T3DB - The Toxin, Toxin-Target Database

David Wishart david.wishart@ualberta.ca
University of Alberta, Edmonton, AB, Canada
April 25, 2013

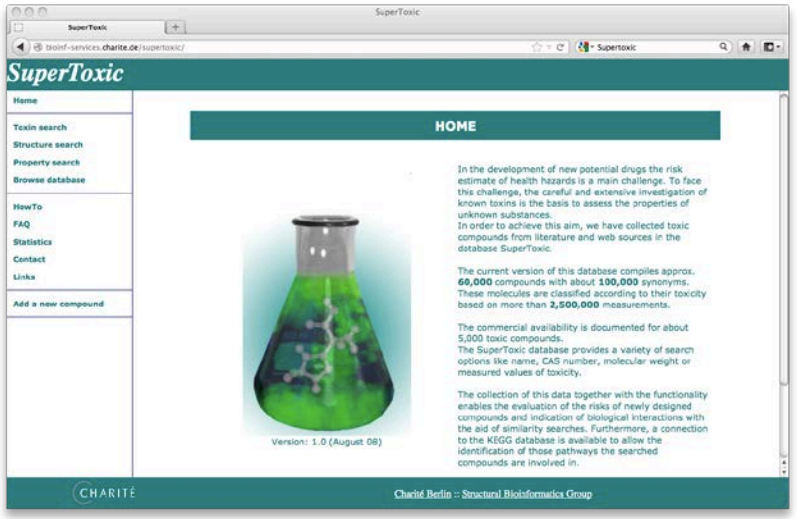
Communities of Practice – US EPA
National Center for Computational Toxicology

Outline

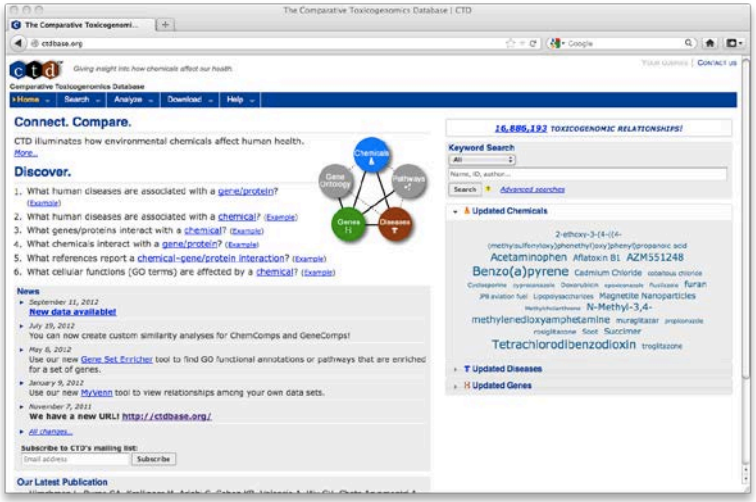
- Brief review of toxicology databases
- Metabolomics and toxicology
- Introducing the toxin, toxin-target database – T3DB
- Systems biology, pathway databases and the small molecule database - SMPDB
- Conclusions & Future Directions

Toxicology Databases

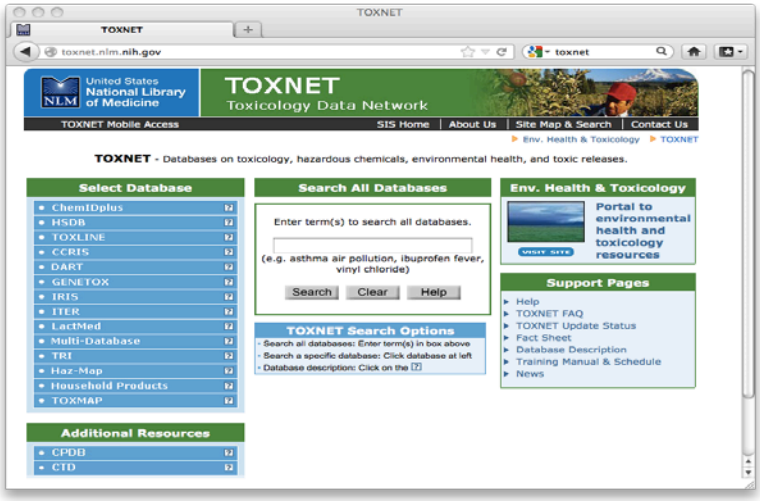
www.epa.gov/actor/



http://bioinf-services.charite.de/supertoxic/

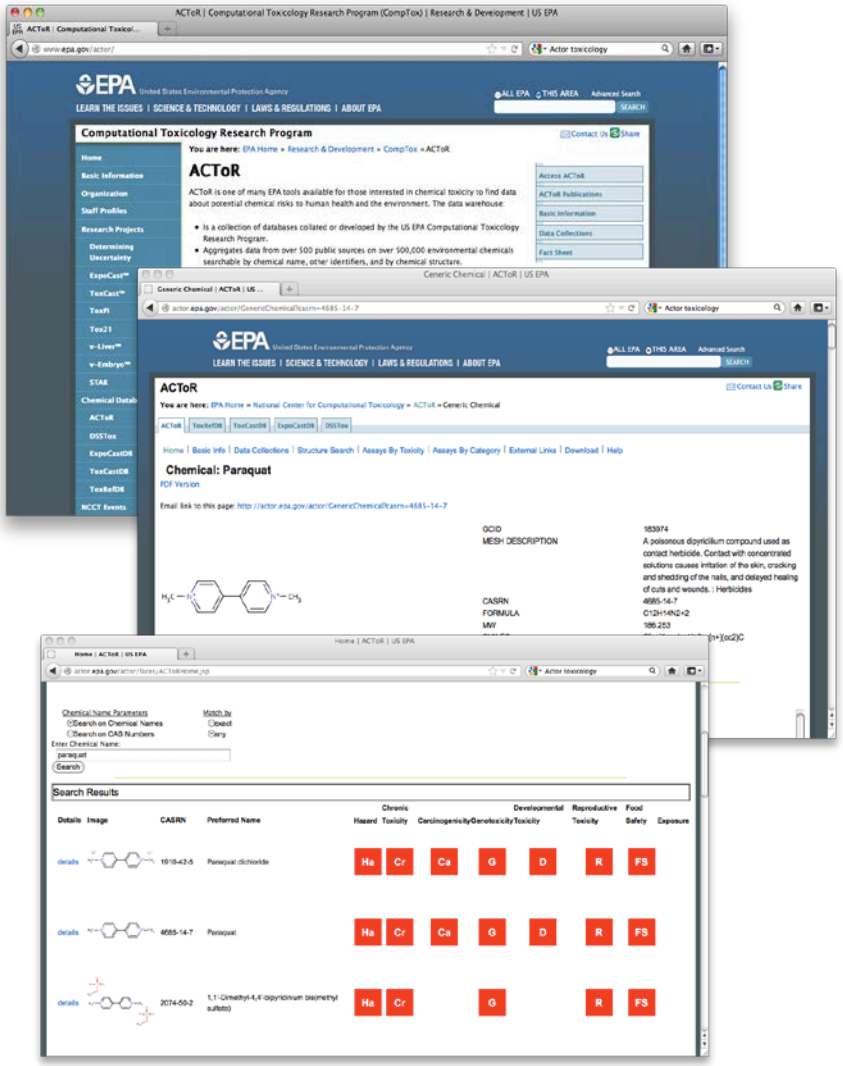


www.ctdbase.org



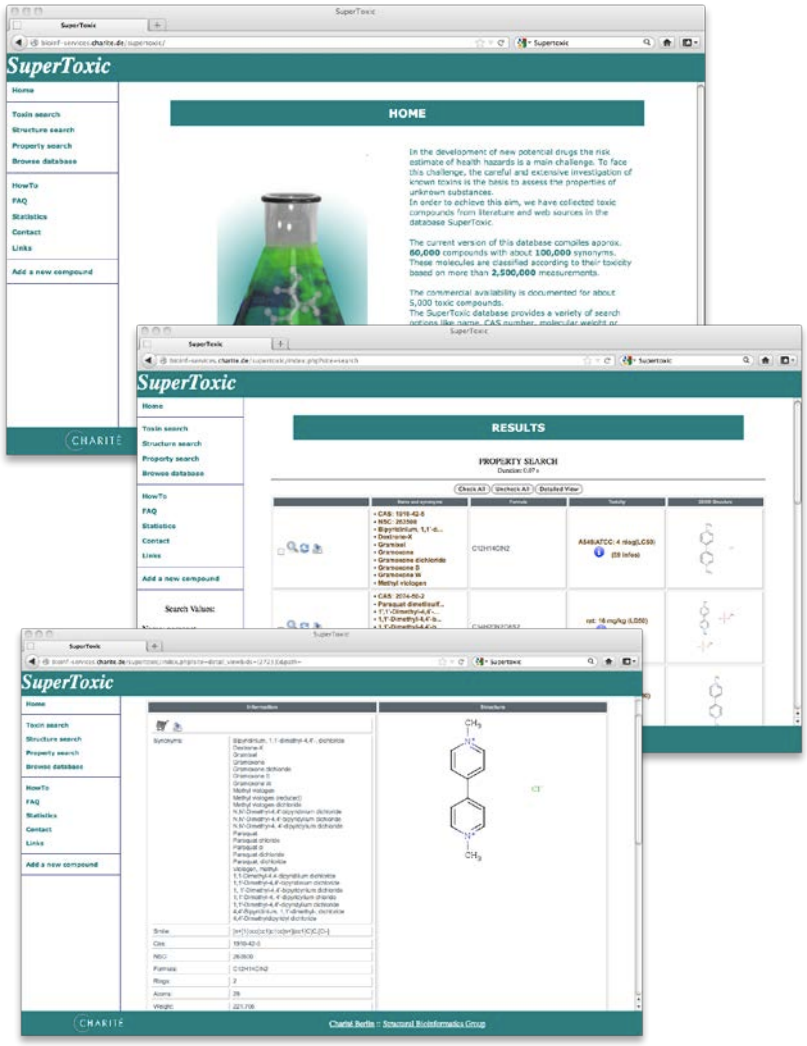
http://toxnet.nlm.nih.gov/

ACToR Database



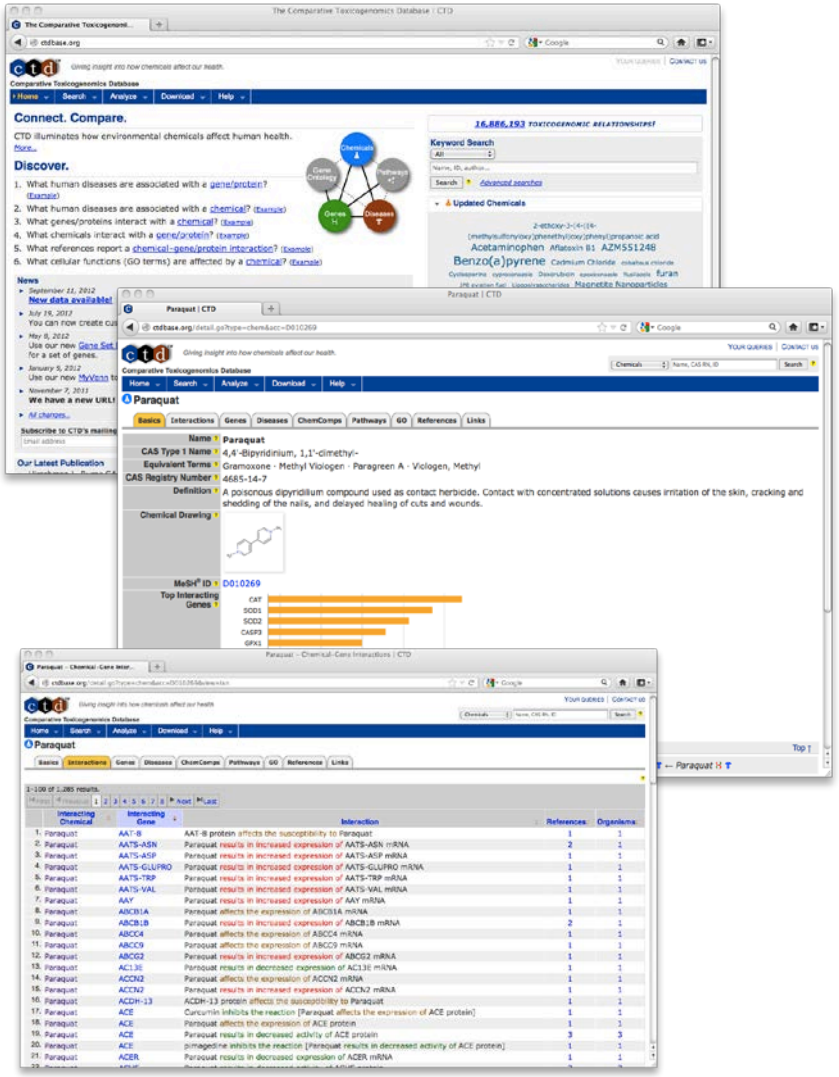
- Maintained by the EPA Computational Toxicology Program
- Aggregate of 500 public resources
- >500,000 compounds
- Data includes chemical structure, physico-chemical values, in vitro assay data and in vivo toxicology data
- Limited target, action or mechanistic data

