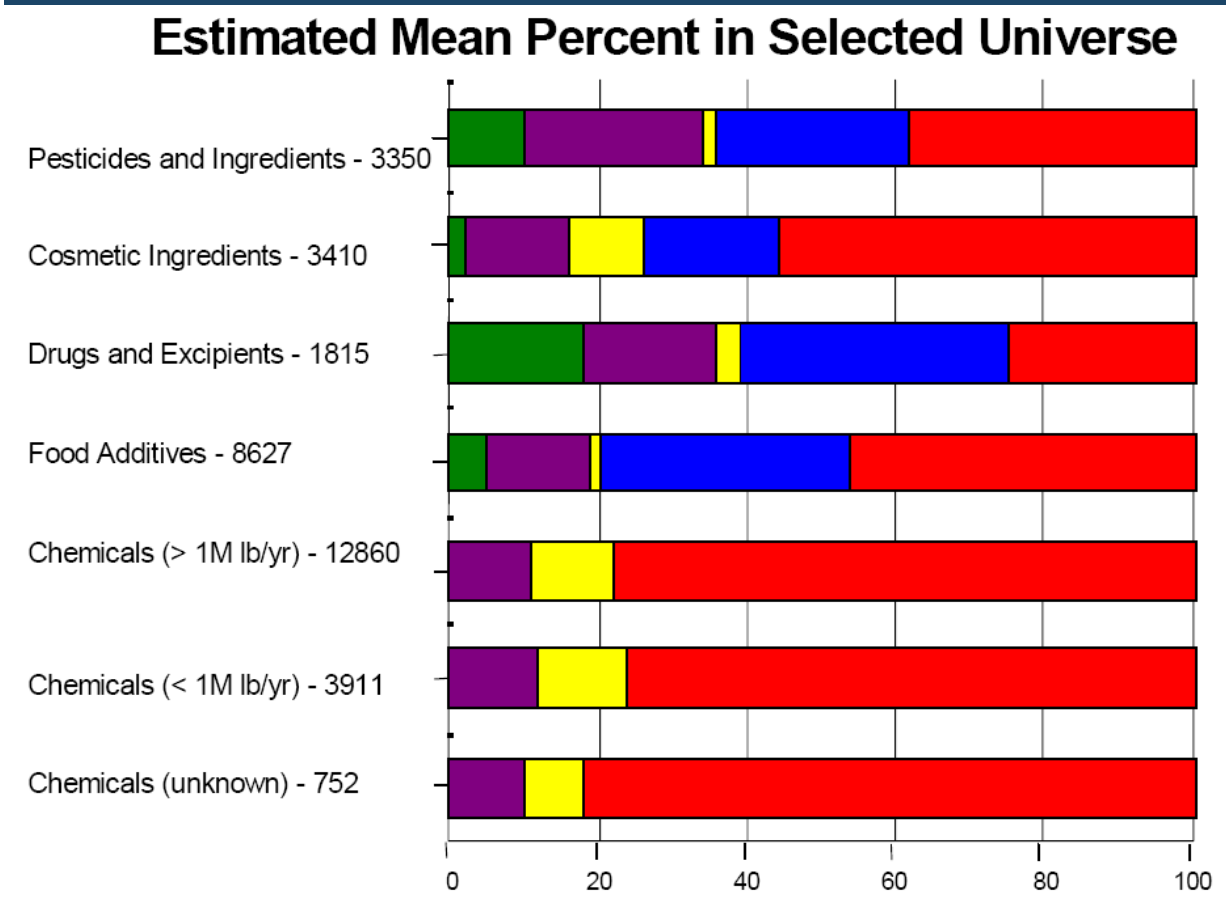
http://www.epa.gov/ncct/

Office of Research and Development
National Center for Computational Toxicology

Part I.

The Problem

Environmental Chemicals: Toxicity Assessment Data Gaps



Complete Hazard Assessment Possible

Minimal Information Available

No Toxicity Information Available

Partial Hazard Assessment Possible

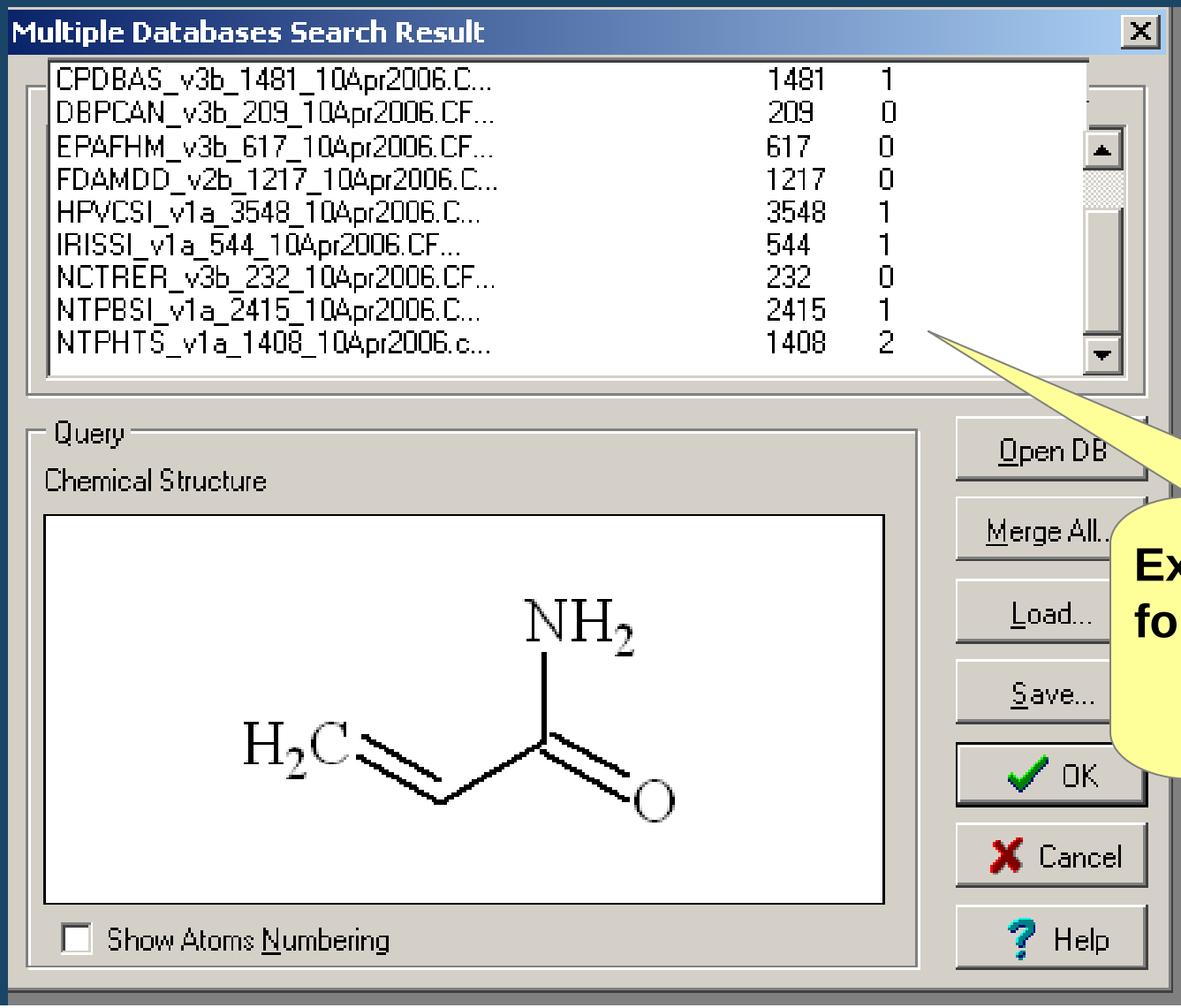
Some Toxicity Information Available

Strategies for Closing the Chemical Data Gap

by John S. Applegate and Katherine Baer

A Center for Progressive Reform Publication *April 2006*

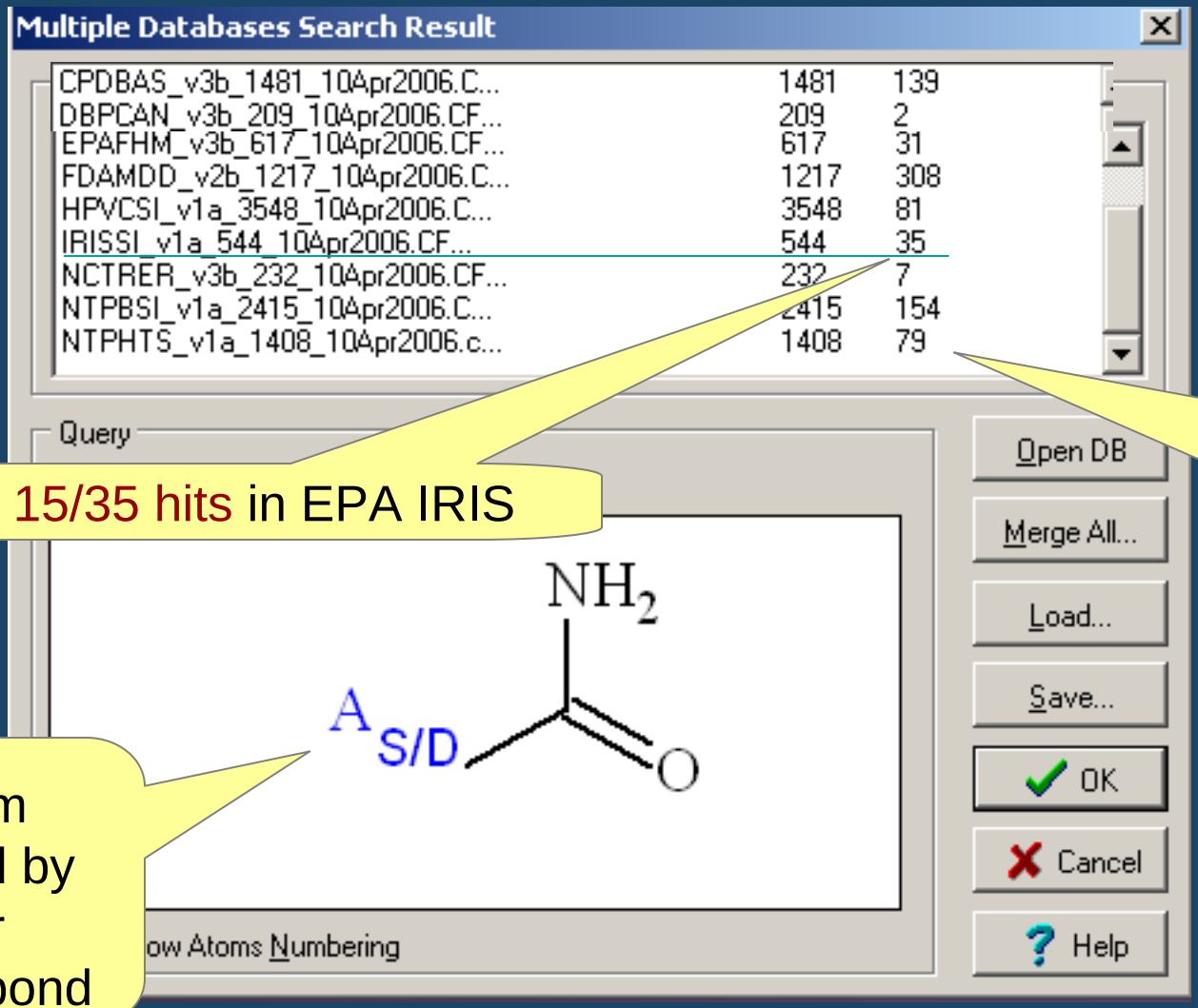
Structure Searching Across 9 Diverse Toxicity Databases:



Exact match search for Acrylamide:

Result: 6 hits

Generalized Sub-Structure Searching Across 9 Diverse Toxicity Databases:



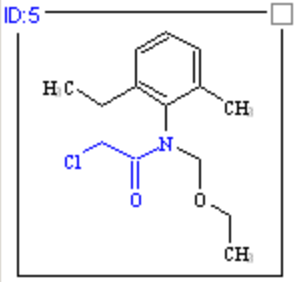
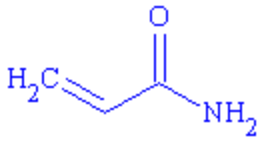
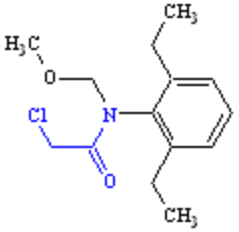
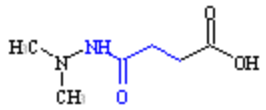
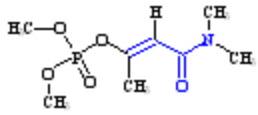
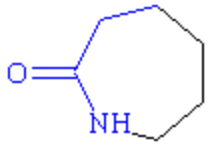
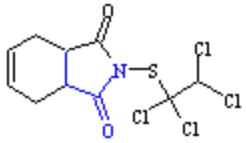
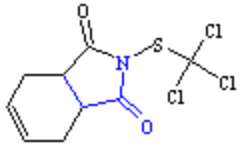
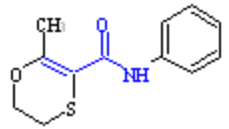
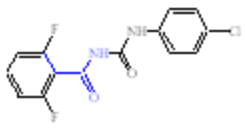
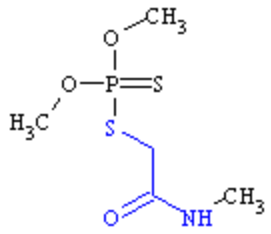
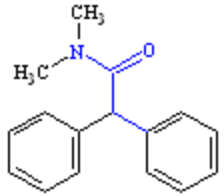
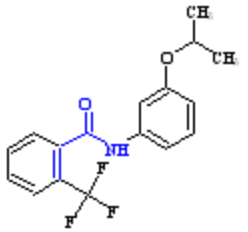
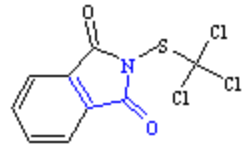
View 15/35 hits in EPA IRIS

Result: 836 hits

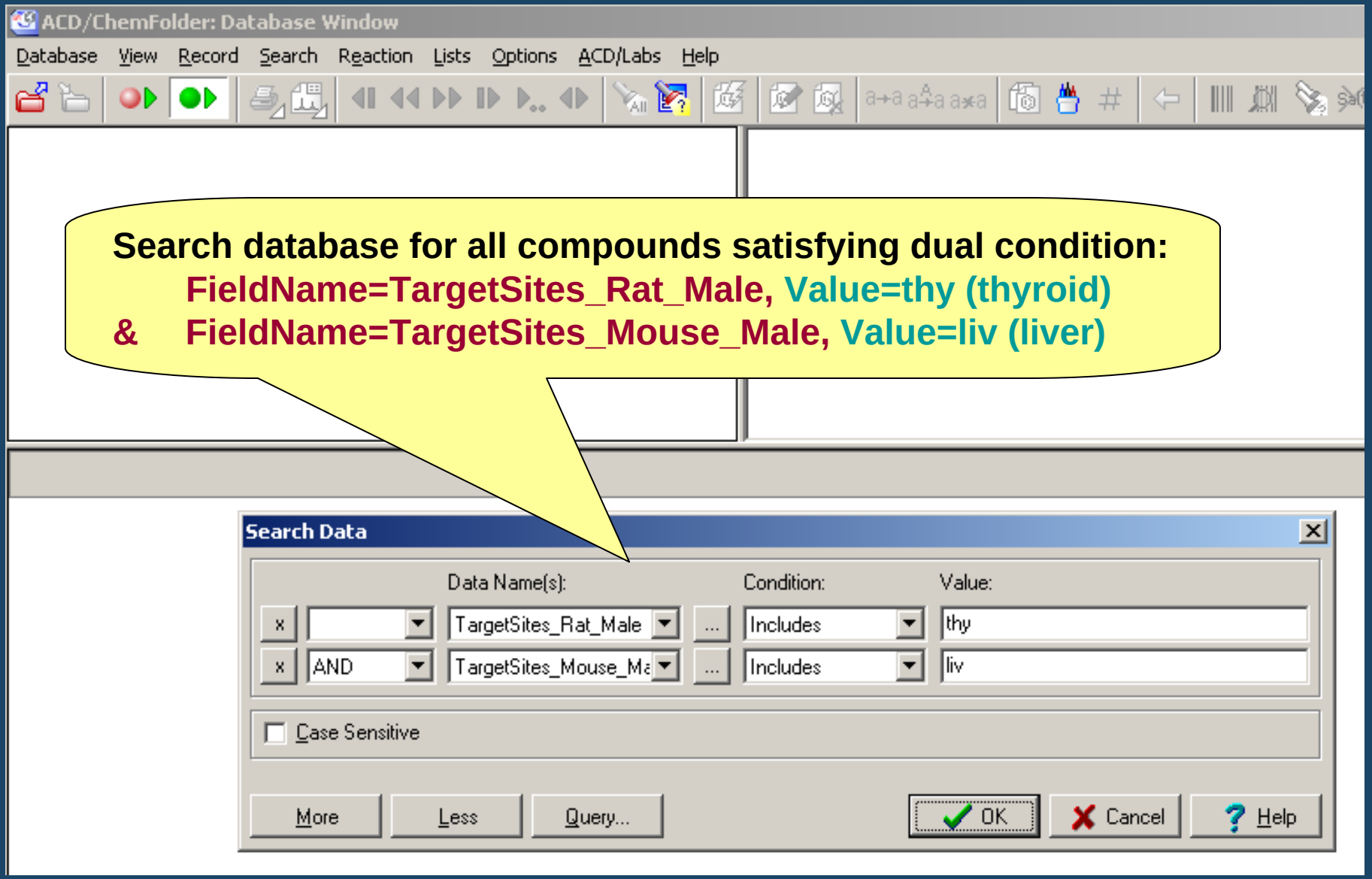
Any atom attached by single or double bond

Generalized Sub-Structure Searching Across 9 Diverse Toxicity Databases:

15/35 Hits in IRIS containing acrylamide-like moiety

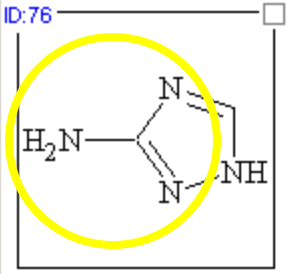
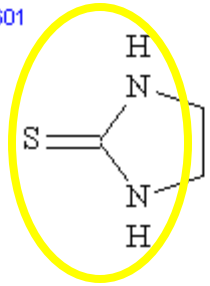
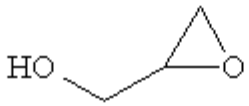
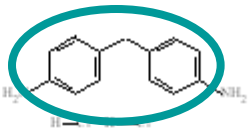
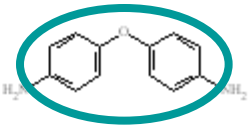
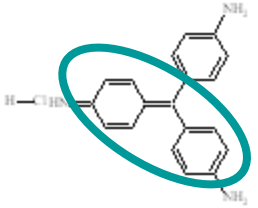
ID:5 	ID:12 	ID:16 	ID:17 	ID:58 
Acetochlor 34256-82-1	Acrylamide 79-06-1	Alachlor 15972-60-8	Daminozide 1596-84-5	Bentazon 25057-89-0
ID:71 	ID:99 	ID:100 	ID:101 	ID:108 
Bidrin 141-66-2	Caprolactam 105-60-2	Captafol 2425-06-1	Captan 133-06-2	Carboxin 5234-68-4
ID:206 	ID:210 	ID:229 	ID:266 	ID:268 
Diflubenzuron 35367-38-5	Dimethoate 60-51-5	Diphenamid 957-51-7	Flutolanil 66332-96-5	N-(Trichloromethylthio)phthali 133-07-3

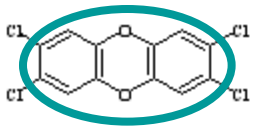
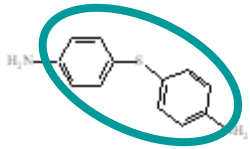
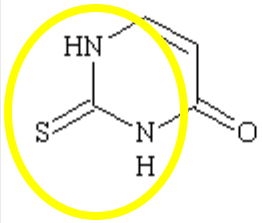
Relational Biological Content Searching: Carcinogenic Potency Database – All Species (CPDBAS_1481)



ACD/ChemFolder: Database Window - [D:\DSSTOX_MISC\ACD_CHEMFOLDERFILES_10APR2006\CPDBAS_V3B_1481_10APR2006.CFD]

Database View Record Search Reaction Lists Options ACD/Labs Help

ID:76	ID:601	ID:666	ID:871	ID:1094	ID:1247
					
76 CPDBAS_v3b_1481_10A	601 CPDBAS_v3b_1481_10	666 CPDBAS_v3b_1481_10	871 CPDBAS_v3b_1481_10	1094 CPDBAS_v3b_1481_1	1247 CPDBAS_v3b_1481_1
3-Aminotriazole	Ethylene thiourea (ETU)	Glycidol	4,4'-Methylenedianiline dihyd	4,4'-Oxydianiline	C.I. Basic red 9 monohydroc
negative	positive	positive	positive	positive	positive
thy	thy	ezy lgi mgl nrv per ski sto thy	liv thy	liv thy	ezy liv ski sub thy
pit thy	thy	cli hmo mgl nrv orc sto thy	thy	liv thy	ezy sub thy
liv	liv pit thy	hag liv lun ski sto	adr liv thy	hag liv	liv
liv	liv pit thy	hag mgl ski sub ute	hmo liv thy	hag liv thy	adr liv

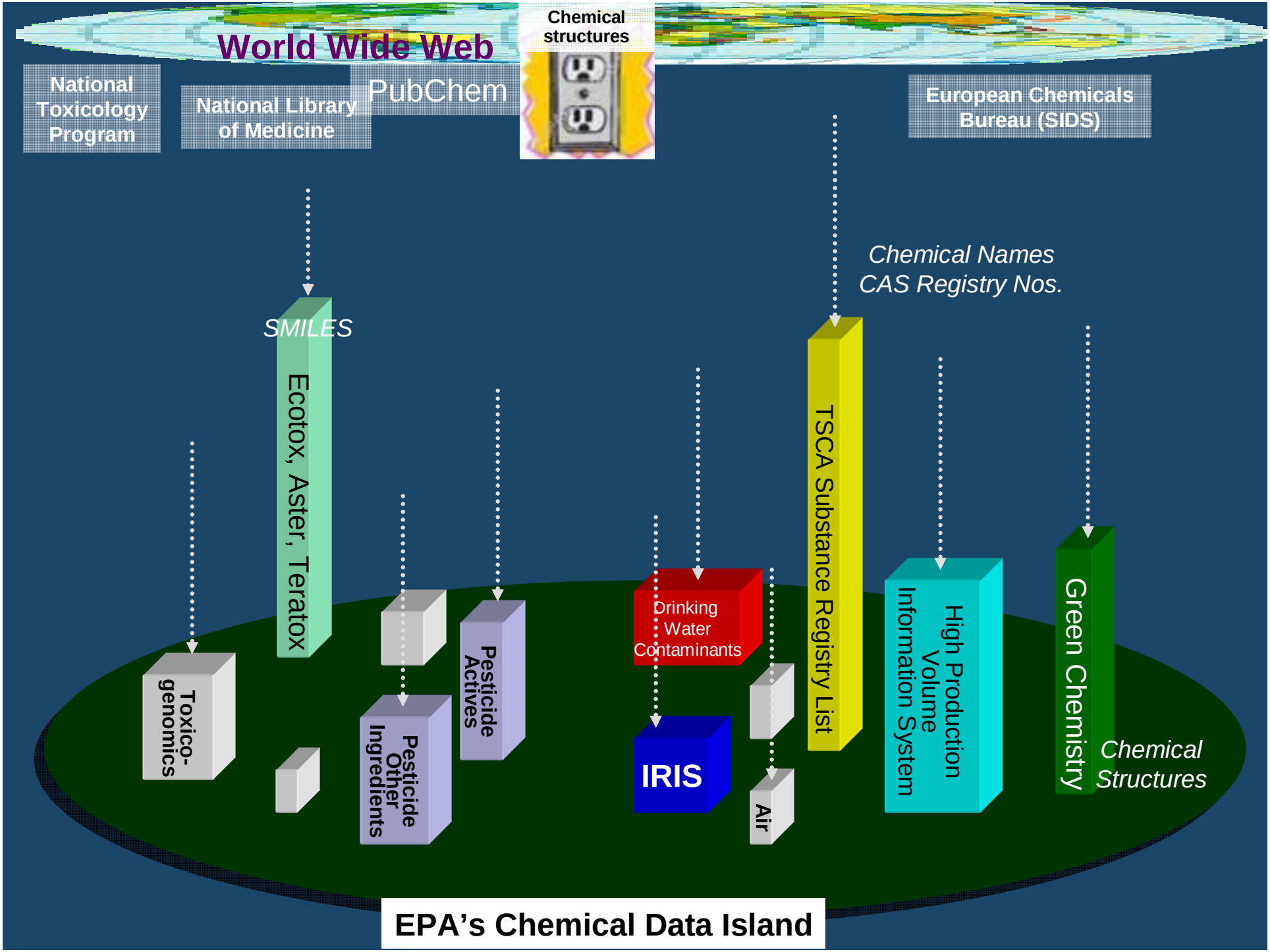
ID:1315	ID:1344	ID:1347
		
1315 CPDBAS_v3b_1481_1	1344 CPDBAS_v3b_1481_1	1347 CPDBAS_v3b_1481_1
2,3,7,8-Tetrachlorodibenzo-p	4,4'-Thiodianiline	Thiouracil
negative	positive	thy
orc thy	ezy lgi liv thy	thy
liv lun	ezy thy ute	liv
liv	liv thy	liv
liv thy	liv thy	

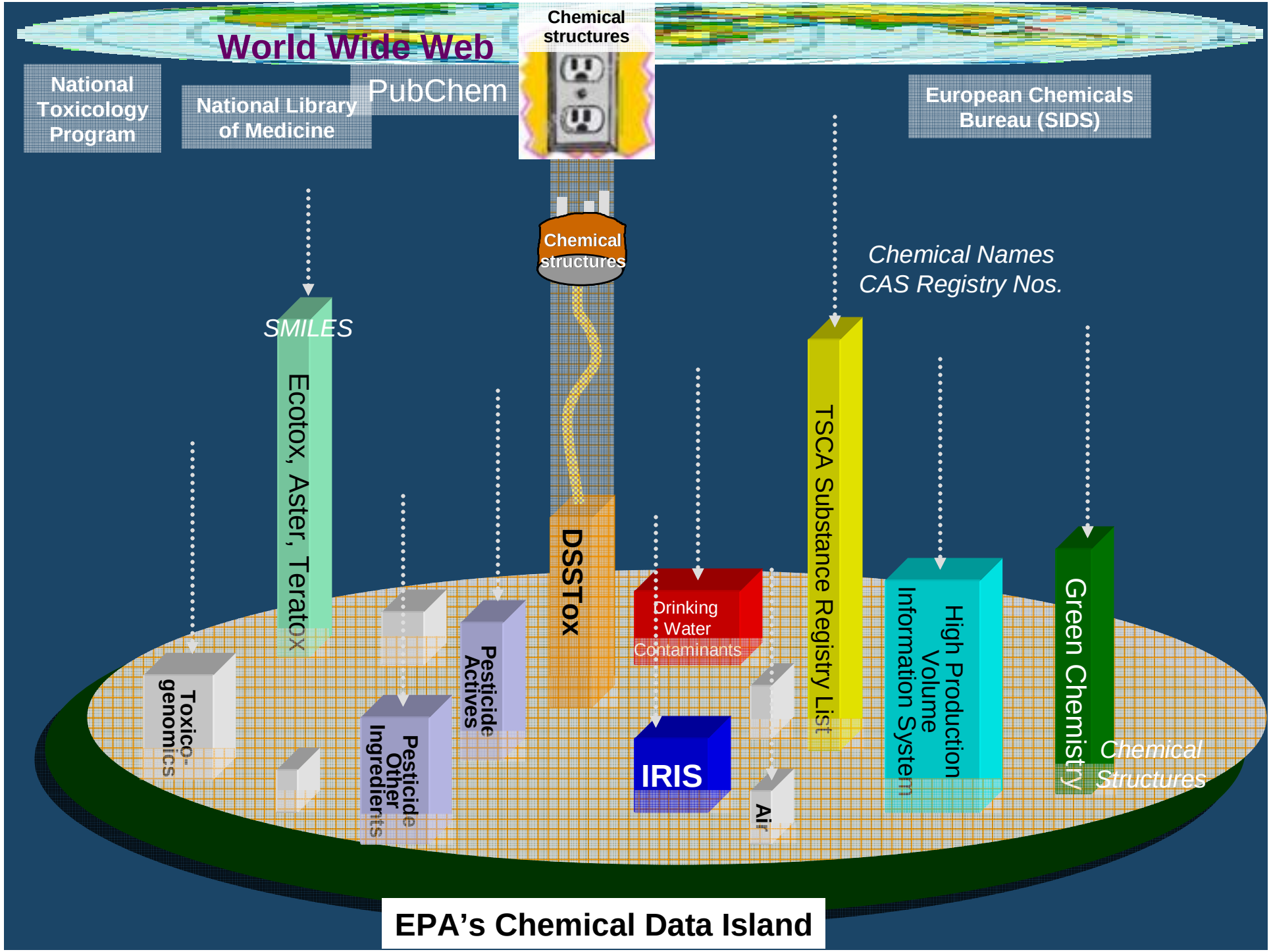
Search Results: 9 hits / 1481 total

TargetSites_Rat_Male = thyroid

& TargetSites_Mouse_Male = liver

EPA's Chemical Data Island


World Wide Web
Chemical structures
National Toxicology Program
National Library of Medicine
PubChem
European Chemicals Bureau (SIDS)
Chemical Names
CAS Registry Nos.
SMILES
Ecotox, Aster, Teratox
TSCA Substance Registry List
High Production Volume Information System
Green Chemistry
Chemical Structures
Toxico-genomics
Pesticide Actives
Pesticide Other Ingredients
Drinking Water Contaminants
IRIS
Air
EPA's Chemical Data Island


World Wide Web
Chemical structures
National Toxicology Program
National Library of Medicine
PubChem
European Chemicals Bureau (SIDS)
Chemical structures
Chemical Names
CAS Registry Nos.
SMILES
Ecotox, Aster, Teratox
DSSTox
TSCA Substance Registry List
High Production Volume Information System
Green Chemistry
Drinking Water Contaminants
Toxico-genomics
Pesticide Actives
Pesticide Other Ingredients
IRIS
Air
Chemical Structures
EPA's Chemical Data Island

Chemical Research in Toxicology

JULY 2007
VOLUME 20, NUMBER 7

Editorial

Aaron T. Jacobs and Lawrence J. Marnett*

A.B. Hancock Jr. Memorial Laboratory for Cancer Research
Departments of Biochemistry, Chemistry, and Pharmacology
Vanderbilt Institute of Chemical Biology
Center in Molecular Toxicology
Vanderbilt-Ingram Cancer Center
Vanderbilt University School of Medicine
Nashville, Tennessee 37232

The Future of Toxicology—Wrap Up

Wither toxicology? We have enjoyed a series of informative, occasionally provocative, commentaries on this subject from a paucity of compelling problems to work on that would generate a broad mandate for large-scale investment in toxicol-

"A major focus for the future of computational toxicology will be integration and analysis of large data sets. The current state of toxicity databases is something of a mess. There are a number of databases, each with differing content, architecture, and searchability, that makes the task of integration extremely difficult."

