NIEHS
National Institute of Environmental Health Sciences

Computational Toxicology: New Approaches for the 21st Century

September 9th, 2009 Session IV: ToxCast and the Comparative Toxicogenomics Database (CTD)

David Dix, Acting Deputy Director of EPA/ORD's National Center for Computational Toxicology

Carolyn Mattingly, Mount Desert Island Biological Laboratory

Srp Superfund Research Program

U.S. Department of Health and Human Services
National Institute of Health
National Institute of Environmental Health Services

EPA United States Environmental Protection Agency

ToxCast- Screening and Prioritization of Environmental Chemicals Based on Bioactivity Profiling and Predictions of Toxicity

David Dix
Acting Deputy Director, EPAs National Center for Computational Toxicology

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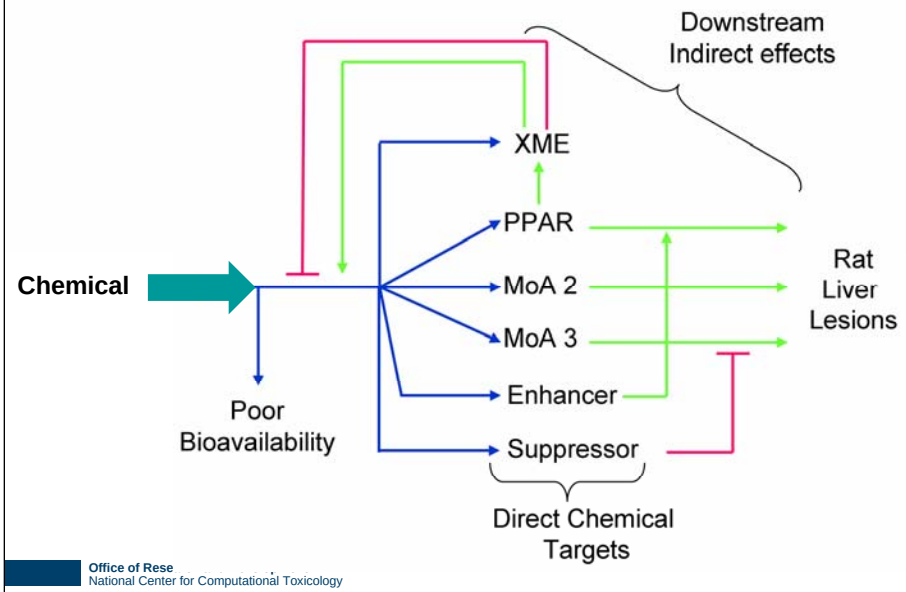
Predicting Toxicity Will Not Be Easy



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Key Challenges Of Pathway Profiling

- Find the Toxicity Pathways
  - Hepato vs developmental nuerotoxicity
- Obtain HTS Assays for Them
  - Including metabolic capability
- Screen Chemical Libraries
  - Coverage of p-chem properties
- Link Results to in vivo Effects
  - Gold standard and dosimetry

ToxCast™ Background

- Research program of EPA's National Center for Computational Toxicology
- Addresses chemical screening and prioritization needs for pesticidal inerts, anti-microbials, CCLs, HPVs and MPVs
- Comprehensive use of HTS technologies
- Coordinated with NTP and NHGRI/NCGC via Tox21

- Committed to stakeholder involvement and public release of data
  - Chemical Prioritization Community of Practice
  - NCCT website- http://www.epa.gov/ncct/

The ToxCast_320

309 Unique Structures

Replicates for QC

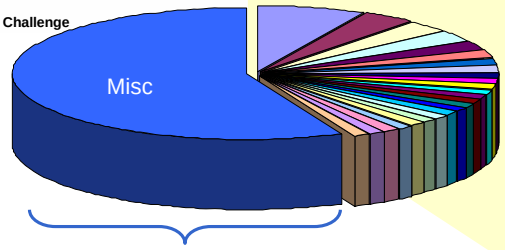
291 Pesticide Actives
9 Industrial Chemicals
8 Metabolites

56/73 Proposed Tier 1 EDSP

53 of 80 with DNTs

122 in IRIS

14 HPV
11 HPV Challenge



Misc MOA classes with
3 or fewer representatives

Classes with
> 3 chemicals

- Acetylcholine esterase inhibitors
- conazole fungicides
- Sodium channel modulators
- pyrethroid ester insecticides
- organothiophosphate acaricides
- dinitroaniline herbicides
- pyridine herbicides
- thiocarbamate herbicides
- imidazolinone herbicides
- organophosphate insecticides
- phenyl organothiophosphate insecticides
- aliphatic organothiophosphate insecticides
- amide herbicides
- aromatic fungicides
- chloroacetanilide herbicides
- chlorotriazine herbicides
- growth inhibitors
- organophosphate acaricides
- oxime carbamate insecticides
- phenylurea herbicides
- pyrethroid ester acaricides
- strobilurin fungicides
- unclassified acaricides
- unclassified herbicides

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ToxRefDB

- Relational phenotypic/toxicity database
- Provides in vivo anchor for ToxCast predictions
- Three study types
  - Chronic/Cancer Rat and Mouse (Martin, et al, EHP 2008)
  - Rat multigenerational Reproduction (Martin, et al, 2009)
  - Rat & Rabbit Developmental Toxicity (Knudsen, et al, 2009)
- Two types of synthesis
  - Supervised (common individual phenotypes)
  - Unsupervised (machine based clustering of phenotype patterns)

ToxRefDB Endpoint Coverage

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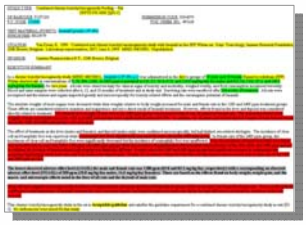
data evaluation records

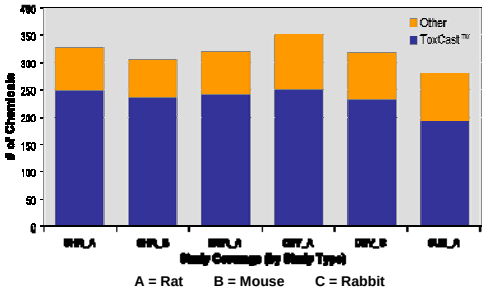


ToxRefDB

CHRONIC/CANCER (CHR)
Martin et al. (2008) Environ Hlth Persp
doi:10.1289/ehp.0800074

MULTIGENERATION REPRODUCTIVE (MGR)
Martin et al. (2009) Toxicol Sci
doi: 10.1093/toxsci/kfp080

PRENATAL DEVELOPMENTAL (DEV)
Knudsen et al. (2009) Reprod Toxicol
doi: 10.1016/j.reprotox.2009.03.016



A = Rat B = Mouse C = Rabbit

SOURCE: Matt Martin, NCCT, 2009

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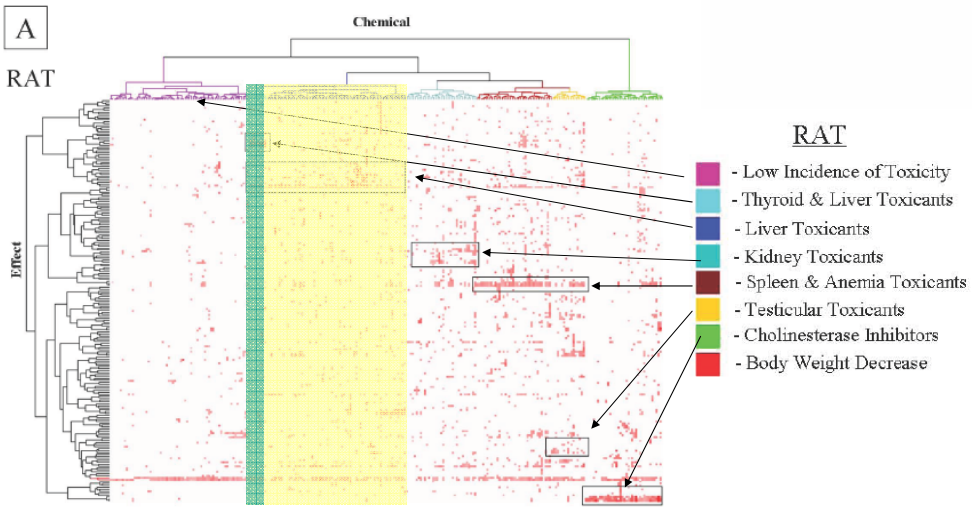
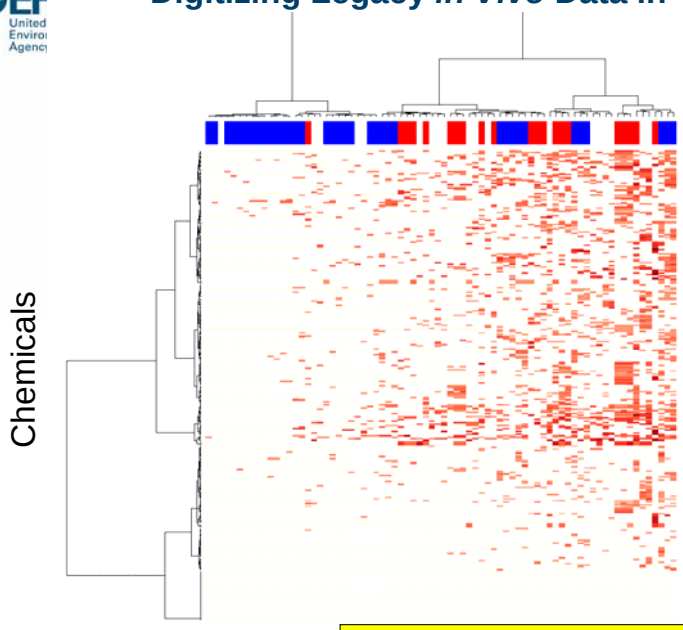
Rat Chronic Bioassay Results



Martin, et al *EHP*, *2009*

Digitizing Legacy *in Vivo* Data in ToxRefDB



Martin et al 2009a,b
Knudsen et al 2009

30 years and more than $2B worth of data

ToxRefDB in Predictive Modeling

STRENGTHS

- Source data from >2,000 guideline studies
- Puts >$2B worth of legacy data into a computable form
- *in vivo* database anchoring HTS *in vitro* assays
- Enables comparison of endpoint incidence between species
- Searchable database will be public (www.epa.gov/ncct/toxrefdb/)

LIMITATIONS

- Endpoints aggregated as independent features
- Data largely qualitative (LELs, LOAELS)
- Not all ToxCast™ chemicals represented in ToxRefDB
- Not all ToxRefDB chemicals represented in ToxCast™
- Species dimorphism may link to biology or study design
- Limited mode of action information available in source DERs

ToxCast Assays

Biochemical Assays

- Protein families
  - GPCR
  - NR
  - Kinase
  - Phosphatase
  - Protease
  - Other enzyme
  - Ion channel
  - Transporter
- Assay formats
  - Radioligand binding
  - Enzyme activity
  - Co-activator recruitment

467 Endpoints

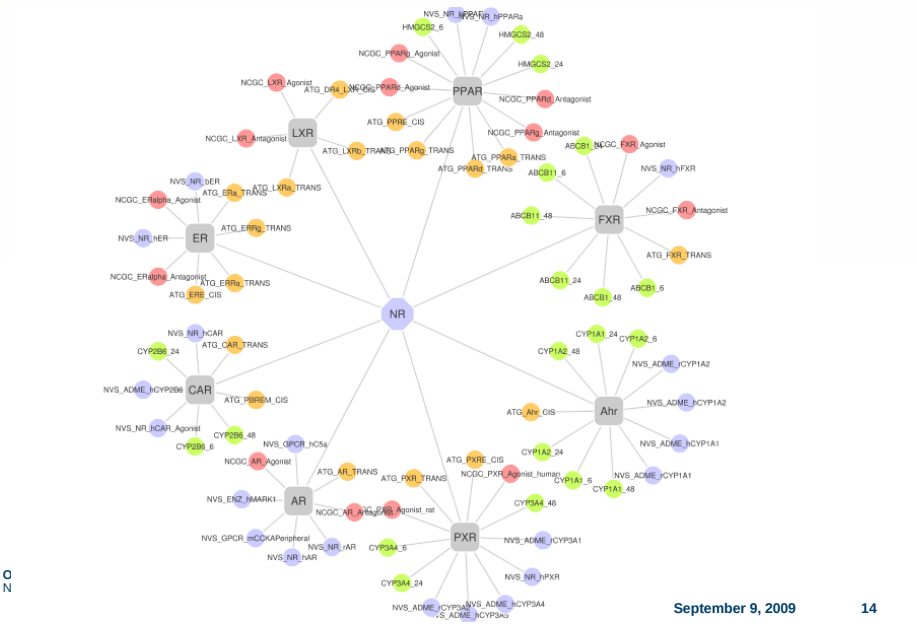
Cellular Assays

- Cell lines
  - HepG2 human hepatoblastoma
  - A549 human lung carcinoma
  - HEK 293 human embryonic kidney
- Primary cells
  - Human endothelial cells
  - Human monocytes
  - Human keratinocytes
  - Human fibroblasts
  - Human proximal tubule kidney cells
  - Human small airway epithelial cells
- Biotransformation competent cells
  - Primary rat hepatocytes
  - Primary human hepatocytes
- Assay formats
  - Cytotoxicity
  - Reporter gene
  - Gene expression
  - Biomarker production
  - High-content imaging for cellular phenotype

Confidence Builders: Some Expected Results…

- Estrogen receptor (ER)
  - Bisphenol A, Methoxychlor, HPTE
- Androgen Receptor (AR)
  - Vinclozolin, Linuron, Prochloraz
- PPAR
  - PFOA, PFOS, Diethylhexyl Phthalate, Lactofen
- Mitochondrial Poisons
  - Azoxystrobin, Fluoxastrobin, Pyraclostrobin
- Acetylcholinesterase Inhibition
  - Multiple organophosphorus pesticides