SuperToxic Database



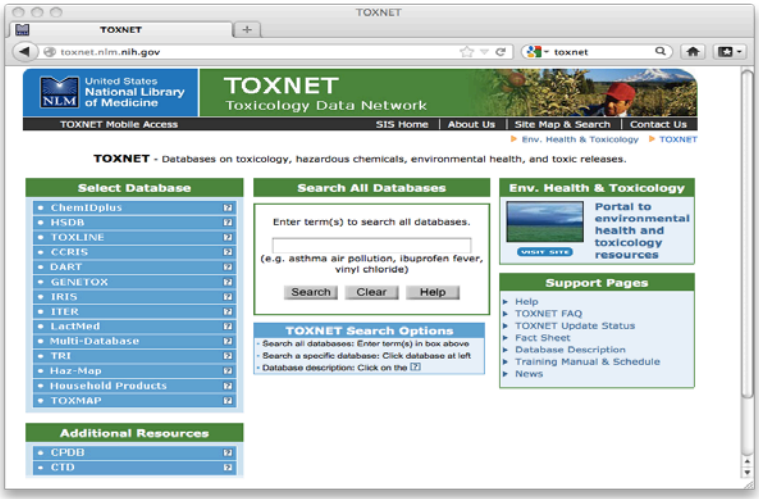
- Maintained by Charite Berlin (Structural Bioinformatics)
- >60,000 compounds, 2,500,000 toxicity measurements
- Data includes chemical structure, physico-chemical values and LC50 data
- No target, no action or mechanistic (MOA) data
- Not updated since 2008

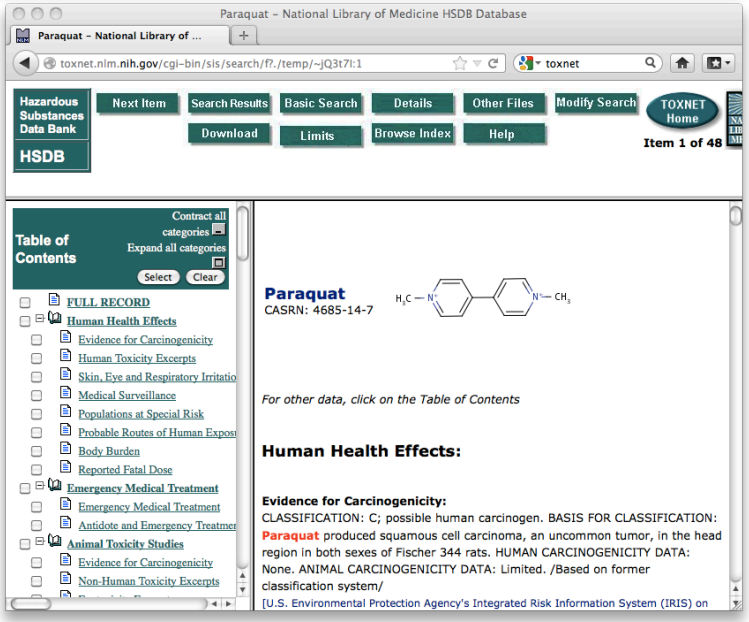
Comparative Toxicogenomics Database



- Maintained by Mount Desert Island Biological Lab
- 11,755 compounds, 599,000 chemical-gene associations, 176,000 chemical-disease associations, 23,000 gene-disease assoc.
- Data mostly *from automated text mining*
- No target or MOA data, no context

ToxNet Database



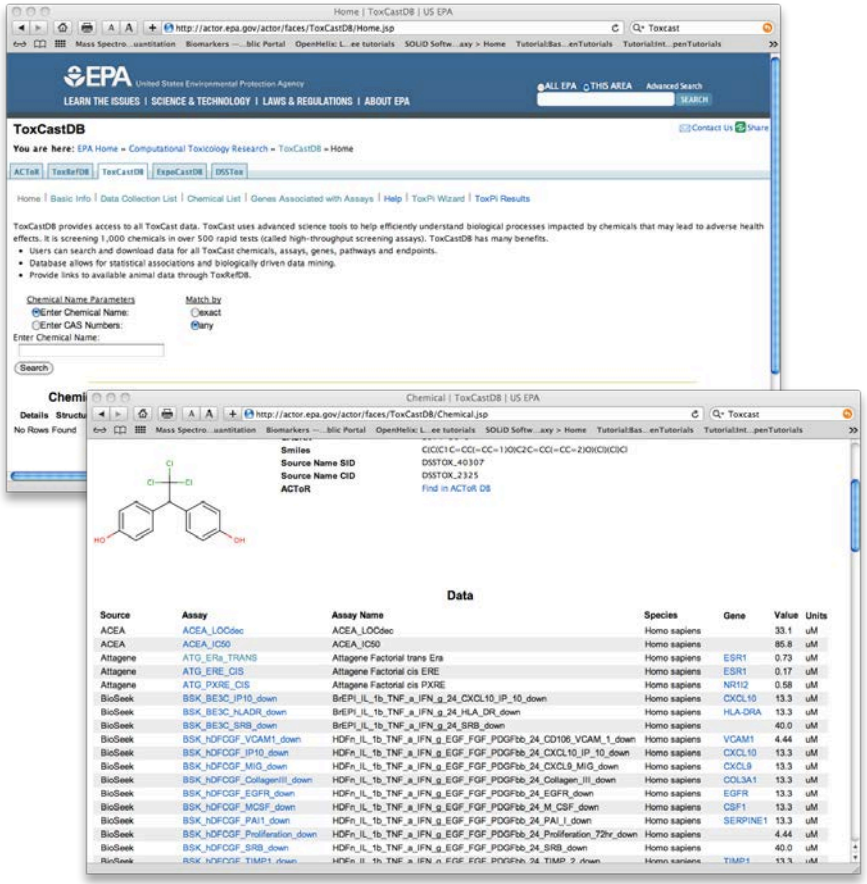


- Maintained by NIH and NLM
- Amalgamation of 15+ different databases on toxicology, hazardous chemicals, environmental health, and toxic releases
- Structure, toxicity, case reports, signs and symptoms
- No target, action or mechanistic data

Toxicology Databases

- General preference for breadth (lots of compounds) over depth (lots of information)
- Most focus on toxicity, not toxicology or molecular mechanisms
- Information content is fragmented, appears in multiple formats, difficult to read, limited search utilities, not linked to other resources and sometimes lightly referenced
- Emerging resources (ToxcastDB, ToxBank Wiki, T3DB) are starting to change this

ToxCastDB



- 310 pesticide compounds in Phase I
- 767 drugs, food adds, pesticide compounds in Phase II
- 500+ HTS assays with gene targeting information

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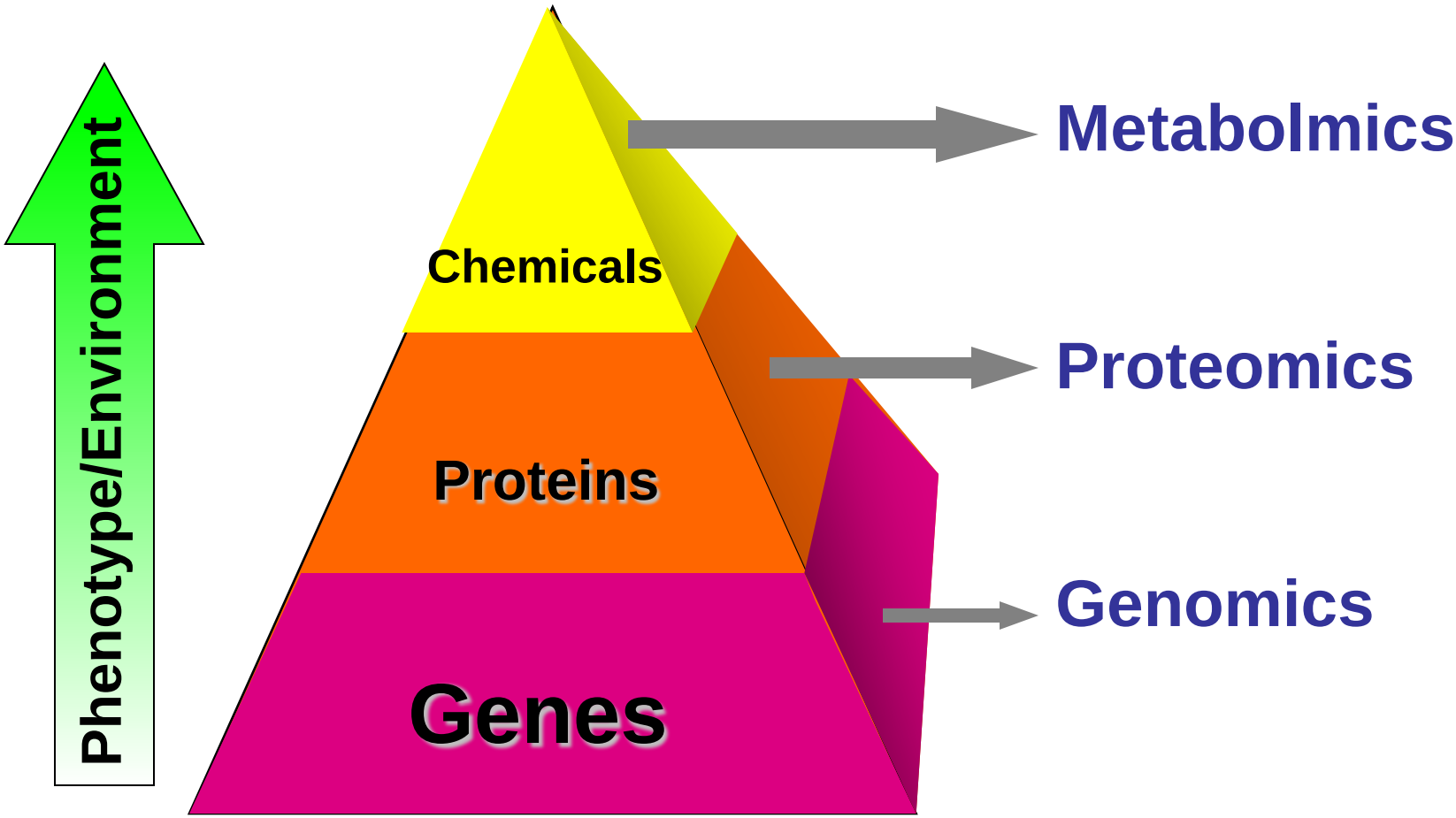
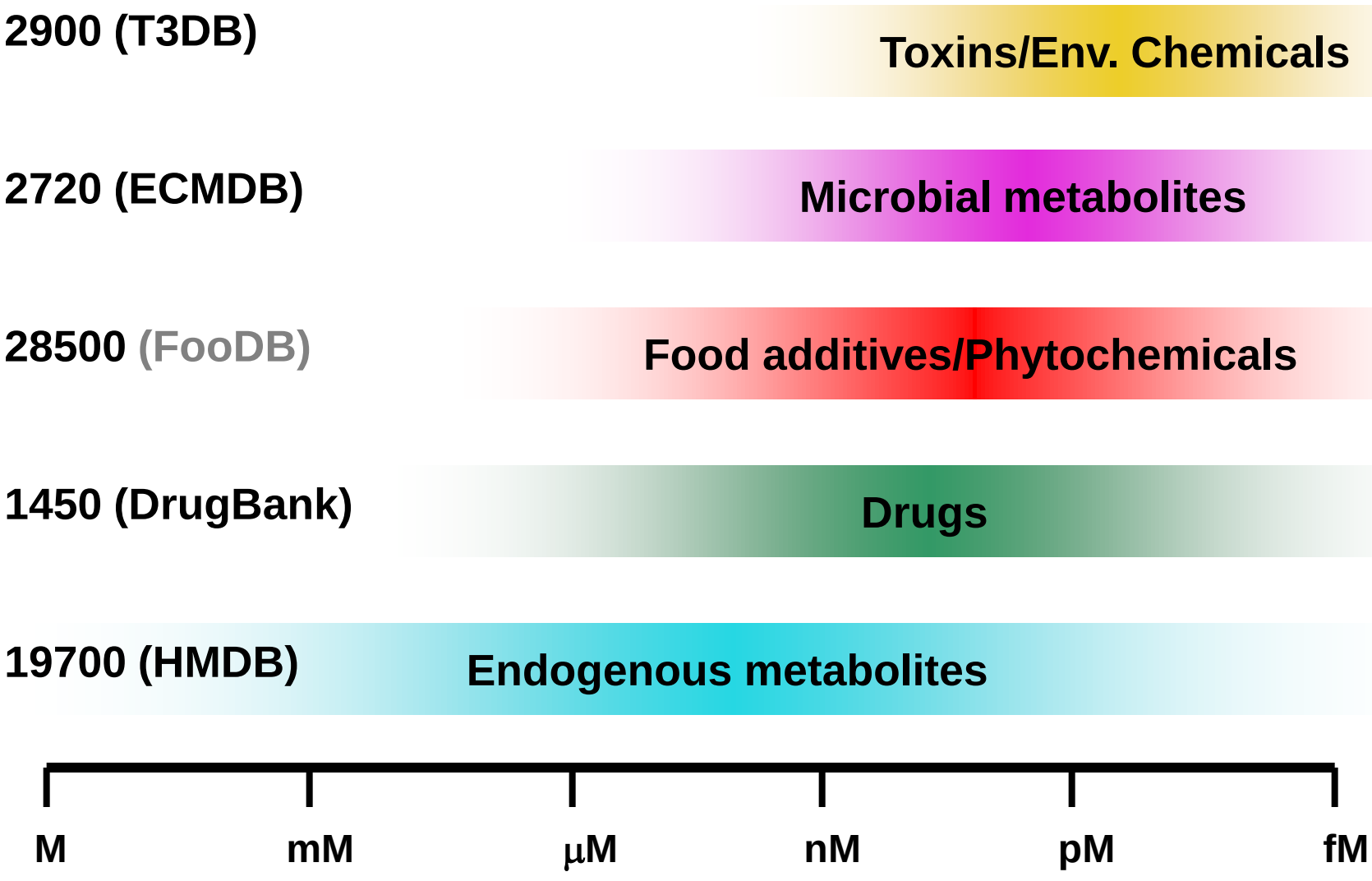
The Pyramid of Life