Part II

Data & Data Linkages

U.S. Environmental Protection Agency

Distributed Structure-Searchable Toxicity (DSSTox) Public Database Network

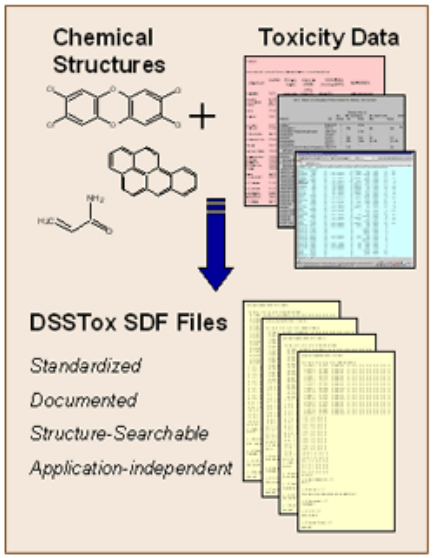
http://www.epa.gov/ncct/dsstox/

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

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.
- Addition of categorical and ranked activity summary fields in 5 DSSTox Data Files (CPDBAS, DBPCAN, EPAFHM, FDAMDD, NCTRER), corresponding to standard PubChem bioassay activity fields:

allows users to search by DSSTox Standard Chemical Fields and includes options for:

- **Text Search:** Chemical Name, CAS RN, InChI, Formula
- **Structure Search (*Exact, Substructure, Similarity*):** SMILES or Structure Drawing Tool entry

***Revised Standard ID Fields for all DSSTox files:**

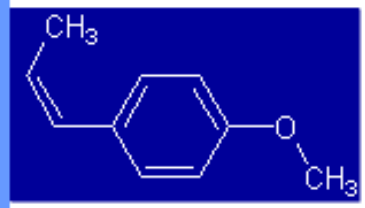
- Modified Record, File, Chemical, and Substance ID fields to index all unique DSSTox structures and substances, also with respect to file record and version

DSSTox Data Files: Details> **All Updated*

CPDBAS_v5b_1547_10Feb2008
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_v2b_2293_15Feb2008
NTPHTS_v1b_1408_15Jul2008
TOXCST_v2b_320_08Feb2008

DSSTox Standard Chemical Fields:

STRUCTURE



DSSTox_CID

STRUCTURE_Formula

STRUCTURE_MolecularWeight

STRUCTURE_ChemicalType

STRUCTURE_TestedForm_DefinedOrganic

STRUCTURE_Chemical Name_IUPAC

STRUCTURE_SMILES

STRUCTURE_Parent_SMILES

STRUCTURE_InChI

STRUCTURE_InChIKey

STRUCTURE_Shown

- tested chemical,
- general form of chemical,
- active ingredient of formulation,
- representative isomer in mixture,
- representative component in mixture,
- monomer of polymer

, simplified to parent

- defined organic
- inorganic
- organometallic

- parent,
- salt Na, Cl, etc
- complex HCl, H2O, mesylate, etc

DSSTox_Generic_SID

TestSubstance_ChemicalName

TestSubstance_CASRN

TestSubstance_Description

- single chemical compound
- macromolecule
- mixture or formulation
- unspecified or multiple forms

ChemicalNote

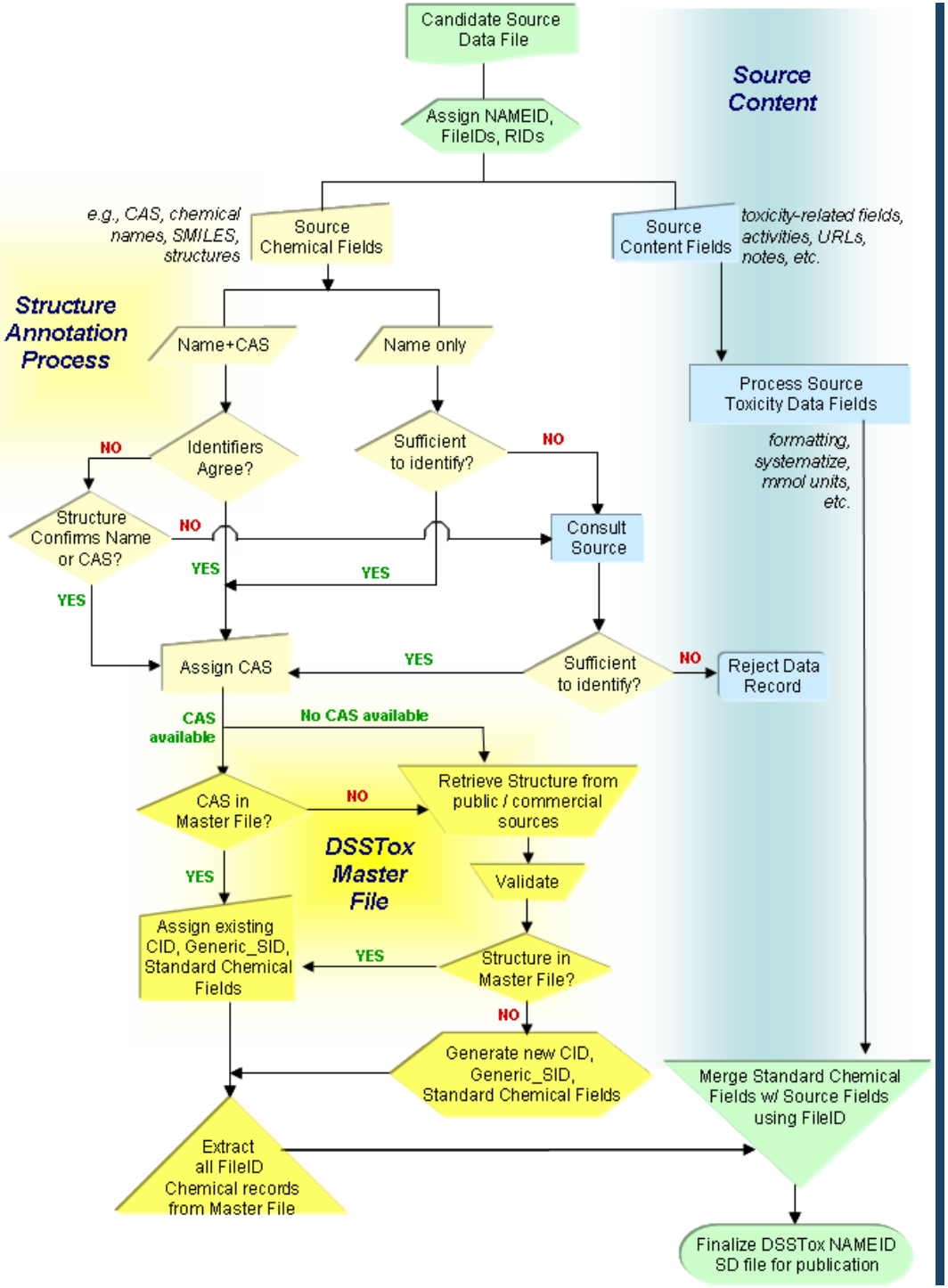
- description of mixture
- nature & CAS of components
- tautomers
- stereochemistry

DSSTox_RID

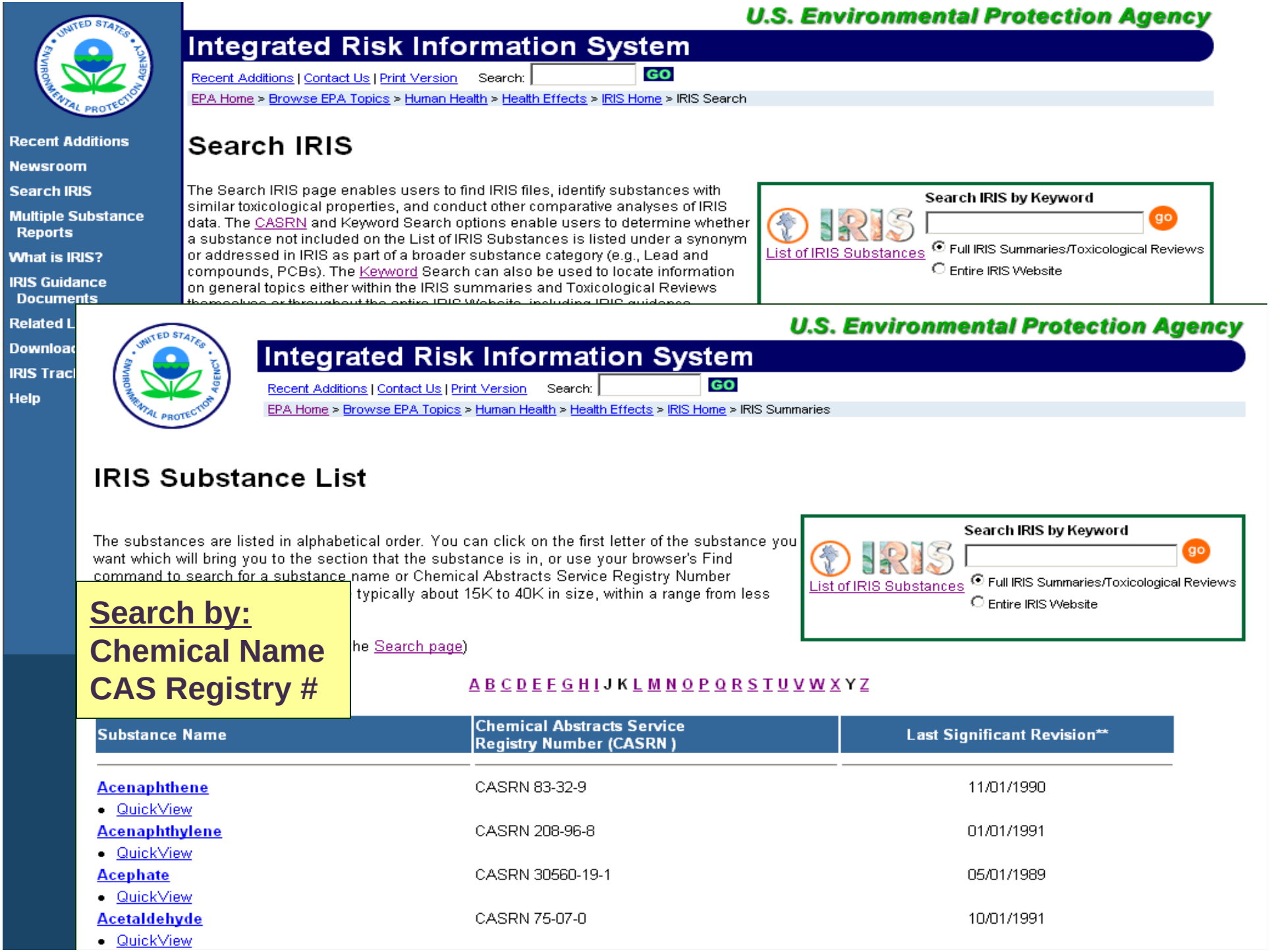
DSSTox_FileID

DSSTox Chemical Quality Assurance Procedures:

- Chemical identification
- Structure annotation
- Internal consistency
- Quality review



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.


U.S. Environmental Protection Agency
Integrated Risk Information System
Recent Additions | Contact Us | Print Version Search: GO
EPA Home > Browse EPA Topics > Human Health > Health Effects > IRIS Home > IRIS Search
Recent Additions
Newsroom
Search IRIS
Multiple Substance Reports
What is IRIS?
IRIS Guidance Documents
Search IRIS
The Search IRIS page enables users to find IRIS files, identify substances with similar toxicological properties, and conduct other comparative analyses of IRIS data. The CASRN and Keyword Search options enable users to determine whether a substance not included on the List of IRIS Substances is listed under a synonym or addressed in IRIS as part of a broader substance category (e.g., Lead and compounds, PCBs). The Keyword Search can also be used to locate information on general topics either within the IRIS summaries and Toxicological Reviews
Search IRIS by Keyword
go
List of IRIS Substances
Full IRIS Summaries/Toxicological Reviews
Entire IRIS Website
U.S. Environmental Protection Agency
Integrated Risk Information System
Recent Additions | Contact Us | Print Version Search: GO
EPA Home > Browse EPA Topics > Human Health > Health Effects > IRIS Home > IRIS Summaries
IRIS Substance List
The substances are listed in alphabetical order. You can click on the first letter of the substance you want which will bring you to the section that the substance is in, or use your browser's Find command to search for a substance name or Chemical Abstracts Service Registry Number
typically about 15K to 40K in size, within a range from less
he Search page)
Search IRIS by Keyword
go
List of IRIS Substances
Full IRIS Summaries/Toxicological Reviews
Entire IRIS Website
Search by:
Chemical Name
CAS Registry #
A B C D E F G H I J K L M N O P Q R S T U V W X Y Z
Substance Name
Chemical Abstracts Service Registry Number (CASRN)
Last Significant Revision**
Acenaphthene
CASRN 83-32-9
11/01/1990
QuickView
Acenaphthylene
CASRN 208-96-8
01/01/1991
QuickView
Acephate
CASRN 30560-19-1
05/01/1989
QuickView
Acetaldehyde
CASRN 75-07-0
10/01/1991
QuickView

U.S. Environmental Protection Agency

Integrated Risk Information System

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You are here: EPA Home » Human Health » IRIS » IRIS Summaries » IRIS Quickviews

Aniline Quickview (CASRN 62-53-3)

Quickview Navigation

- view Anilin

Health assessm
comprehensive
Regional Offices

Disclaimer: Thi
the Full IRIS Sur

For definitions

Status of

File First On-Lin
Last Significant

Category (sec
Oral RfD Assess
Inhalation RfC As
Carcinogenicity As

Chronic Health Hazard Assessments for Noncarcinogenic Effects

Carcinogenicity Assessment for Lifetime Exposure

Weight of Evi

Weight of Evider

B2 (Probable hum

Weight of Evider

Induction of tumo
genetic toxicologi

This may be a syn

Principal and

- 20-26

Confidence in

- Study
- Databa
- RfC -- L

Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Oral Slope Factor(s)	Extrapolation Method
5.7×10^{-3} per mg/kg-day	Linearized multistage procedure, extra risk

Drinking Water Unit Risks
1.6×10^{-7} per ug/L

Risk Level	Concentration
E-4 (1 in 10,000)	6×10^{2} ug/L
E-5 (1 in 100,000)	6×10^{1} ug/L
E-6 (1 in 1,000,000)	6 ug/L

Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type: Spleen, combined fibrosarcoma, stromal sarcoma, capsular sarcoma and hemangiosarcoma
Test Species: Rat/CD-F, male
Route: Oral, Diet
Reference: CIIT, 1982

Home
About DSSTox
Work in Progress
Frequent Questions
Structure Data Files
Central Field Definition Table
Apps, Tools & More
DSSTox Community
Site Map
Glossary of Terms
Help

SDF Download Page:

IRISTR: EPA Integrated Risk Information System (IRIS) Toxicity Review Data *Database File*

** *New DSSTox* Database File *28July2007:*
- Replaces previously published IRISSI_v1a Structure-Index Locater File
- Added 34 new IRIS Source-Specific data fields.

New Users: For general inform… and their use in Chemical Relation…

Description: *The following des…*

EPA's Integrated Risk Infor… National Center for Environ… found in the environment. IR… substances for use in risk a… training in toxicology, but w… following categories:

- Oral reference doses
- Hazard identification,

File Types	Description	File Size	Format
Documentation Files			
Log File	IRISTR_LogFile_28Jul2007.pdf (PDF, 4 pp.)	38KB	PDF
Field Definition File	IRISTR_FieldDefFile_28Jul2007.pdf (PDF, 8 pp.)	75KB	PDF
	IRISTR_FieldDefFile_28Jul2007.doc	204KB	DOC
Data Files: *IRISTR*			
SDF Structure Data File	IRISTR_v1a_544_28Jul2007.sdf	*.zip 1.1 MB	SDF
• Data Table (no structures)	IRISTR_v1a_544_28Jul2007_nostructures.xls		XLS
• Structures Table	IRISTR_v1a_544_28Jul2007_structures.pdf (PDF, 11pp., 1.8MB)		PDF

File Error Report

IRISTR SDF Fields (55 total)

DSSTox Standard Chemical Fields (18)

DSSTox Standard Toxicity Fields (3)

Oral_RfD_Assessed
Oral_RfD_CriticalEffects
Oral_RfD_mg_per_kg_day
Oral_RfD_mmol_per_kg_day
Oral_RfD_Notes
Oral_RfD_Confidence

Inhalation_RfC_Assessed
Inhalation_RfC_CriticalEffects
Inhalation_RfC_mg_per_m3
Inhalation_RfC_mmol_per_m3
Inhalation_RfC_Notes
Inhalation_RfC_Confidence

WtOfEvidence_Cancer_Assessed
WtOfEvidence_Cancer_Concern
WtOfEvidence_1986GuidelineCategories
WtOfEvidence_UpdatedGuidelineUsed
WtOfEvidence_Cancer_Narrative

DrinkingWater_OralSlope_Assessed
DrinkingWater_PrecursorEffect_TumorType
DrinkingWater_OralSlopeFactor_mg_per_kg_day
DrinkingWater_OralSlopeFactor_mmol_per_kg_day
DrinkingWater_ExtrapolationMethod_Notes
DrinkingWater_UnitRisk_microg_per_L
DrinkingWater_UnitRisk_micromol_per_L
DrinkingWater_StudyRoute

Inhalation_UnitRisk_Assessed
Inhalation_PrecursorEffect_TumorType
Inhalation_UnitRisk_microg_per_m3
Inhalation_UnitRisk_micromol_per_m3
Inhalation_StudyRoute
Inhalation_ExtrapolationMethod_Notes

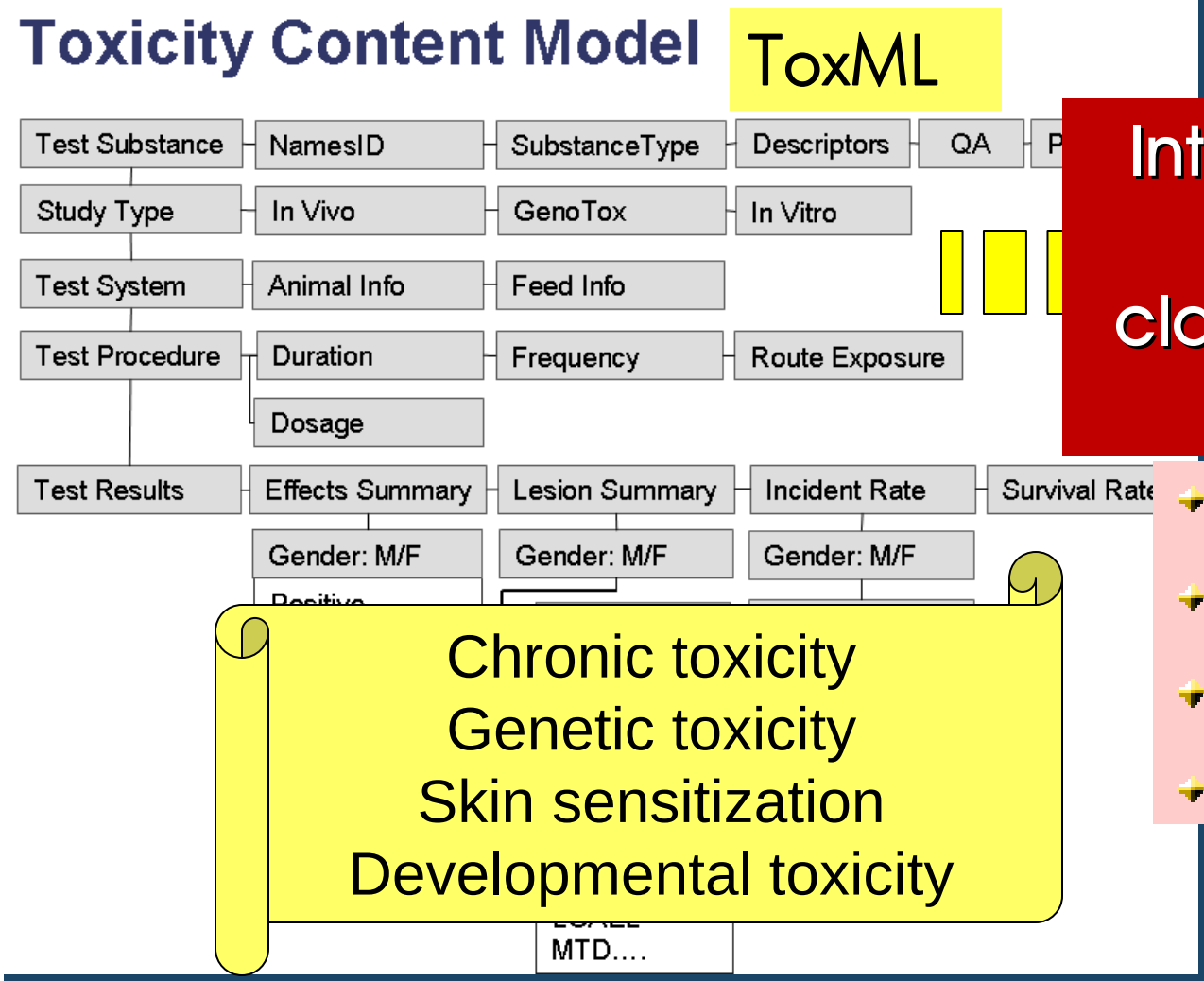
TotalAssessments
Note_IRISTR
Website_URL (field contains chemical-specific links to IRIS "Quick View

IRISTR Toxicity Review Areas	Totals_v1a*
Oral RfDs	357
Inhalation RfCs	70
Weight of Evidence Characterizations	243
Oral Slope Factors/Drinking Water Unit Risks	76
Air Unit Risks	54
Total Assessments	800

Number of IRISTR Toxicity Review Assessments per Chemical	Totals_v1a**
0	(39)
1	323
2	101
3	54
4	22
5	5
Total Assessments	800

Toxicity Experimental Data → Summary Data:

ToxML / LIST Collaborations: FDA CDER/CFSAN



Intermediate toxicity classifications for SAR

+

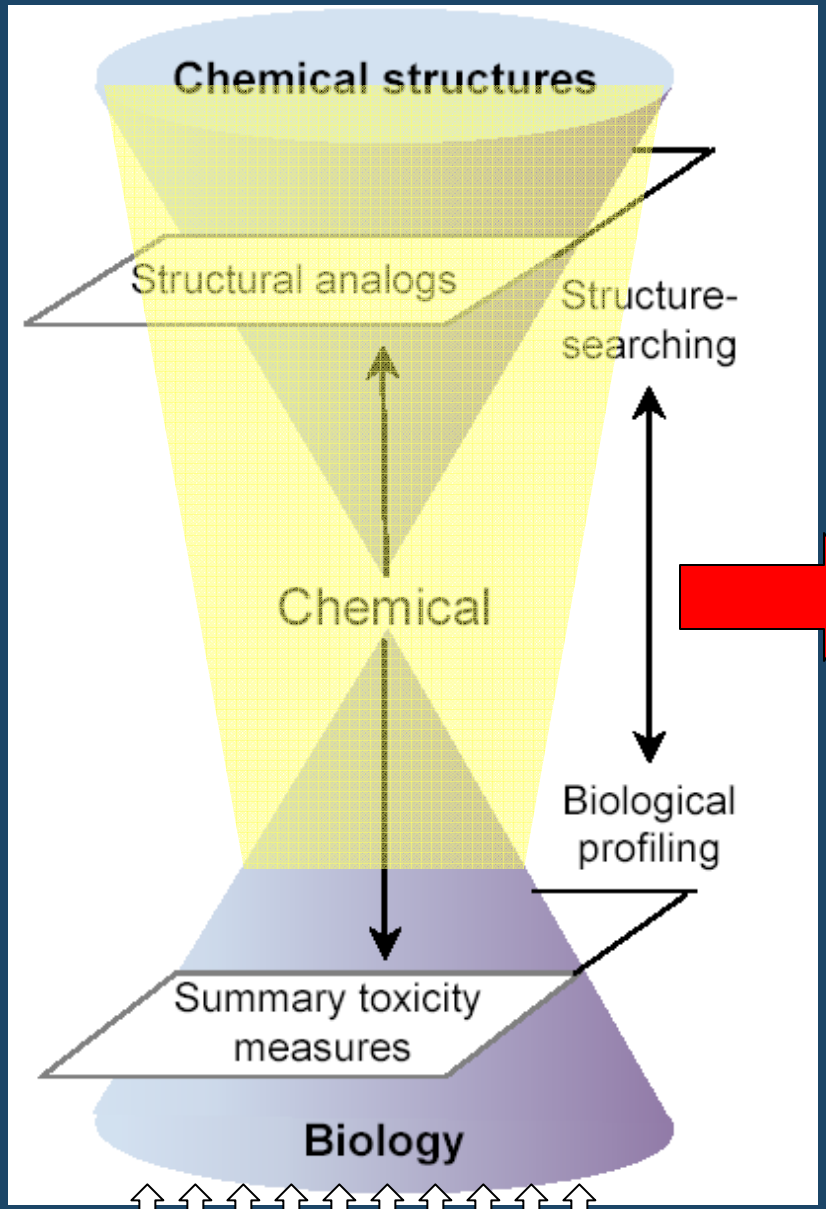
−

- Activity categories
- Potency categories
- Mode of action categories
- Summary calls