Confidence Builders (2): Multiple Assays and Technologies per Target



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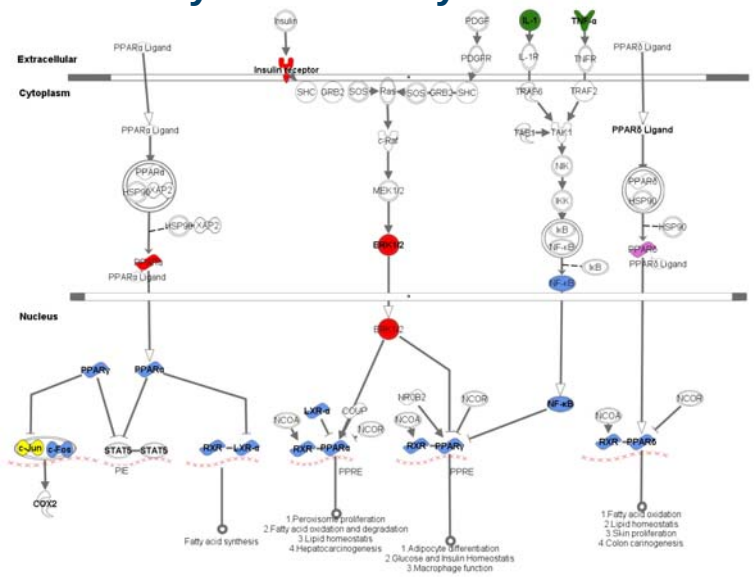
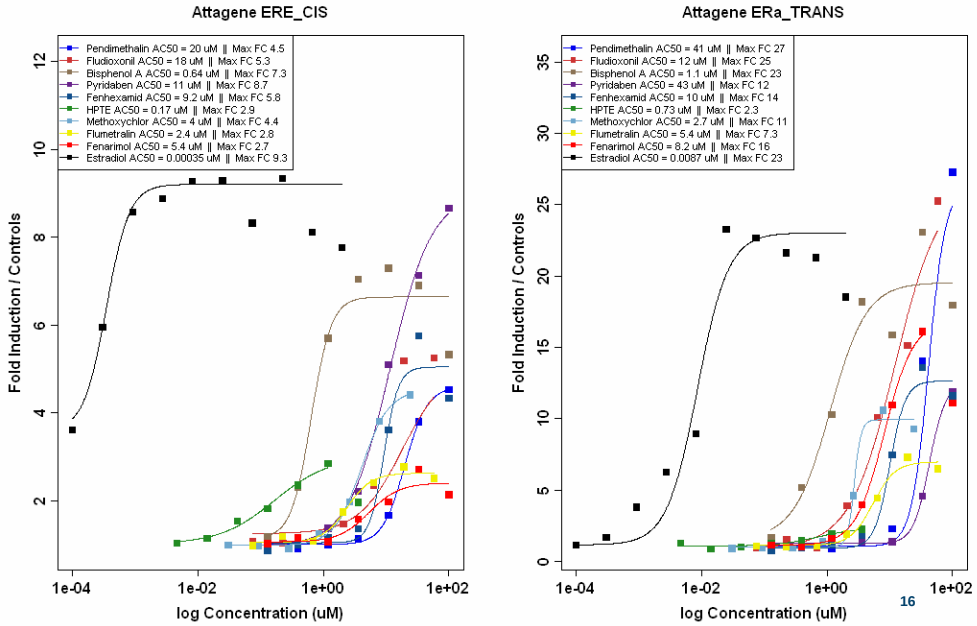
Confidence Builders (3): Pathway Based Analysis

- **Biologically Multiplexed Activity Profiling (BioMAP)**
- **Multiplex Transcription Reporter Assay**
- **Cell-based HTS Assays**
- **Cell-free HTS Assays**
- **High Content Cell Imaging Assays**



Data Analysis:

What is a hit?



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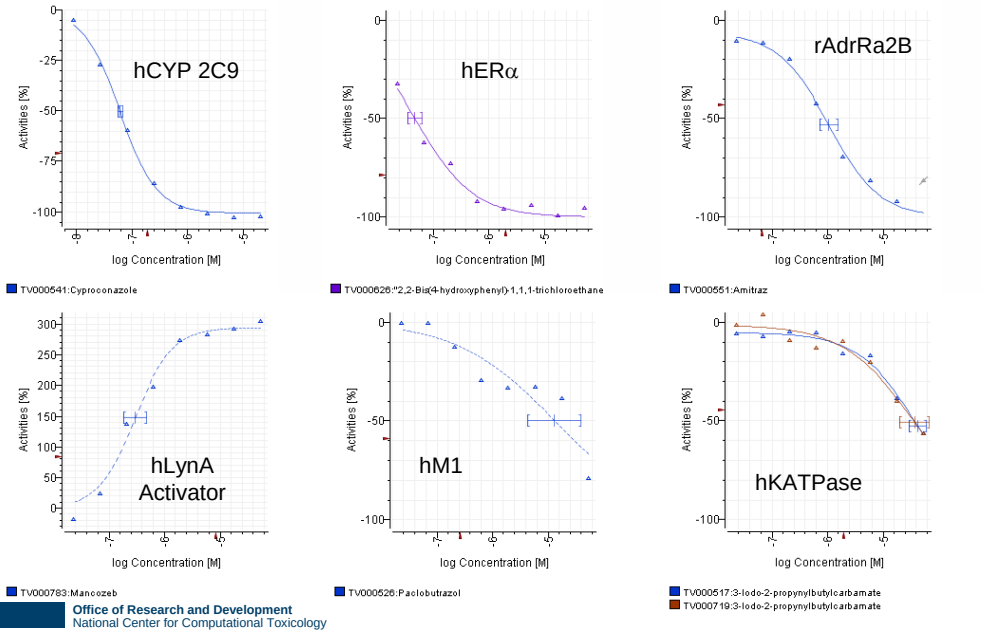
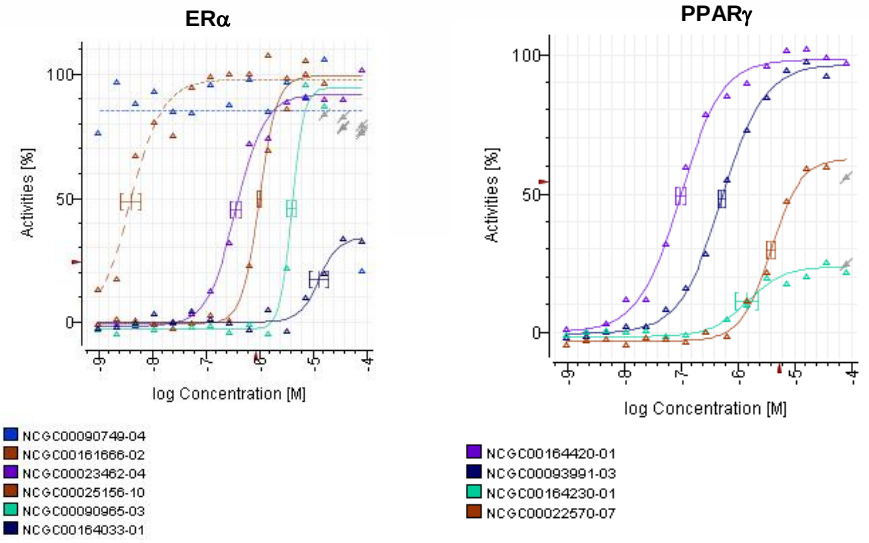
Biochemical HTS from Novascreen



qHTS from the NCGC on NRs



Attagene: *cis* and *trans* Assays

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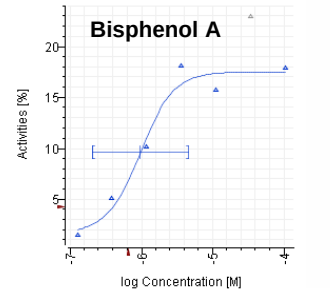
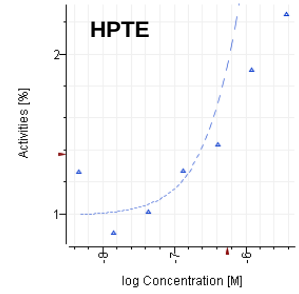
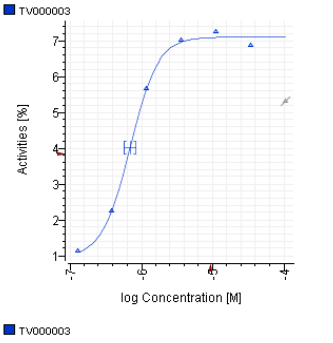
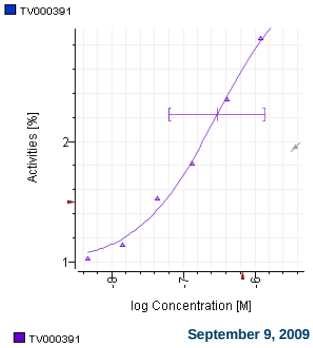
***trans*: ERa**

***cis*: ERE**



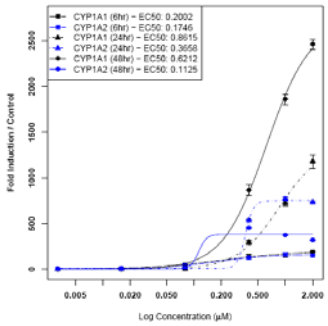


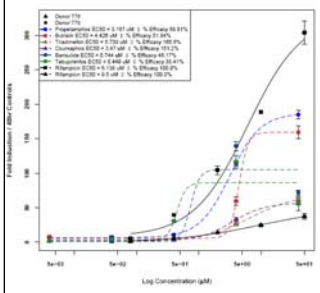




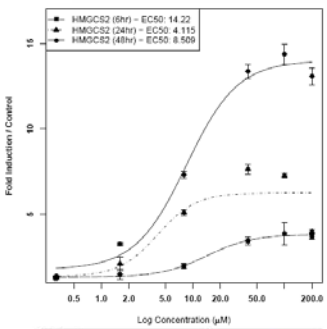
CellzDirect: Data Examples

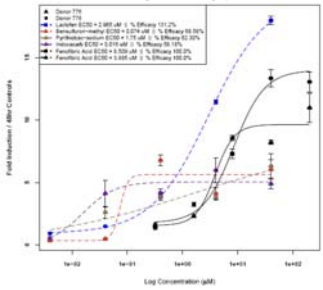
CYP1A1-AhR



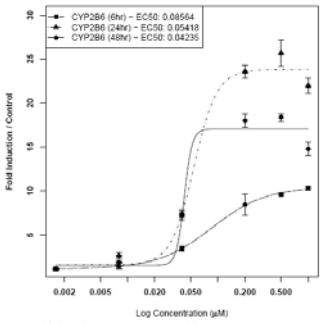


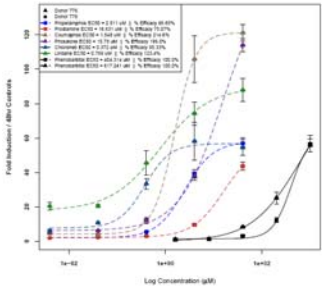
HMGCS2-PPARα





CYP2B6-CAR





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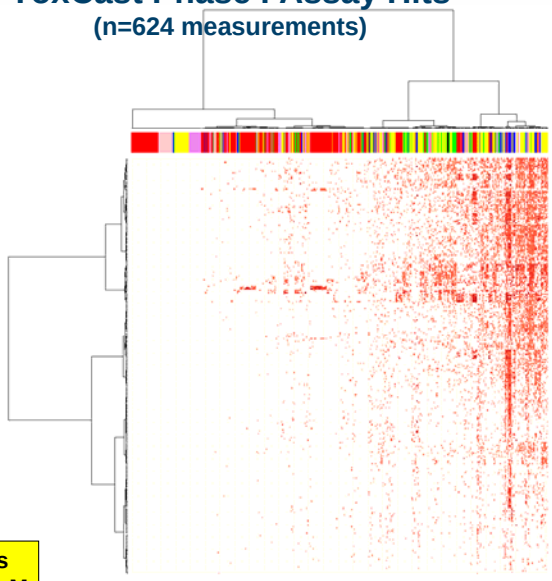
ToxCast Phase I Assay Hits

(n=624 measurements)

- Cell Free HTS
- Multiplexed TF
- Human BioMap
- HCS
- qNPAs
- XMEs
- Impedance
- Genotoxicity



828 Assay-Chemical Pairs had AC50s of less than 1μM

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Judson et al, submitted

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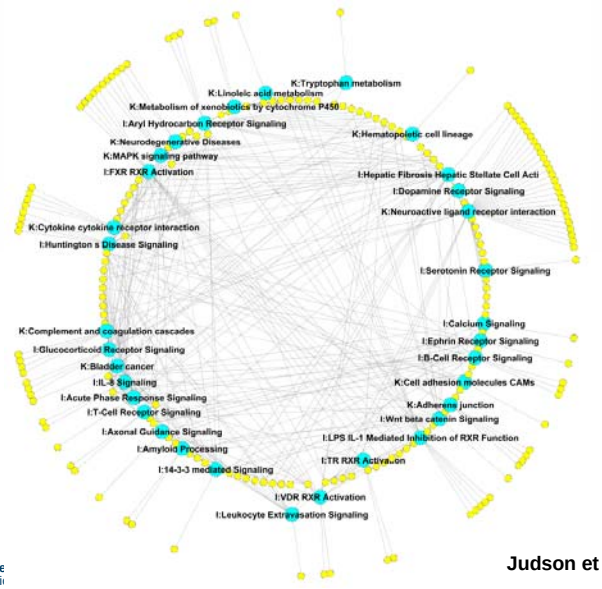
Minimum Human Pathways in ToxCast Phase I



Judson et al, submitted

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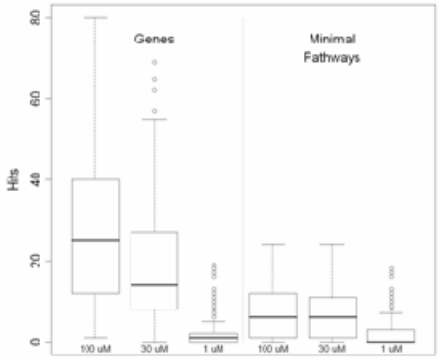
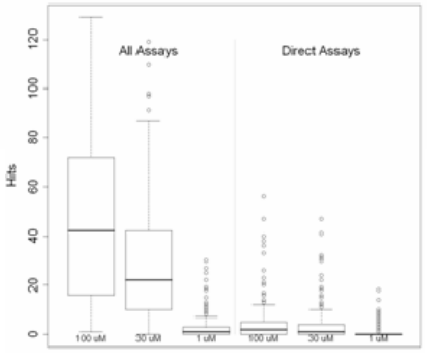
"Hits" per Chemical
As a Function of AC50/LEC Cutoff