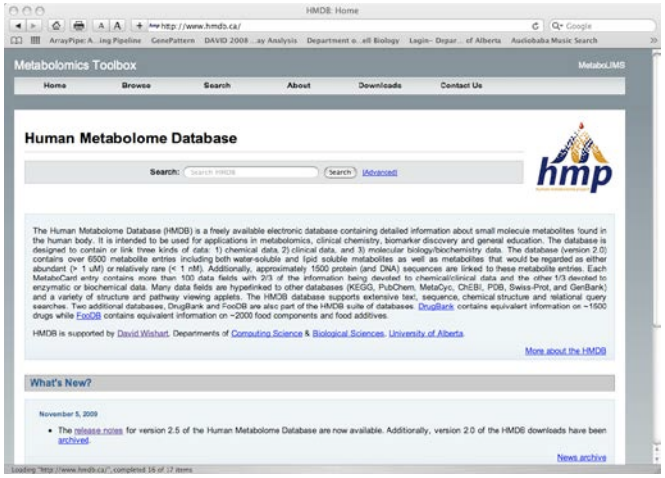
The Human Metabolome Project

- **$7.5 million Genome Canada Project launched in Jan. 2005 - Based at the University of Alberta**
- **Key objective was to create a comprehensive database of *all* human metabolites that included compound data, source data, concentration data and a wide range (NMR, GC-MS, MS/MS) of spectral data**
- **Special focus on metabolites in biofluids such as urine, CSF and blood as well as tissues using HT experiments and text analysis (~40,000 cmpds to date)**
- **Associate metabolite concentrations to ~600 diseases or conditions**
- **Make all data freely and electronically accessible**

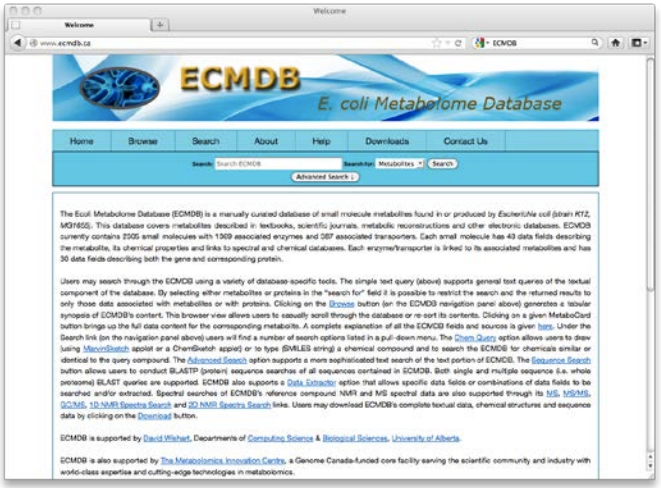
Human Metabolomes



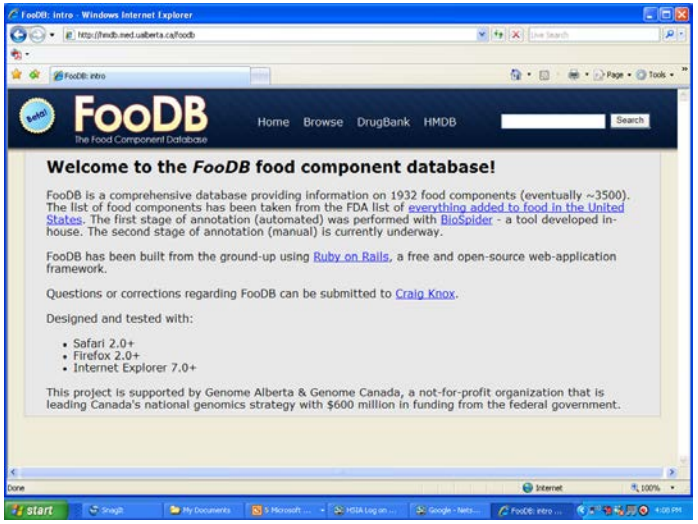
Meet the Metabolomes…



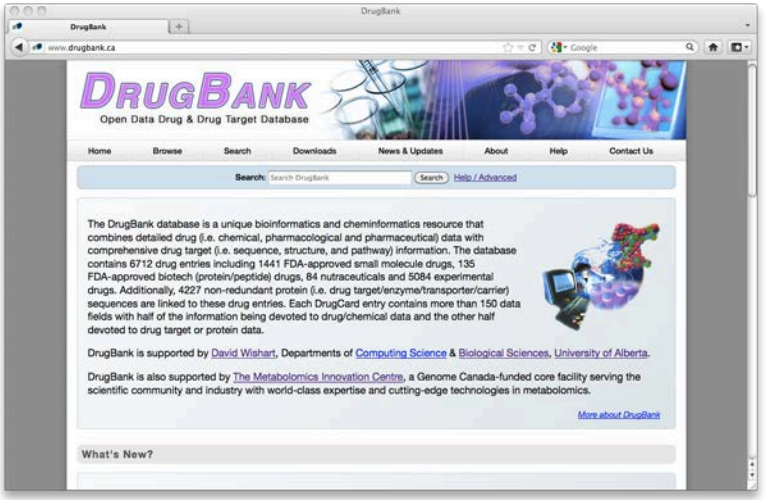
http://www.hmdb.ca



http://www.ecmdb.ca

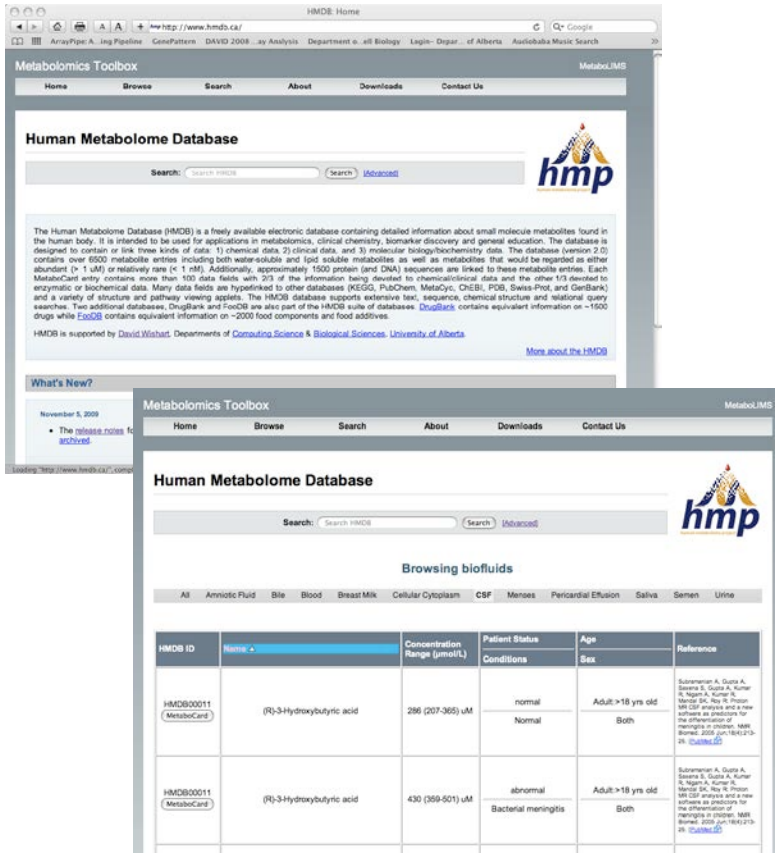


http://www.foodb.ca



http://www.drugbank.ca

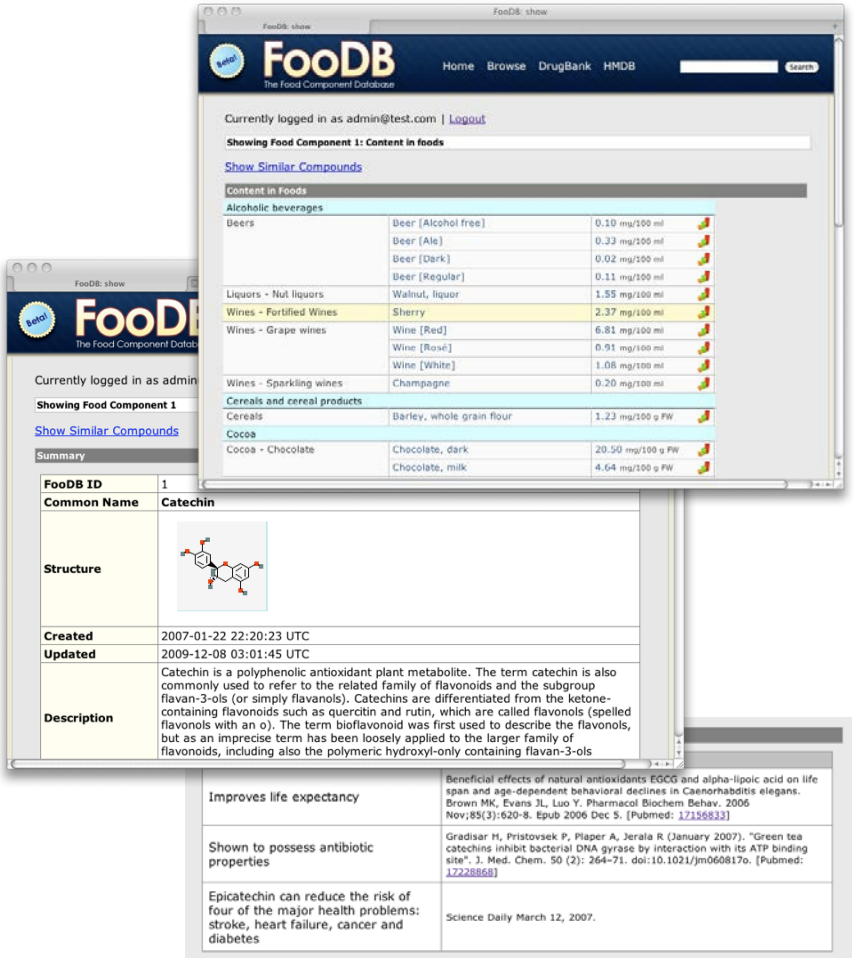
The Human Metabolome Database (HMDB)



http://www.hmdb.ca

- A web-accessible resource containing detailed information on 40214 “quantified”, “detected” and “expected” metabolites
- Normal/abnormal concentrations
- 600+ disease links
- 1000’s of reference spectra
- 1000’s of reactions & pathways
- Supports sequence, spectral, structure and text searches as well as compound browsing
- Full data downloads