Chronic toxicity
Genetic toxicity
Skin sensitization
Developmental toxicity

LeadScope

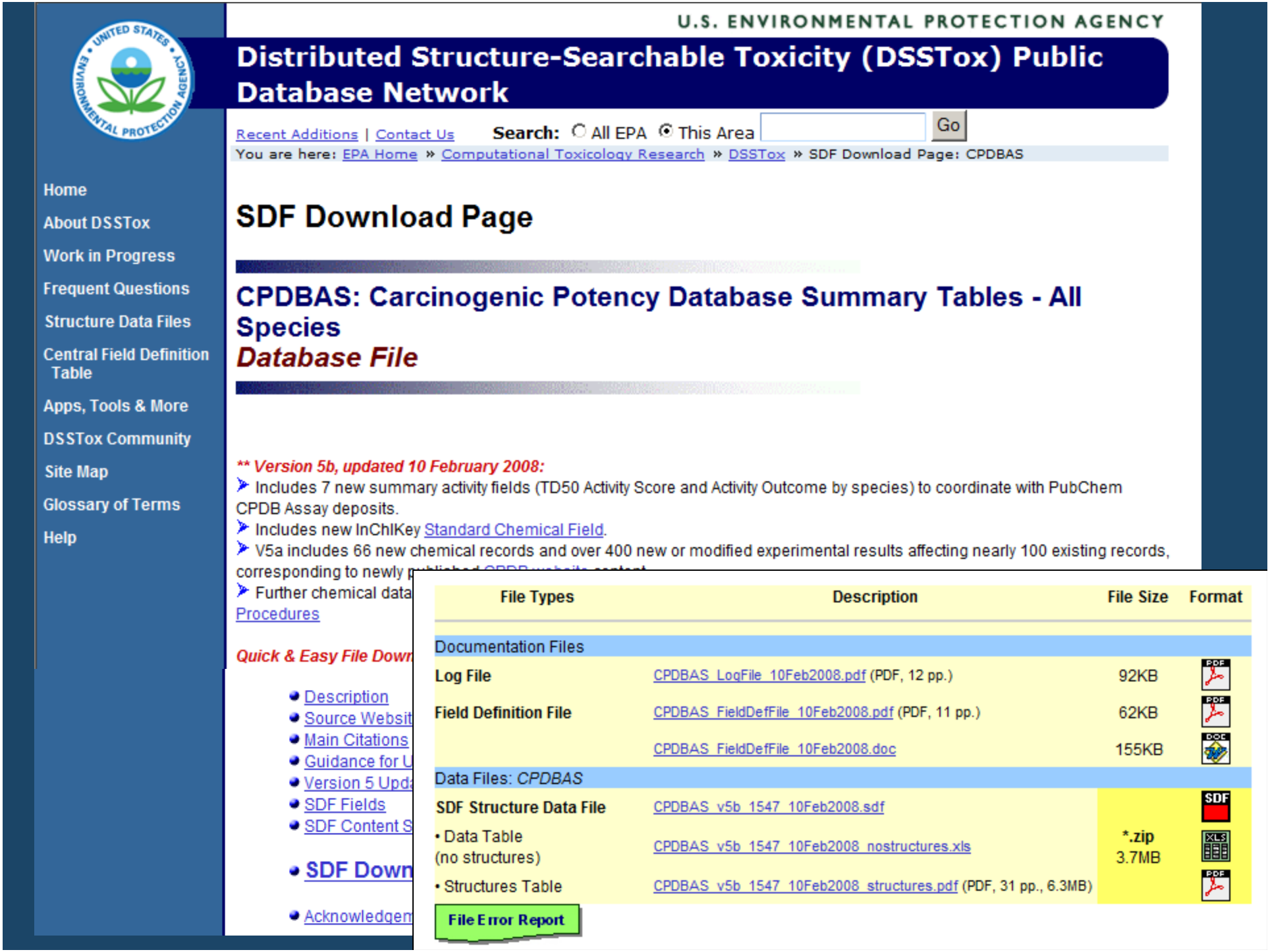
DSSTox Summary Toxicity Data Files



DSSTox Summary Toxicity Data Files

Compound	Tox1	Tox2	Tox3	Tox4	...
Chem1	rat	male	+	lung	...
Chem2					
Chem3					
Chem4					
Chem5					
Chem6					
Chem7					
Chem8					
...					

Toxicity Data Models


U.S. ENVIRONMENTAL PROTECTION AGENCY
Distributed Structure-Searchable Toxicity (DSSTox) Public Database Network
Recent Additions | Contact Us
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Go
You are here: EPA Home » Computational Toxicology Research » DSSTox » SDF Download Page: CPDBAS
Home
About DSSTox
Work in Progress
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Structure Data Files
Central Field Definition Table
Apps, Tools & More
DSSTox Community
Site Map
Glossary of Terms
Help
SDF Download Page
CPDBAS: Carcinogenic Potency Database Summary Tables - All Species
Database File
** Version 5b, updated 10 February 2008:
Includes 7 new summary activity fields (TD50 Activity Score and Activity Outcome by species) to coordinate with PubChem CPDB Assay deposits.
Includes new InChIKey Standard Chemical Field.
V5a includes 66 new chemical records and over 400 new or modified experimental results affecting nearly 100 existing records, corresponding to newly
Further chemical data
Procedures
Quick & Easy File Down
Description
Source Websit
Main Citations
Guidance for U
Version 5 Upd
SDF Fields
SDF Content S
SDF Down
Acknowledgen
File Types
Description
File Size
Format
Documentation Files
Log File
CPDBAS_LogFile_10Feb2008.pdf (PDF, 12 pp.)
92KB
Field Definition File
CPDBAS_FieldDefFile_10Feb2008.pdf (PDF, 11 pp.)
62KB
CPDBAS_FieldDefFile_10Feb2008.doc
155KB
Data Files: CPDBAS
SDF Structure Data File
CPDBAS_v5b_1547_10Feb2008.sdf
• Data Table (no structures)
CPDBAS_v5b_1547_10Feb2008_nostructures.xls
*.zip 3.7MB
• Structures Table
CPDBAS_v5b_1547_10Feb2008_structures.pdf (PDF, 31 pp., 6.3MB)
File Error Report

CPDBAS_v5a_1547

STRUCTURE
DSSTox_RID
DSSTox_CID
DSSTox_Generic_SID
DSSTox_FileID
STRUCTURE_Formula
STRUCTURE_MolecularWeight
STRUCTURE_ChemicalType
STRUCTURE_TestedForm
_DefinedOrganic
STRUCTURE_Shown
TestSubstance_ChemicalName
TestSubstance_CASRN
TestSubstance_Description
ChemicalNote
STRUCTURE_ChemicalName
_IUPAC
STRUCTURE_SMILES
STRUCTURE_Parent_SMILES
STRUCTURE_InChI
StudyType
Endpoint
Species

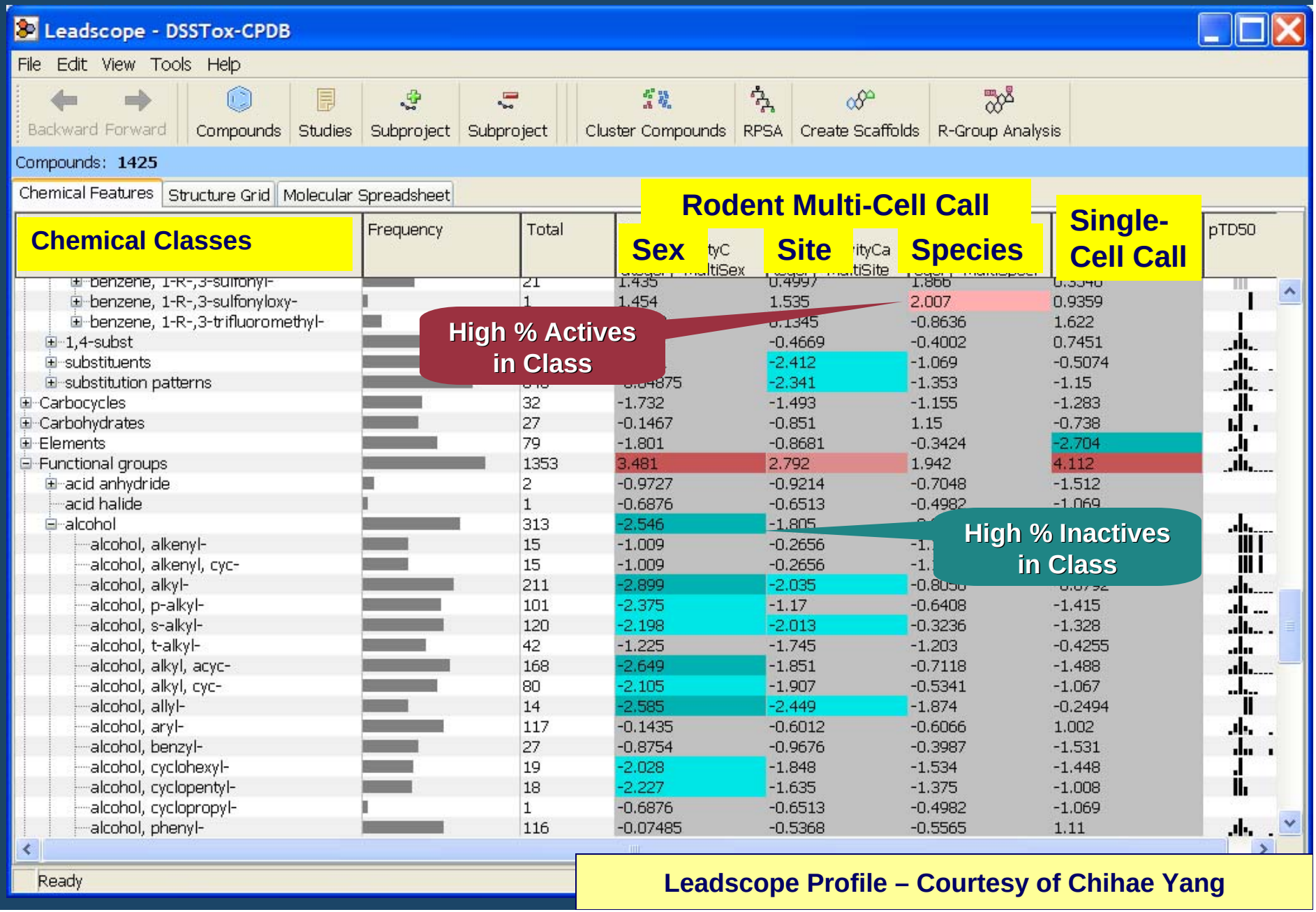
Mutagenicity_SAL_CPDB
TD50_Rat_mg
TD50_Rat_mmol
TD50_Rat_Note
TargetSites_Rat_Male, Female, Both Sexes
TD50_Mouse_mg
TD50_Mouse_mmol
TD50_Mouse_Note
TargetSites_Mouse_Male, Female, Both Sexes
TD50_Hamster_mg
TD50_Hamster_mmol
TD50_Hamster_Note
TargetSites_Hamster_Male, Female, Both Sexes
TD50_Dog_mg
TargetSites_Dog
TD50_Rhesus_mg
TargetSites_Rhesus
TD50_Cynomolgus_mg
TargetSites_Cynomolgus
TD50_Dog_Rhesus_Cynomolgus_Note
ActivityCategory_SingleCellCall
ActivityCategory_MultiCellCall
ActivityCategory_MultiCellCall_Details
ToxicityNote
NTP_TechnicalReport
Website_URL

0
1

multisite active;
multisex active;
multispecies active
multisex inactive;
multispecies inactive

adrenal gland;
bone;
clitoral gland;
esophagus;
ear/Zymbal's gland;
gall bladder;
harderian gland;
hematopoietic system;
kidney;
large intestine;
liver;
lung;
mesovarium;
mammary gland;
mixture;
myocardium;
nasal cavity
nervous system;
oral cavity
ovary;
pancreas;
peritoneal cavity;
pituitary gland;
preputial gland;
prostate;
skin;
small intestine;
spleen;
stomach;
subcutaneous tissue;
bearing animals;
nd;
adder;
system.

Chemical-Biological Profiling of CPDBAS Activities

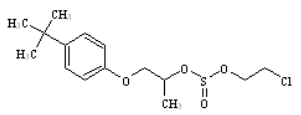
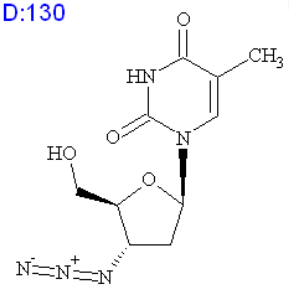
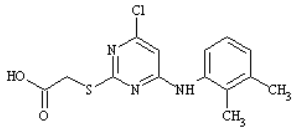
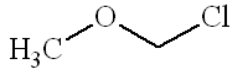
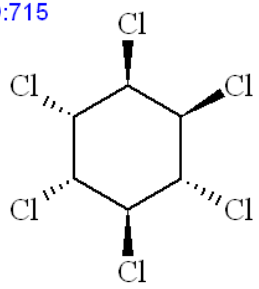
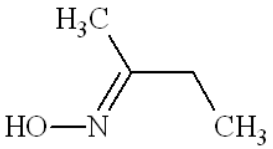
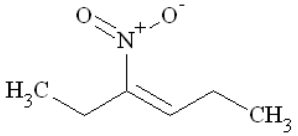
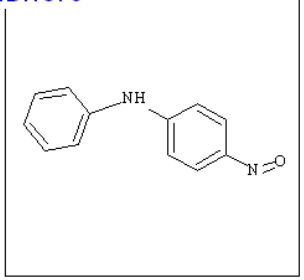


Leadscope Profile – Courtesy of Chihae Yang

CPDBAS_v5b_1547_10Feb2008

	ActivityCategory_		ActivityCategory_MultiCellCall_Details**			
Call	SingleCellCall	MultiCellCall**	multisite***	multisex	multispecies	Total Incidences* (CPDBAS_v5)
Active (1)	active					223
	active	active	✓			81
	active	active		✓		113
	active	active			✓	8
	active	active				
	active	active				
	active	active				
	active	active				
	active	active				
Inactive (0)	inactive					
	inactive	inactive				
	inactive	inactive				
	inactive	inactive				
	inactive	inactive				

If chemical is

ID:98 	ID:130 	ID:299 	ID:316 
Aramite 140-57-8	AZT 30516-87-1	[4-Chloro-6-(2,3-xylidino)-2-p 50892-23-4	Chloromethyl methyl ether 107-30-2
ID:715 	ID:912 	ID:1000 	ID:1076 
alpha-1,2,3,4,5,6-Hexachloro 319-84-6	Methylethylketoxime 96-29-7	3-Nitro-3-hexene 4812-22-0	p-Nitrosodiphenylamine 156-10-5

CPDBAS SDF Fields (61 total)*

DSSTox Standard Chemical Fields (19) * STRUCTURE_InChIKey *field added in v5b*

DSSTox Standard Toxicity Fields (3)

ActivityOutcome_CPDBAS_Mutagenicity ***modified in v5b*** (formerly **Mutagenicity_SAL_CPDB**)

TD50_Rat_mg
TD50_Rat_mmol
ActivityScore_CPDBAS_Rat ***new to v5b***
TD50_Rat_Note
TargetSites_Rat_Male
TargetSites_Rat_Female
TargetSites_Rat_BothSexes
ActivityOutcome_CPDBAS_Rat ***new to v5b***
TD50_Mouse_mg
TD50_Mouse_mmol
ActivityScore_CPDBAS_Mouse ***new to v5b***
TD50_Mouse_
TargetSites_M
TargetSites_M
TargetSites_M
ActivityOutcon
TD50_Hamste
TD50_Hamste
ActivityScore_
TD50_Hamste
TargetSites_H
TargetSites_H
TargetSites_H
ActivityOutcon
TD50_Dog_mg

TD50_Dog_mg
TargetSites_Dog
TD50_Rhesus_mg
TargetSites_Rhesus
TD50_Cynomolgus_mg
TargetSites_Cynomolgus
TD50_Dog_Primates_Note ***modified in v5b***
ActivityOutcome_CPDBAS_Dog_Primates ***new to v5b***
ActivityOutcome_CPDBAS_SingleCellCall ***modified in v5b***
ActivityOutcome_CPDBAS_MultiCellCall ***modified in v5b***
ActivityOutcome_CPDBAS_MultiCellCall_Details ***modified in v5b***
Note_CPDBAS .....contains controlled text entries for version content updates
NTP_TechnicalReport
ChemicalPage_URL .....(formerly **Website_URL** in v4a), contains link to the record-specific CPDB Chemical Index data page, e.g. see ACETALDEHYDE EXIT Disclaimer .

NCBI

PubChem Substance

Search PubChem Substance for dsstox Go Clear Save Search

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Display Summary Show 20 Sort by Send to

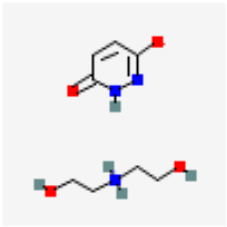
Tools: Links: Related Structures, BioAssays, Literature, Other Links

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

12940 DSSTox Substances

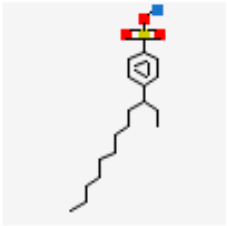
Items 1 - 20 of 12940

1: SID: 48423627 Related Structures

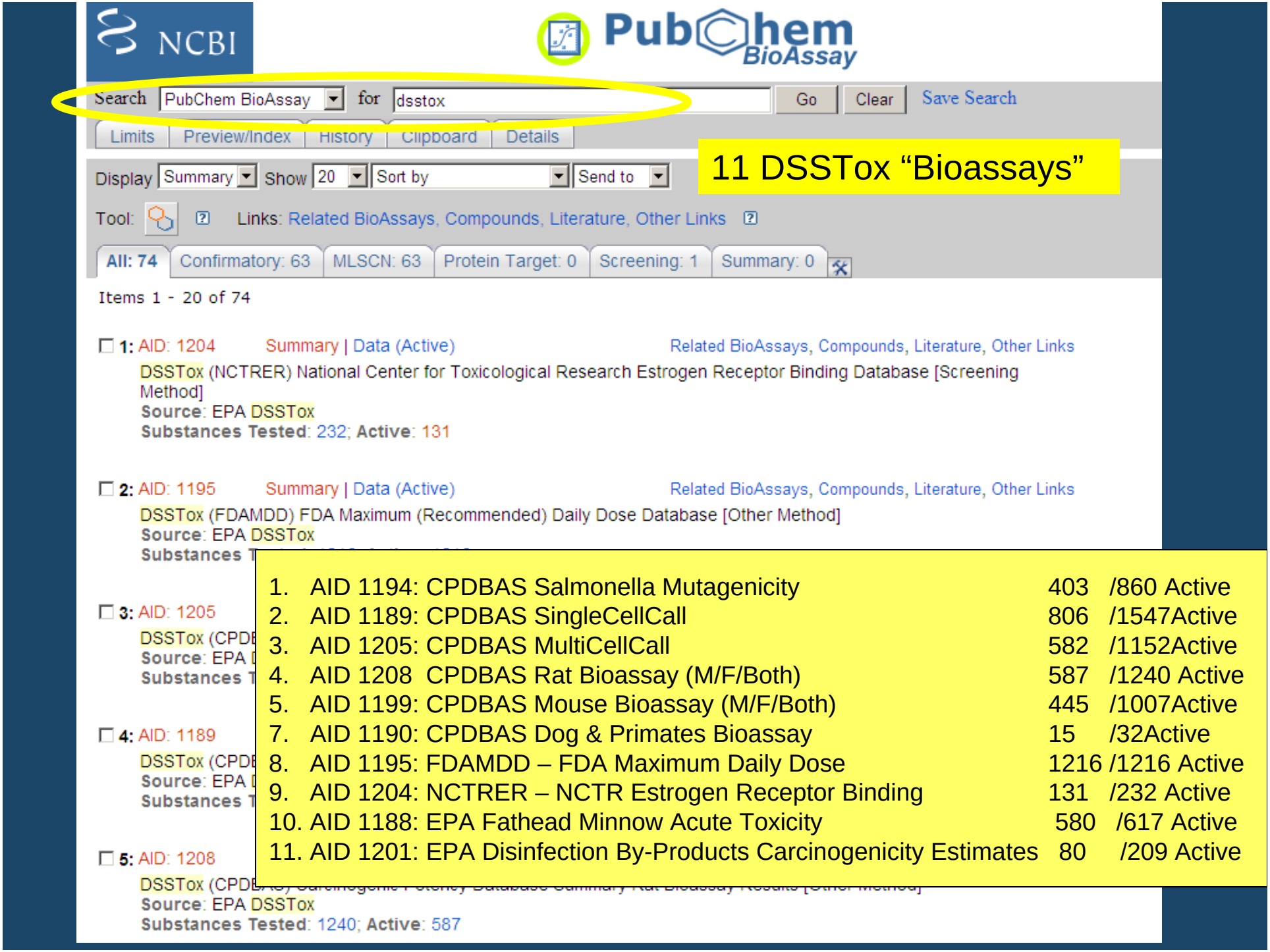


MALEIC HYDRAZIDE DIETHANOLAMINE; 2-hydroxy-N-(2-hydroxyethyl)ethanaminium 6-oxo-1,2,3,6-tetrahydropyridazin-3-olate; 5716-15-4
Compound ID: 24180705
Source: EPA DSSTox (31555) → **DSSTox NTPHTS Download Page**
IUPAC: bis(2-hydroxyethyl)azanium; 6-oxo-1H-pyridazin-3-olate
MW: 217.222400 g/mol | **MF**: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

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 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

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

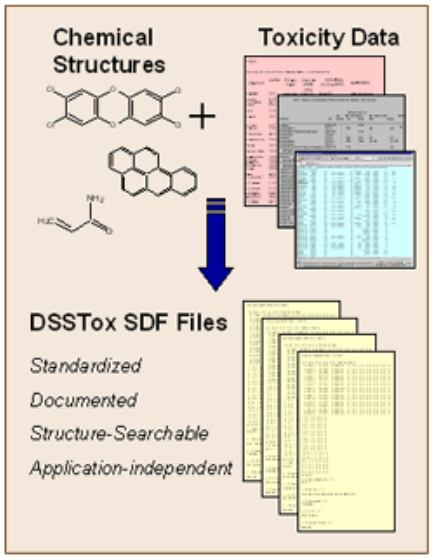
About DSSTox
Work in Progress
Frequent Questions
Structure Data Files
Central Field Definition Table
Apps, Tools & More
DSSTox Community
Site Map
Glossary of Terms
Help

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

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.
- Addition of categorical and ranked activity summary fields in 5 DSSTox Data Files (CPDBAS, DBPCAN, EPAFHM, FDAMDD, NCTRER), corresponding to standard PubChem bioassay activity fields:

allows users to search by DSSTox Standard Chemical Fields and includes options for:

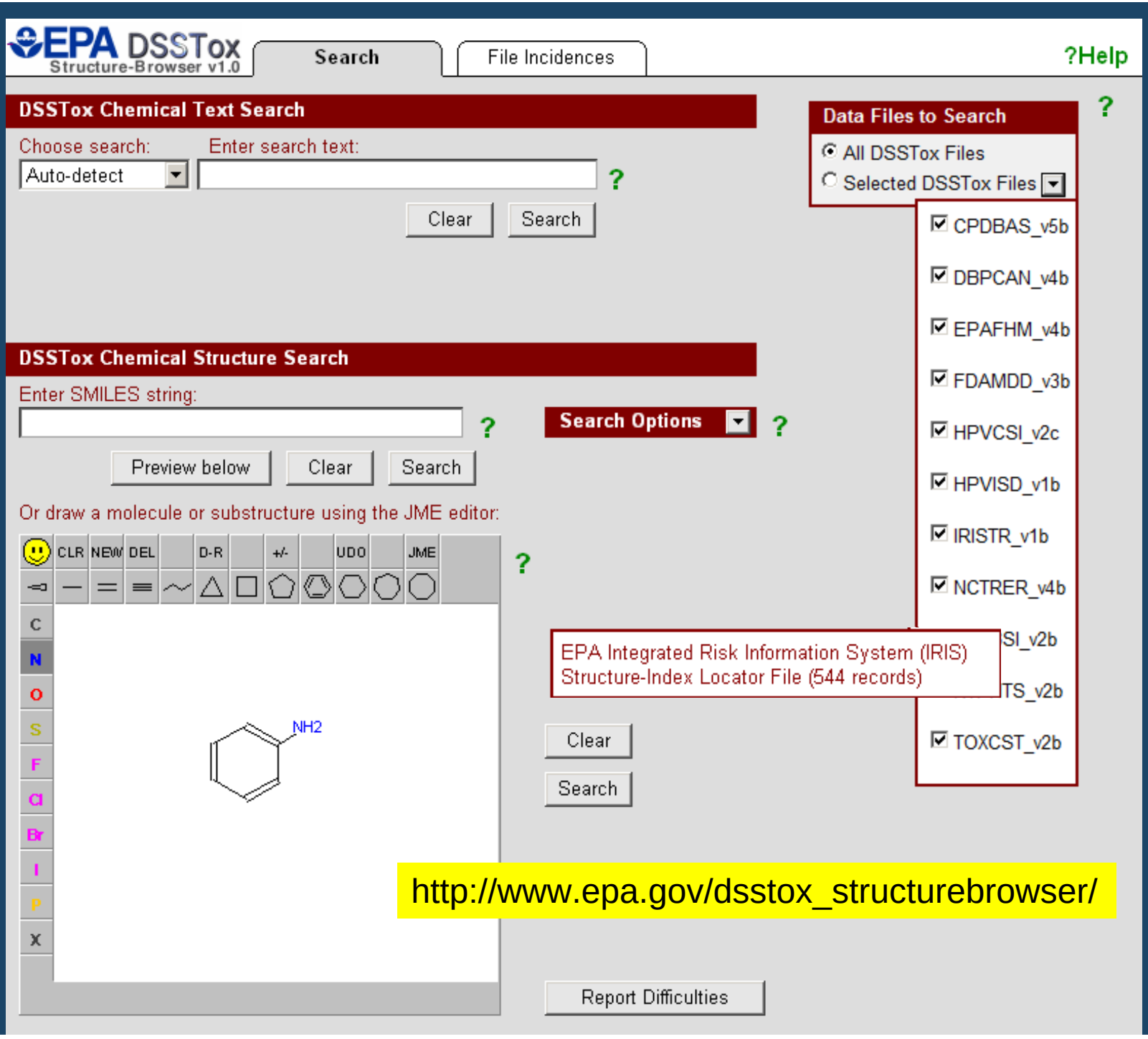
- **Text Search:** Chemical Name, CAS RN, InChI, Formula
- **Structure Search (*Exact, Substructure, Similarity*):** SMILES or Structure Drawing Tool entry

***Revised Standard ID Fields for all DSSTox files:**

- Modified Record, File, Chemical, and Substance ID fields to index all unique DSSTox structures and substances, also with respect to file record and version

DSSTox Data Files: Details> **All Updated*

CPDBAS_v5b_1547_10Feb2008
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_v2b_2293_15Feb2008
NTPHTS_v1b_1408_15Jul2008
TOXCST_v2b_320_08Feb2008


EPA DSSTox
Structure-Browser v1.0
Search
File Incidences
?Help
DSSTox Chemical Text Search
Choose search:
Auto-detect
Enter search text:
Clear
Search
Data Files to Search
All DSSTox Files
Selected DSSTox Files
CPDBAS_v5b
DBPCAN_v4b
EPAFHM_v4b
FDAMDD_v3b
HPVCSI_v2c
HPVISD_v1b
IRISTR_v1b
NCTRER_v4b
SI_v2b
TS_v2b
TOXCST_v2b
DSSTox Chemical Structure Search
Enter SMILES string:
Search Options
Preview below
Clear
Search
Or draw a molecule or substructure using the JME editor:
CLR
NEW
DEL
D-R
+/-
UDO
JME
C
N
O
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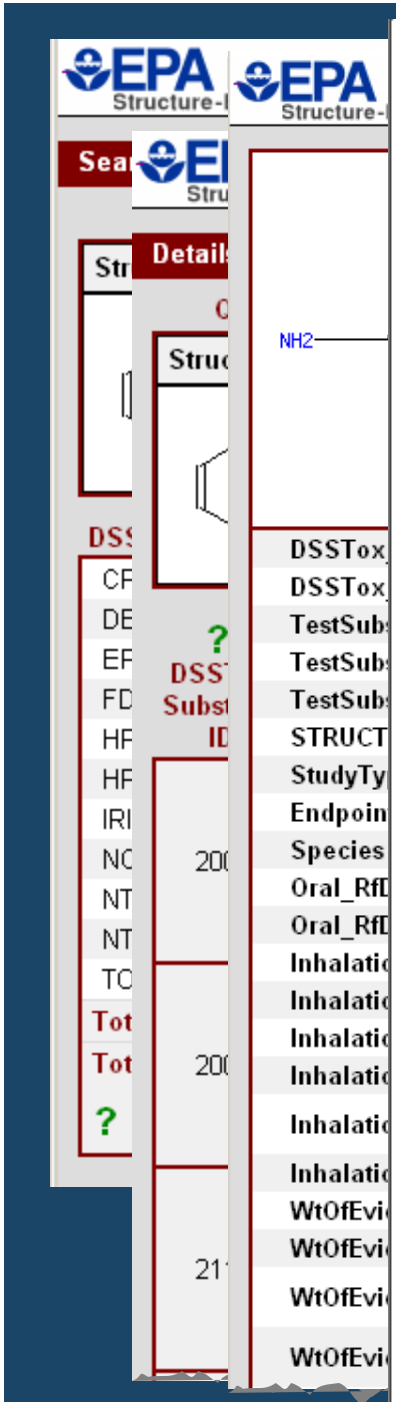
F
Cl
Br
I
P
X
NH2
EPA Integrated Risk Information System (IRIS)
Structure-Index Locator File (544 records)
Clear
Search
Report Difficulties
http://www.epa.gov/dsstox_structurebrowser/



U.S. Environmental Protection Agency

Integrated Risk Information System (IRIS)

Aniline Quickview (CASRN 62-53-3)

Quickview Navigation
+ Expand navigation:

- view Aniline Summary

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of toxicity data by U.S. EPA health scientists from several Program Offices, Regional Offices, and the Office of Research and Development.