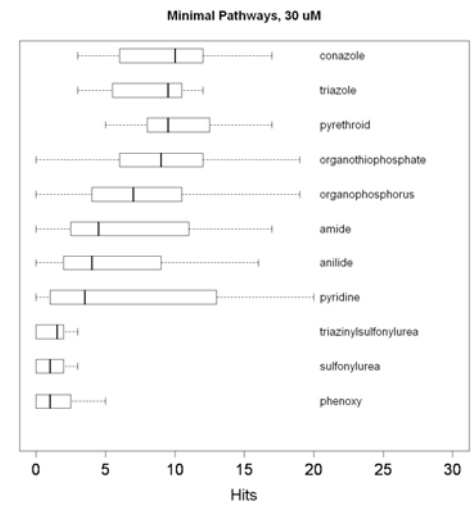


9 Chemicals have at least 20 hits at an AC50 of <30µM

Judson et al, submitted

"Hit" Distribution for Chemical Classes Against 33 Minimal Pathways

(at least 10 chemicals per class)



Judson et al, submitted

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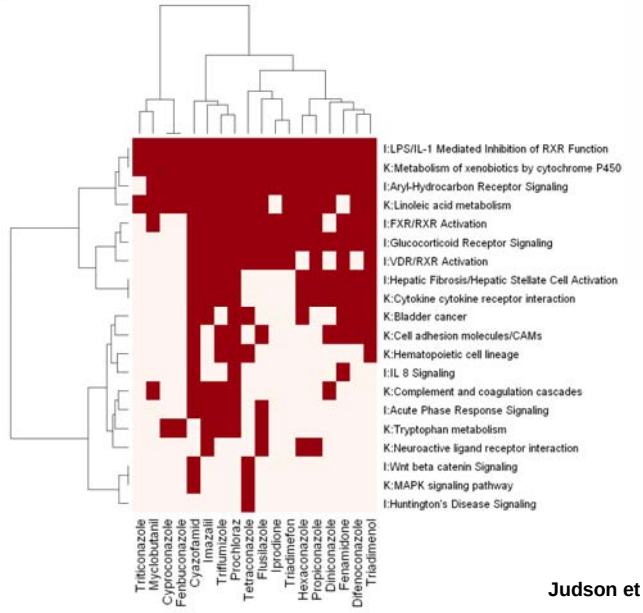
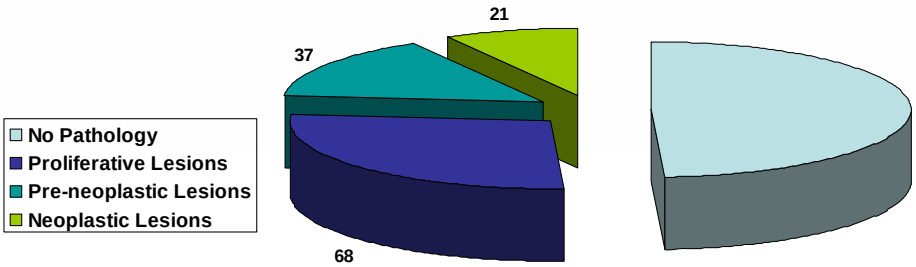
Activity of Conazoles Against Minimal Pathway Set



Judson et al, submitted

Rat Liver Histopathology from Chronic Bioassays



N = 248 Chemicals

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Martin et al, 2009

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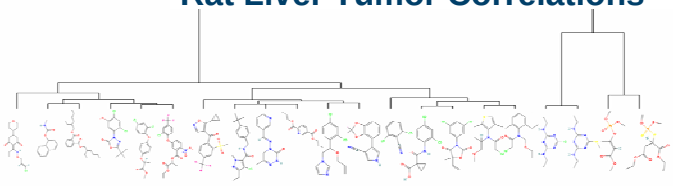
Rat Liver Tumor Correlations



Tepraloxydim	Carbaryl	Diethylhexyl phthalate	Oxadiazon	Diclofop-methyl	Lactofen	Isoxaflutole	Tebufenpyrad	Pymetrozine	2,5-Pyridinedicarboxylic acid, dipropyl ester	Imazalil	Fludioxonil	Dichlobenil	Cyclanilide	Vinclozolin	Dimethenamid	Acetochlor	Simazine	Ametryn	Mevinphos	Malathion	
			■	■	■									■	■	■				■	AR
		■		■	■					■											PPARA
	■	■	■	■	■	■	■		■	■	■		■	■	■	■	■	■	■	■	PPARG
					■		■						■			■		■			HMGCS2
			■	■		■			■								■		■		CCL2

Fisher's Exact test, p<0.01

Judson, et al, ***submitted***

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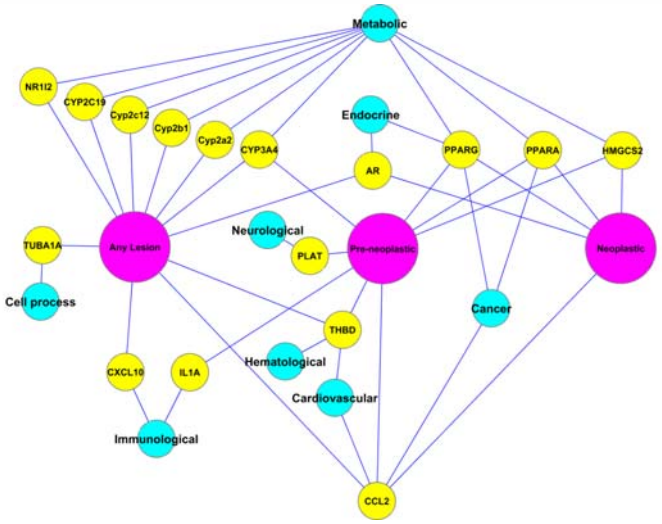
Gene Networks Associated with Progression of Rat Liver Tumor Endpoints



SEVERITY

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National Center for Computational Toxicology

Judson et al, submitted

Some Challenges Faced or to be Faced

- Organizing the chemical library
- Quality control of the chemical library
  - Acceptable purity, stability
- Defining concentration response ranges to the assayed
- Definition/Calculation of a hit
  - Minimum fold change; minimum r-squared; limit on Hill function
- Assay performance
  - Replicates, artifacts
- Sufficient coverage of biological pathways
  - Including those that represent tissue level processes
- Incorporation of metabolic competency
- Establishment of target prediction
  - Pathway perturbation
  - Rodent bioassay data
  - Rodent mechanistic studies
  - Human effects
- Sufficient representation of positives to predict against

Prioritization Product Timeline

Phase	Number of Chemicals	Chemical Criteria	Purpose	Number of Assays	Cost per Chemical	Target Date
Ia	320	Data Rich (pesticides)	Signature Development	552	$20k	FY07-09
Ib	15	Nanomaterials	Pilot	166	$10K	FY09
IIa	>300	Data Rich Chemicals	Validation	>400	~$20-25k	FY09-11
IIb	>100	Known Human Toxicants	Extrapolation	>400	~$20-25k	FY09-11
IIc	>300	Expanded Structure and Use Diversity	Extension	>400	~$20-25k	FY09-11
IId	>12	Nanomaterials	PMN	>200	~$15-20K	FY10-11
III	Thousands	Data poor	Prediction and Prioritization	>300	~$15-20k	FY11-12

FY07 FY08 FY09 FY10 FY11 FY12

Proof of Concept: ToxCast

Verification/Extension

Reduce to Practice

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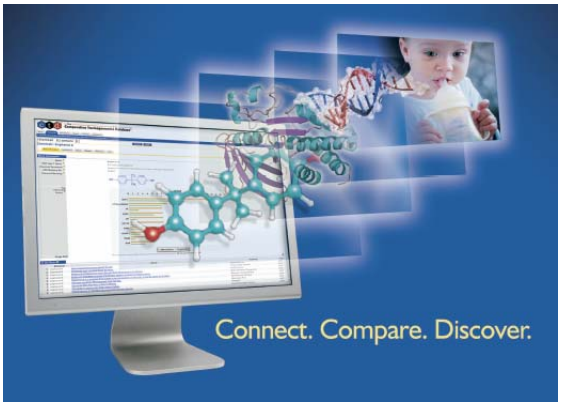
Tox21

Phase II Plans

- Done in conjunction with Tox21 10k Library
  - Subset of 700 will seed Phase II
- Chemical Diversity
  - More food use pesticides
  - Failed pharmaceuticals (preclinical and clinical)
  - "Green" chemicals
  - HPV Categories
  - Liver toxicants
  - OECD Molecular Screening Group nominations
- Evaluation of Phase I Assays
- Addition of new assays via competitive procurements
- Timing
  - Chemical procurement completed 4thQ FY09
  - Launch of Assays, 1st Q FY10
  - Results Available early FY11

The Comparative Toxicogenomics Database (CTD)



Carolyn J. Mattingly
The Mount Desert Island Biological Laboratory
Salisbury Cove, Maine

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Helping scientists explore the etiologies of environmental diseases

- What diseases are associated with arsenic?
- Arsenic affects which genes and proteins?
- What biological processes are affected by arsenic?
- Which molecular pathways are affected by arsenic?
- Which other chemicals affect the same molecular pathways?
- Which diseases are implicated with other chemicals?

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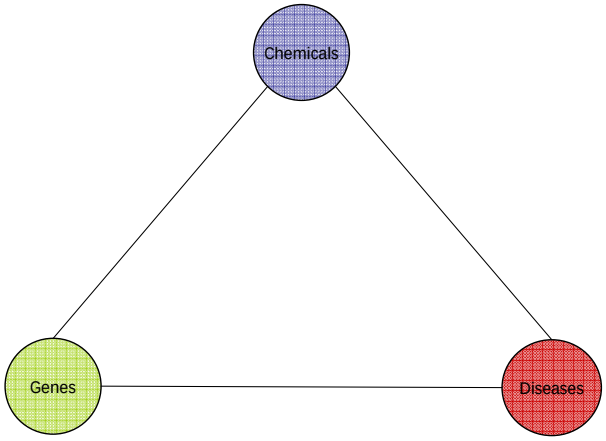
Curated Data



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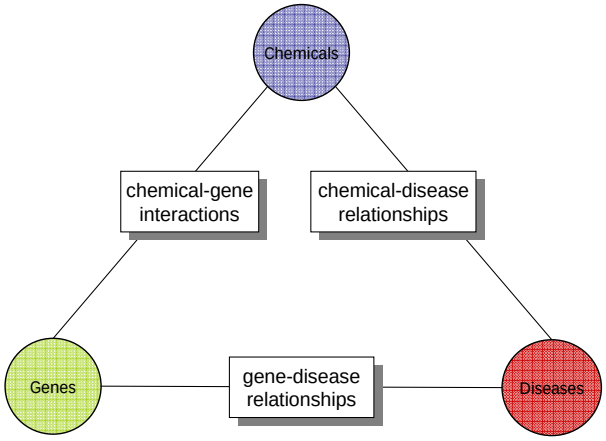
Curated Data



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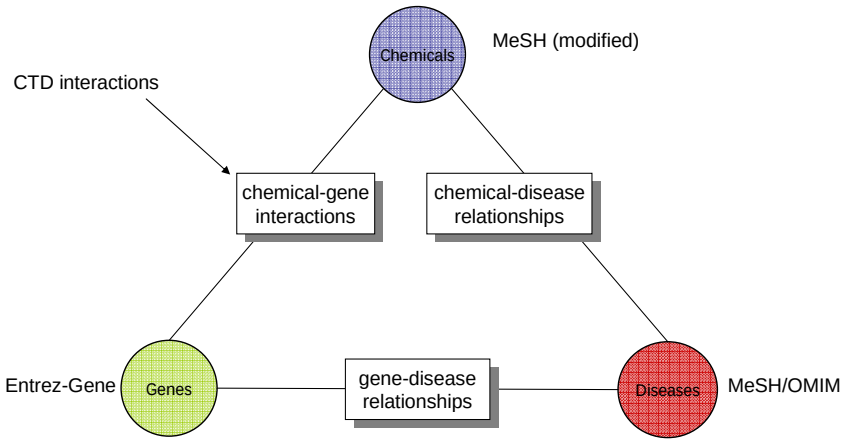
Curated Data



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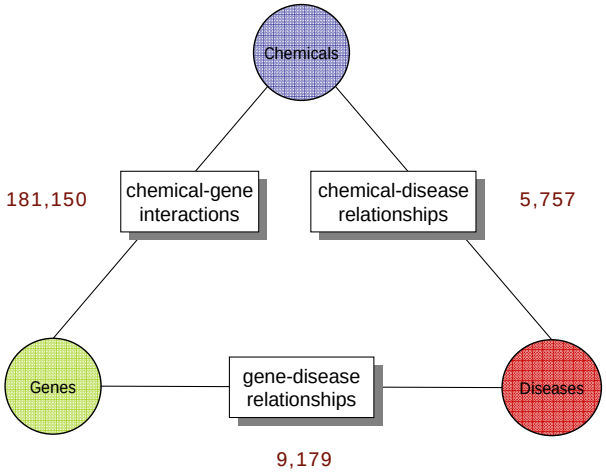
Curated Data