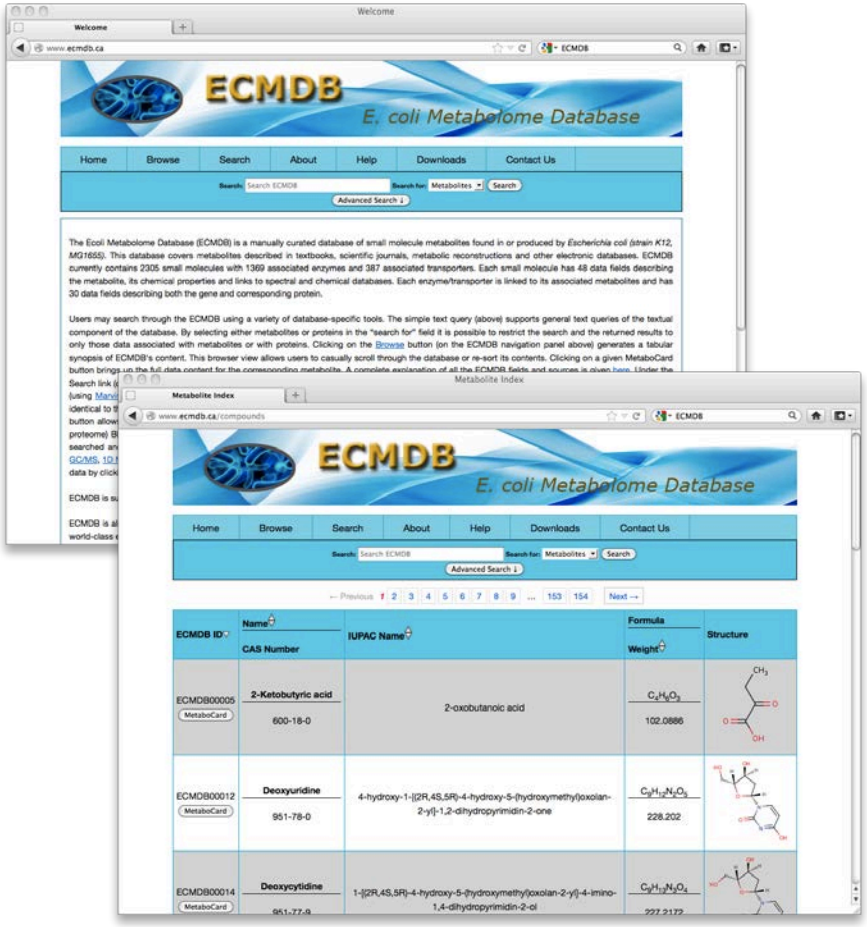
The Food Constituent Database (FooDB)



http://www.foodb.ca

- 28,543 compounds, 24,579 structures with 21,843 descriptions
- 131,867 synonyms
- 3000 flavour-compound associations
- Content data on 635 “pure” foods
- >60,000 hyperlinks to 11 different external DBs
- Supports sequence, structure & text searches
- >100 data fields/cmpd
- Not quite “Live”

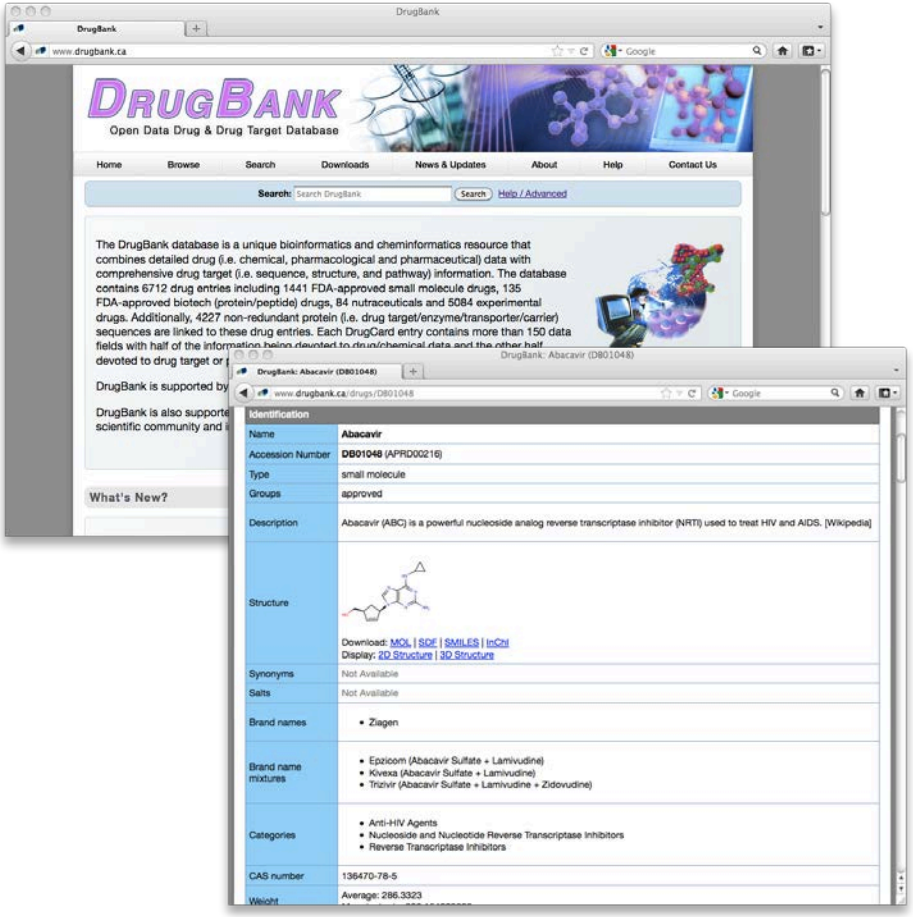
The E. coli Metabolome Database (ECMDB)



- 2717 E. coli metabolites
- 1573 genes (1205 enzymes, 299 transporters)
- 3145 chemical reactions
- 4300 references
- 125 pathways
- Supports sequence, structure & text searches as well as compound browsing
- 80 data fields per compound
- 4965 NMR and MS spectra
- Corrects many errors and erroneous entries in EcoCyc

http://www.ecmdb.ca

The Drug Database (DrugBank)



http://www.drugbank.ca

- 1447 small molecule drugs
- 85 nutraceuticals
- >500 drug metabolites
- >5200 experimental drugs
- 148 data fields/drug
- >1000 food/drug interacts
- 1637 drug targets
- >200 drug pathways
- Supports sequence, spectral, structure and text searches as well as compound browsing
- Full data downloads

A Word About DrugBank..

- First database to link drugs to drug targets
- Intended to facilitate systems and predictive pharmacology and to accelerate drug R&D pipeline
- Receives ~7 million web hits/year, linked to all major bioinformatic databases and used by all major pharmaceutical companies
- Has been used to discover, design and repurpose a number of drugs
- Our model for T3DB…

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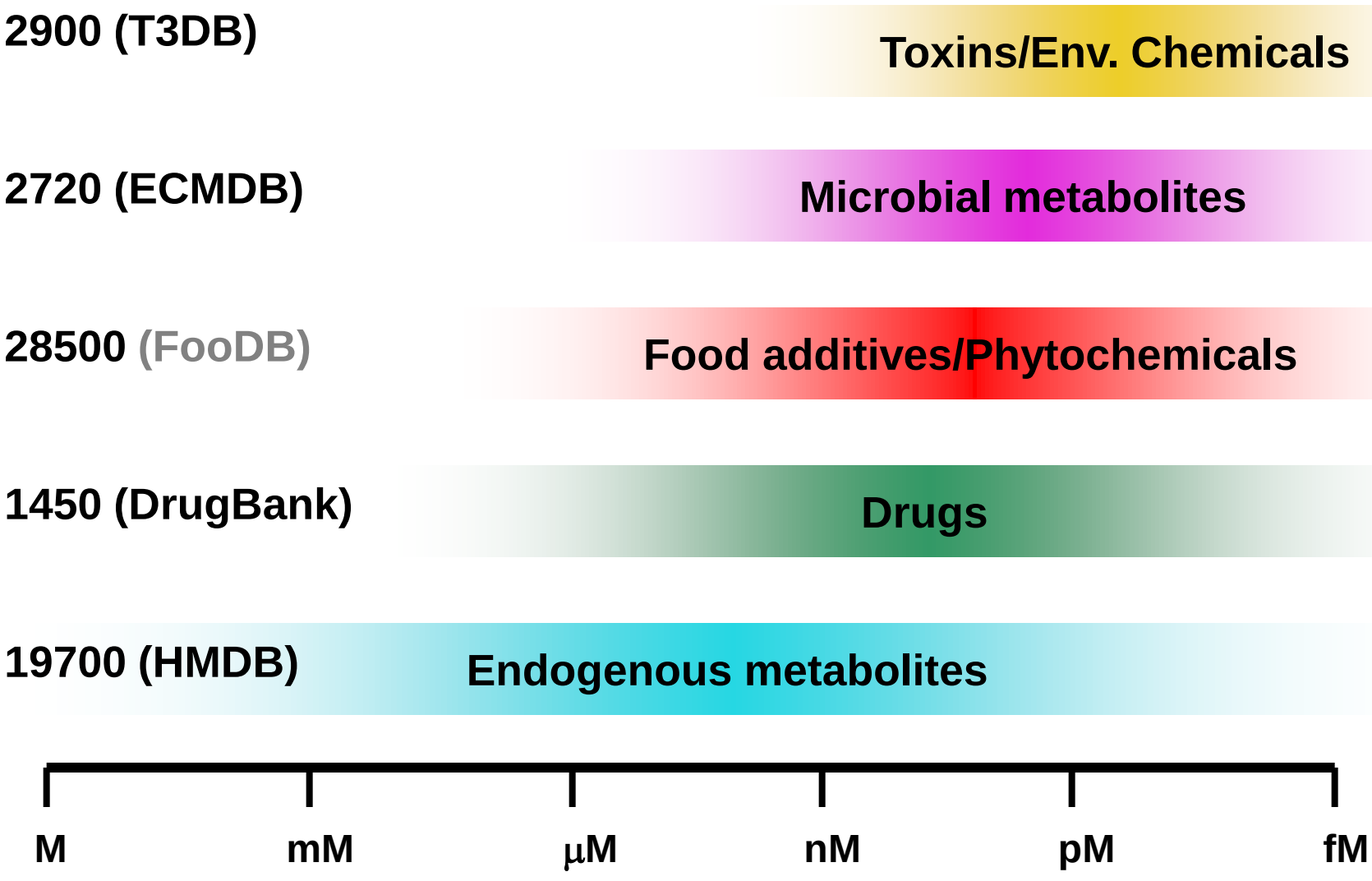
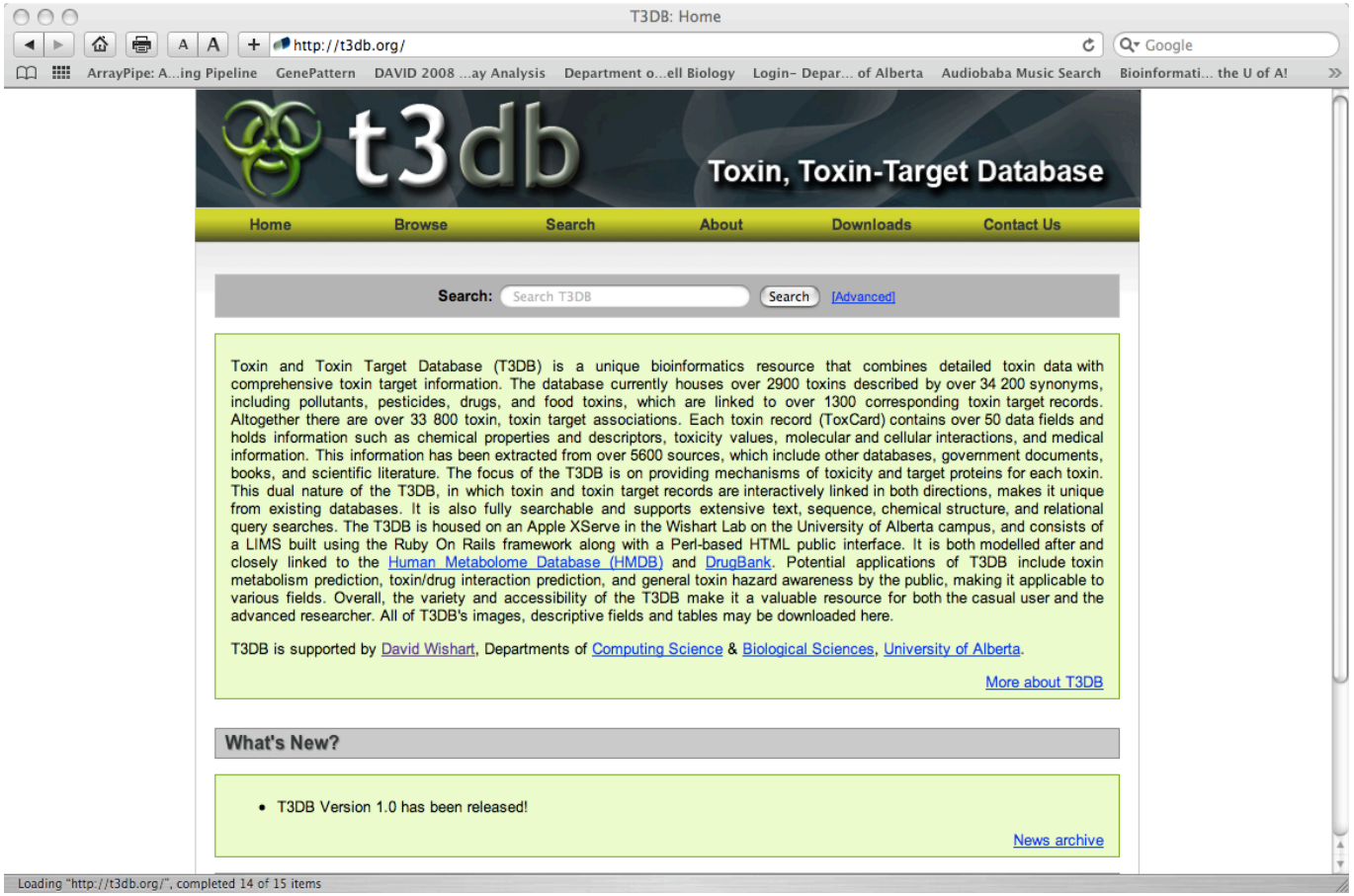