Disclaimer: This QuickView represents a snapshot of key information. We suggest that you read the IRIS Summary to put this information into complete context.

For definitions of terms in the IRIS Web site, refer to the IRIS Glossary.

Status of Data for Aniline

File First On-Line: 09/07/1988
Last Significant Revision: 11/01/1990

Category (section)	Status	Last Revised
Oral RfD Assessment	No data	
Inhalation RfC Assessment	On-line	12/01/1993
Carcinogenicity Assessment	On-line	02/01/1994

Chronic Health Hazard Assessments for Noncarcinogenic Effects

Reference Dose for Chronic Oral Exposure (RfD)

Not Assessed under the IRIS Program.

Reference Concentration for Chronic Inhalation Exposure (RfC)

Critical Effect	Point of Departure	UF	MF	RfC
Lack of toxicity (other effect: Mild spleen toxicity.)	NOAEL (HEC): 3.4 mg/m3	3000	1	$1x10^{-3}$ mg/m3

U.S. Environmental Protection Agency

Integrated Risk Information System (IRIS)

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You are here: EPA Home » Research & Development » NCEA » IRIS Home » Integrated Risk Information System (IRIS)

- IRIS Home
- Basic Information
- IRIS Process
- A to Z List of IRIS Substances
- Advanced Search
- Compare IRIS Values
- IRIS Guidance
- Download IRIS
- IRIS Track
- Site Help & Tools
  - Site Overview
  - IRIS Glossary
  - Frequent Questions
  - Tools & Databases
- Related Links

IRIS (Integrated Risk Information System) is a compilation of electronic reports on specific substances found in the environment and their potential to cause human health effects. IRIS was initially developed for EPA staff in response to a growing demand for consistent information on substances for use in risk assessments, decision-making and regulatory activities. The information in IRIS is intended for those without extensive training in toxicology, but with some knowledge of health sciences.

Getting Started with IRIS

- An overview of the web site
- What is IRIS?
- How does EPA decide which substances to add or update?

More frequent questions >>

Using the

Upcoming

Top of page

Search IRIS by Keyword

go

- IRIS Summaries/Toxicological Reviews
- Entire IRIS Website

List of IRIS Substances >>

Ask Peter

I'm Peter, the IRIS Virtual

Advanced Search

By Keyword, Substance, or CASRN | By Critical Effect or Tumor Type | By Toxicity Value | By Human Carcinogenicity | By Uncertainty Factor

+ Search Tips

Search by Keyword, Substance, or CASRN Go

Enter a Keyword, Substance, or CASRN:

EPA DSSTox Structure-Browser GO

- IRIS Summary/Toxicological Review
- Entire IRIS Website

Go

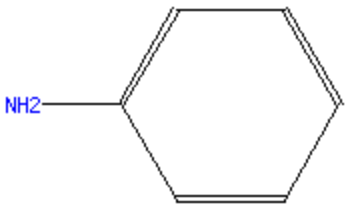
Search Scope

The search by **Keyword** allows you to enter any keyword or string of keywords to locate information on that topic. The search by Chemical Name or CAS Registry Number (CASRN) allows you to enter any chemical name or CASRN and retrieve a list of IRIS substances that match or are a synonym for that chemical name or CASRN.


EPA IRIS Website
DSSTox Structure-Browser

EPA DSSTox Structure-Browser v1.0

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



IRISTR:
EPA Integrated Risk Information System (IRIS) Structure-Index Locator File (544 records)

IRISTR_v1a_544_28Jul2007

IRISTR Source Website

Output Options

Choose Format | Save | Print

?

PubChem

Links directly to chemical data page for Aniline in PubChem

DSSTox_RID	23877
DSSTox_Generic_SID	20090
StudyType	Human Health Exposure Toxicity Review for Risk Assessment
Endpoint	cancer; acute; short-term; sub-chronic; chronic; developmental
Species	rodent; human; dog; rabbit
STRUCTURE_Shown	tested chemical
TestSubstance_ChemicalName	Aniline
TestSubstance_CASRN	62-53-3
TestSubstance_Description	single chemical compound
Oral_RfD_Assessed	0
Oral_RfD_CriticalEffects	Not assessed under the IRIS program.
Inhalation_RfC_Assessed	1
Inhalation_RfC_CriticalEffects	mild spleen toxicity
Inhalation_RfC_mg_per_m3	0.001 mg/m3
Inhalation_RfC_mmol_per_m3	1.07380820711613E-05 mmol/m3
Inhalation_RfC_Notes	NOAEL (No observed adverse effect level) HEC (Human Equivalent Concentration): 3.4 mg/m3
Inhalation_RfC_Confidence	Low
WtOfEvidence_Cancer_Assessed	1
WtOfEvidence_Cancer_Concern	Medium
WtOfEvidence_1986GuidelineCategories	B2; Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals
WtOfEvidence_Cancer_Narrative	Induction of tumors of the spleen and the body cavity in two strains of rat; and some supporting genetic toxicological evidence.

NCBI

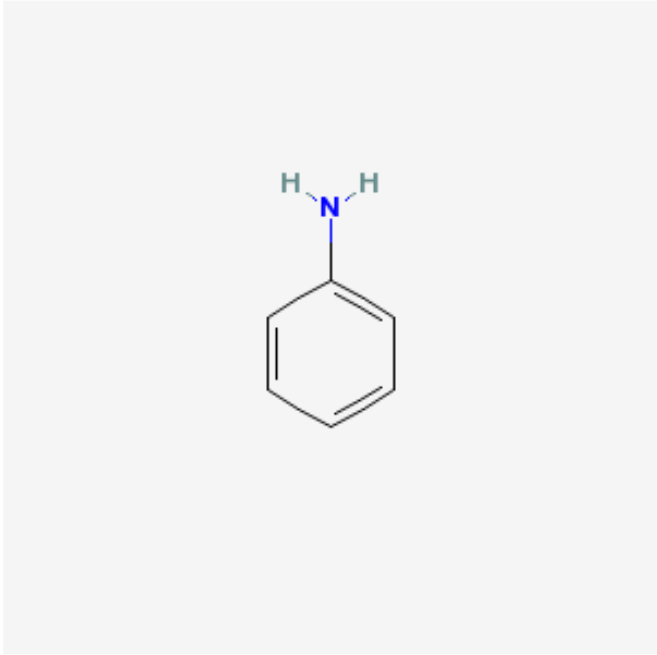
PubChem

Information on biological activities of small molecules

HOME | SEARCH | SITE MAP | PubMed | Entrez | Structure | GenBank | PubChem | Help

Search PubChem Compound GO

Compound Summary:



CID: 6115

BioActivity: Summary
All: 53 Links
Active: 6 Links
Inactive: 45 Links
Inconclusive: 1 Link

Protein Structures: 3 Links

Protein Sequences: 15 Links

NLM Toxicology: Link

Substances:
All: 270 Links
Same: 28 Links
Mixture: 242 Links

Related Compounds:
Same, Connectivity: 13 Links

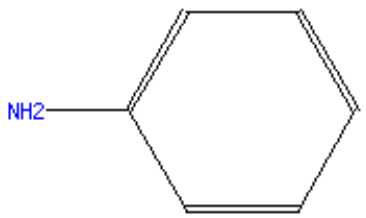
Similar Compounds: 164 Links

Structure Search

MeSH | Synonyms | Properties | Descriptors | Category | Exports

EPA DSSTox Structure-Browser v1.0

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



IRISTR:
EPA Integrated Risk Information System (IRIS) Structure-Index Locator File (544 records)

IRISTR_v1a_544_28Jul2007

IRISTR Source Website

Output Options

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PubChem

EPA ACToR

Links directly to chemical data page for Aniline in EPA ACToR

DSSTox_RID	23877
DSSTox_Generic_SID	20090
StudyType	Human He
Endpoint	cancer; ac
Species	rodent; human; dog; rabbit
STRUCTURE_Shown	tested chemical
TestSubstance_ChemicalName	Aniline
TestSubstance_CASRN	62-53-3
TestSubstance_Description	single chemical compound
Oral_RfD_Assessed	0
Oral_RfD_CriticalEffects	Not assessed under the IRIS program.
Inhalation_RfC_Assessed	1
Inhalation_RfC_CriticalEffects	mild spleen toxicity
Inhalation_RfC_mg_per_m3	0.001 mg/m3

Weight-of-Evidence (WOE) for Carcinogenicity is a system used by the U.S. EPA for characterizing the extent to which the available data support the hypothesis that an agent causes cancer in humans. Revised guidelines published in 1996, 1999, and 2005 have modified these cancer risk characterizations. The approach outlined in EPA"s guidelines for carcinogen risk assessment (2005) considers all scientific information in determining whether and under what conditions an agent may cause cancer in humans, and provides a narrative approach to characterize carcinogenicity rather than categories. Click the ? for more details.

E-05 mmol/m3

ed adverse effect level) HEC (Human Equivalent

mg/m3

n carcinogen - based on sufficient evidence of

nimals

ACToR Home
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Data Collections
Search by Name
Search By Structure
Browse Assays
Downloads
ToxRefDB
DSSTox
ToxMiner
ToxCast
Chemical Prioritization
National Center for Computational Toxicology
Links
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Search Results

Search Term: NAMES : EXACT : aniline

GCID	CASRN	Name	Structure	Bioassay	Literature	MESH	MSDS	Genomics	Hazard	Carcinogenicity	GeneTox	DevTox	ReproTox	DevNeuroTox	NeuroTox	ImmunoTox	ChronicTox	SubchronicTox	DermalTox	RespiratoryTox	AcuteTox	OtherTox	EcoTox	Regulation
88	62-53-3	Aniline	S	B		M	M		H	C	M	D	R		N	I	C		D		A	T	E	R
89	142-04-1	Aniline.HCl	S	B		M	M			C	M	D	R		N	I	C					T		R
131913	45497-73-2	142-04-1	S	B		M																		

Chemical Summary

ACToR Home
About ACToR
Data Collections
Search by Name
Search By Structure
Browse Assays
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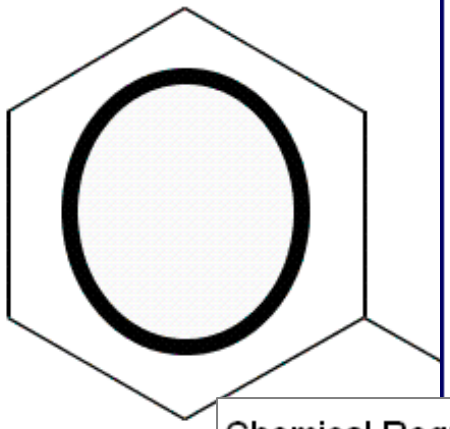


Substances

SCID	Name
90	aniline
1722	aniline
3552	aniline
7104	aniline
8664	aniline

10634	aniline	NTPHTS_DSSTOX	DSSTOX_33195
18522	Aniline	ATSDR_ToxFaq	ATSDR_ToxFaq_9
18890	Aniline	CalEPA	CalEPA_110
28360	aniline	HCPSL_1999	HCPSL_1999_50
28493	Aniline	HCPSL_1999	HCPSL_1999_183
28839	Benzenamine	HCPSL_2006	HCPSL_2006_205
29118	Benzenamine	HPVChallenge	HPVChallenge_22
32512	Benzenamine	HPV	HPV_27
35643	Aniline	INCHEM_IARC	INCHEM_IARC_241
39894	Aniline	ITER_TERA	ITER_TERA_51
54058	Benzenamine	IUR2002	IUR2002_42
60499	62-53-3	NTP1408	NTP1408_29
64301	Aniline (8CA)	OPPIN_Active	OPPIN_Active_2424
68513	Aniline (8CA)	OPPIN_FoodUseActive	OPPIN_FoodUseActive_1244
71389	Aniline (8CA)	OPPIN_Inert	OPPIN_Inert_2243
73926	Aniline	PAN	PAN_929
77727	ANILINE	RBC	RBC_17
79230	ANILINE	Scorecard	Scorecard_929

Chemical Regulations

SCID	Regulation AID	Regulation Name
83185	SRS_CAA112_b_HON_AID_1	CAA112 (b) HON - Hazardous Organic Substance
221301	SRS_CWA_311_AID_1	Clean Water Act Hazardous Substance
221522	SRS_HAP_AID_1	Hazardous Air Pollutant
221681	SRS_NJ_RTK_HS_AID_1	New Jersey Right to Know Hazardous Substance
223688	SRS_RCRA_Appendix_VIII_AID_1	RCRA Hazardous Waste Constituent
223986	SRS_RCRA_U_Waste_AID_1	Hazardous Discarded Commercial Chemical Product (U)
224030	SRS_SARA_110_AID_1	SARA Hazardous Substance
224786	SRS_SARA_302A_AID_1	SARA Extremely Hazardous Substance
225057	SRS_TSCA_4_Tests_AID_1	Testing of Existing Chemicals

Data Collection: IRISTR_DSSTOX

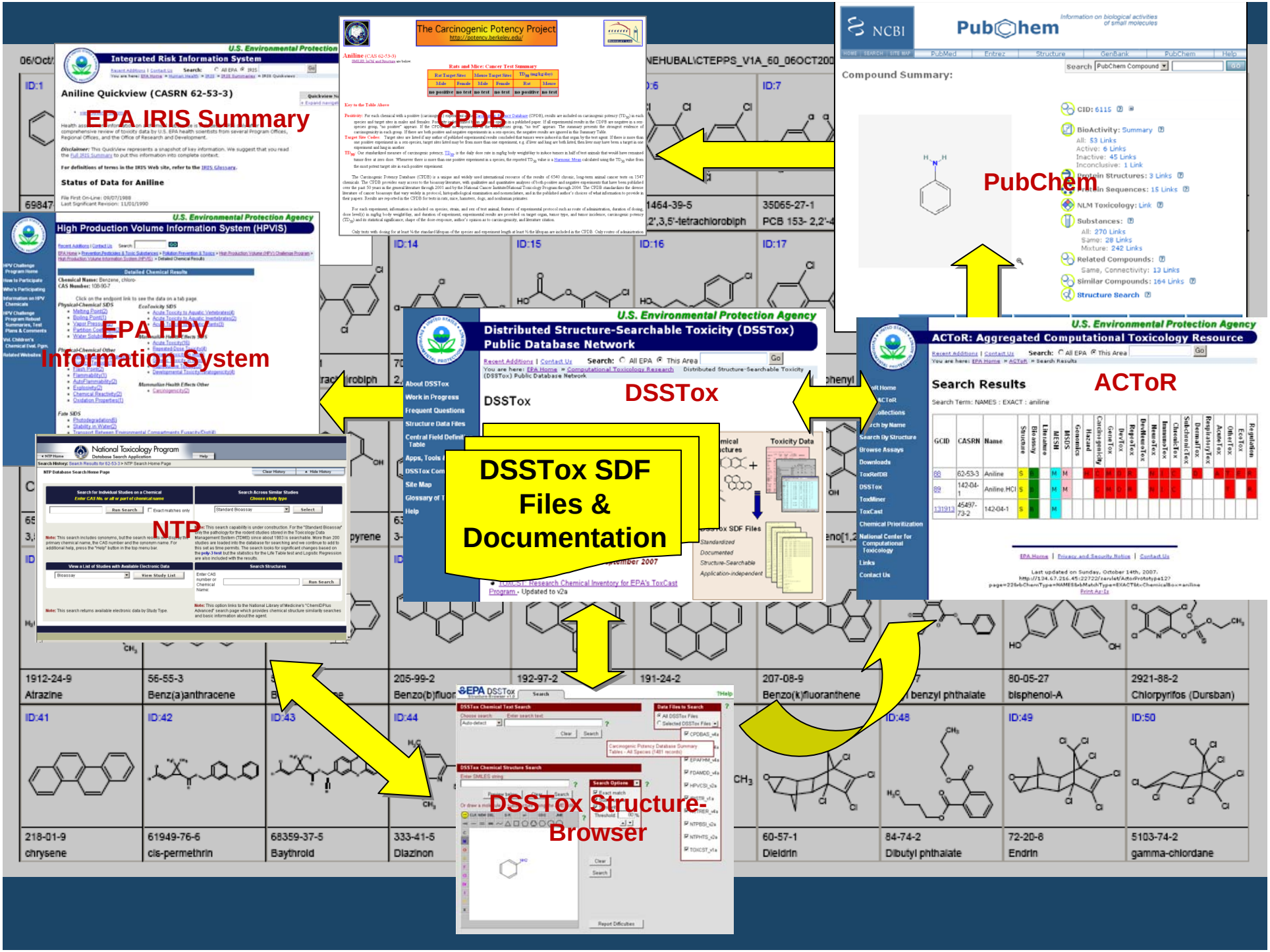
Name:	IRISTR_DSSTOX
Description	EPA Integrated Risk Information System http://www.epa.gov/iris/. A structure index file with links to webpage for each chemical (DSSTOX)
ID	7
Source Type	DSSTox Collection
Number of Substances	544
Number of Generic Chemicals	555

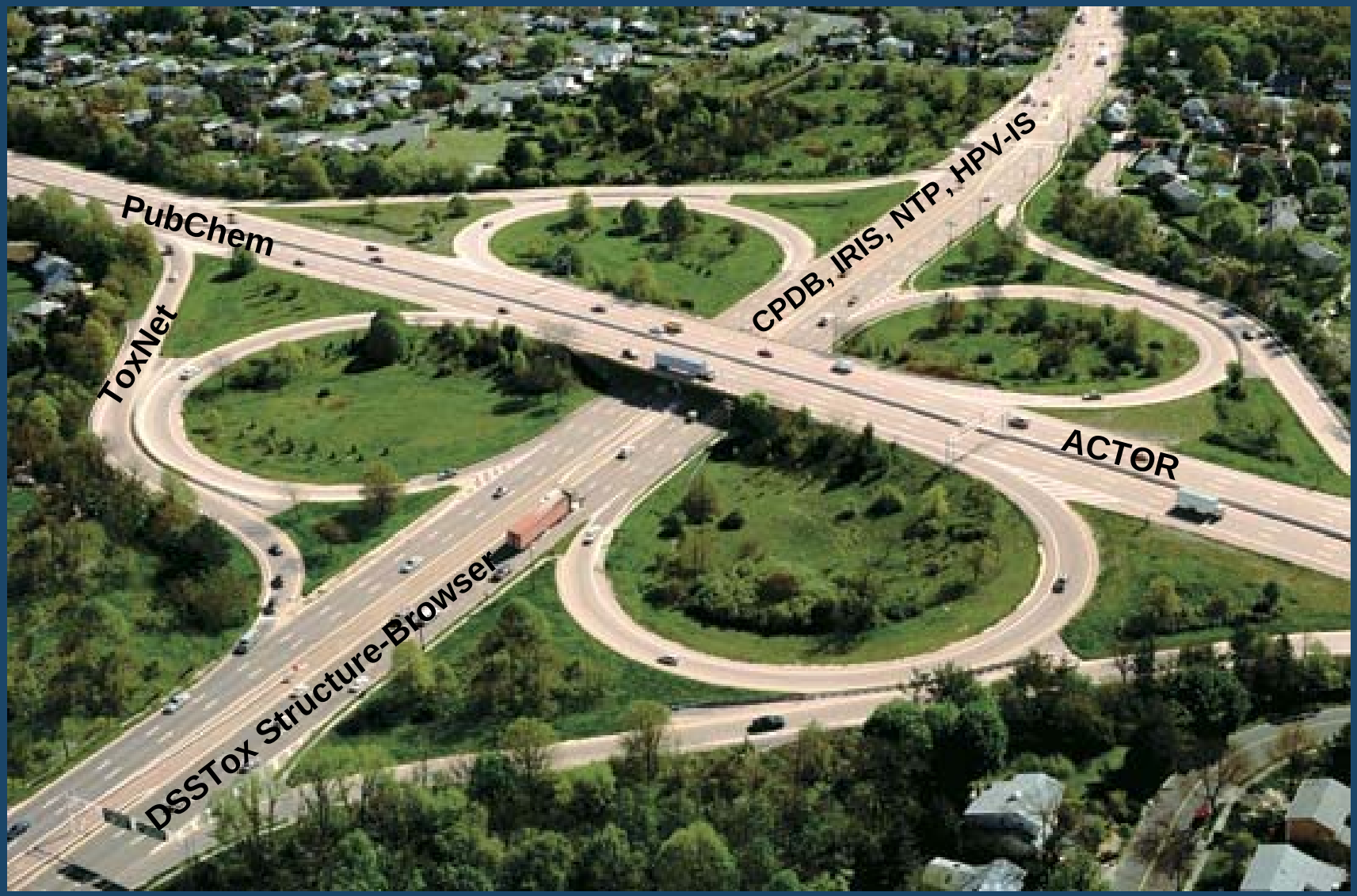
Show Assay Data

Page 1 of 6 : Next

1 2 3 4 5 6

SCID	GCID	Source SID	CASRN	Name	Structure	Bioassay	Literature	MESH	MSDS	Genomics	Hazard	Carcinogenicity	GeneTox	DevTox	ReproTox	DevNeuroTox	NeuroTox	ImmunoTox	ChronicTox	SubchronicTox	DermalTox	RespiratoryTox	Acute Tox	OtherTox	EcoTox	Regulation	Description	Category	FoodSafe
7072	1670	DSSTOX_23845	83-32-9	1,2-dihydroacenaphthylene	S	B		M	M		H	C	M	D	R		N	I	C				A	T	E	R			
7073	6292	DSSTOX_23846	208-96-8	acenaphthylene	S			M			H	C	M	D	R		N	I	C		D		A	T	E	R			
7074	6293	DSSTOX_23847	30560-19-1	O,S-dimethyl acetylamidothiophosphate	S			M	M		H	C	M	D	R		N	I	C		D		A	T	E	R			
7075	2	DSSTOX_23848	75-07-0	acetaldehyde	S	B		M	M		H	C	M	D	R		N	I	C		D		A	T	E	R			F
7076	6294	DSSTOX_23849	34256-82-1	2-chloro-N-(ethoxymethyl)-N-(2-ethyl-6-methylphenyl)acetamide	S	B		M			H	C	M	D	R		N	I	C				A	T	E				
7077	1446	DSSTOX_23850	67-64-1	acetone	S	B		M	M		H	C	M	D	R		N	I	C		D		A	T	E	R			F
7078	9	DSSTOX_23851	75-05-8	acetonitrile	S	B		M	M		H	C	M	D	R		N	I	C		D		A	T	E	R			


EPA IRIS Summary
CPDB
PubChem
EPA HPV Information System
DSSTox
ACToR
NTP
DSSTox SDF Files & Documentation
DSSTox Structure Browser


PubChem
ToxNet
CPDB, IRIS, NTP, HPV-IS
ACTOR
DSSTox Structure-Browser

Part III

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

Inside EPA
Online access provided by InsideEPA.com

Date: June 22, 2007 -

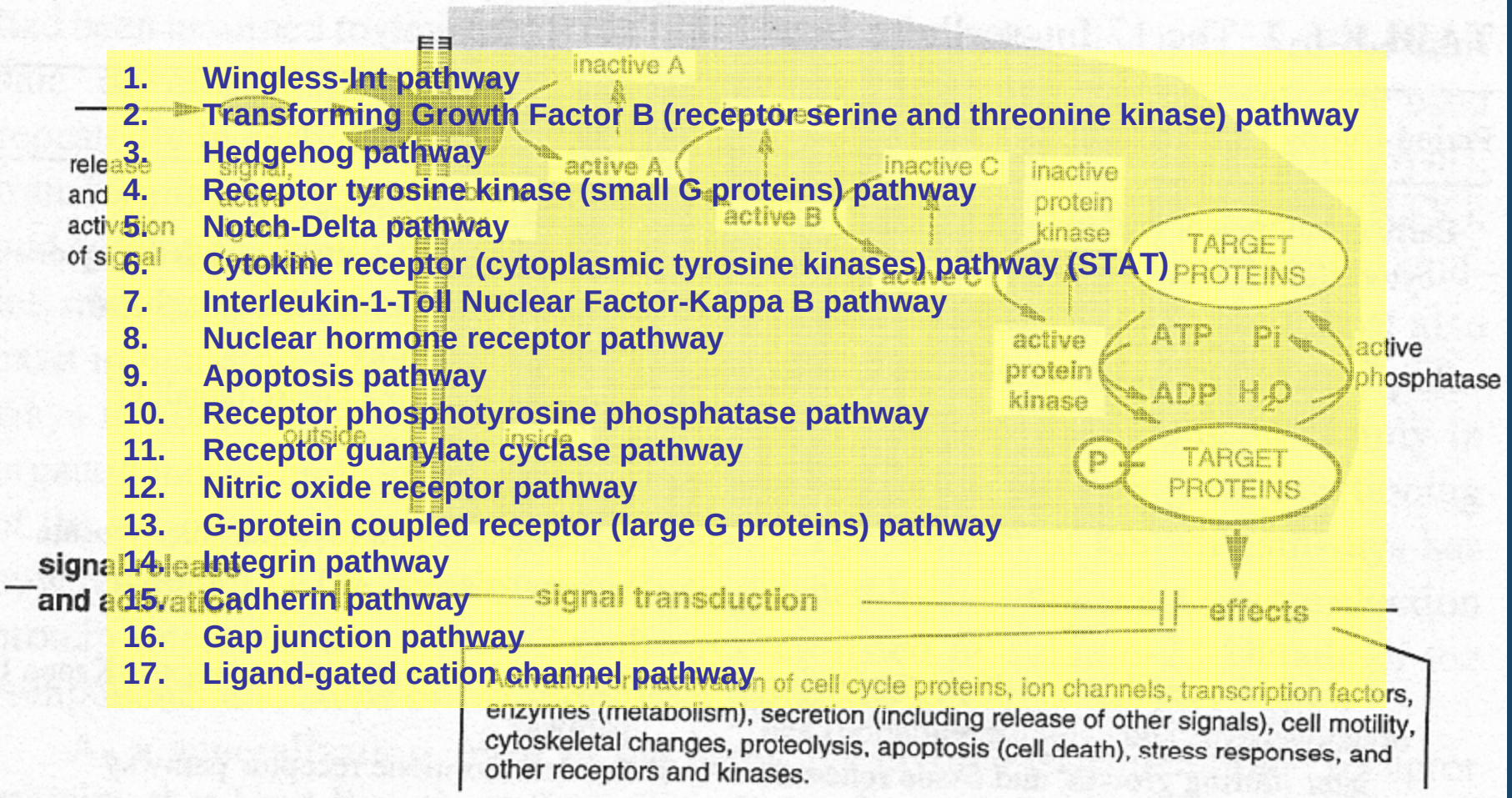
A National Academy of Sciences (NAS) panel is calling for a major shift in how EPA assesses chemicals' toxicity, recommending that the agency base its toxicological research and regulatory processes on how substances affect biological pathways -- which send information within and between cells -- rather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

The new studies envisioned by the panel would evaluate chemicals' effects on biological processes using cells or cell lines, preferably human, to examine how they react to exposure to different substances. Rather than focusing research and basing regulations on endpoints, such as a substance's apparent ability to create tumor cells or harm brain development in fetuses, EPA should center toxicity testing around "the perturbations in toxicity pathways that are expected to lead to adverse effects," the report says.