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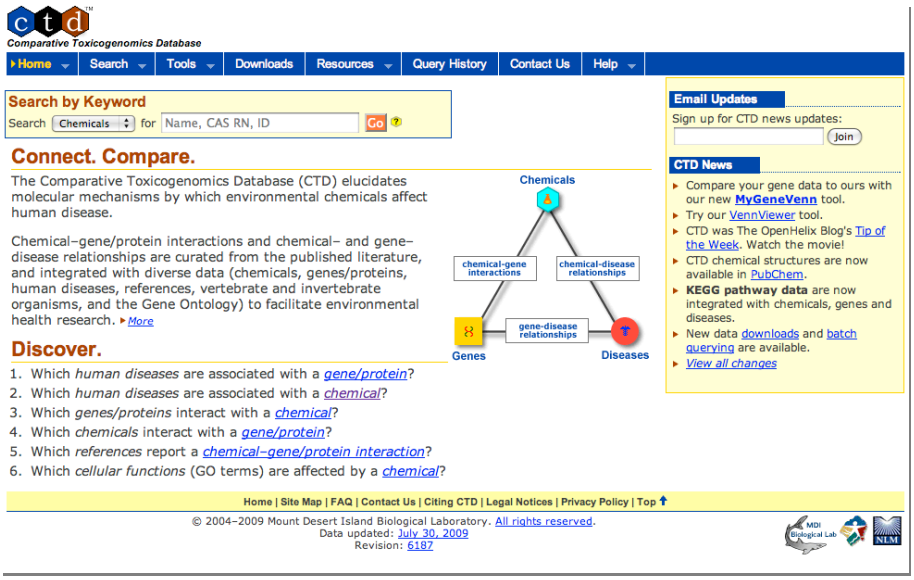
ctd
Comparative Toxicogenomics Database
Home
Search
Tools
Downloads
Resources
Query History
Contact Us
Help
Search by Keyword
Search Chemicals for Name, CAS RN, ID
Go
Connect. Compare.
The Comparative Toxicogenomics Database (CTD) elucidates molecular mechanisms by which environmental chemicals affect human disease.
Chemical–gene/protein interactions and chemical– and gene–disease relationships are curated from the published literature, and integrated with diverse data (chemicals, genes/proteins, human diseases, references, vertebrate and invertebrate organisms, and the Gene Ontology) to facilitate environmental health research. More
Chemicals
chemical-gene interactions
chemical-disease relationships
gene-disease relationships
Genes
Diseases
Discover.
1. Which human diseases are associated with a gene/protein?
2. Which human diseases are associated with a chemical?
3. Which genes/proteins interact with a chemical?
4. Which chemicals interact with a gene/protein?
5. Which references report a chemical–gene/protein interaction?
6. Which cellular functions (GO terms) are affected by a chemical?
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CTD chemical structures are now available in PubChem.
KEGG pathway data are now integrated with chemicals, genes and diseases.
New data downloads and batch querying are available.
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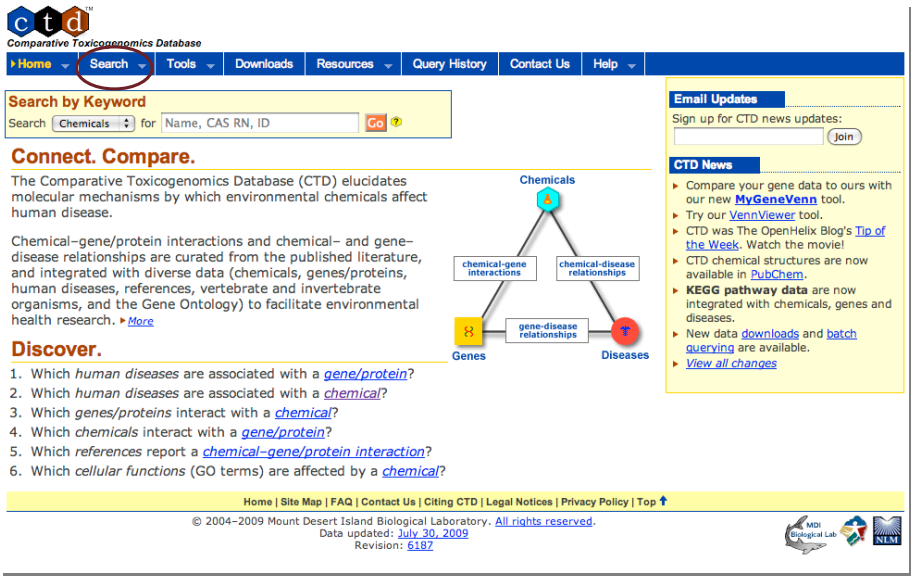
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Connect. Compare.
The Comparative Toxicogenomics Database (CTD) elucidates molecular mechanisms by which environmental chemicals affect human disease.
Chemical–gene/protein interactions and chemical– and gene–disease relationships are curated from the published literature, and integrated with diverse data (chemicals, genes/proteins, human diseases, references, vertebrate and invertebrate organisms, and the Gene Ontology) to facilitate environmental health research.
More
Chemicals
chemical-gene interactions
chemical-disease relationships
gene-disease relationships
Genes
Diseases
Discover.
1. Which human diseases are associated with a gene/protein?
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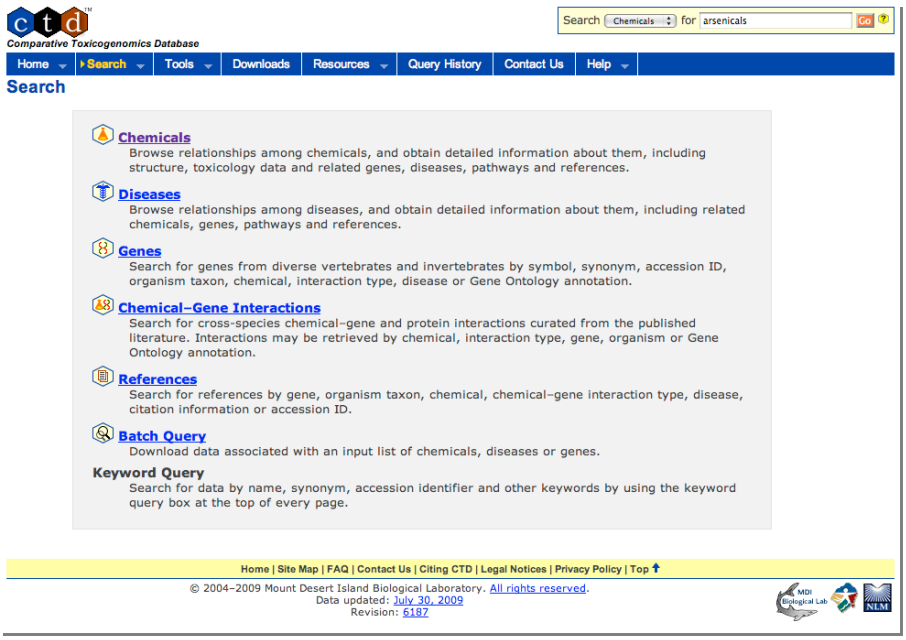
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Browse relationships among chemicals, and obtain detailed information about them, including structure, toxicology data and related genes, diseases, pathways and references.
Diseases
Browse relationships among diseases, and obtain detailed information about them, including related chemicals, genes, pathways and references.
Genes
Search for genes from diverse vertebrates and invertebrates by symbol, synonym, accession ID, organism taxon, chemical, interaction type, disease or Gene Ontology annotation.
Chemical–Gene Interactions
Search for cross-species chemical–gene and protein interactions curated from the published literature. Interactions may be retrieved by chemical, interaction type, gene, organism or Gene Ontology annotation.
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Search for references by gene, organism taxon, chemical, chemical–gene interaction type, disease, citation information or accession ID.
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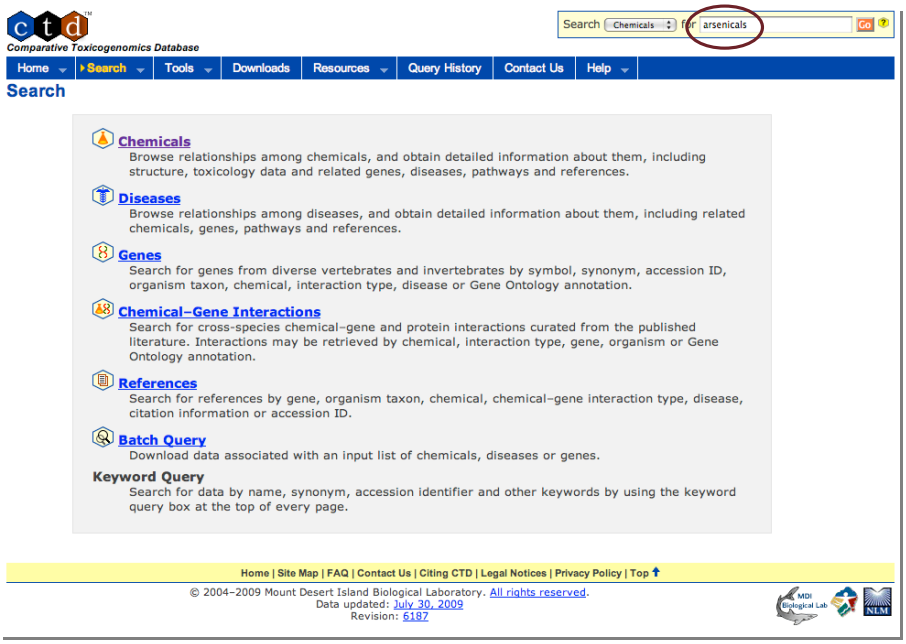
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Chemicals
Browse relationships among chemicals, and obtain detailed information about them, including structure, toxicology data and related genes, diseases, pathways and references.
Diseases
Browse relationships among diseases, and obtain detailed information about them, including related chemicals, genes, pathways and references.
Genes
Search for genes from diverse vertebrates and invertebrates by symbol, synonym, accession ID, organism taxon, chemical, interaction type, disease or Gene Ontology annotation.
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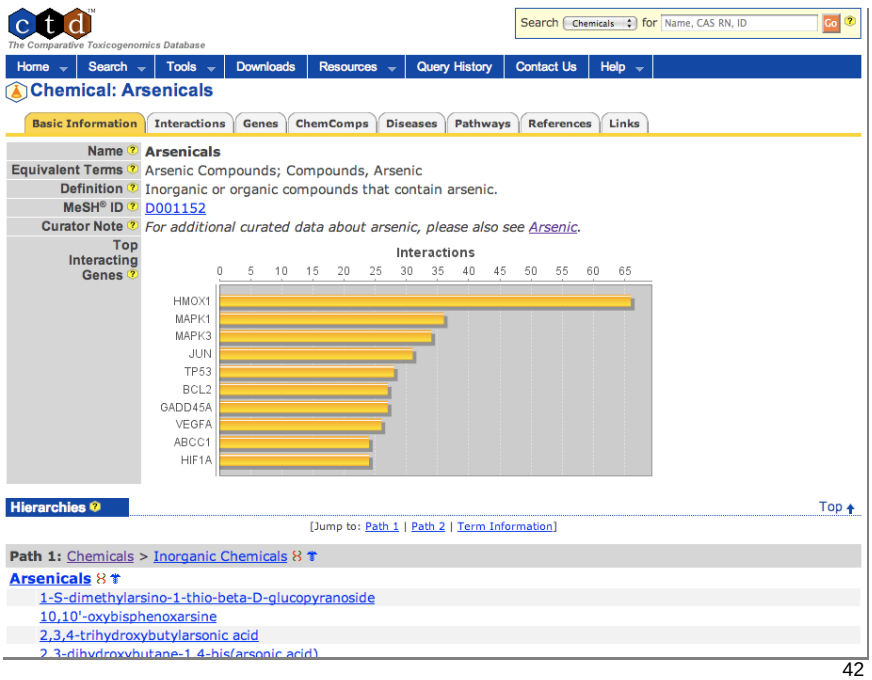
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Chemical: Arsenicals
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Name Arsenicals
Equivalent Terms Arsenic Compounds; Compounds, Arsenic
Definition Inorganic or organic compounds that contain arsenic.
MeSH® ID D001152
Curator Note For additional curated data about arsenic, please also see Arsenic.
Top Interacting Genes
Interactions
0 5 10 15 20 25 30 35 40 45 50 55 60 65
HMOX1
MAPK1
MAPK3
JUN
TP53
BCL2
GADD45A
VEGFA
ABCC1
HIF1A
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Arsenicals
1-S-dimethylarsino-1-thio-beta-D-glucopyranoside
10,10'-oxybisphenoxarsine
2,3,4-trihydroxybutylarsonic acid
2,3-dihydroxybutane-1,4-bis(arsonic acid)

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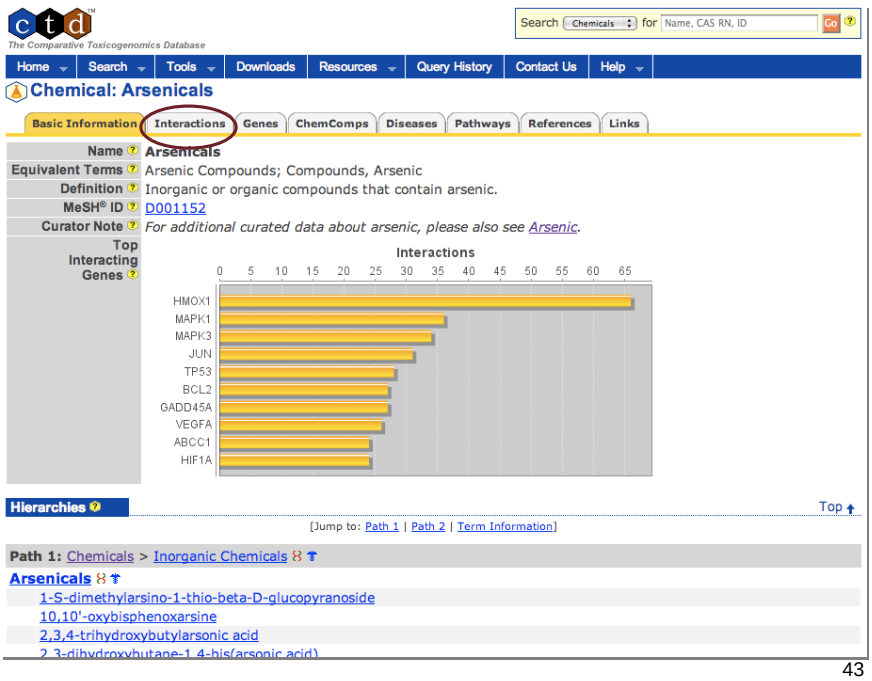
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Chemical: Arsenicals
Basic Information Interactions Genes ChemComps Diseases Pathways References Links
Name Arsenicals
Equivalent Terms Arsenic Compounds; Compounds, Arsenic
Definition Inorganic or organic compounds that contain arsenic.
MeSH® ID D001152
Curator Note For additional curated data about arsenic, please also see Arsenic.
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Interactions
0 5 10 15 20 25 30 35 40 45 50 55 60 65
HMOX1
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BCL2
GADD45A
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Path 1: Chemicals > Inorganic Chemicals
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10,10'-oxybisphenoxarsine
2,3,4-trihydroxybutylarsonic acid
2,3-dihydroxybutane-1,4-bis(arsonic acid)
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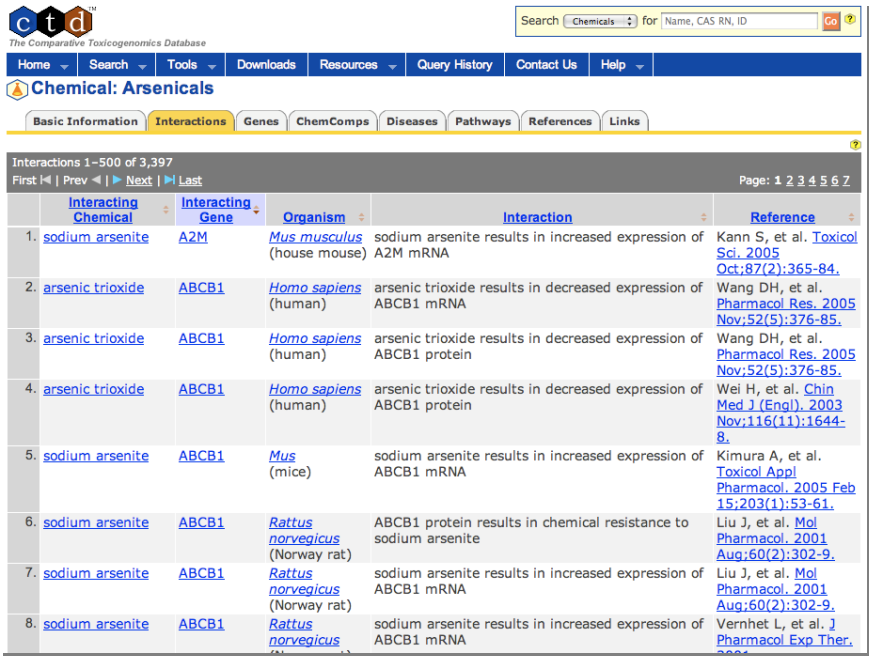