The Toxin, Toxin-Target Database (T3DB)



Lim E, Pon A, Djoumbou Y, Knox C, Shrivastava S, Guo AC, Neveu V, Wishart DS. T3DB: a comprehensively annotated database of common toxins and their targets. Nucleic Acids Res. 2010 Jan 38(Database issue):D781-6. **http://www.t3db.org**

The Toxin, Toxin-Target Database (T3DB)

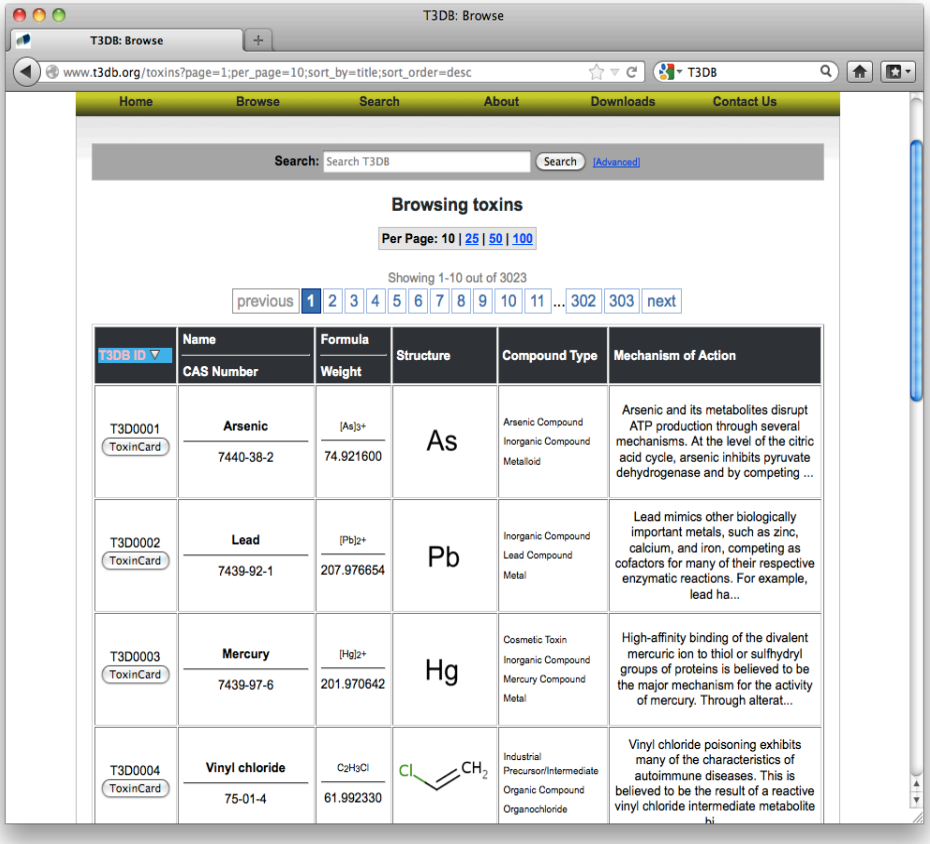
http://www.t3db.org

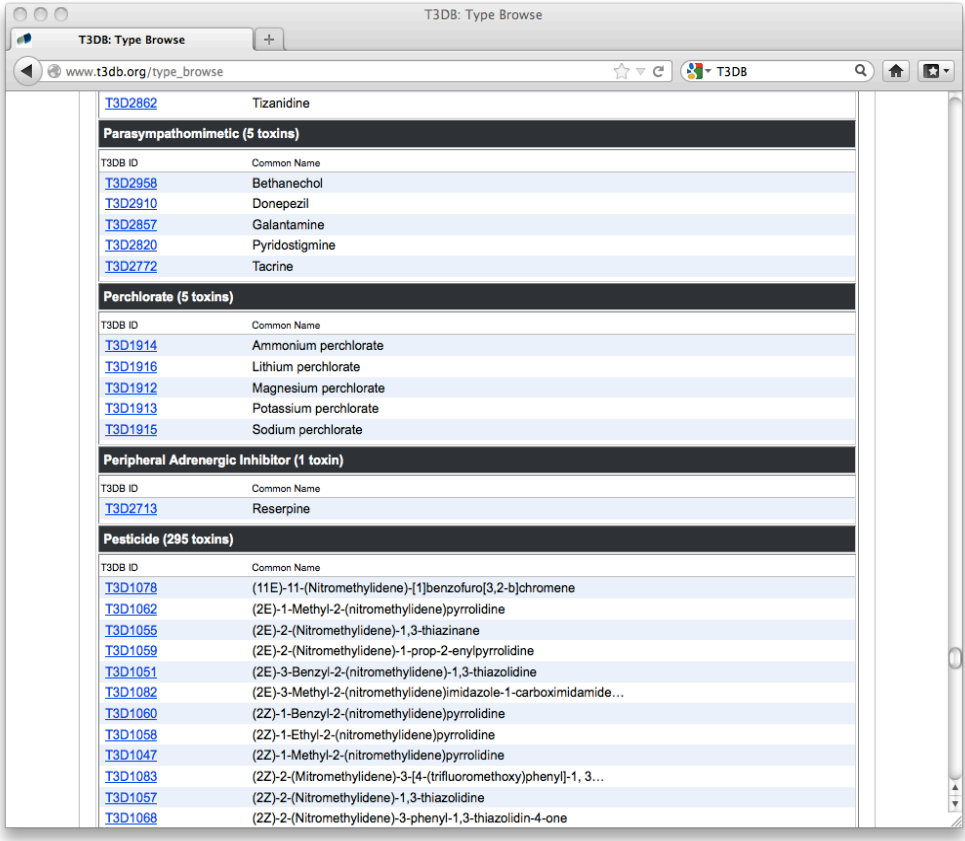
- >2900 common toxins (drugs, pesticides, herbicides, cosmetic compounds, cleaners, solvents, PCBs, furans, etc.)
- 1550 toxin targets – *now including ToxCast targets*
- 406 toxin “classes”
- Describes MOA, toxic effects, treatment, lethal or harmful dose
- 80 data fields per compound including data on protein targets (if known)

A Word About T3DB..

- First database to link common toxins/poisons to specific human targets
- Intended to help with systems toxicology
- Intended to facilitate *in silico* toxicity or mechanism of action testing
- Intended to enable predictive toxicology (via sequence/structure/QSAR mapping)
- Largely unknown in the tox community
- Hoping to find out ways of making it more useful/appealing to the community