"In this framework, the goals of toxicity testing are to identify critical pathways that when perturbed can lead to adverse health outcomes and to . . . understand the effects of perturbations on human populations," says the report, *Toxicity Testing in the Twenty-first Century: A Vision and a Strategy* .

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**



U.S. ENVIRONMENTAL PROTECTION AGENCY

National Center for Computational Toxicology

Contact Us **Search:** All EPA This Area Go

You are here: EPA Home » National Center for Computational Toxicology » ToxCast™ Program

- Home
- Basic Information
- Organization
  - Post Doc Profiles
- Framework
- Databases and Models
- Research Activities
  - ACToR
  - ToxCast™
  - Virtual Liver
- Conferences and Seminars
- Publications

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

ToxCast™ Program

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

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.

ToxCast™ Navigation

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

POLICYFORUM

Science: Feb 15, 2008

TOXICOLOGY

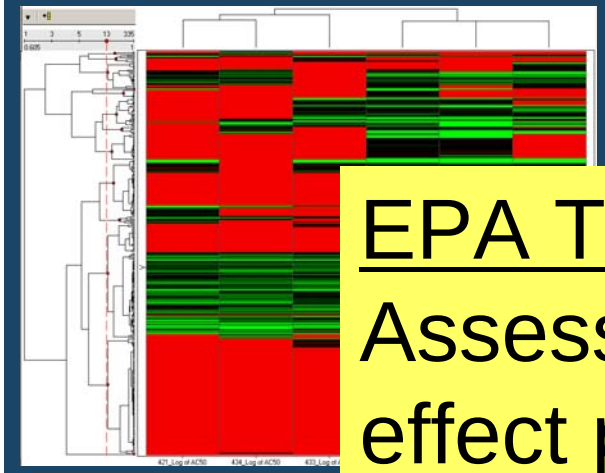
Transforming Environmental Health Protection

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

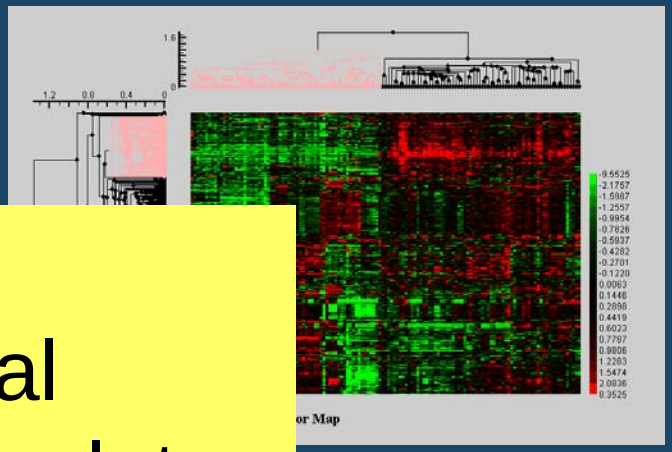
We propose a shift from primarily in vivo animal studies to in vitro assays, in vivo assays with lower organisms, and computational modeling for toxicity assessments.

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

Correlating Domain Outputs

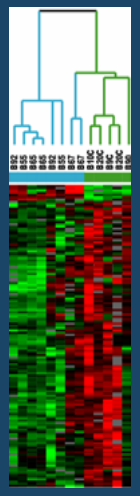


CellularA

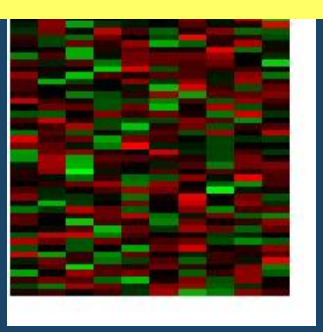


emical properties

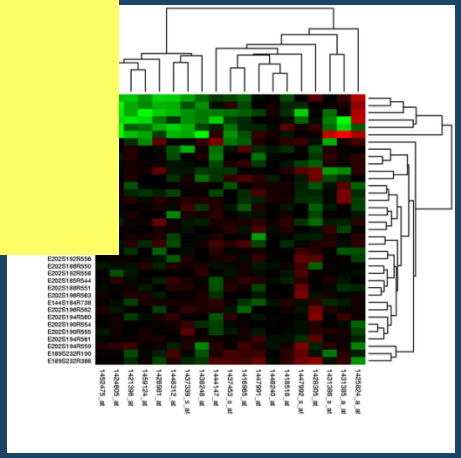
EPA ToxCast Goal:
Assess broad biological effect patterns and correlate with the patterns of known toxicants for forecasting potential for hazard



Biochemical Assays

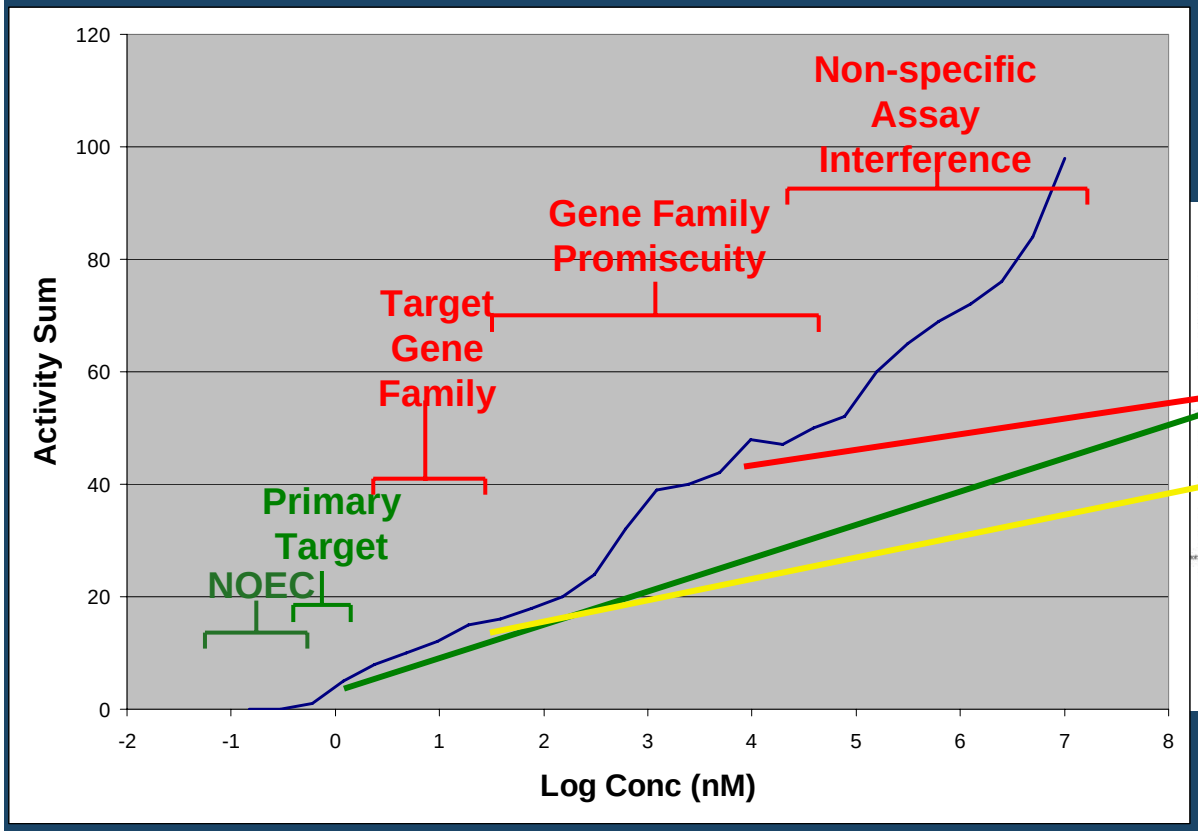


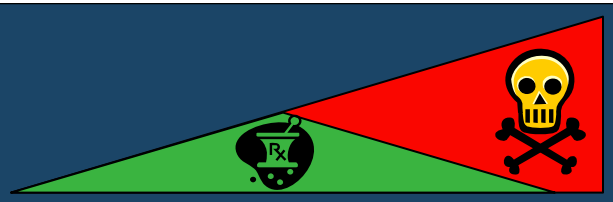
Genomic Signatures



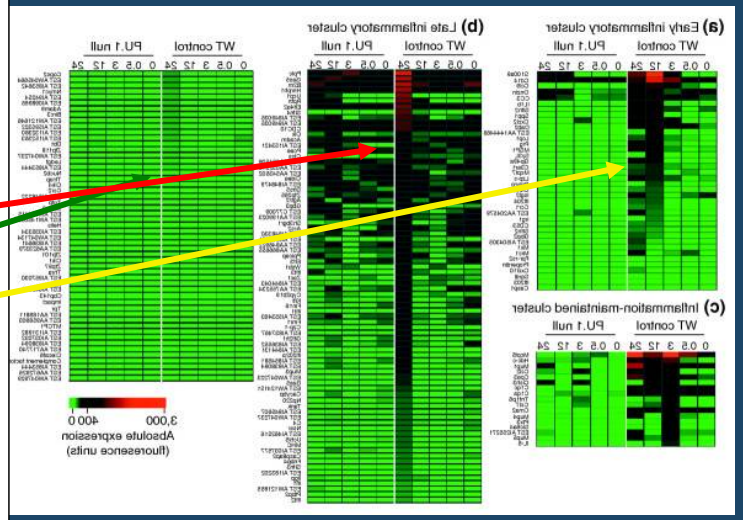
Toxicology Endpoints

Bioactivity Profiling of Pharmaceuticals vs Environmental Chemicals





HTS Target Assay Panels



Heat map profiles of activity in different assays (columns) arranged by compound (rows). Inactive (green) to highly active (red).

Slide courtesy of Keith Houck, EPA NCCT

United States Environmental Protection Agency

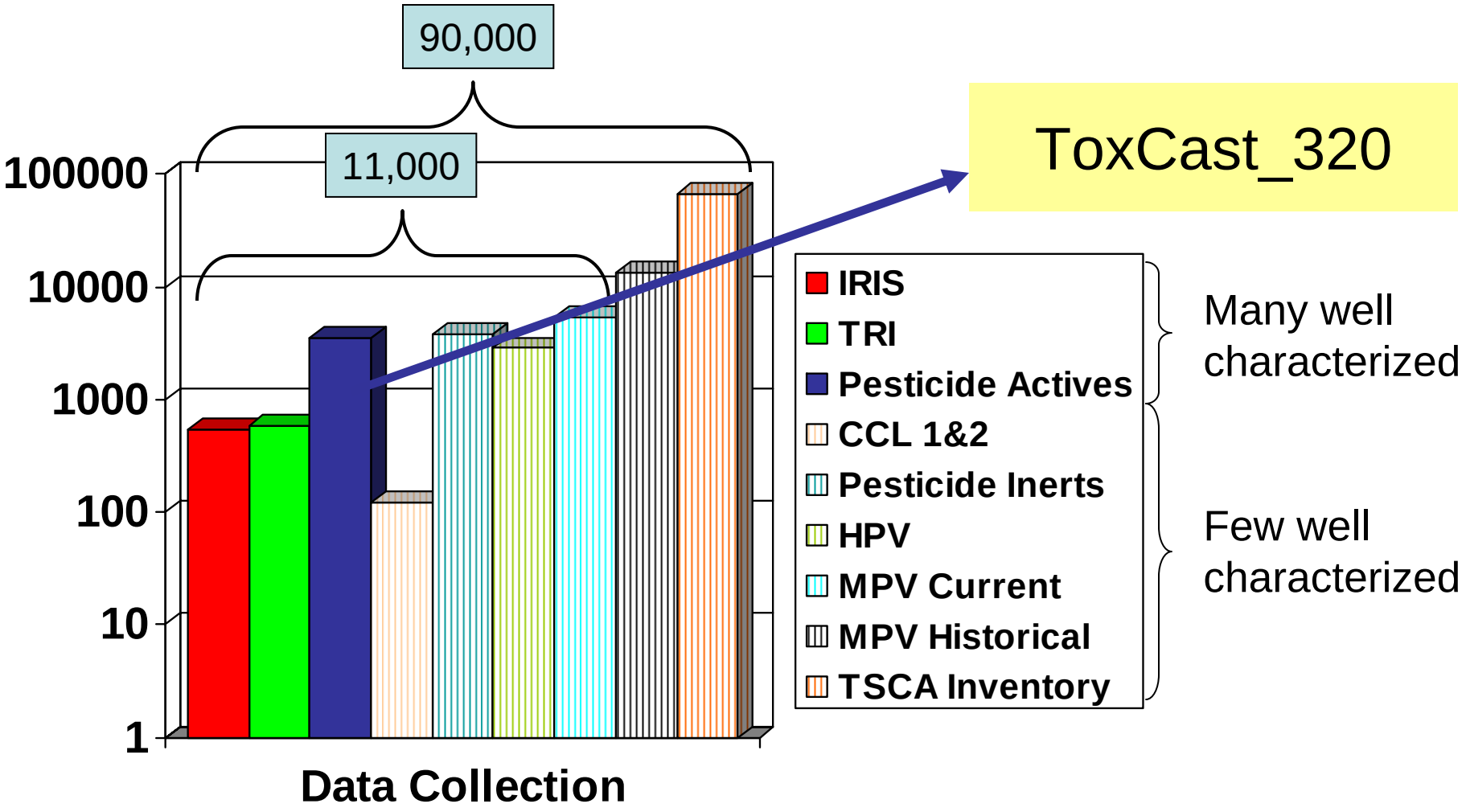
ToxCast Phase I Objective:

Derive Predictive Signatures for Chemical Prioritization

Requirements for Chemical Selection:

- Sufficient number and diversity of chemicals
- Availability of high quality reference *in vivo* toxicity data covering broad range of endpoints
- Expectation of broad spectrum biological activity
- Properties suitable for HTS
- Cost and availability

ToxCast Phase I Chemicals



Prioritize List of ~840 Pesticide Actives

- Data availability
- Toxicological interest
- Environmental relevance

CAS_NO	Parent Molecular Weight	ALogP	PCCODE	CHEMICALNAME	Exclude(X) Additional(+)	DER_TOTAL	Comment	Pesticides (3448)	Pesticides (Actives Supported) (1082)	Pesticide (Food Use Actives) (336)	AntiMicrobial (754)	AntiMicrobial (Food Use) (26)	Inerts (3305)	Inerts (List 1) (8)	Inerts (List 2) (96)	HPV (2843)	HPV Challenge (1973)	EDSP (79)	CCL (41)	Number of lists	Activity/Chemical Classes	Activity/Pesticidal MOA
135158-54-2	210.3	2.19	061402	1,2,3-Benzothiadiazole-7-		6		1	1	1	0	0	0	0	0	0	0	0	0	3		unclass
123312-89-0	217.2	0.82	101103	1,2,4-Triazin-3(2H)-one, 4,5-		6		1	1	1	0	0	0	0	0	0	0	0	0	3	Triazine	
68049-83-2	338.2	3.74	119016	1,2,4-Triazolo(4,3-a)pyridin-3(2H)-		6		1	1	0	0	0	0	0	0	0	0	0	0	2		unclass
139-40-2	229.7	2.17	080808	1,3,5-Triazine-2,4-diamine, 6-		5		1	1	0	0	0	0	0	0	0	0	0	0	2	Triazine	chlorotri
122-34-9	201.7	1.39	080807	1,3,5-Triazine-2,4-diamine, 6-		6		1	1	1	1	1	0	0	0	0	0	1	0	6	Triazine	chlorotri
101-05-3	275.5	3.58	080811	1,3,5-Triazine-2-amine, 4,6-		6	Mouse	1	1	0	0	0	0	0	0	0	0	0	0	2	Triazine	triazine
29091-21-2	350.3	3.73	110201	1,3-Benzenediamine, 2,6-dinitro-		6		1	1	0	0	0	0	0	0	0	0	0	0	2	Amine,	phenyle
118134-30-8	297.5	4.07	120759	1,4-Dioxaspiro?4,5Udecane-2-		6		1	1	0	0	0	0	0	0	0	0	0	0	2		unclass
116255-48-2	377.1	3.66	120503	1H-1,2,4-Tria																2	Bromin	conazol
119168-77-3	333.9	3.86	090102	1H-Pyrazole-																2	Amide,	pyrazol
119515-38-7	229.3	2.16	070705	1-Piperidinec																2	Alcohol	
101-10-0	200.6	2.19	021201	2-(m-Chlorop																2	Phenox	phenox
21564-17-0	238.3	3.56	035603	2-		6		1	1	0	1	0	1	0	0	0	0	0	0	4	Thiazol	benzoth
2971-36-0				2,2-Bis(4-hydroxyphenyl)-1,1,1-	+	0	metabol	0	0	0	0	0	0	0	0	0	0	0	0	0		organoc
94-75-7	221	2.46	030001	2,4-Dichlorophenoxyacetic acid		6	Repro	1	1	1	0	0	0	0	0	1	1	1	0	6	Carbox	phenox
16079-88-2	241.5	1.49	006315	2,4-Imidazolidinedione, 1-bromo-		6		1	1	0	1	0	0	0	0	1	0	0	0	4	Imidazo	
136-45-8	251.3	2.22	047201	2,5-Pyridinedicarboxylic acid,		6		1	1	1	0	0	0	0	0	0	0	0	0	3	Ester,	
120-32-1	218.7	3.64	062201	2-Benzyl-4-chlorophenol		5		1	1	0	1	0	1	0	0	0	0	0	0	4	Cresol,	
7786-34-7	224.1	0.41	015801	2-Butenoic acid, 3-		6		1	1	0	0	0	0	0	0	0	0	1	0	3	Organo	organop
1929-82-4	230.9	3.56	069203	2-Chloro-6-		6		1	1	1	0	0	0	0	0	1	1	0	0	5	Organo	

Pesticide Registration Records

Testsubstance_ChemicalName	Molecular Weight	ADMET_SolubilityLeve	ALogP	PChem Sum (1-3)	EPAPTC 826	NTPHTS 1408	EPADNT 82	DNT GRADN	IMMTOX 87	HPVCSI 3548	ICCVAM 87	NCTRER 232	NTPCSI 2415	NTPGTZ 1931	IRISSI 544	ECODEM 399	EPAFHM 617	FDAMDD 1217
1-Naphthaleneacetic acid	186.2	3	2.47	1	30	86										5		
2,4-D, dimethylamine salt	266.1	3	2.46	1	44	157							1373	509				
2-4,D	221	3	2.46	1	52	167				250		119	233	507	193	6		
Octhilinone	213.3	3	3.35	1	584	280							382	1418		143		
Acetaminophen	151.2	4	1.35	1	104	436							725	1029			165	3
Acetochlor	269.8	3	3.12	1	114	440							731		5	17		
Alachlor	269.8	3	2.99	1	118	459						103	782		16	18	575	
Aldicarb	190.3	4	1.47	1	119	460	6	3	2				783	43	18	19	264	
Atrazine	215.7	3	1.78	1	149	501			52	1127	8	49	869	158	48	25		
Benomyl	290.3	3	2.57	1	156	511				2998			895	175	57	27		
1H-Purine-2,6-dione, 3,7-dihyd	194.2	4	0.06	1	26	584				20		168	1065	329			24	181
Capsaicin	305.4	3	3.79	1	222	587							1074					
Carbaryl	201.2	3										126	1620		102	38	33	
Carbendazim	191.2	3								2985			1079	342		293		
Chloropicrin	164.4	3											1124	419		48		
Citric acid	192.1	5								129								288
Dazomet	162.3	3	0.8	1	320	683				859			1224	515		379		
Diazinon	304.3	3	4.24	1	326	697	26						1256	546		302	334	
Dicloran	207	3	2.48	1	332	707				319			1273	575		67		
Dichlorvos	221	4	1.61	1	330	710	27			2786			1280	628	197	66		
Disulfoton	274.4	3	4.42	1	360	763	30						1364		233	365	328	
Camphor	152.2	3	2.4	1	221	767							1069					
Carbamothioic acid, dipropyl-	189.3	3	2.98	1	231	773	32						2135	865	248	84		
Fluometuron	232.2	3	2.8	1	428	808							1452	940	260	315		
Malathion	330.3	3	2.77	1	497	916	50	2					1664	1128	322	121	282	
Methyl parathion	263.2	3	3.14	1	539	961	54						1734	1259	348	153		

DSSTox File Incidence

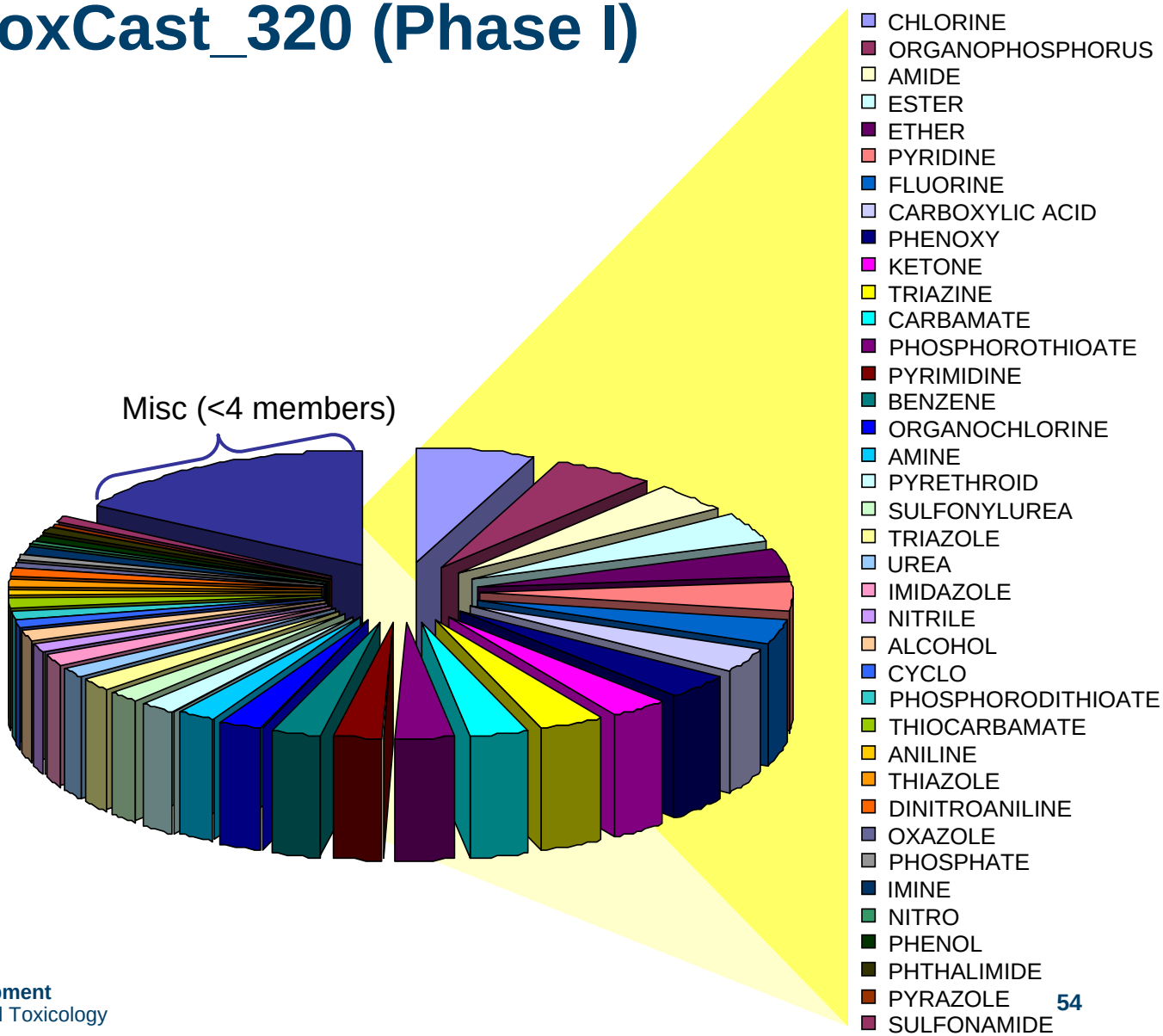
United States Environmental Protection Agency