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	Interacting Chemical	Interacting Gene	Organism	Interaction	Reference
1.	sodium arsenite	A2M	*Mus musculus* (house mouse)	sodium arsenite results in increased expression of A2M mRNA	Kann S, et al. Toxicol Sci. 2005 Oct;87(2):365-84.
2.	arsenic trioxide	ABCB1	*Homo sapiens* (human)	arsenic trioxide results in decreased expression of ABCB1 mRNA	Wang DH, et al. Pharmacol Res. 2005 Nov;52(5):376-85.
3.	arsenic trioxide	ABCB1	*Homo sapiens* (human)	arsenic trioxide results in decreased expression of ABCB1 protein	Wang DH, et al. Pharmacol Res. 2005 Nov;52(5):376-85.
4.	arsenic trioxide	ABCB1	*Homo sapiens* (human)	arsenic trioxide results in decreased expression of ABCB1 protein	Wei H, et al. Chin Med J (Engl). 2003 Nov;116(11):1644-8.
5.	sodium arsenite	ABCB1	*Mus* (mice)	sodium arsenite results in increased expression of ABCB1 mRNA	Kimura A, et al. Toxicol Appl Pharmacol. 2005 Feb 15;203(1):53-61.
6.	sodium arsenite	ABCB1	*Rattus norvegicus* (Norway rat)	ABCB1 protein results in chemical resistance to sodium arsenite	Liu J, et al. Mol Pharmacol. 2001 Aug;60(2):302-9.
7.	sodium arsenite	ABCB1	*Rattus norvegicus* (Norway rat)	sodium arsenite results in increased expression of ABCB1 mRNA	Liu J, et al. Mol Pharmacol. 2001 Aug;60(2):302-9.
8.	sodium arsenite	ABCB1	*Rattus norvegicus*	sodium arsenite results in increased expression of ABCB1 mRNA	Vernhet L, et al. J Pharmacol Exp Ther.

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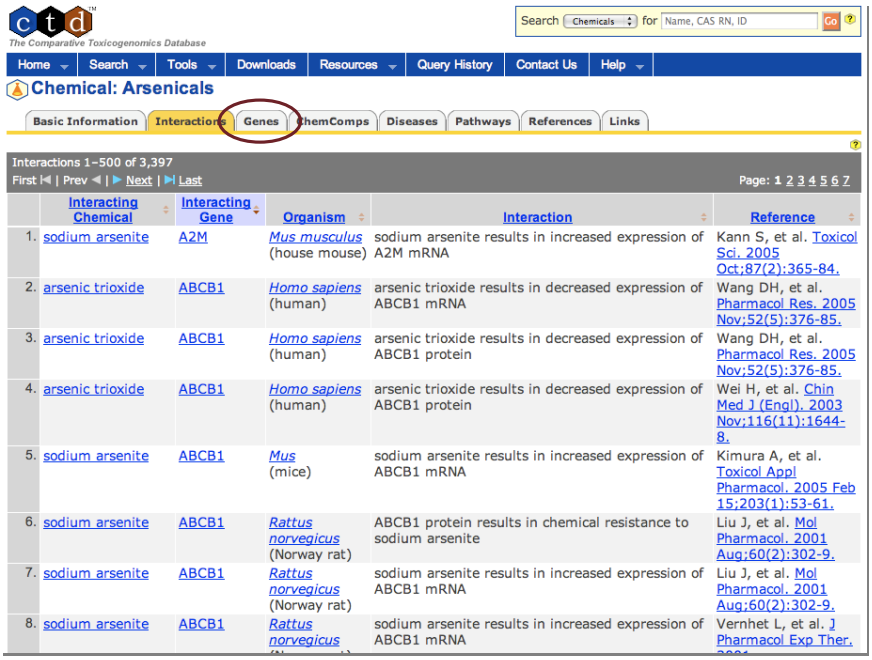

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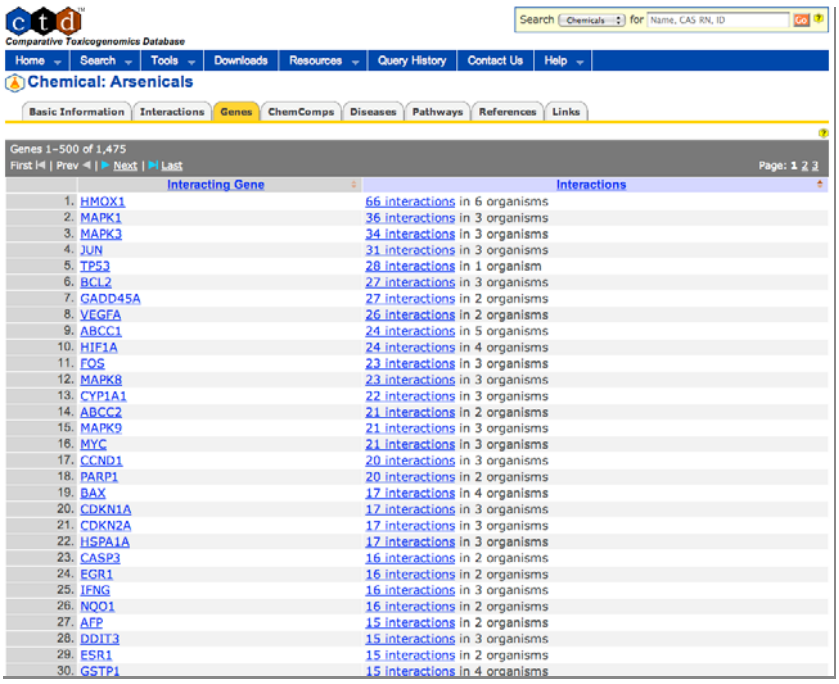
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6. BCL2 27 interactions in 3 organisms
7. GADD45A 27 interactions in 2 organisms
8. VEGFA 26 interactions in 2 organisms
9. ABCC1 24 interactions in 5 organisms
10. HIF1A 24 interactions in 4 organisms
11. FOS 23 interactions in 3 organisms
12. MAPK8 23 interactions in 3 organisms
13. CYP1A1 22 interactions in 3 organisms
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19. BAX 17 interactions in 4 organisms
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21. CDKN2A 17 interactions in 3 organisms
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23. CASP3 16 interactions in 2 organisms
24. EGR1 16 interactions in 2 organisms
25. IFNG 16 interactions in 3 organisms
26. NQO1 16 interactions in 2 organisms
27. AFP 15 interactions in 2 organisms
28. DDIT3 15 interactions in 3 organisms
29. ESR1 15 interactions in 2 organisms
30. GSTP1 15 interactions in 4 organisms

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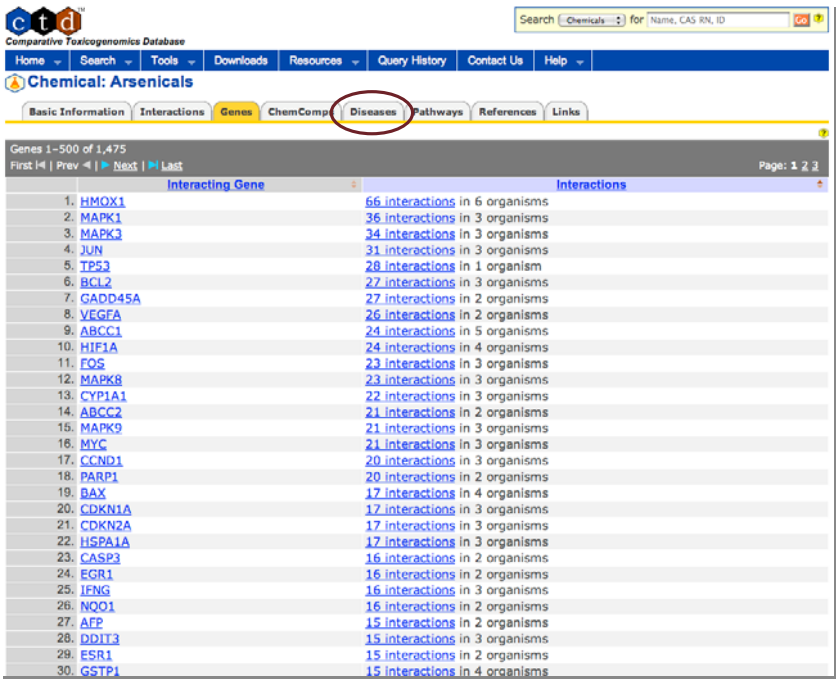
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13. CYP1A1 22 interactions in 3 organisms
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16. MYC 21 interactions in 3 organisms
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23. CASP3 16 interactions in 2 organisms
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25. IFNG 16 interactions in 3 organisms
26. NQO1 16 interactions in 2 organisms
27. AFP 15 interactions in 2 organisms
28. DDIT3 15 interactions in 3 organisms
29. ESR1 15 interactions in 2 organisms
30. GSTP1 15 interactions in 4 organisms

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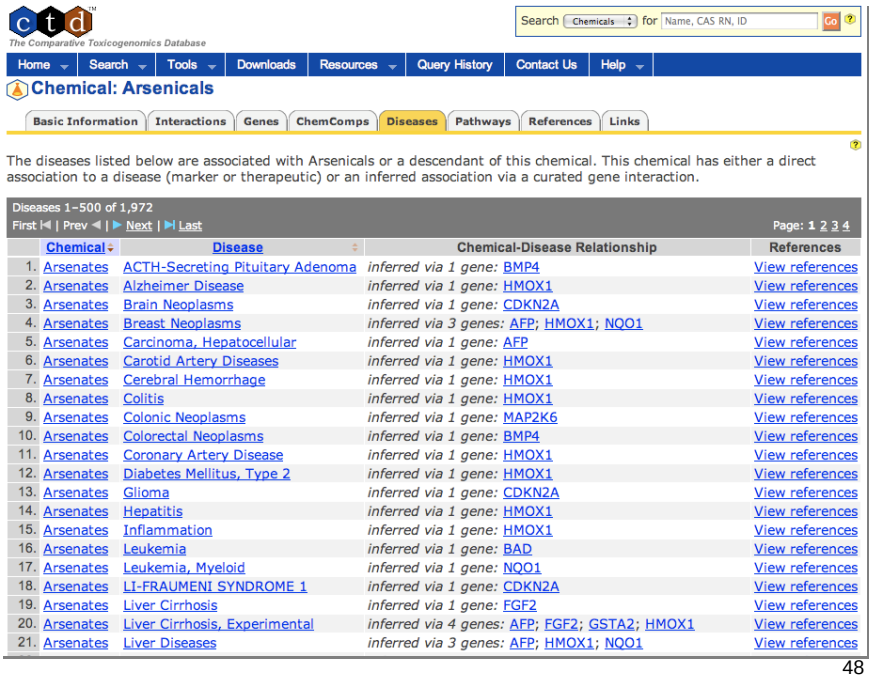

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Chemical: Arsenicals

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The diseases listed below are associated with Arsenicals or a descendant of this chemical. This chemical has either a direct association to a disease (marker or therapeutic) or an inferred association via a curated gene interaction.

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	Chemical	Disease	Chemical-Disease Relationship	References
1.	Arsenates	ACTH-Secreting Pituitary Adenoma	*inferred via 1 gene:* BMP4	View references
2.	Arsenates	Alzheimer Disease	*inferred via 1 gene:* HMOX1	View references
3.	Arsenates	Brain Neoplasms	*inferred via 1 gene:* CDKN2A	View references
4.	Arsenates	Breast Neoplasms	*inferred via 3 genes:* AFP; HMOX1; NQO1	View references
5.	Arsenates	Carcinoma, Hepatocellular	*inferred via 1 gene:* AFP	View references
6.	Arsenates	Carotid Artery Diseases	*inferred via 1 gene:* HMOX1	View references
7.	Arsenates	Cerebral Hemorrhage	*inferred via 1 gene:* HMOX1	View references
8.	Arsenates	Colitis	*inferred via 1 gene:* HMOX1	View references
9.	Arsenates	Colonic Neoplasms	*inferred via 1 gene:* MAP2K6	View references
10.	Arsenates	Colorectal Neoplasms	*inferred via 1 gene:* BMP4	View references
11.	Arsenates	Coronary Artery Disease	*inferred via 1 gene:* HMOX1	View references
12.	Arsenates	Diabetes Mellitus, Type 2	*inferred via 1 gene:* HMOX1	View references
13.	Arsenates	Glioma	*inferred via 1 gene:* CDKN2A	View references
14.	Arsenates	Hepatitis	*inferred via 1 gene:* HMOX1	View references
15.	Arsenates	Inflammation	*inferred via 1 gene:* HMOX1	View references
16.	Arsenates	Leukemia	*inferred via 1 gene:* BAD	View references
17.	Arsenates	Leukemia, Myeloid	*inferred via 1 gene:* NQO1	View references
18.	Arsenates	LI-FRAUMENI SYNDROME 1	*inferred via 1 gene:* CDKN2A	View references
19.	Arsenates	Liver Cirrhosis	*inferred via 1 gene:* FGF2	View references
20.	Arsenates	Liver Cirrhosis, Experimental	*inferred via 4 genes:* AFP; FGF2; GSTA2; HMOX1	View references
21.	Arsenates	Liver Diseases	*inferred via 3 genes:* AFP; HMOX1; NQO1	View references