Inside T3DB – Browsing Options

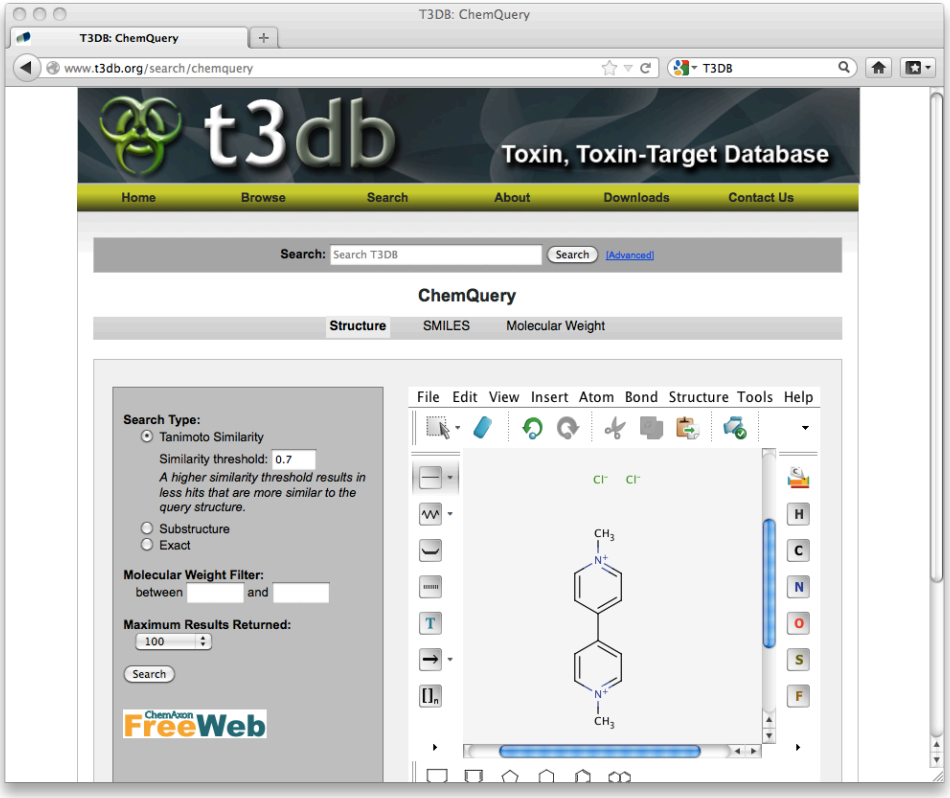




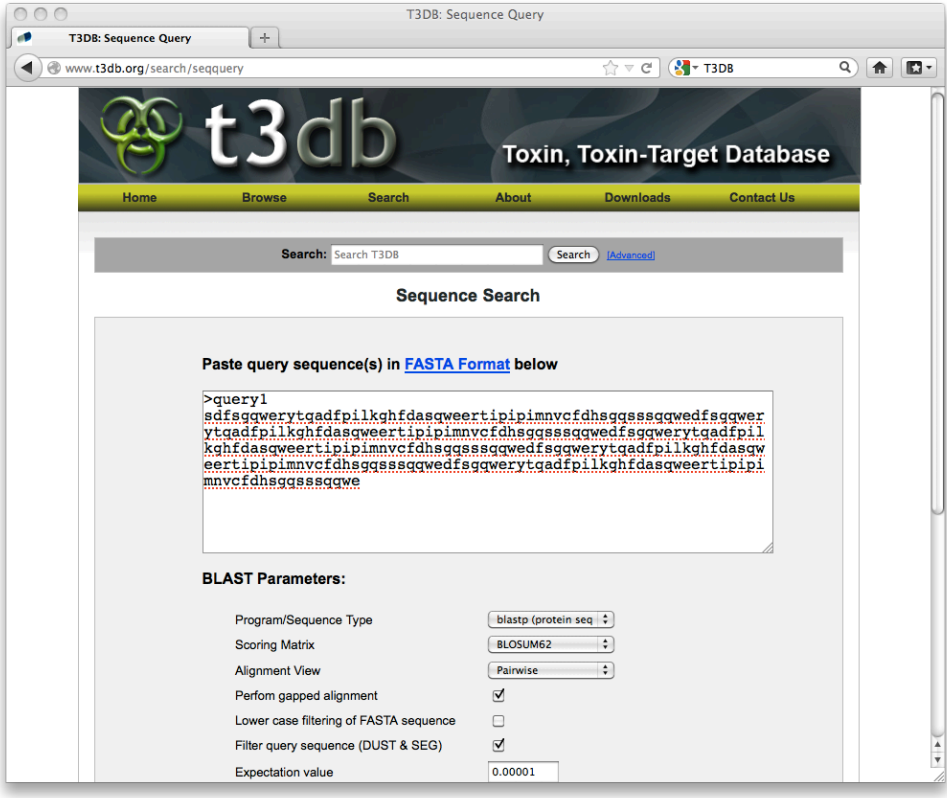
Browse by Compound

Browse by Toxin Type

Inside T3DB – Search Options

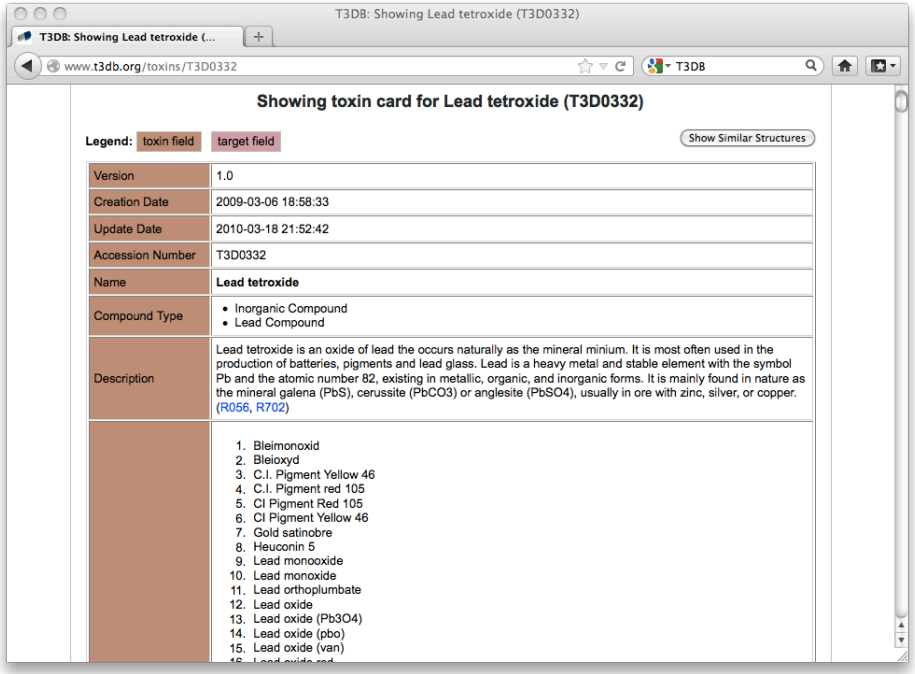


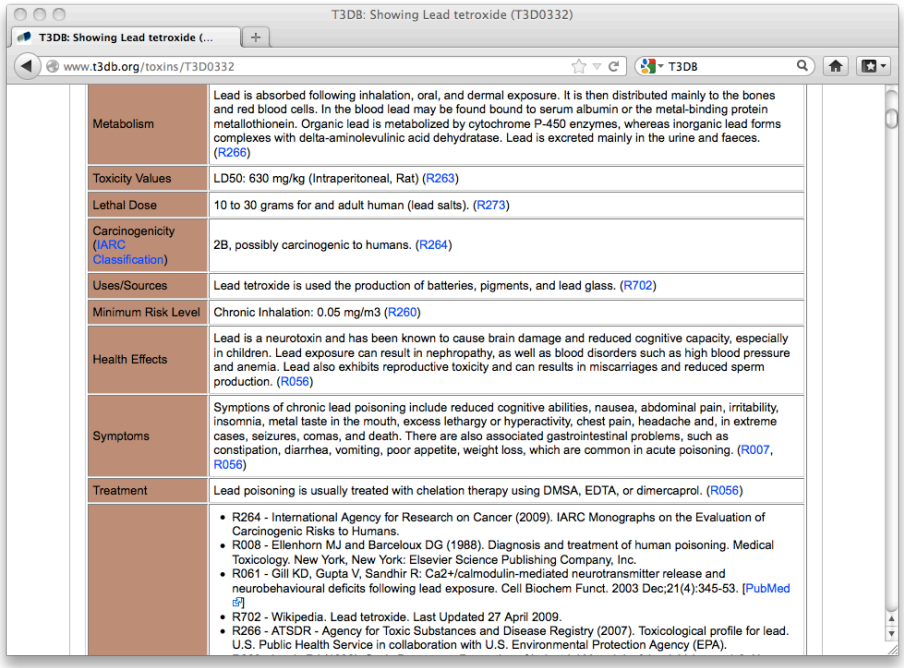
Search by Structure



Search by Sequence

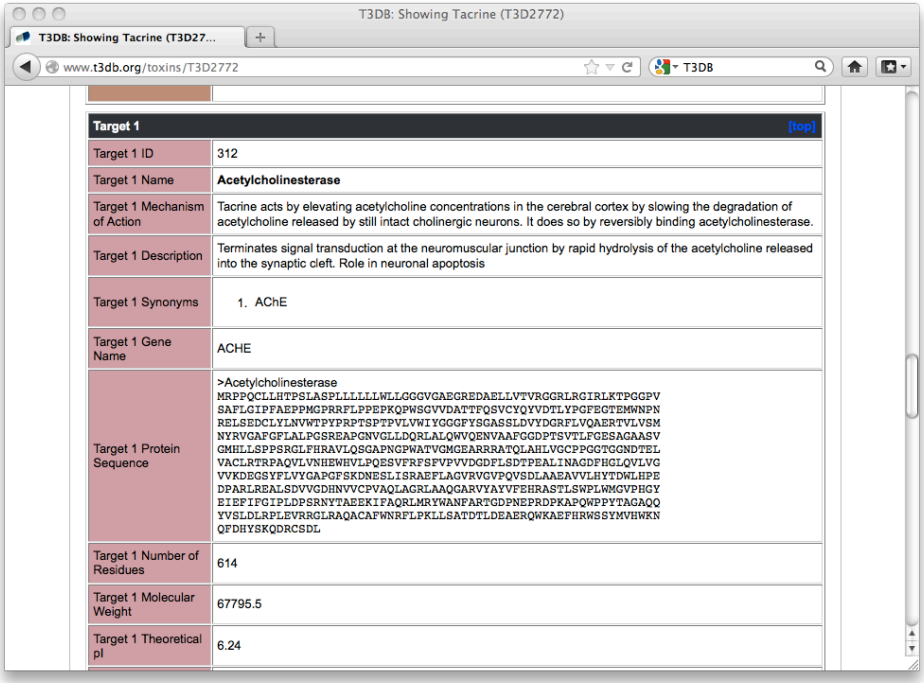
Inside T3DB – Toxin Cards or ToxCards





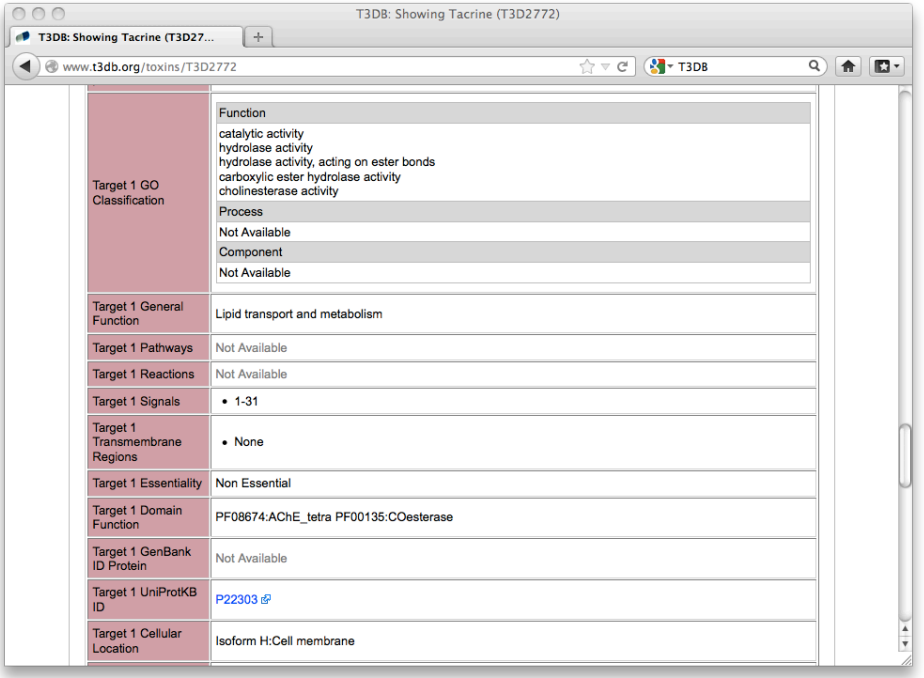
Lead Tetraoxide

Inside T3DB – Protein (Target) Cards



Target 1 [top]

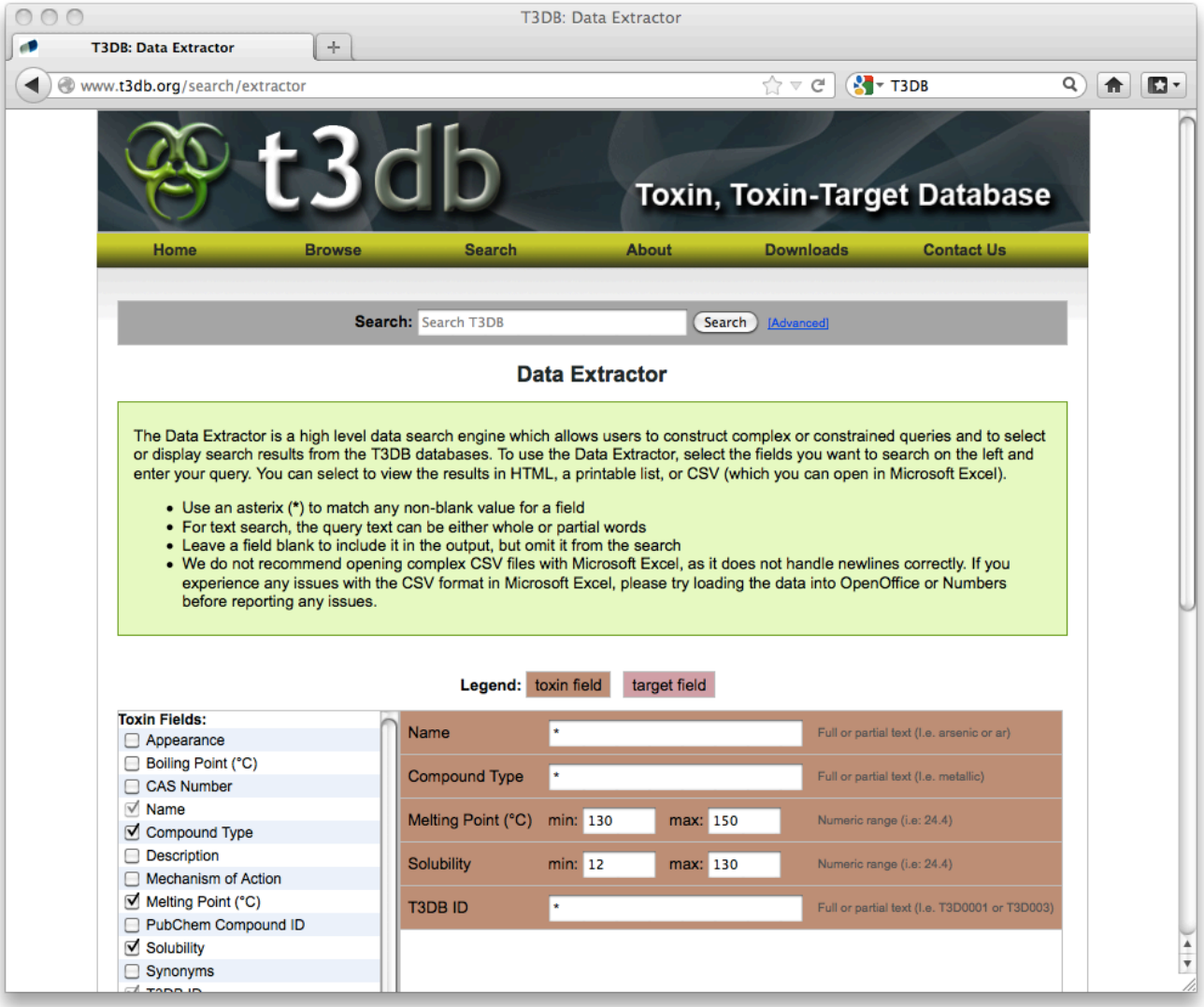
Target 1 ID	312
Target 1 Name	**Acetylcholinesterase**
Target 1 Mechanism of Action	Tacrine acts by elevating acetylcholine concentrations in the cerebral cortex by slowing the degradation of acetylcholine released by still intact cholinergic neurons. It does so by reversibly binding acetylcholinesterase.
Target 1 Description	Terminates signal transduction at the neuromuscular junction by rapid hydrolysis of the acetylcholine released into the synaptic cleft. Role in neuronal apoptosis
Target 1 Synonyms	1. AChE
Target 1 Gene Name	ACHE
Target 1 Protein Sequence	>Acetylcholinesterase MRPPQCLLHTPSLASPLLLLLLWLLGGGVGAEGREDAELLVTVRGGRLRGIRLKTPGGPV SAFLGIPFAEPPMGPRRFLPPEPKQPWSGVVDATTFQSVCYQYVDTLYPGFEGTEMWNPN RELSEDCLYLNVWTPYPRPTSPTPVLVWIYGGGFYSGASSLDVYDGRFLVQAERTVLVSM NYRVGAFGFLALPGSREAPGNVGLLDQRLALQWVQENVAAFGGDPTSVTLFGESAGAASV GMHLLSPPSRGLFHRAVLQSGAPNGPWATVGMGEARRRATQLAHLVGCPPGGTGGNDTEL VACLRTRPAQVLVNHEWHVLPQESVFRFSFVPVVDGDFLSDTPEALINAGDFHGLQVLVG VVKDEGSYFLVYGAPGFSKDNESLISRAEFLAGVRVGVPQVSDLAAEAVVLHYTDWLHPE DPARLREALSDVVGDHNVVCPVAQLAGRLAAQGARVYAYVFEHRASTLSWPLWMGVPHGY EIEFIFGIPLDPSRNYTAEEKIFAQRLMRYWANFARTGDPNEPRDPKAPQWPPYTAGAQQ YVSLDLRPLEVRRGLRAQACAFWNRFLPKLLSATDTLDEAERQWKAEFHRWSSYMVHWKN QFDHYSKQDRCSDL
Target 1 Number of Residues	614
Target 1 Molecular Weight	67795.5
Target 1 Theoretical pI	6.24