Prioritize Chemicals for ToxCast Phase I: Chemical Characteristics

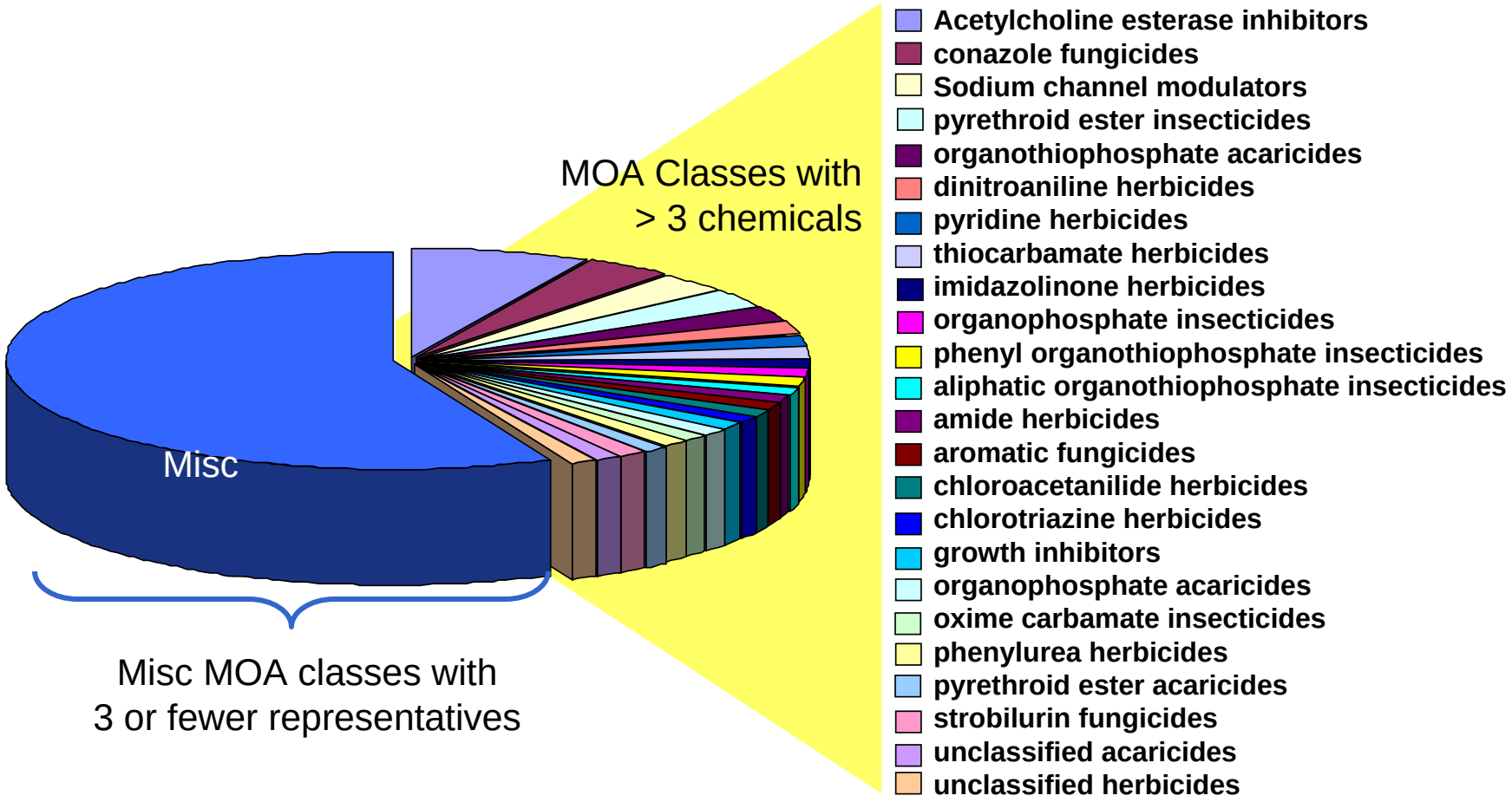
- Meet minimal HTS phys-chem requirements
  - Soluble in DMSO / water
  - Not highly volatile
  - Molecular Weight in approx range [100-1,000]
  - Available in ~pure or standard form with structure
- Span diverse structural space
- Include clusters of similar chemicals

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

Home
About DSSTox
Work in Progress
Frequent Questions
Structure Data Files
Central Field Definition Table
Apps, Tools & More
DSSTox Community
Site Map
Glossary of Terms
Help

SDF Download Page

TOXCST: Research Chemical Inventory for EPA' *Structure-Index File*

** *Version 2b DSSTox* Structure-Index File *08 February 2008*

➢ *Incorporates new InChIKey field and a few structure modifications after additional quali of Analysis (COAs) of purchased chemicals.*

Quick & Easy File Downloads: FTP Download Instructions

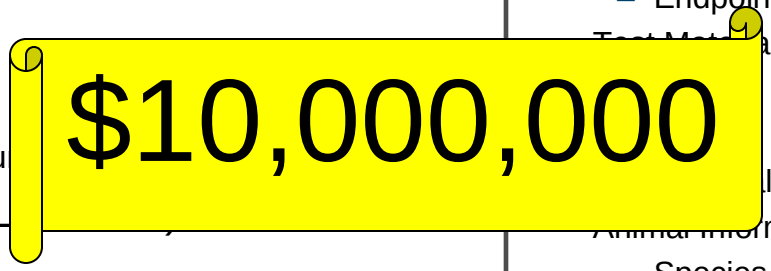
File Types	Description	File Size
Documentation Files: *TOXCST*		
Log File	TOXCST_LogFile_08Feb2008.pdf	37KB
Data Files: *TOXCST*		
SDF Structure Data File	TOXCST_v2b_320_08Feb2008.sdf	922KB
• Data Table (no structures)	TOXCST_v2b_320_08Feb2008_nostructures.xls	207KB
• Structures Table	TOXCST_v2b_320_08Feb2008_structures.pdf (7 pp.)	1.4 MB

TOXCST SDF Content Summary

TOXCST SDF Content	Totals_v2b*
# Records	320
DSSTox Standard Chemical Fields	19
TOXCST Source Fields	2
Total # Fields	21
Chemical Content	**Counts_v2b**
STRUCTURE_ChemicalType:	
defined organic	313
inorganic	1
organometallic	6
no structure	0
STRUCTURE_TestedForm_DefinedOrganic:	
parent	299
complex	8
salt	6
salt complex	0
TestSubstance_Description:	
single chemical compound	308
macromolecule	0
unspecified or multiple forms	0
mixture or formulation	12

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

Extraction of DER information

United States Environmental Protection Agency

STUDY TYPE: Combined chronic toxicity/oncogenicity feeding – Rat
OPPTS 870.4300 [§83-5]

DP BARCODE: D257223
P.C. CODE: 111901

SUBMISSION CODE: S564270
TOX. CHEM. NO.: 497AB

TEST MATERIAL (PURITY): Imazalil (purity ≥97.4%)
SYNONYMS: R023979

CITATION: Van Deun, K. 1999. Combined oral chronic toxicity/carcinogenicity study with Imazalil in the SPF Wistar rat. Dept. Toxicology, Janssen Research Foundation, 2340 Beerse, Belgium. Laboratory report number, 3817, June 8, 1999. MRID 44858001. Unpublished.

SPONSOR: Janssen Pharmaceutica N.V., 2340 Beerse, Belgium

EXECUTIVE SUMMARY:

In a chronic toxicity/oncogenicity study (MRID 44858001), Imazalil (≥97.4% a.i.) was administered in the diet to groups of 50 male and 50 female Hannover substrain (SPF) Wistar-derived rats at concentrations of 0, 50, 200, 1200, or 2400 ppm (equivalent to 0.0, 2.7, 10.8, 65.8, and 134.8 mg/kg/day for males and 0.0, 3.6, 14.6, 85.2, and 168.8 mg/kg/day for females) for two years. All rats were observed daily for clinical signs of toxicity and morbidity, weighed weekly, and food consumption monitored biweekly. Blood and urine samples were collected after 6, 12, and 18 months of treatment and at study end. Surviving rats were sacrificed after 104 weeks of treatment. All rats were necropsied and the tissues and organs inspected grossly and microscopically for toxicity-related effects and the carcinogenic potential of Imazalil.

The absolute weights of most organs were decreased while their weights relative to body weight increased for male and female rats in the 1200 and 2400 ppm treatment groups. These effects are considered related to inanition and inappetence and not a direct result of Imazalil treatment. However, effects found in the liver and thyroid was considered directly related to treatment. The absolute liver weight of male rats in the 2400 ppm group was increased while it was decreased in female rats. The associated relative liver weights of male and female rats in the 1200 and 2400 ppm groups were significantly increased 9-26%. In addition, the absolute and relative thyroid weights of male but not female rats in the 1200 and 2400 ppm groups were increased.

The effect of treatment on the liver (males and females) and thyroid (males only) were confirmed microscopically, but had distinct sex-related etiologies. The incidence of clear cell and basophilic foci was equivocal while eosinophilic foci were significantly increased for male rats in the 2400 ppm group. In female rats of the 2400 ppm group, the incidences of clear cell and basophilic foci were significantly decreased but the incidence of eosinophilic foci was unaffected. Also, the incidence of hepatocyte fatty vacuolation was increased only in male rats of the 1200 ppm and 2400 ppm groups while the incidence of pigmentation was increased only in females of the 200, 1200, and 2400 ppm groups. In addition, the location of hepatocellular hypertrophy was distinctly different. Female rats in the 1200 and 2400 ppm groups had significant increases in centriacinar and periacinar hypertrophy while male rats only had centriacinar hypertrophy. Finally, the incidence of thyroid follicular cell hyperplasia was increased only in male rats of the 1200 and 2400 ppm groups.

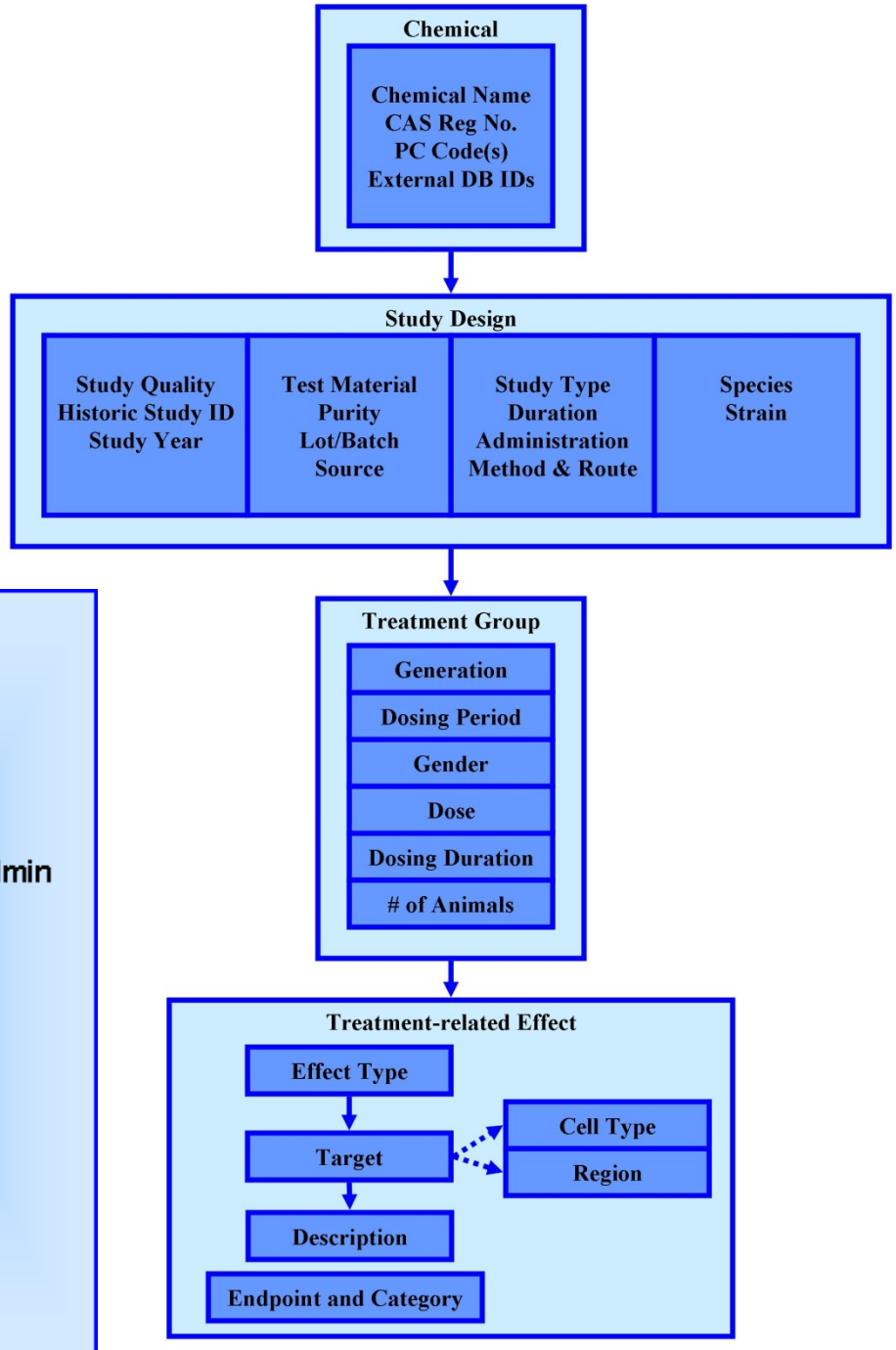
The lowest observed adverse effect level (LOAEL) for male and female rats was 1200 ppm (65.8 and 85.2 mg/kg/day, respectively) with a corresponding no observed adverse effect level (NOAEL) of 200 ppm (10.8 mg/kg/day males, 14.6 mg/kg/day females). These are based on the effects found on body weight, weight gain, and the macro- and microscopic effects noted in the liver of all rats and the thyroid of male rats.

Male rats had a significant increase in the incidence of hepatocellular adenomas and thyroid follicular neoplasia while no increase was found for female rats. These results indicate a difference in the disposition of Imazalil between the sexes increases hepatic and thyroid neoplasia in male rats, likely through differences in metabolic activation of the test material.

This chronic toxicity/oncogenicity study in the rat is **Acceptable/guideline** and satisfies the guideline requirement for a combined chronic toxicity/oncogenicity study in rats [83-5]. No deficiencies were noted for this study.

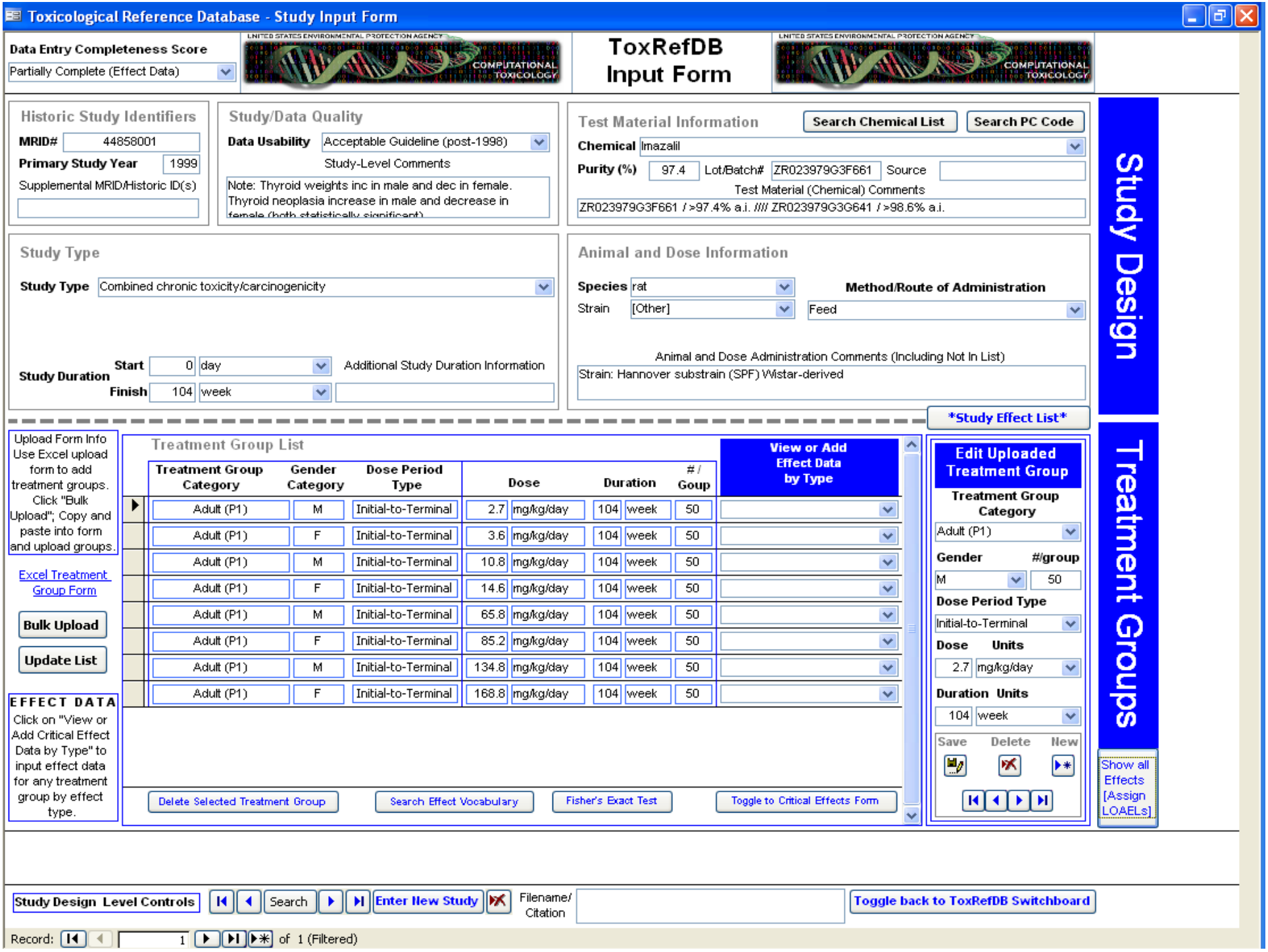
EPA United States Environmental Protection Agency

ToxRefDB: *Toxicity Reference Database*



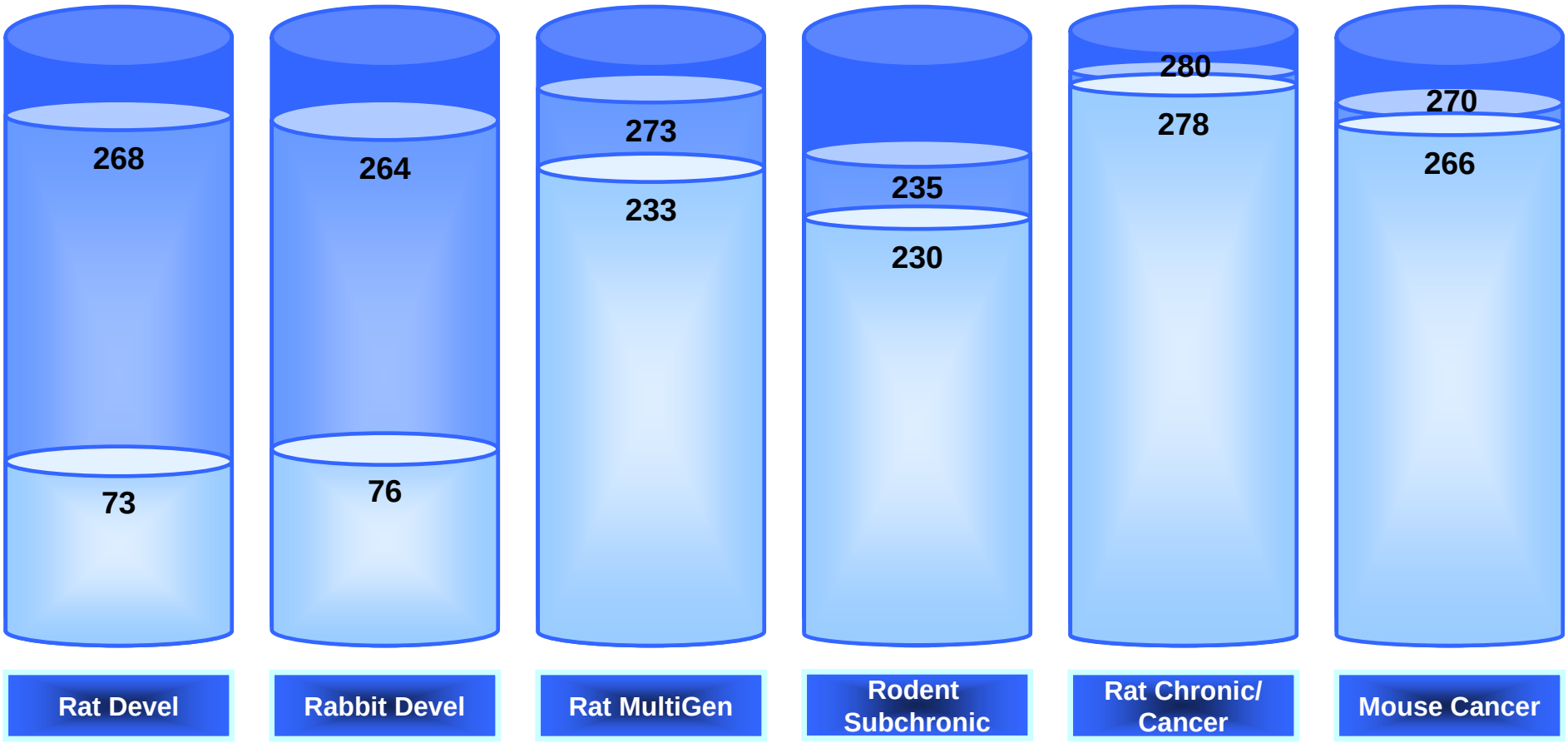
Fields/Data Elements Utilizing Standardized Vocabulary

- Chemical
- Study Quality
- Study Type
- Method & Route of Admin
- Species
- Strain
- Generation
- Dosing Period
- Gender
- Dosing Duration
- Effect Type
- Effect Target
- Effect Description
- Target Cell Type
- Target Region


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)

Data Entry Status

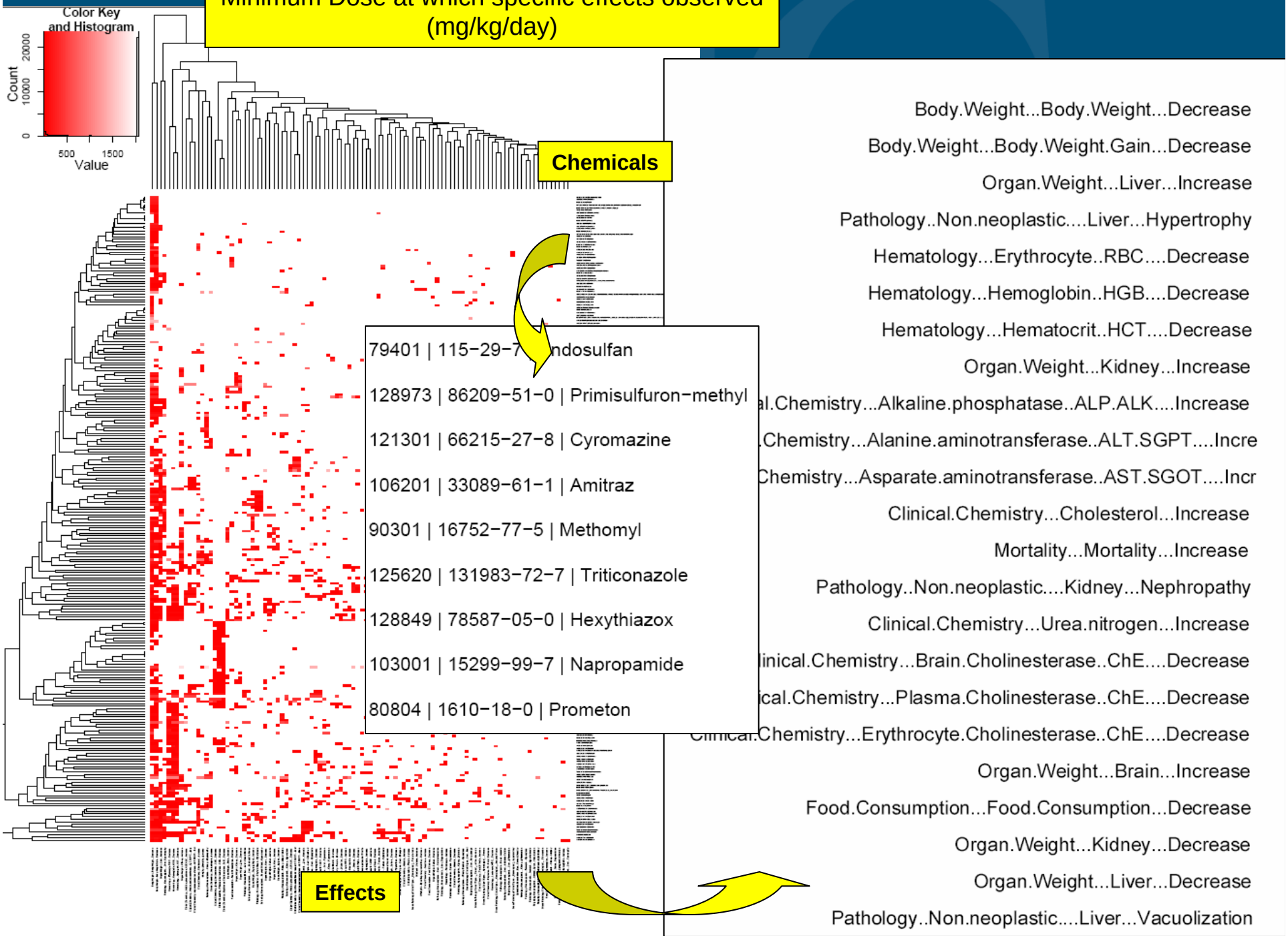
ToxCast Phase I Chemicals Only
Total: 291 Pesticides



Office of Research and Development
National Center for Computational Toxicology

Current as of February 8, 2008

Minimum Dose at which specific effects observed (mg/kg/day)



ToxCast HTS Assay Contractors and Collaborators

Compound Focus, a subsidiary of BioFocus DPI (A Galápagos Company)

NovaScreen (a Caliper Life Sciences company)

Phylonix (Zebrafish Assays for Drug Screening)

BioSeek

attagene (The Home of TFomics™)

Nine contracts, one IAG and an MOU provide chemical procurement; hundreds of biochemical, cellular, tissue and genomic assays; model organisms; and the capacity to screen up to 10,000 chemicals

CellLumen

NCGC (NIH Chemical Genomics Center)

ACEA Biosciences, Inc.