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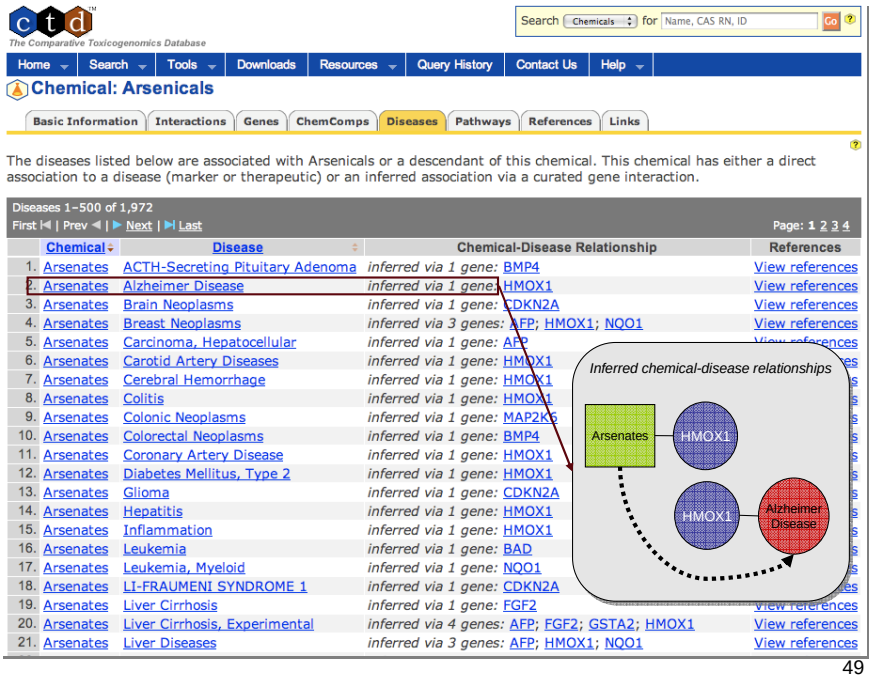
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Chemical | Disease | Chemical-Disease Relationship | References
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2. Arsenates Alzheimer Disease inferred via 1 gene: HMOX1 View references
3. Arsenates Brain Neoplasms inferred via 1 gene: CDKN2A View references
4. Arsenates Breast Neoplasms inferred via 3 genes: AFP; HMOX1; NQO1 View references
5. Arsenates Carcinoma, Hepatocellular inferred via 1 gene: AFP
6. Arsenates Carotid Artery Diseases inferred via 1 gene: HMOX1
7. Arsenates Cerebral Hemorrhage inferred via 1 gene: HMOX1
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9. Arsenates Colonic Neoplasms inferred via 1 gene: MAP2K6
10. Arsenates Colorectal Neoplasms inferred via 1 gene: BMP4
11. Arsenates Coronary Artery Disease inferred via 1 gene: HMOX1
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13. Arsenates Glioma inferred via 1 gene: CDKN2A
14. Arsenates Hepatitis inferred via 1 gene: HMOX1
15. Arsenates Inflammation inferred via 1 gene: HMOX1
16. Arsenates Leukemia inferred via 1 gene: BAD
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18. Arsenates LI-FRAUMENI SYNDROME 1 inferred via 1 gene: CDKN2A
19. Arsenates Liver Cirrhosis inferred via 1 gene: FGF2
20. Arsenates Liver Cirrhosis, Experimental inferred via 4 genes: AFP; FGF2; GSTA2; HMOX1 View references
21. Arsenates Liver Diseases inferred via 3 genes: AFP; HMOX1; NQO1 View references
Inferred chemical-disease relationships
Arsenates
HMOX1
HMOX1
Alzheimer Disease

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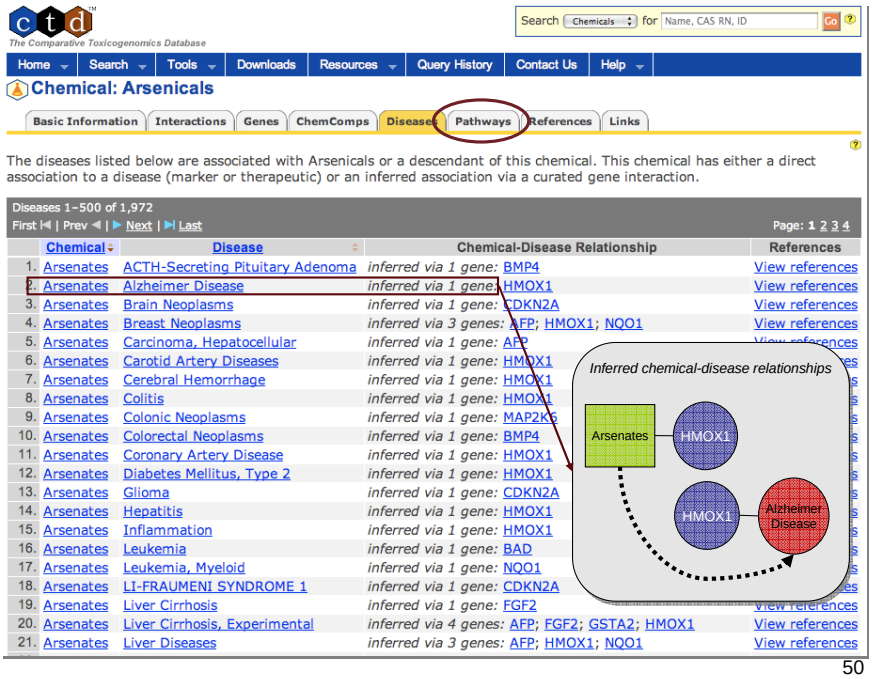
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21. Arsenates Liver Diseases inferred via 3 genes: AFP; HMOX1; NQO1 View references
Inferred chemical-disease relationships
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HMOX1
HMOX1
Alzheimer Disease

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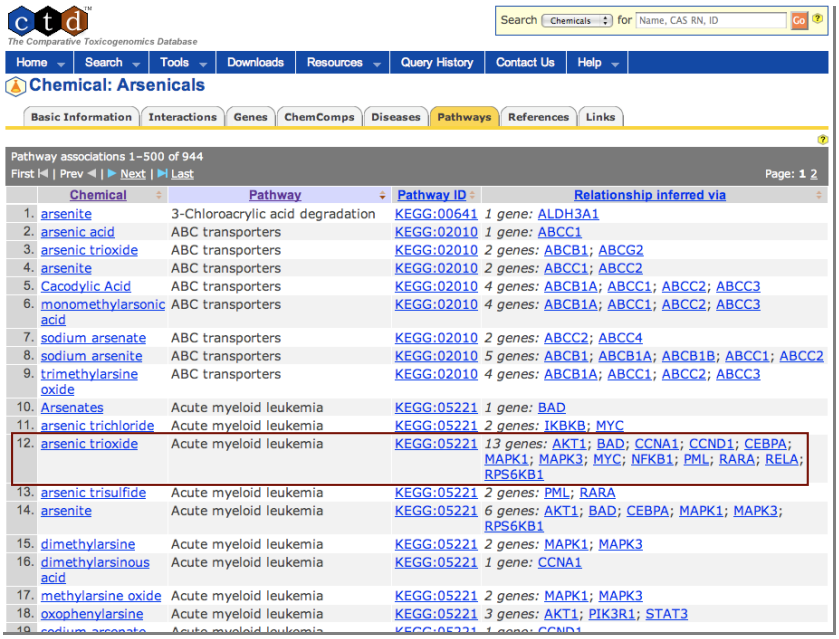

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	Chemical	Pathway	Pathway ID	Relationship inferred via
1.	arsenite	3-Chloroacrylic acid degradation	KEGG:00641	*1 gene:* ALDH3A1
2.	arsenic acid	ABC transporters	KEGG:02010	*1 gene:* ABCC1
3.	arsenic trioxide	ABC transporters	KEGG:02010	*2 genes:* ABCB1; ABCG2
4.	arsenite	ABC transporters	KEGG:02010	*2 genes:* ABCC1; ABCC2
5.	Cacodylic Acid	ABC transporters	KEGG:02010	*4 genes:* ABCB1A; ABCC1; ABCC2; ABCC3
6.	monomethylarsonic acid	ABC transporters	KEGG:02010	*4 genes:* ABCB1A; ABCC1; ABCC2; ABCC3
7.	sodium arsenate	ABC transporters	KEGG:02010	*2 genes:* ABCC2; ABCC4
8.	sodium arsenite	ABC transporters	KEGG:02010	*5 genes:* ABCB1; ABCB1A; ABCB1B; ABCC1; ABCC2
9.	trimethylarsine oxide	ABC transporters	KEGG:02010	*4 genes:* ABCB1A; ABCC1; ABCC2; ABCC3
10.	Arsenates	Acute myeloid leukemia	KEGG:05221	*1 gene:* BAD
11.	arsenic trichloride	Acute myeloid leukemia	KEGG:05221	*2 genes:* IKBKB; MYC
12.	arsenic trioxide	Acute myeloid leukemia	KEGG:05221	*13 genes:* AKT1; BAD; CCNA1; CCND1; CEBPA; MAPK1; MAPK3; MYC; NFKB1; PML; RARA; RELA; RPS6KB1
13.	arsenic trisulfide	Acute myeloid leukemia	KEGG:05221	*2 genes:* PML; RARA
14.	arsenite	Acute myeloid leukemia	KEGG:05221	*6 genes:* AKT1; BAD; CEBPA; MAPK1; MAPK3; RPS6KB1
15.	dimethylarsine	Acute myeloid leukemia	KEGG:05221	*2 genes:* MAPK1; MAPK3
16.	dimethylarsinous acid	Acute myeloid leukemia	KEGG:05221	*1 gene:* CCNA1
17.	methylarsine oxide	Acute myeloid leukemia	KEGG:05221	*2 genes:* MAPK1; MAPK3
18.	oxophenylarsine	Acute myeloid leukemia	KEGG:05221	*3 genes:* AKT1; PIK3R1; STAT3

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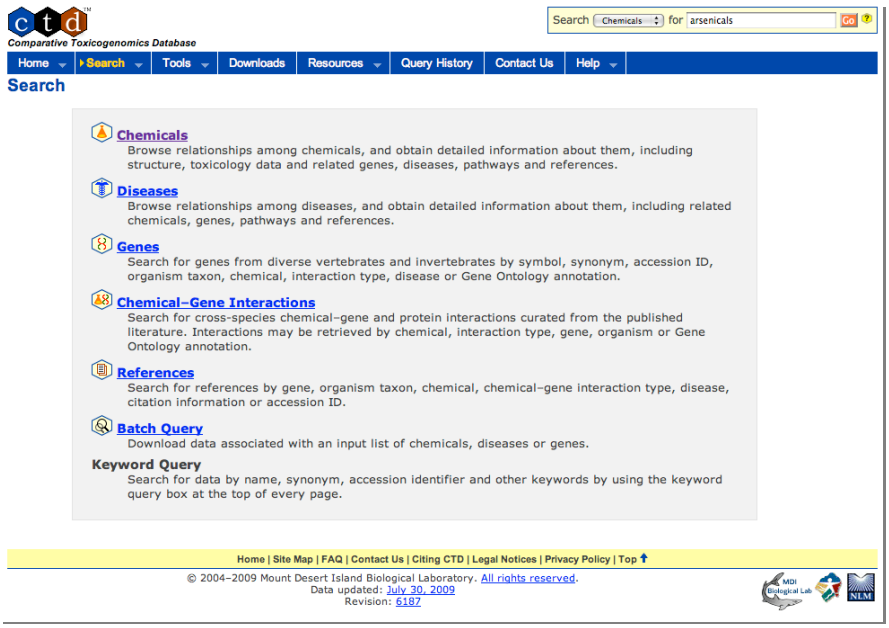
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Chemicals
Browse relationships among chemicals, and obtain detailed information about them, including structure, toxicology data and related genes, diseases, pathways and references.
Diseases
Browse relationships among diseases, and obtain detailed information about them, including related chemicals, genes, pathways and references.
Genes
Search for genes from diverse vertebrates and invertebrates by symbol, synonym, accession ID, organism taxon, chemical, interaction type, disease or Gene Ontology annotation.
Chemical–Gene Interactions
Search for cross-species chemical–gene and protein interactions curated from the published literature. Interactions may be retrieved by chemical, interaction type, gene, organism or Gene Ontology annotation.
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Search for references by gene, organism taxon, chemical, chemical–gene interaction type, disease, citation information or accession ID.
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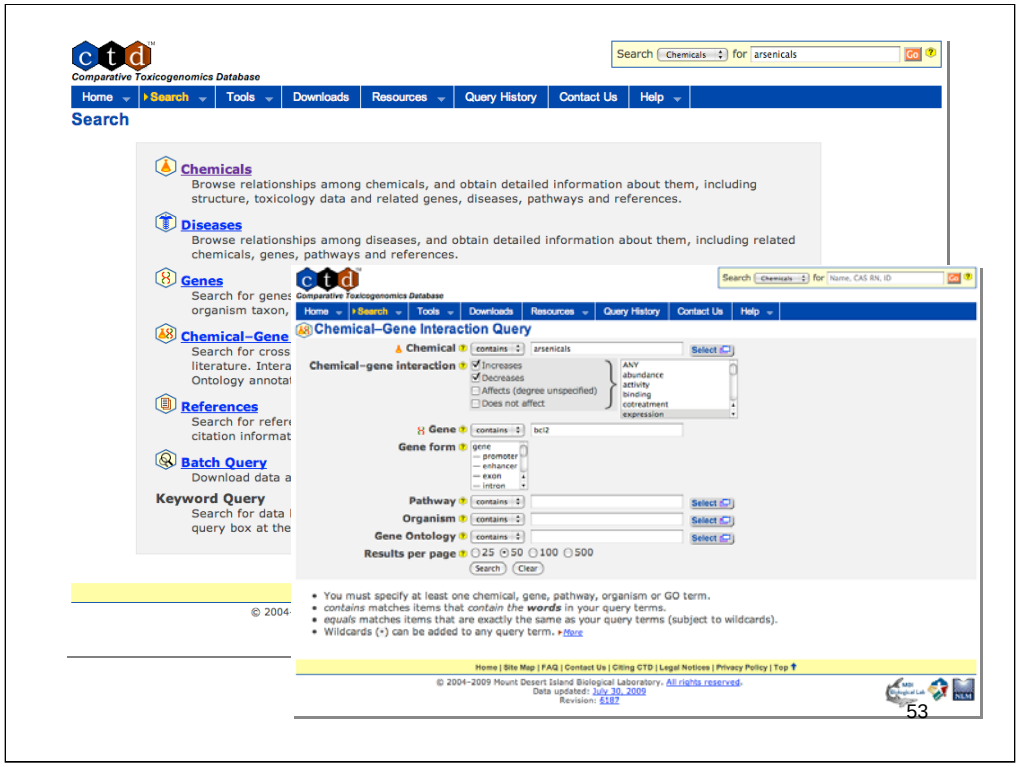
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Search Chemicals for arsenicals
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Search
Chemicals
Browse relationships among chemicals, and obtain detailed information about them, including structure, toxicology data and related genes, diseases, pathways and references.
Diseases
Browse relationships among diseases, and obtain detailed information about them, including related chemicals, genes, pathways and references.
Genes
Search for genes
organism taxon,
Chemical–Gene
Search for cross
literature. Intera
Ontology annotat
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Search for refer
citation informat
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Chemical–Gene Interaction Query
Chemical contains arsenicals Select
Chemical–gene interaction
Increases
Decreases
Affects (degree unspecified)
Does not affect
ANY
abundance
activity
binding
cotreatment
expression
Gene contains bcl2
Gene form
gene
promoter
enhancer
exon
intron
Pathway contains Select
Organism contains Select
Gene Ontology contains Select
Results per page 25 50 100 500
Search Clear
You must specify at least one chemical, gene, pathway, organism or GO term.
contains matches items that contain the words in your query terms.
equals matches items that are exactly the same as your query terms (subject to wildcards).
Wildcards (*) can be added to any query term. More
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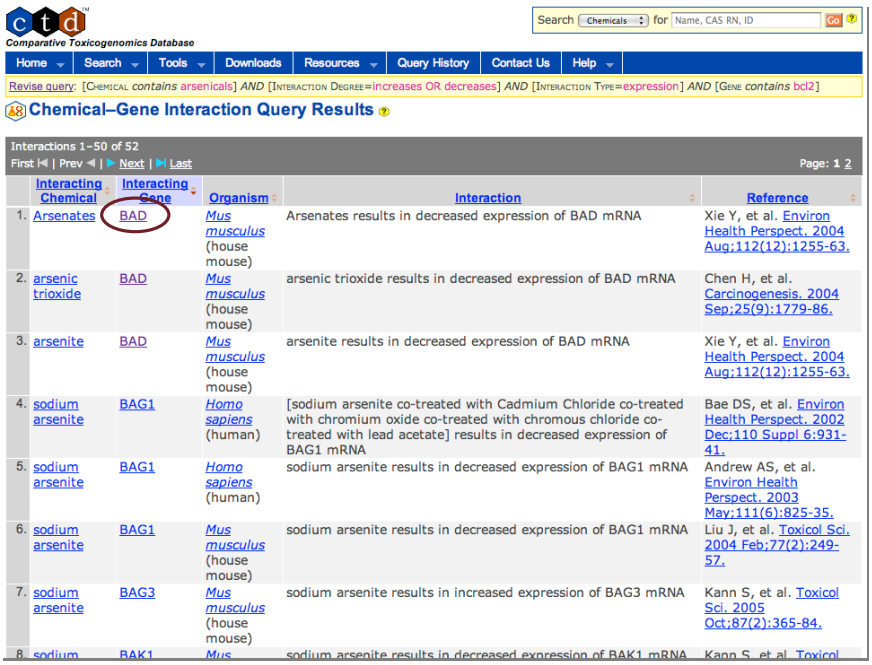