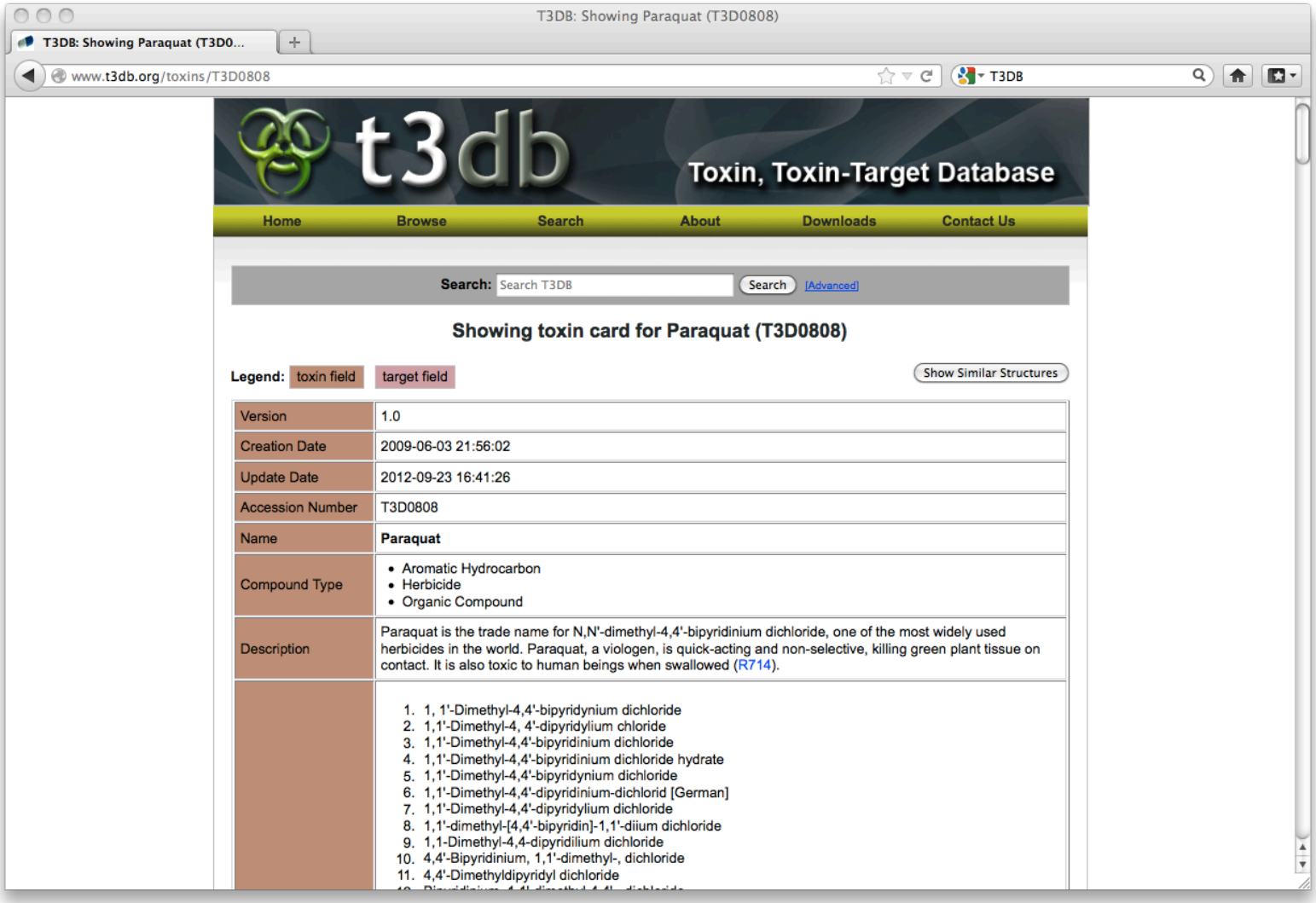
Target 1 GO Classification	**Function** catalytic activity hydrolase activity hydrolase activity, acting on ester bonds carboxylic ester hydrolase activity cholinesterase activity **Process** Not Available **Component** Not Available
Target 1 General Function	Lipid transport and metabolism
Target 1 Pathways	Not Available
Target 1 Reactions	Not Available
Target 1 Signals	• 1-31
Target 1 Transmembrane Regions	• None
Target 1 Essentiality	Non Essential
Target 1 Domain Function	PF08674:AChE_tetra PF00135:COesterase
Target 1 GenBank ID Protein	Not Available
Target 1 UniProtKB ID	P22303
Target 1 Cellular Location	Isoform H:Cell membrane

Acetylcholinesterase

Inside T3DB – Complex Queries & Data Extraction



ToxCard - Paraquat



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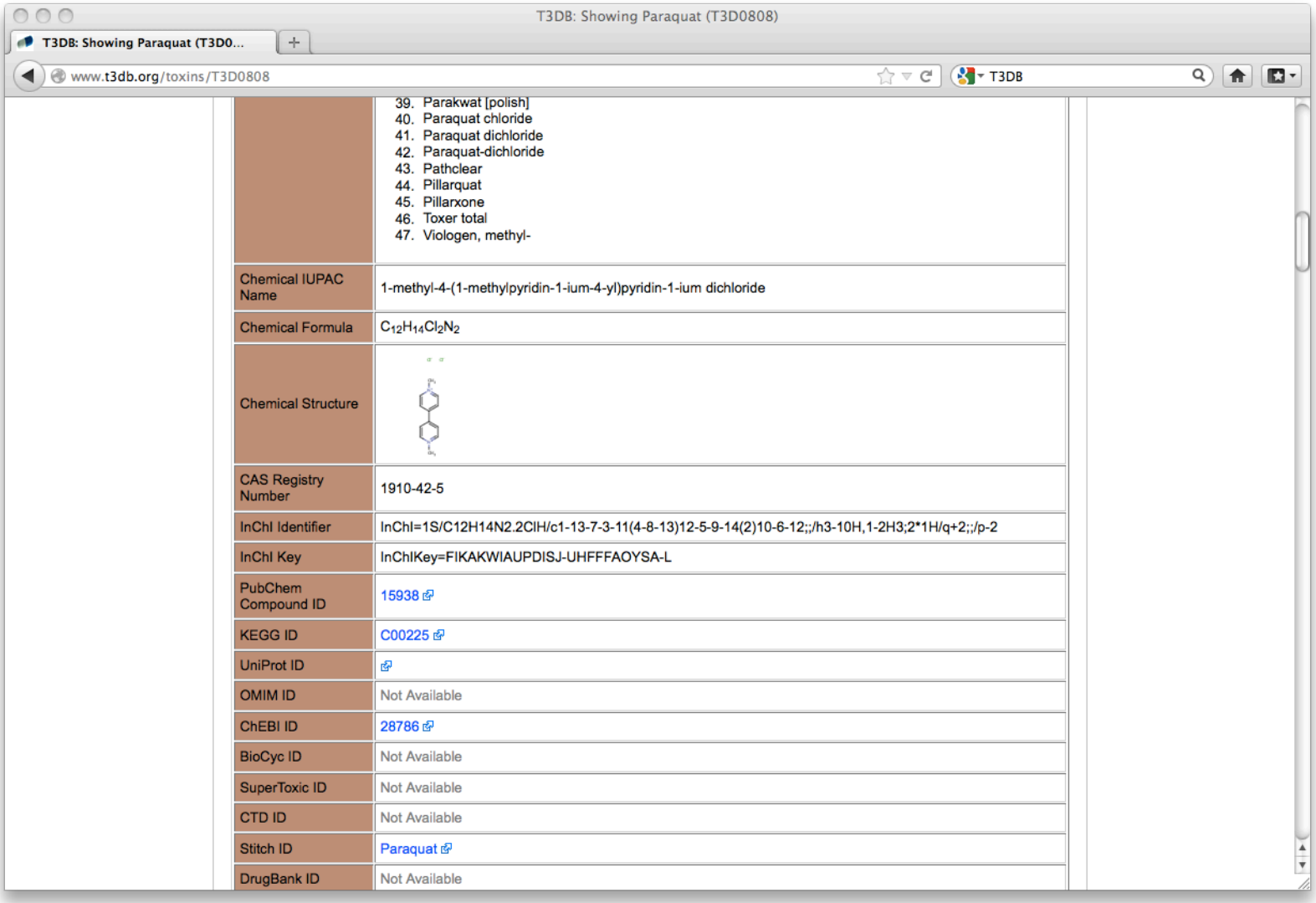
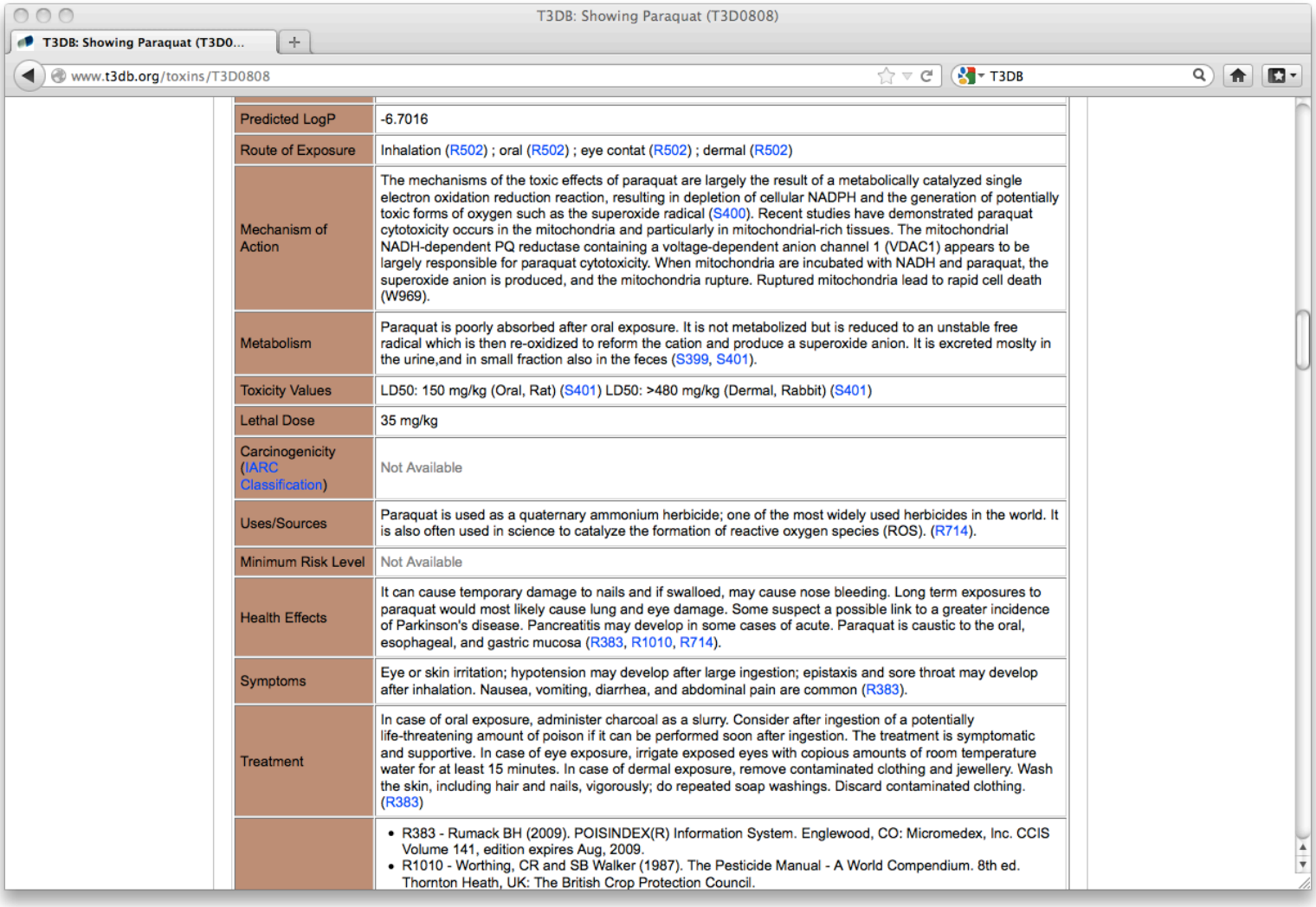