The Hamner Institutes for Health Sciences (Where Great Minds and Medicine Meet)

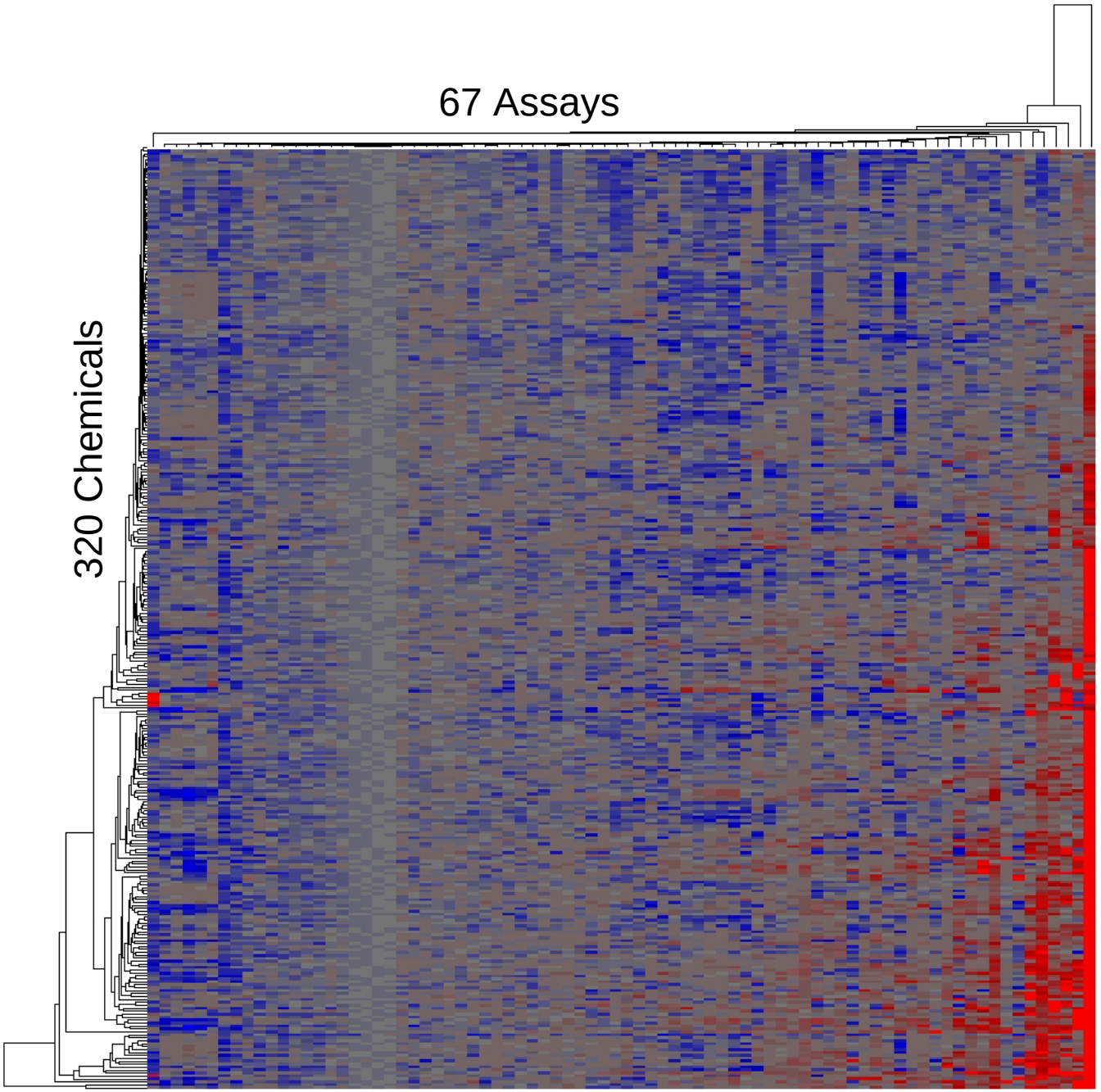
iVAL

Expression Analysis

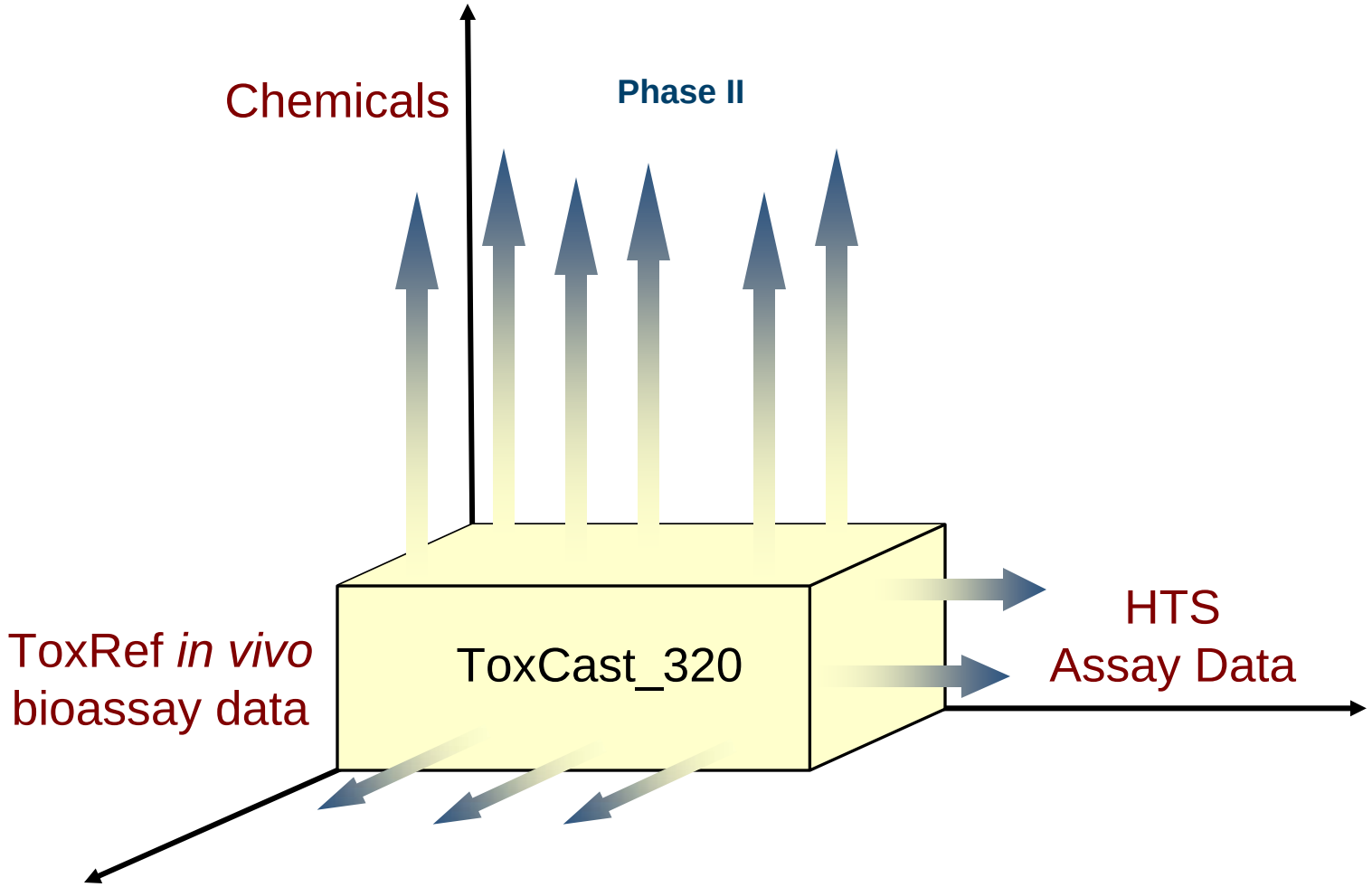
Assay Type	# Assays	# Endpoints	Assay Source	Comment	Source	ToxCast_320 Status 04dec2007
HTS	**240**	**240**	**Human, rat, other**	**Enzyme inhibition, receptor binding**	**NovaScreen**	Single concentration data delivered; multiple concentration to follow
uHTS	**10+**	**10+**	**Human and rodent**	**Nuclear 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**				

EPA
United States
Environmental Protection
Agency

Attagene Heatmap



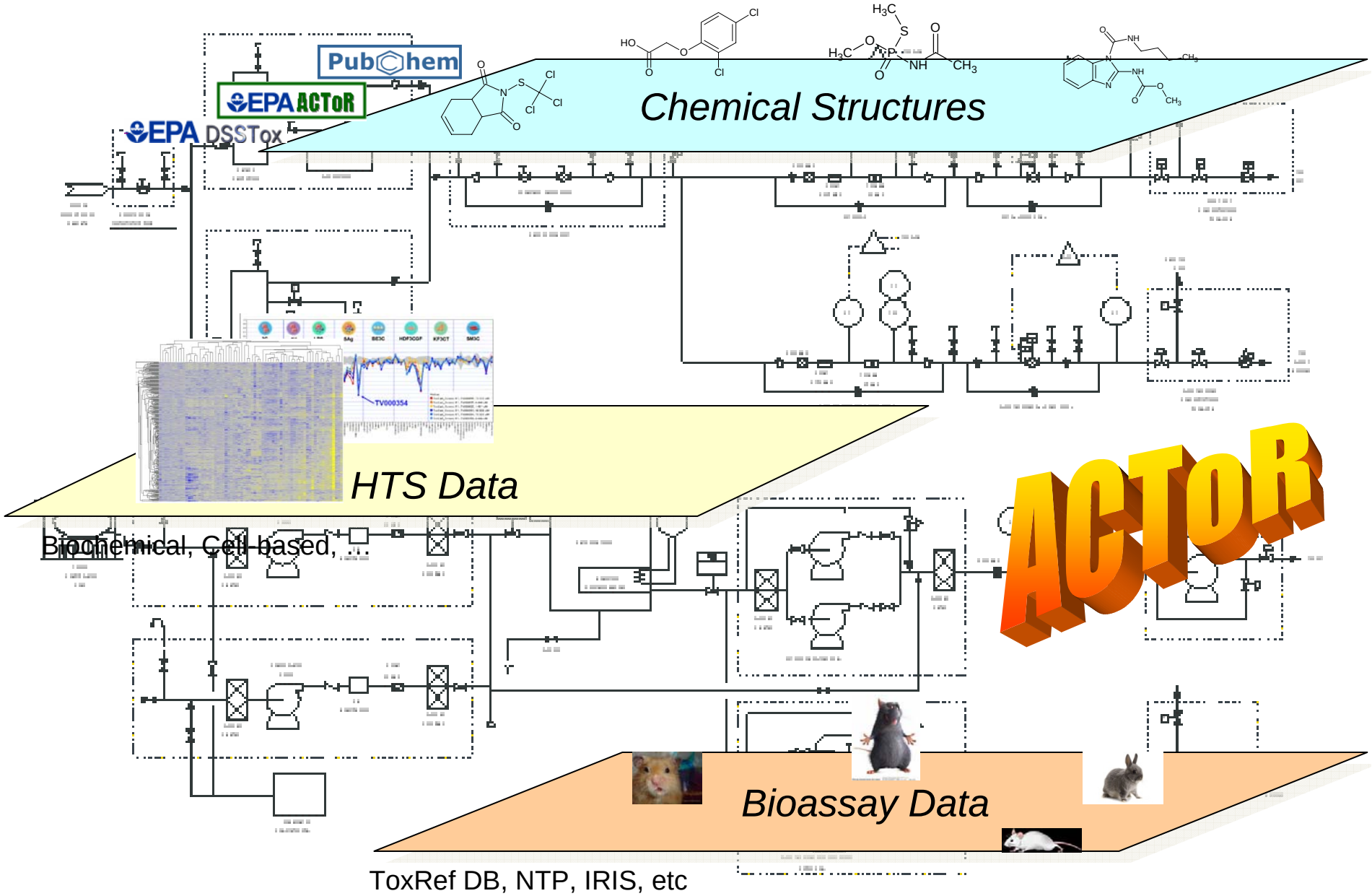
ToxCast Phase I: Proof of Concept



Part IV

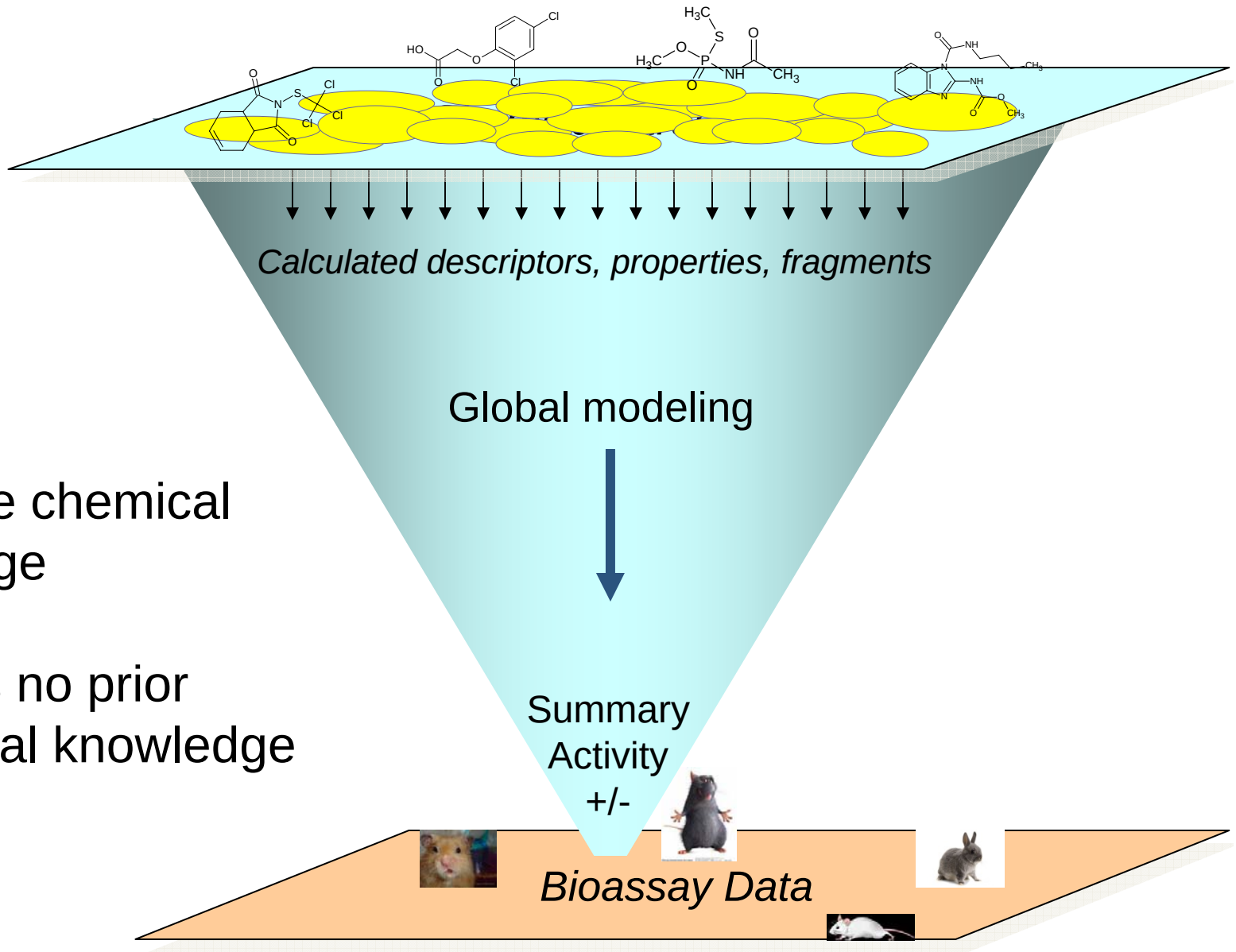
Incorporating SAR Concepts into ToxCast

ToxCast: Multidimensional Data



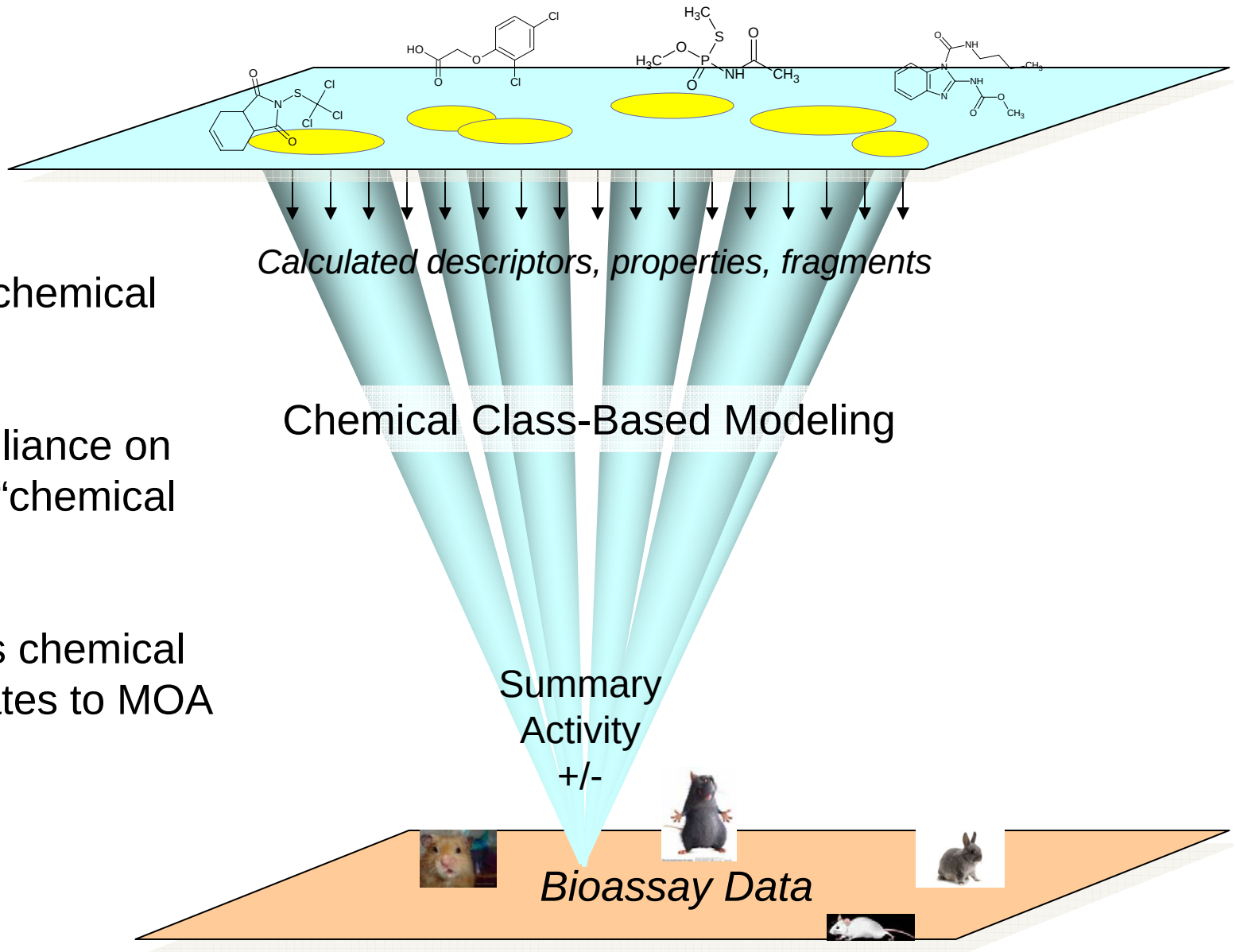
Structure-Activity Approaches to Toxicity Prediction

- 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



Oncologic Carcinogenicity Estimation Expert System:
Chemical Class – Based Prediction Modules

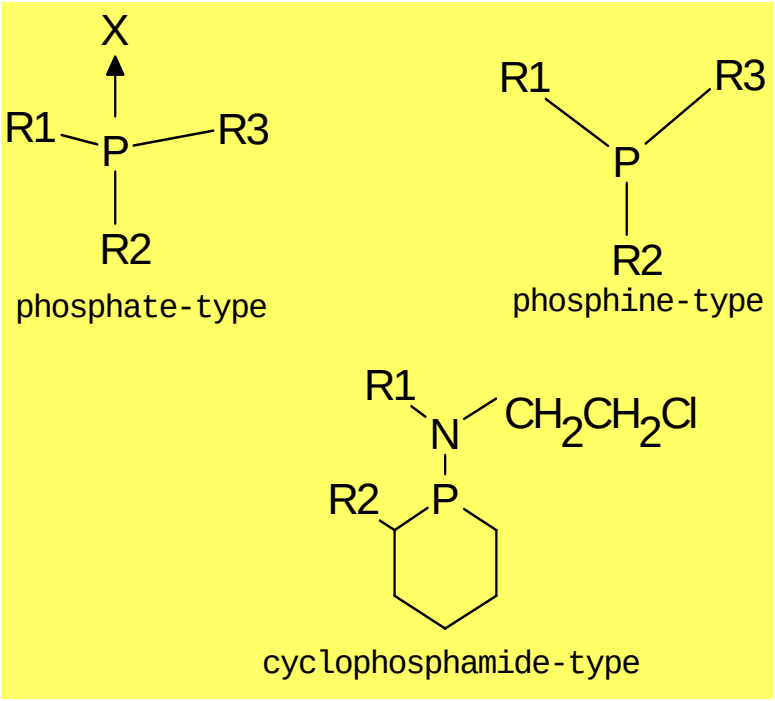
Acyl and Benzoyl Halide Type Compounds
Acrylate Reactive Functional Groups
Acrylamide Reactive Functional Groups
Aflatoxin Type Compounds
Aldehyde Type Compounds
Aliphatic Azo and Azoxy Type Compounds
Alkanesulfonoxy Ester Type Compounds
Alkyl Sulfate and Alkyl Alkanesulfonate Type Compounds
Aromatic Amine Type Compounds
Anhydride Type Compounds
Arylazo Type Compounds
Aryldiazonium Salts
C-Nitroso and Oxime Type Compounds
Carbamate Type Compounds
Carbamyl Halide Type Compounds
Coumarin and Furocoumarin Type Compounds
Dicarbonyl Type Compounds
Epoxide Reactive Functional Groups
Ethyleneimine Reactive Functional Groups
Haloalkylamine Reactive Functional Groups
Haloether Reactive Functional Groups
Halogenated Aromatic Hydrocarbon Type Compounds
Halogenated Cycloalkane Type Compounds
ortho-Halogenated Heterocyclic Type Compounds
Halogenated Nitroaromatic Type Compound
Halogenated Linear Aliphatic Type CompoundsHalothioether Reactive Functional Groups
Hydrazo Type Compounds
Reactive Ketone Reactive Functional Groups
Lactone Type Reactive Functional Groups
Nitrosamide Type Compounds
Nitrosamine Type Compounds
Nitroalkane and Nitroalkene Type Compounds
Nitrogen Mustard Reactive Functional Groups
Organophosphorus Type Compound
Peroxide Type Compounds
Phenol Type Compounds
Phosgene Type Compounds
Polycyclic Aromatic Hydrocarbons - HeterocyclicPolycyclic Aromatic Hydrocarbons - Homocyclic Siloxane Type Compounds
Reactive Sulfone Reactive Functional Groups
Sulfur Mustard Reactive Functional Groups
Sultone Reactive Functional Groups
Thiocarbamate Type Compounds
Thiocarbonyl Type Compounds
Triazene Type Compounds
Urea Type Compounds

Oncologic Carcinogenicity Estimation Expert System:

Organophosphate

R1/R2/R3 = alkyl groups or aryl groups

P X-alkyl or X-aryl where X is oxygen, sulfur or in some cases nitrogen, linking the phosphorus to the alkyl/aryl group



phosphine-type → phosphine and phosphine-oxide

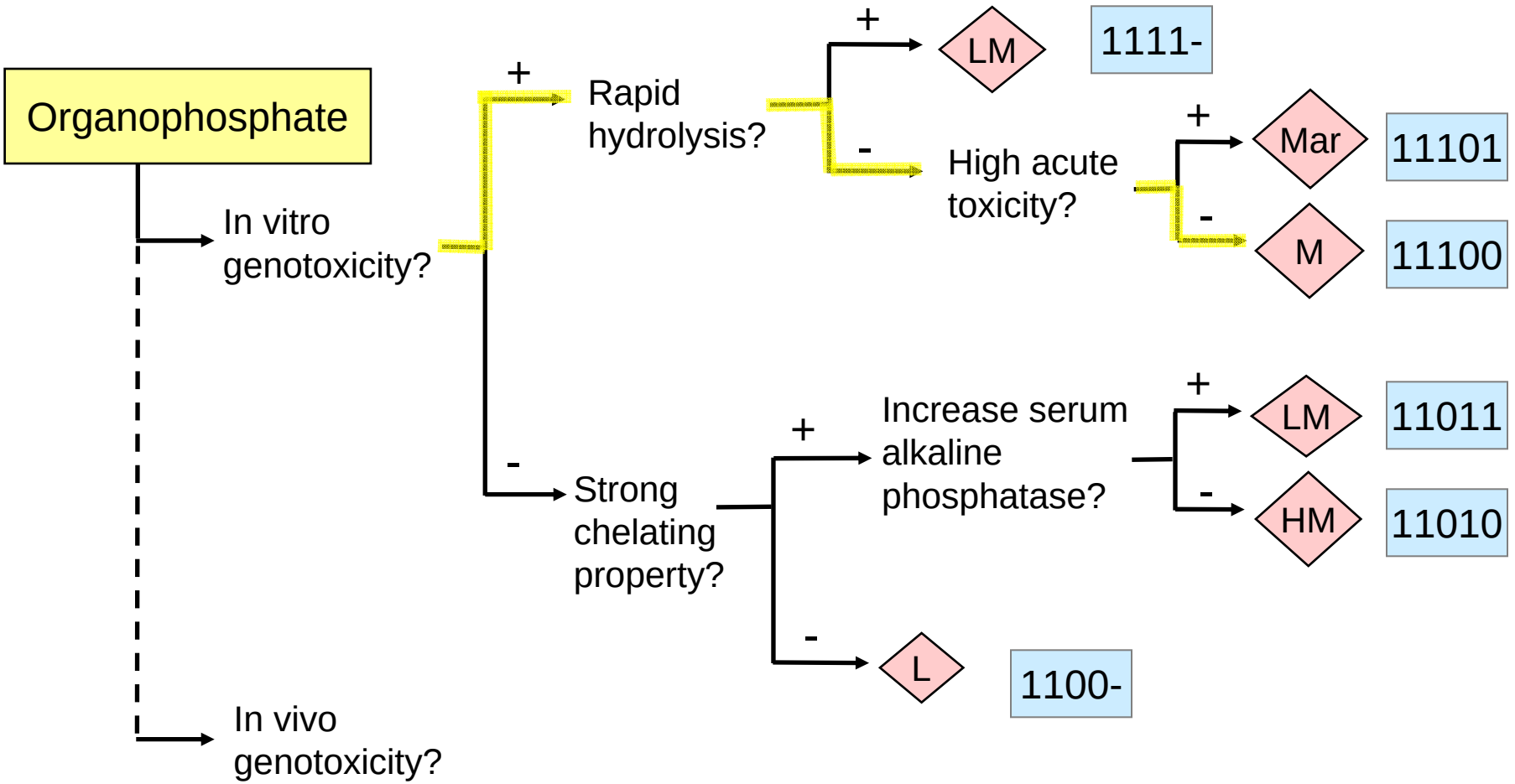
cyclophosphamide-type → cyclophosphamide, isophosphamide, trophosphamide

R1/R2/R3: alkyl (Cn), hydrogen (H), benzyl (CH2C6H5), phenyl (C6H5), Morpholino, NR'R" (where R'R" can be one of the above).

X1/X2/X3/X4: Oxygen (O), Sulfur (S)

Substituents: Halogens (Cl, Br, I, F), hydroxyl (OH), carboxylic acid (COOH), sulfonic acid (SO3H) and additionally alkyl (Cn) on the aryl ring..