Comparative Toxicogenomics Database

Search Chemicals for Name, CAS RN, ID

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Revise query: [Chemical *contains* arsenicals] *AND* [Interaction Degree=increases OR decreases] *AND* [Interaction Type=expression] *AND* [Gene *contains* bcl2]

Chemical–Gene Interaction Query Results

Interactions 1–50 of 52

First | Prev | Next | Last

Page: 1 2

	Interacting Chemical	Interacting Gene	Organism	Interaction	Reference
1.	Arsenates	BAD	*Mus musculus* (house mouse)	Arsenates results in decreased expression of BAD mRNA	Xie Y, et al. Environ Health Perspect. 2004 Aug;112(12):1255-63.
2.	arsenic trioxide	BAD	*Mus musculus* (house mouse)	arsenic trioxide results in decreased expression of BAD mRNA	Chen H, et al. Carcinogenesis. 2004 Sep;25(9):1779-86.
3.	arsenite	BAD	*Mus musculus* (house mouse)	arsenite results in decreased expression of BAD mRNA	Xie Y, et al. Environ Health Perspect. 2004 Aug;112(12):1255-63.
4.	sodium arsenite	BAG1	*Homo sapiens* (human)	[sodium arsenite co-treated with Cadmium Chloride co-treated with chromium oxide co-treated with chromous chloride co-treated with lead acetate] results in decreased expression of BAG1 mRNA	Bae DS, et al. Environ Health Perspect. 2002 Dec;110 Suppl 6:931-41.
5.	sodium arsenite	BAG1	*Homo sapiens* (human)	sodium arsenite results in decreased expression of BAG1 mRNA	Andrew AS, et al. Environ Health Perspect. 2003 May;111(6):825-35.
6.	sodium arsenite	BAG1	*Mus musculus* (house mouse)	sodium arsenite results in decreased expression of BAG1 mRNA	Liu J, et al. Toxicol Sci. 2004 Feb;77(2):249-57.
7.	sodium arsenite	BAG3	*Mus musculus* (house mouse)	sodium arsenite results in increased expression of BAG3 mRNA	Kann S, et al. Toxicol Sci. 2005 Oct;87(2):365-84.
8.	sodium	BAK1	*Mus*	sodium arsenite results in decreased expression of BAK1 mRNA	Kann S, et al. Toxicol

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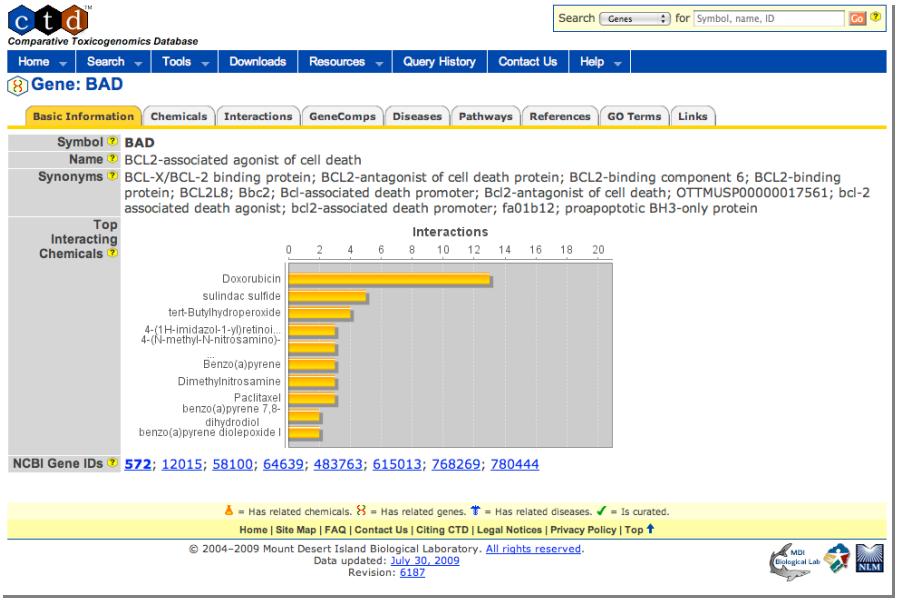
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Search Genes for Symbol, name, ID Go
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Gene: BAD
Basic Information Chemicals Interactions GeneComps Diseases Pathways References GO Terms Links
Symbol BAD
Name BCL2-associated agonist of cell death
Synonyms BCL-X/BCL-2 binding protein; BCL2-antagonist of cell death protein; BCL2-binding component 6; BCL2-binding protein; BCL2L8; Bbc2; Bcl-associated death promoter; Bcl2-antagonist of cell death; OTTMUSP00000017561; bcl-2 associated death agonist; bcl2-associated death promoter; fa01b12; proapoptotic BH3-only protein
Top Interacting Chemicals
Interactions
0 2 4 6 8 10 12 14 16 18 20
Doxorubicin
sulindac sulfide
tert-Butylhydroperoxide
4-(1H-imidazol-1-yl)retinoi... 4-(N-methyl-N-nitrosamino)-
Benzo(a)pyrene
Dimethylnitrosamine
Paclitaxel
benzo(a)pyrene 7,8-dihydrodiol benzo(a)pyrene diolepoxide I
NCBI Gene IDs 572; 12015; 58100; 64639; 483763; 615013; 768269; 780444
= Has related chemicals. = Has related genes. = Has related diseases. ✓ = Is curated.
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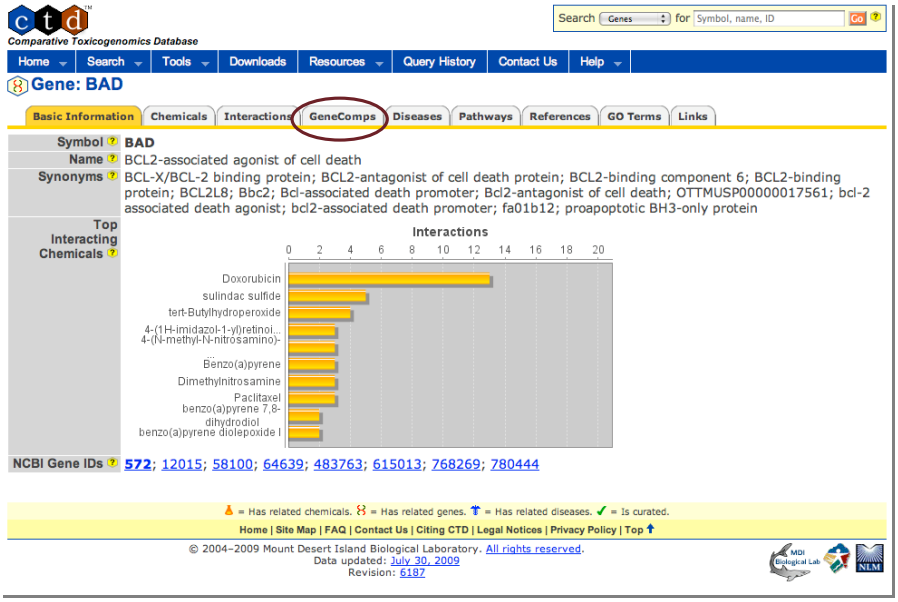
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Gene: BAD
Basic Information Chemicals Interactions GeneComps Diseases Pathways References GO Terms Links
Symbol BAD
Name BCL2-associated agonist of cell death
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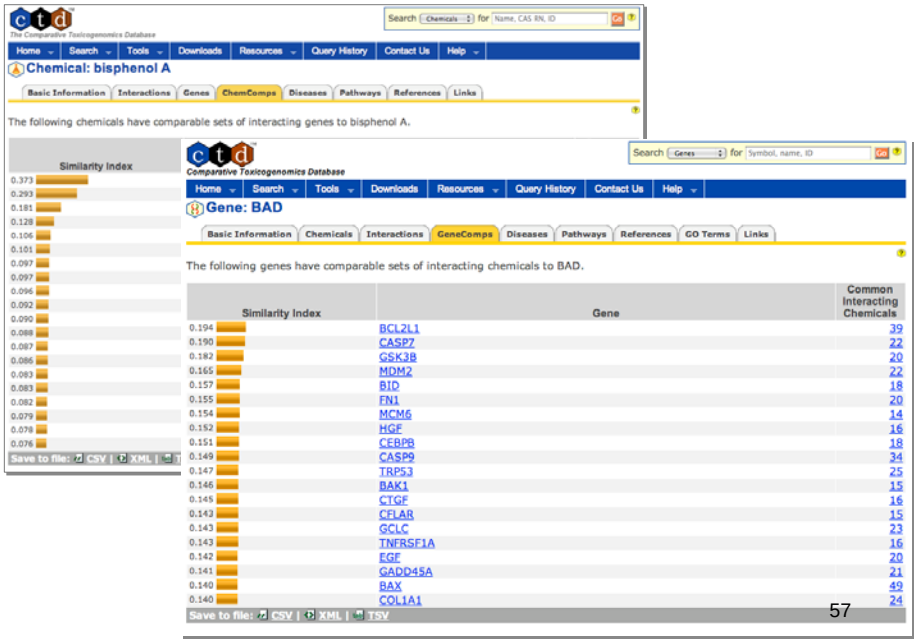
Chem/Gene Comps



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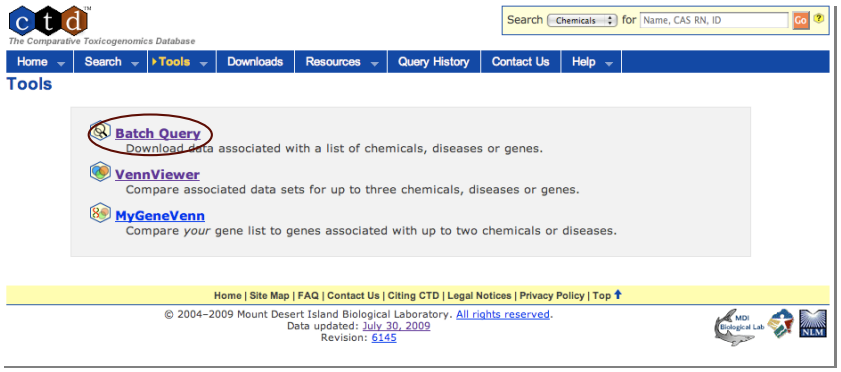
Tools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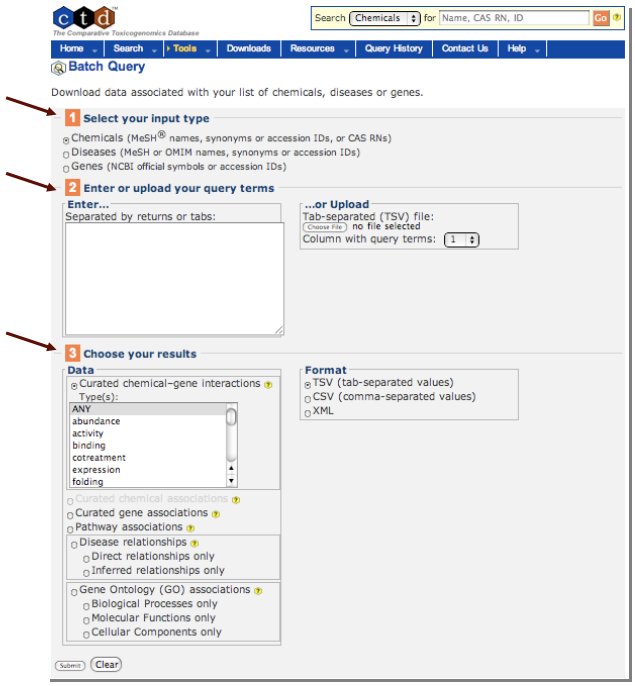
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Diseases (MeSH or OMIM names, synonyms or accession IDs)
Genes (NCBI official symbols or accession IDs)
2 Enter or upload your query terms
Enter...
Separated by returns or tabs:
...or Upload
Tab-separated (TSV) file:
Choose File no file selected
Column with query terms: 1
3 Choose your results
Data
Curated chemical–gene interactions
Type(s):
ANY
abundance
activity
binding
cotreatment
expression
folding
Curated chemical associations
Curated gene associations
Pathway associations
Disease relationships
Direct relationships only
Inferred relationships only
Gene Ontology (GO) associations
Biological Processes only
Molecular Functions only
Cellular Components only
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CSV (comma-separated values)
XML
Submit
Clear