Combining SAR and Biofunctional Information in Oncologic: *Predicting Carcinogenicity of Organophosphates*



Woo et al. (1996) Environ. Carc. & Ecotox. Revs., C14:1-42

Oncologic Carcinogenicity Estimation Expert System:
Chemical Class – Based Prediction Modules

Acyl and Benzoyl Halide Type Compounds
Acrylate Reactive Functional Groups
Acrylamide Reactive Functional Groups
Aflatoxin Type Compounds
Aldehyde Type Compounds
Aliphatic Azo and Azoxy Type Compounds
Alkanesulfonoxy Ester Type Compounds
Alkyl Sulfate and Alkyl Alkanesulfonate Type Compounds
Aromatic Amine Type Compounds
Anhydride Type Compounds
Arylazo Type Compounds
Aryldiazonium Salts
C-Nitroso and Oxime Type Compounds
Carbamate Type Compounds
Carbamyl Halide Type Compounds
Coumarin and Furocoumarin Type Compounds
Dicarbonyl Type Compounds
Epoxide Reactive Functional Groups
Ethylene
Haloalky
Haloether Reactive Functional Groups
Halogenated Aromatic Hydrocarbon Type Compounds
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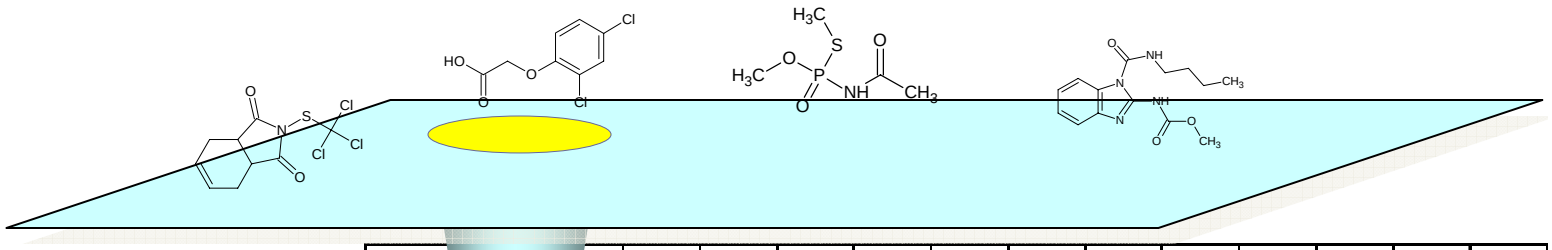
Homocyclic Siloxane Type Compounds
Reactive Sulfone Reactive Functional Groups
Sultone Reactive Functional Groups
Thiocarbamate Type Compounds
Thiocarbonyl Type Compounds
Triazene Type Compounds
Urea Type Compounds

1111-
11101
11100
11011
11010

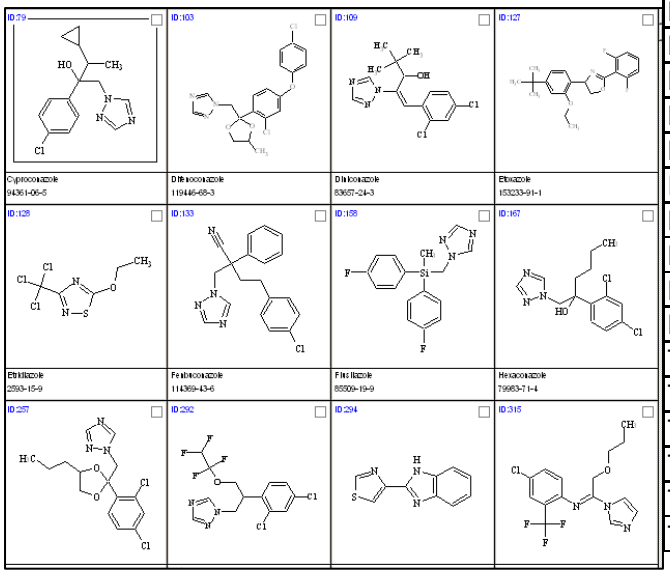
1100101010000…
1010011111000000000001010000000101001…
1100-
0

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**

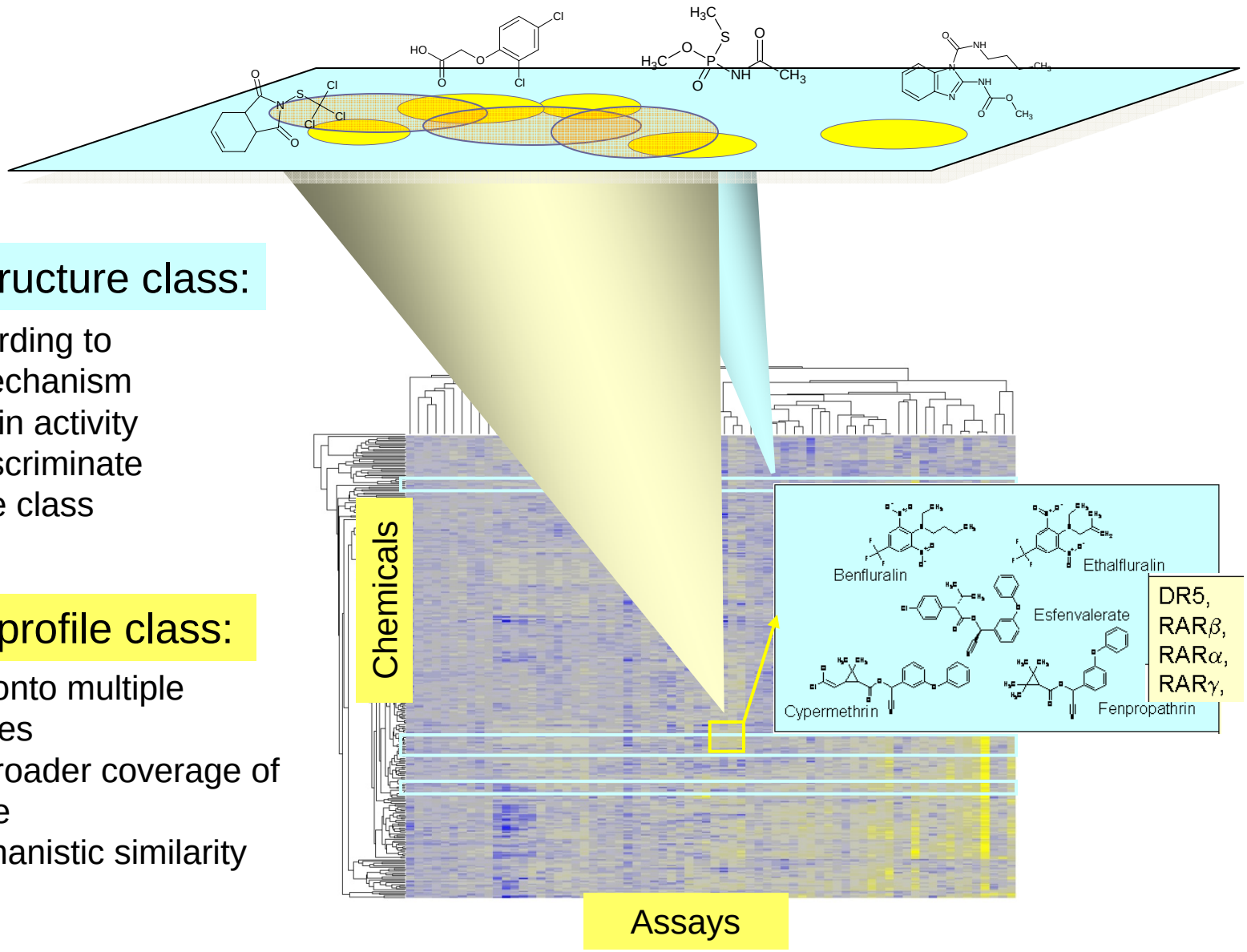
Structure Class vs Bioactivity Class

Chemical structure class:

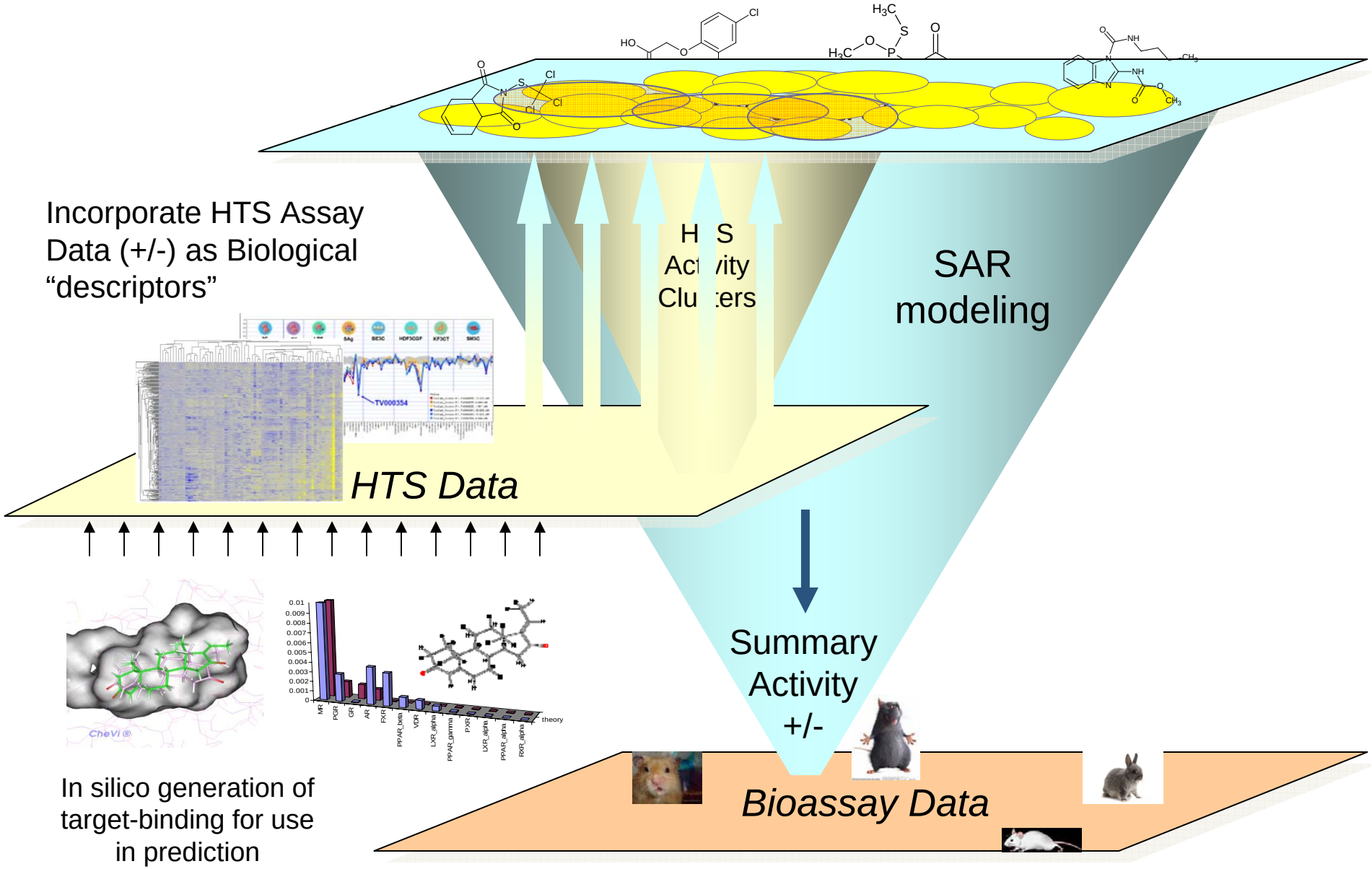
- Cluster according to activity and mechanism
- Differences in activity profiles can discriminate within structure class

Bioactivity profile class:

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

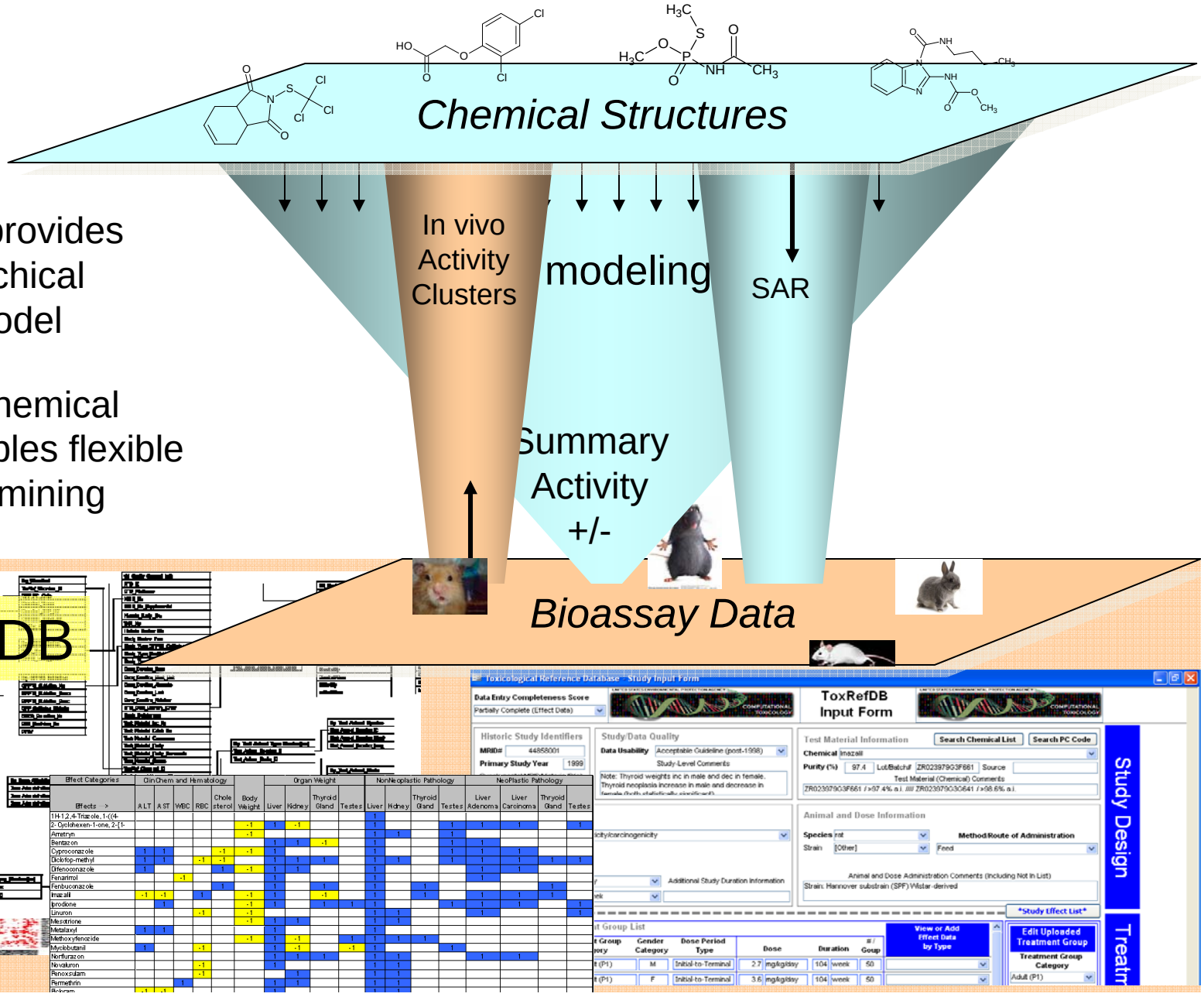


Structure-Activity Approaches to Toxicity Prediction



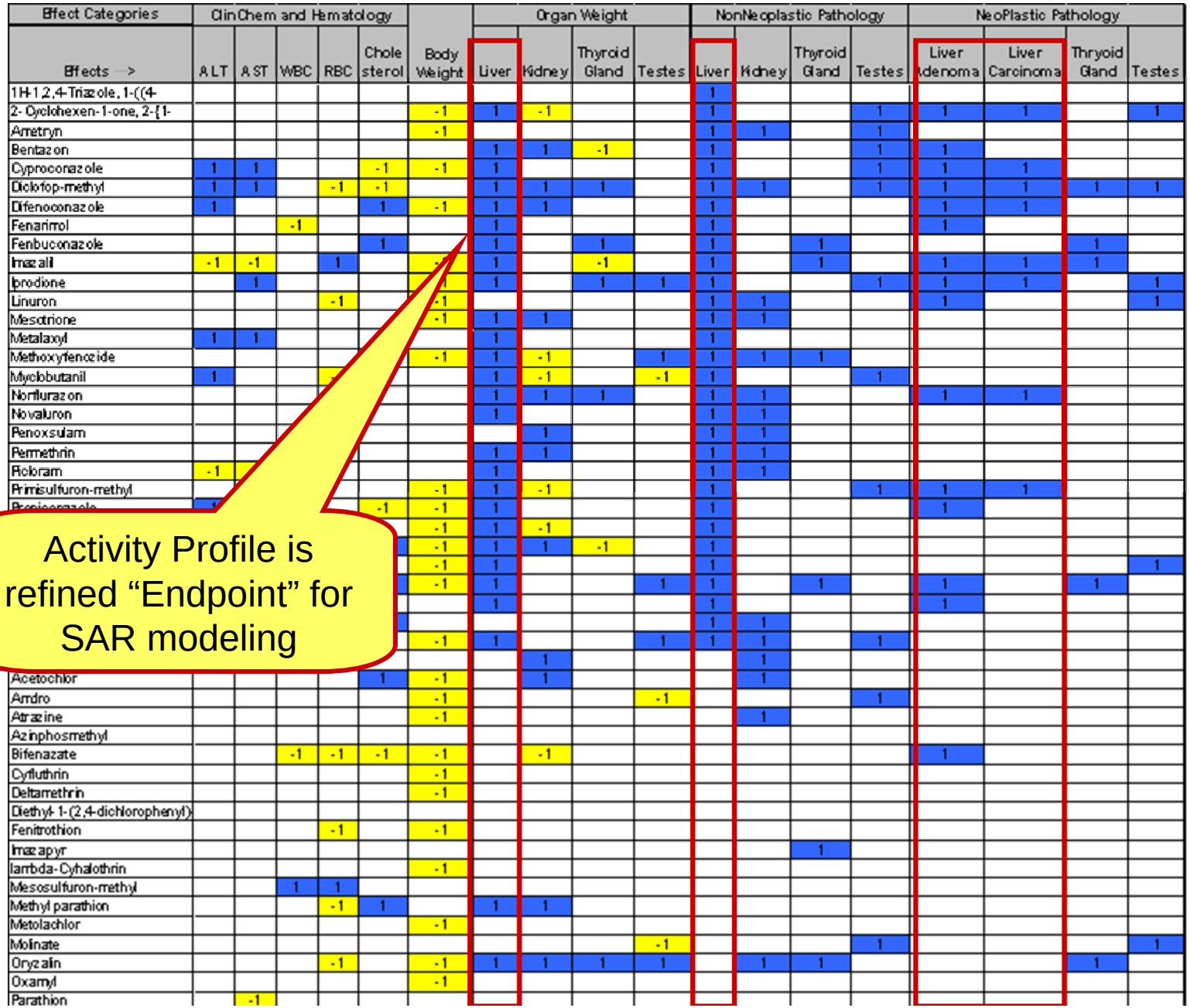
Use of Bioassay Activity Categories in SAR

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

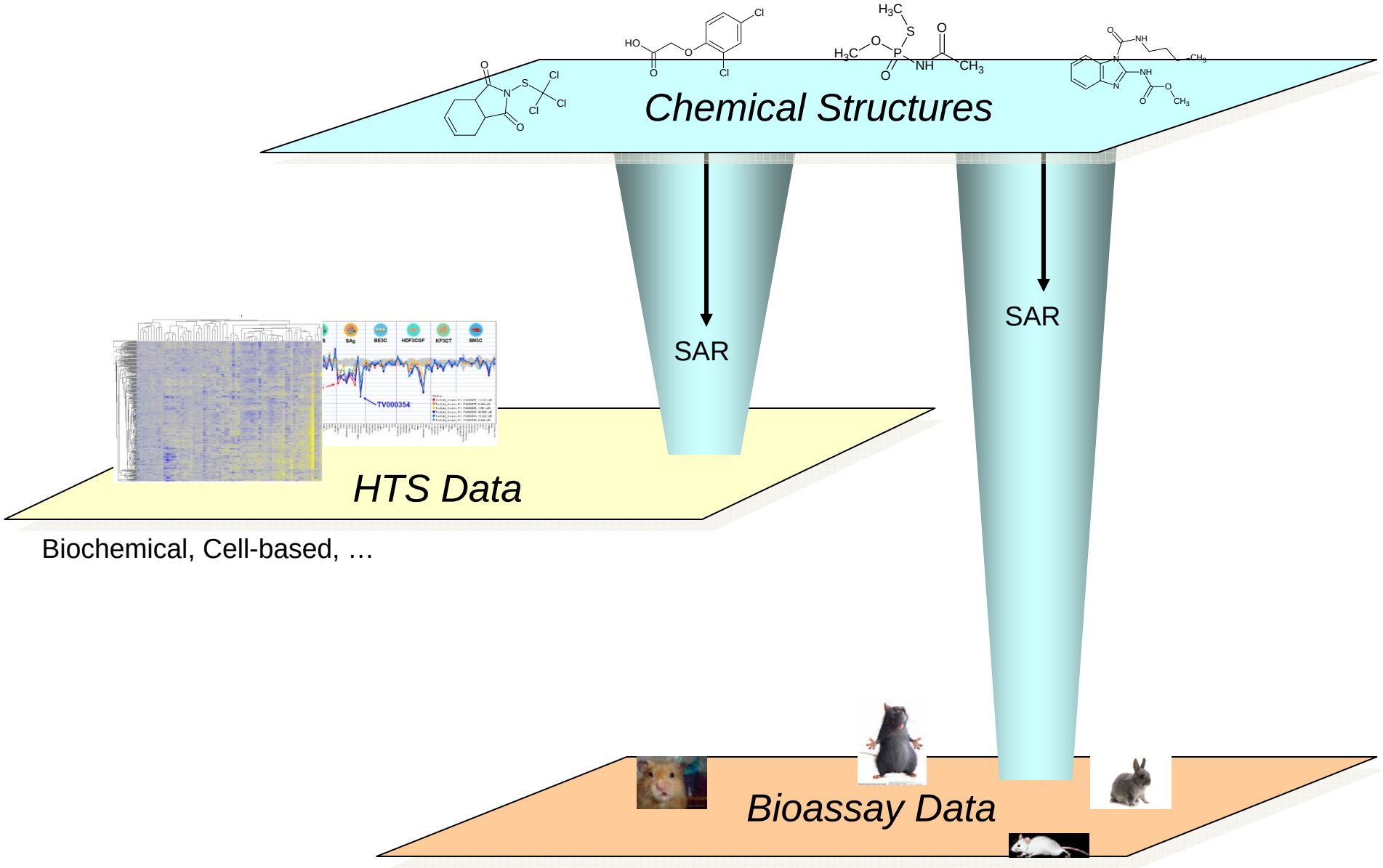


ToxRefDB Profiling of Liver Effects for Pesticides

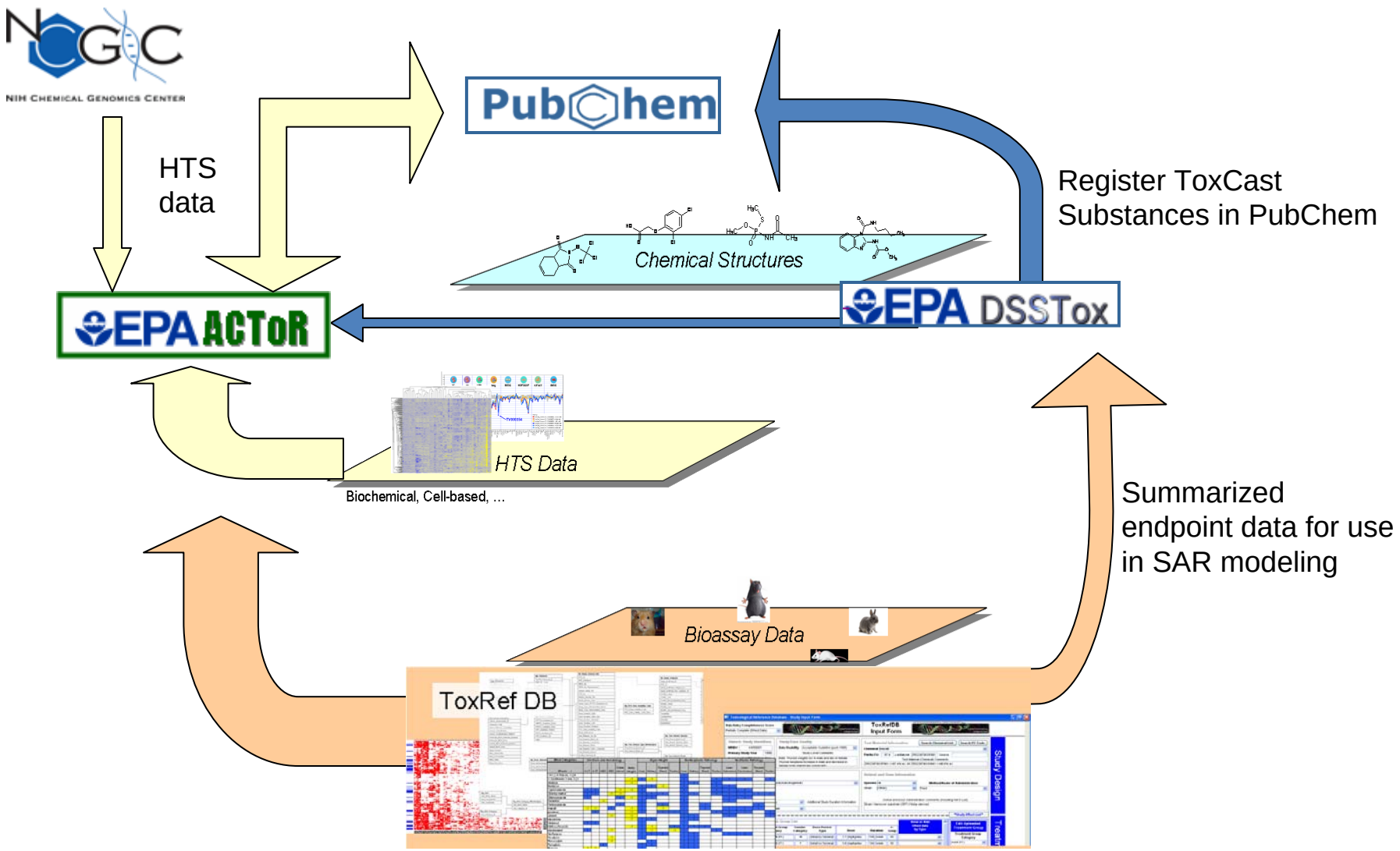
Liver non-neoplastic histopathology and increased organ weight are often associated with tumors and cancer



Structure-Analog Approaches



ToxCast: Data Publication & Exploration

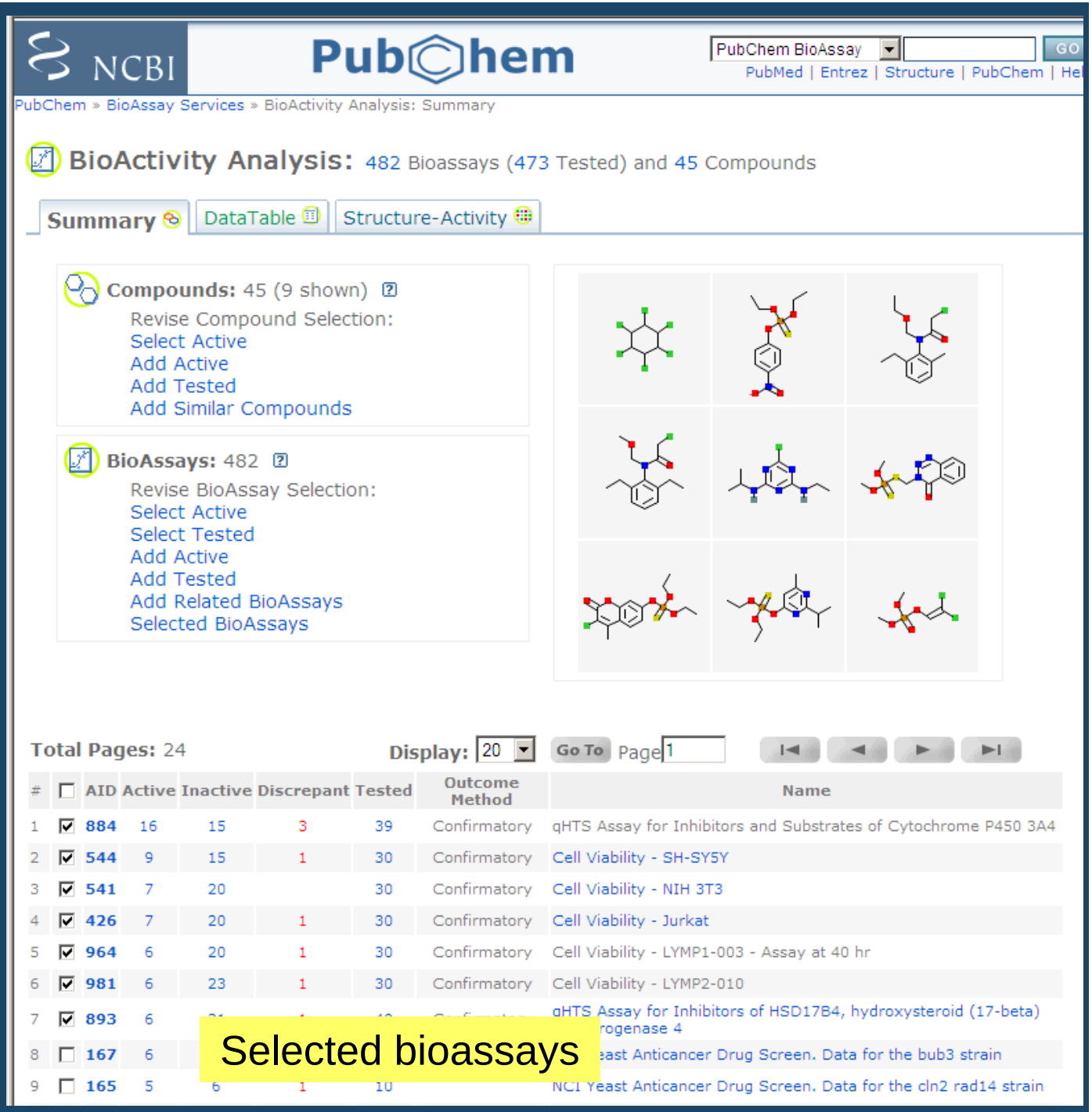


ToxCast_320

Bioactivity Analysis:

Retrieve all bioassay data in PubChem for ToxCast_320

482 Bioassays
45 Compounds



Incorporating SAR Concepts into ToxCast: Conclusions

- HTS data offers:
  - activity-based clustering of chemicals
  - biofunctional information for refining class-based SAR
  - new “biological” descriptors for global SAR
- In vivo bioassay profiles expanding “endpoints” for SAR
- Structure-analog approaches coupled with HTS and ToxRef in vivo data offer powerful data mining tools
- Public tools for structure-based exploration of data becoming available

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