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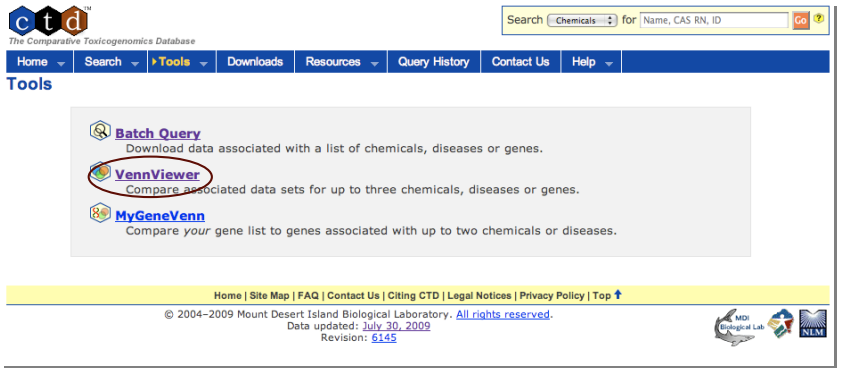
Tools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Tools: VennViewer

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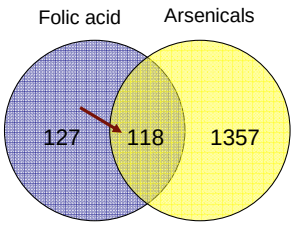
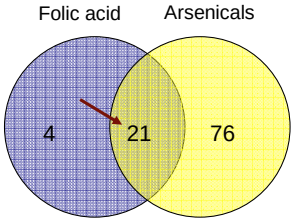
Tools: VennViewer

Interacting Genes/Proteins



Pathways



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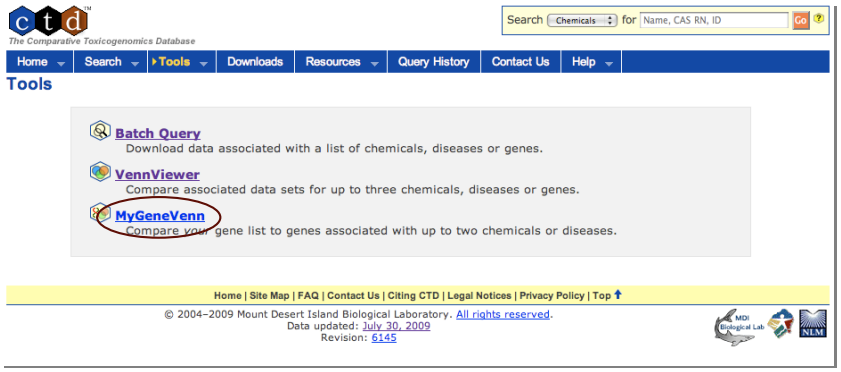
Tools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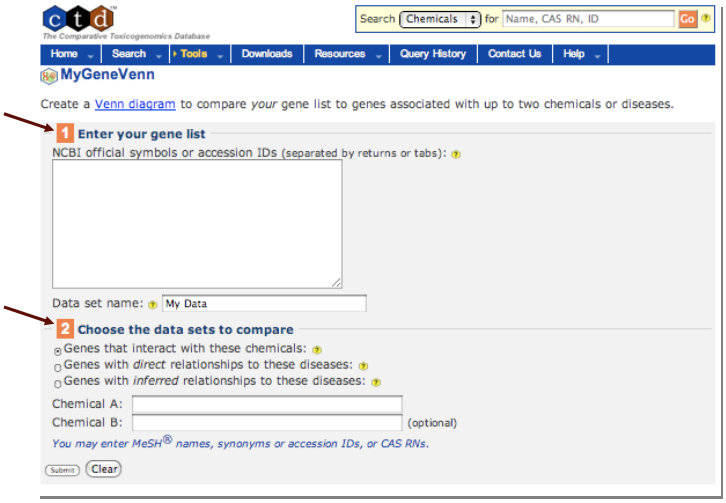
Tools: MyGeneVenn



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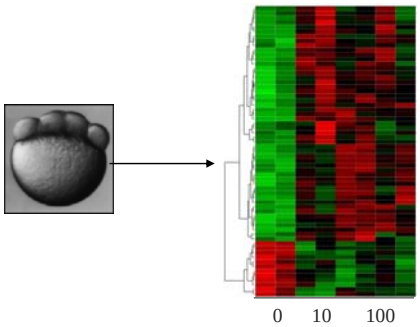

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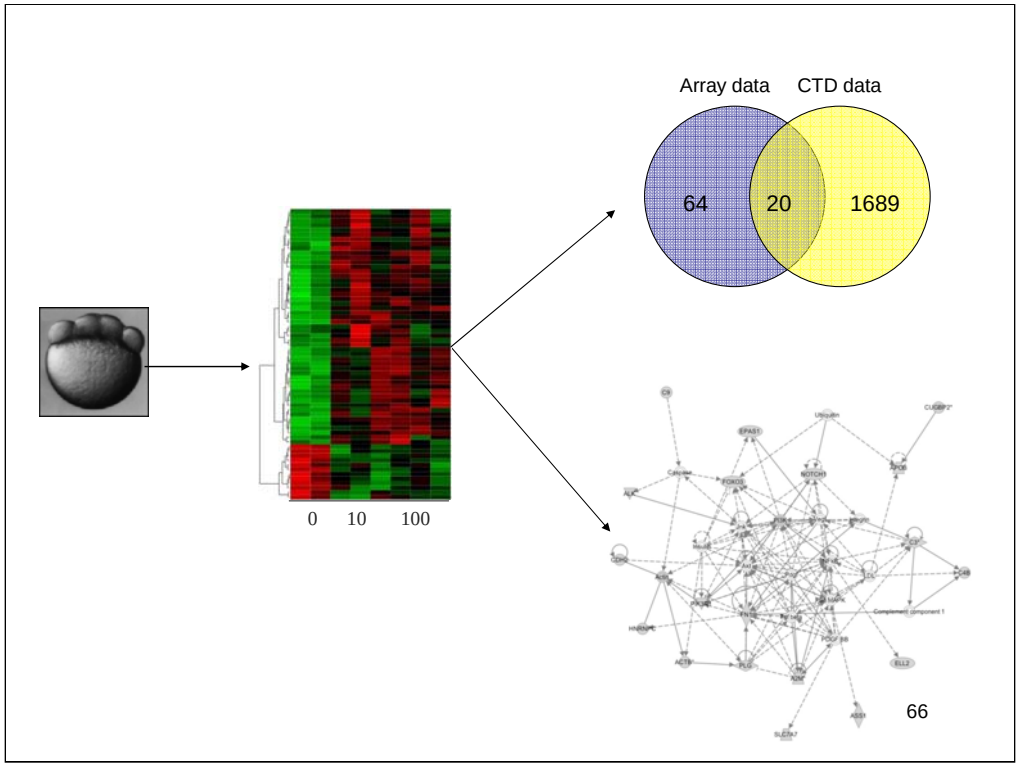
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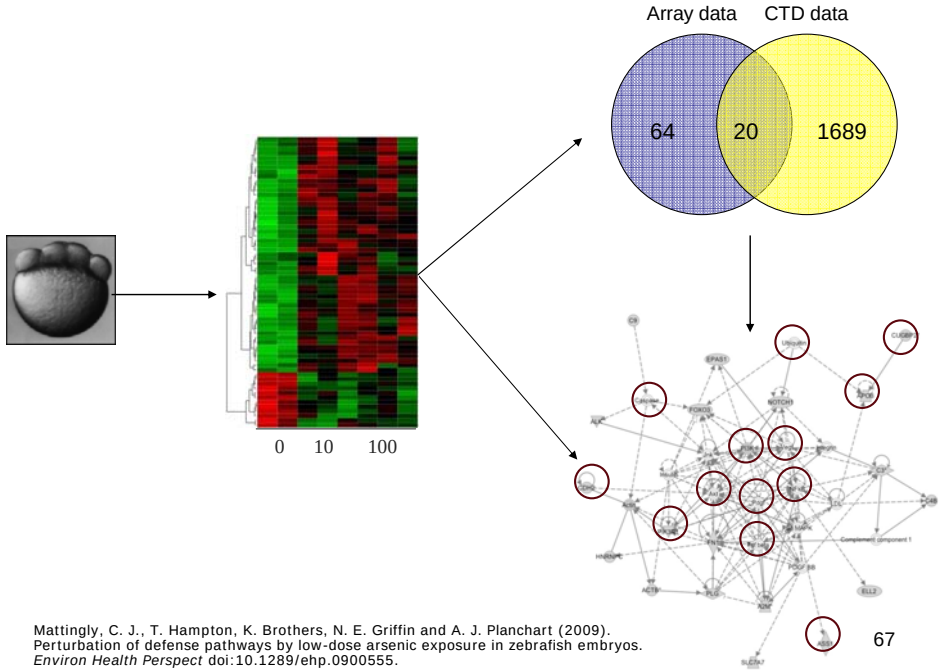

Mattingly, C. J., T. Hampton, K. Brothers, N. E. Griffin and A. J. Planchart (2009). Perturbation of defense pathways by low-dose arsenic exposure in zebrafish embryos. *Environ Health Perspect* doi:10.1289/ehp.0900555.

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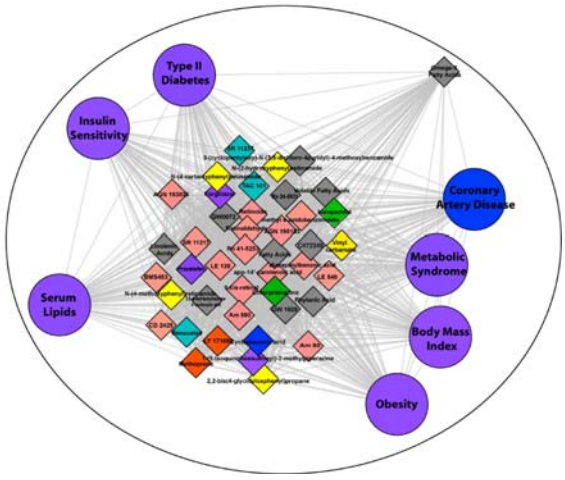
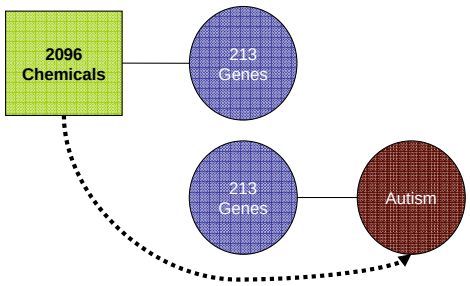


Gohlke, J., R. Thomas, Y. Zhang, M. D. Rosenstein, A. P. Davis, C. Murphy, C. J. Mattingly, K. G. Becker and C. J. Portier (2009). The Genetic And Environmental Pathways to Complex Diseases. *BMC Syst Biol*.May 5 3:46.

Environmental etiology of autistic disorders



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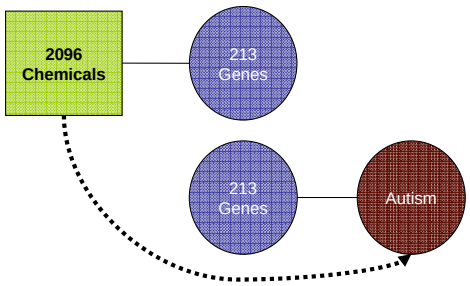
Environmental etiology of autistic disorders

- What do these chemicals have in common?
  - Structure
  - Regulatory features (e.g., High production, Carcinogen)
  - Function (e.g., Associated pathways)
  - Other associated diseases (e.g., Neurological)



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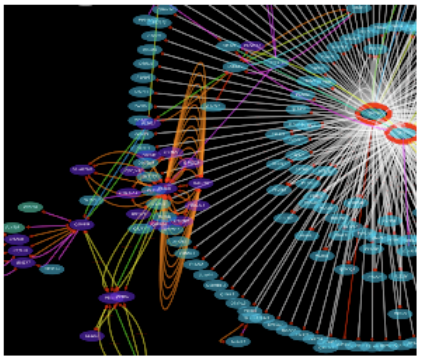
Next

- Analysis tools and visualization capabilities
- Integration of additional data sets
- Text mining



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Recent CTD references

- Gohlke, J., R. Thomas, Y. Zhang, M. D. Rosenstein, A. P. Davis, C. Murphy, C. J. Mattingly, K. G. Becker and C. J. Portier (2009). The Genetic And Environmental Pathways to Complex Diseases. *BMC Syst Biol*.May 5 3:46.
- Mattingly, C. J., T. Hampton, K. Brothers, N. E. Griffin and A. J. Planchart (2009). Perturbation of defense pathways by low-dose arsenic exposure in zebrafish embryos. *Environ Health Perspect* doi:10.1289/ehp.0900555.
- Davis, A. P., C. G. Murphy, C. A. Saraceni-Richards, M. C. Rosenstein, T. C. Wiegers and C. J. Mattingly (2009). Comparative Toxicogenomics Database: a knowledgebase and discovery tool for chemical-gene-disease networks. *Nucleic Acids Res* 37(Database issue): D786-92.
- Mattingly, C. J. (2009). Chemical databases for environmental health and clinical research. *Toxicol Lett*. 186(1):62-5.
- Davis, A. P., C. G. Murphy, M. C. Rosenstein, T. C. Wiegers and C. J. Mattingly (2008). The Comparative Toxicogenomics Database facilitates identification and understanding of chemical-gene-disease associations: arsenic as a case study. *BMC Med Genomics* 1: 48.

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Acknowledgements

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