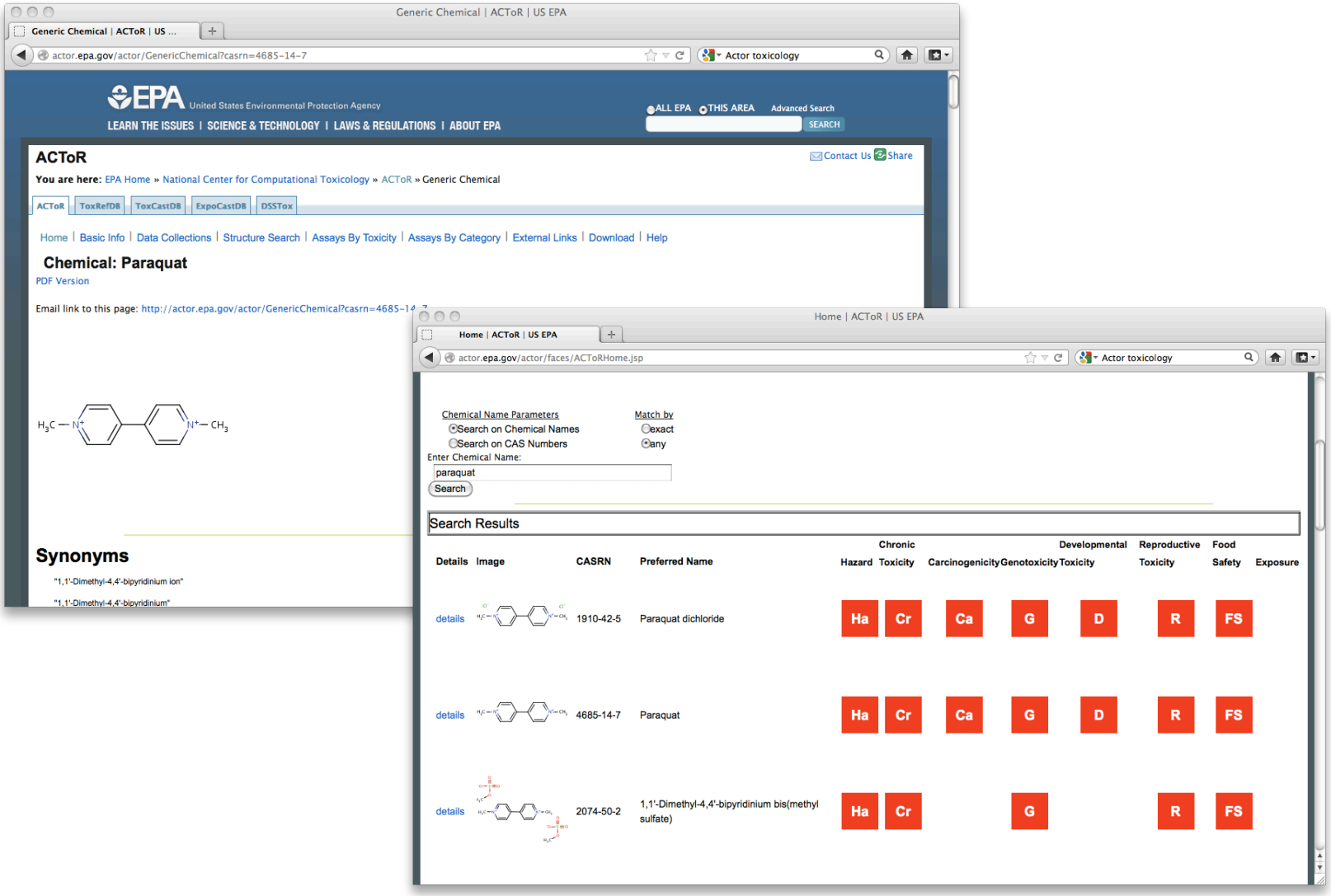
	39. Parakwat [polish] 40. Paraquat chloride 41. Paraquat dichloride 42. Paraquat-dichloride 43. Pathclear 44. Pillarquat 45. Pillarxone 46. Toxer total 47. Viologen, methyl-
Chemical IUPAC Name	1-methyl-4-(1-methylpyridin-1-ium-4-yl)pyridin-1-ium dichloride
Chemical Formula	$C_{12}H_{14}Cl_2N_2$
Chemical Structure	
CAS Registry Number	1910-42-5
InChI Identifier	InChI=1S/C12H14N2.2ClH/c1-13-7-3-11(4-8-13)12-5-9-14(2)10-6-12;;/h3-10H,1-2H3;2*1H/q+2;;/p-2
InChI Key	InChIKey=FIKAKWIAUPDISJ-UHFFFAOYSA-L
PubChem Compound ID	15938
KEGG ID	C00225
UniProt ID	
OMIM ID	Not Available
ChEBI ID	28786
BioCyc ID	Not Available
SuperToxic ID	Not Available
CTD ID	Not Available
Stitch ID	Paraquat
DrugBank ID	Not Available

ToxCard - Paraquat

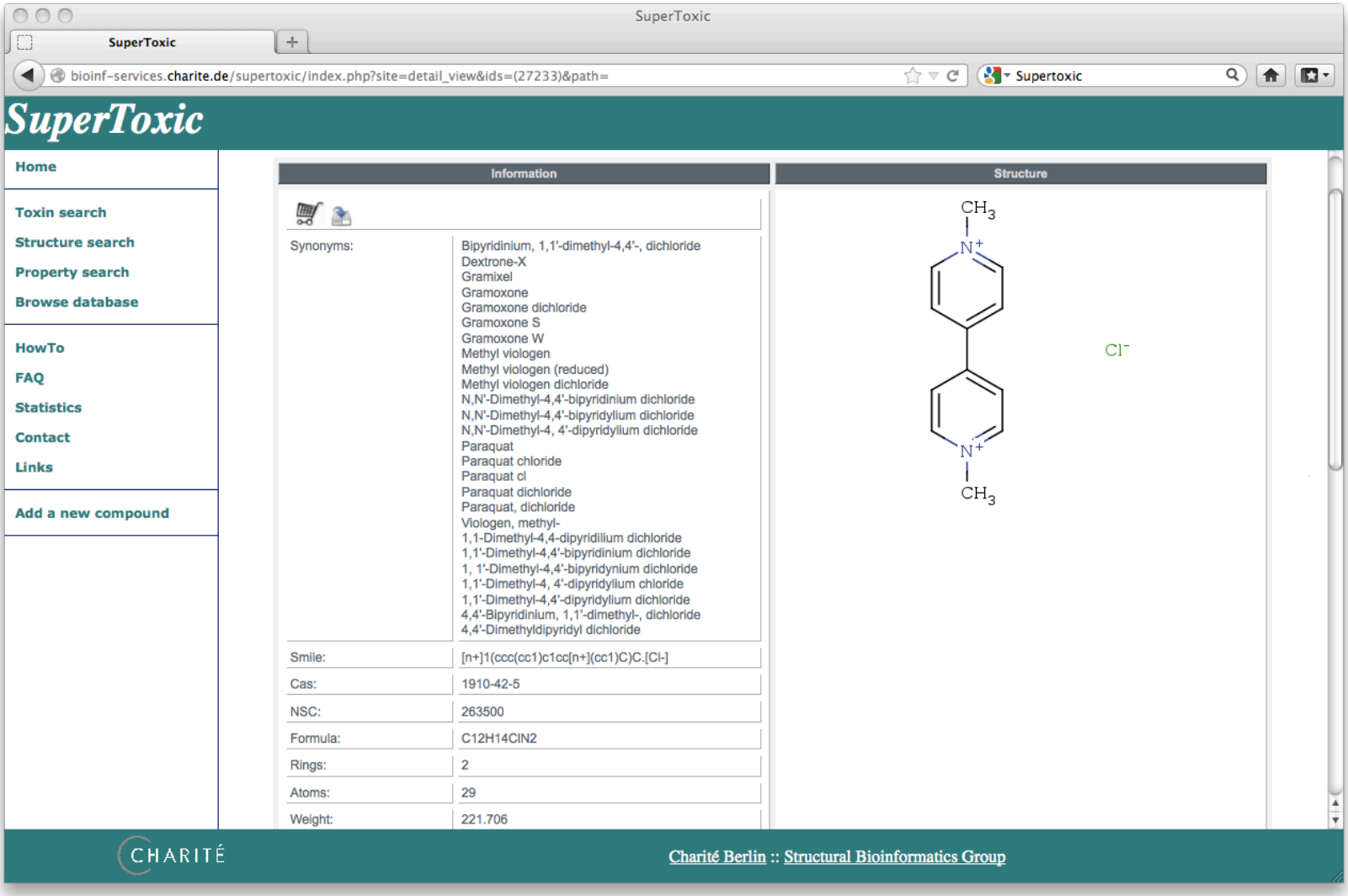


Predicted LogP	-6.7016
Route of Exposure	Inhalation (R502) ; oral (R502) ; eye contat (R502) ; dermal (R502)
Mechanism of Action	The mechanisms of the toxic effects of paraquat are largely the result of a metabolically catalyzed single electron oxidation reduction reaction, resulting in depletion of cellular NADPH and the generation of potentially toxic forms of oxygen such as the superoxide radical (S400). Recent studies have demonstrated paraquat cytotoxicity occurs in the mitochondria and particularly in mitochondrial-rich tissues. The mitochondrial NADH-dependent PQ reductase containing a voltage-dependent anion channel 1 (VDAC1) appears to be largely responsible for paraquat cytotoxicity. When mitochondria are incubated with NADH and paraquat, the superoxide anion is produced, and the mitochondria rupture. Ruptured mitochondria lead to rapid cell death (W969).
Metabolism	Paraquat is poorly absorbed after oral exposure. It is not metabolized but is reduced to an unstable free radical which is then re-oxidized to reform the cation and produce a superoxide anion. It is excreted mosity in the urine,and in small fraction also in the feces (S399, S401).
Toxicity Values	LD50: 150 mg/kg (Oral, Rat) (S401) LD50: >480 mg/kg (Dermal, Rabbit) (S401)
Lethal Dose	35 mg/kg
Carcinogenicity (IARC Classification)	Not Available
Uses/Sources	Paraquat is used as a quaternary ammonium herbicide; one of the most widely used herbicides in the world. It is also often used in science to catalyze the formation of reactive oxygen species (ROS). (R714).
Minimum Risk Level	Not Available
Health Effects	It can cause temporary damage to nails and if swalloed, may cause nose bleeding. Long term exposures to paraquat would most likely cause lung and eye damage. Some suspect a possible link to a greater incidence of Parkinson's disease. Pancreatitis may develop in some cases of acute. Paraquat is caustic to the oral, esophageal, and gastric mucosa (R383, R1010, R714).
Symptoms	Eye or skin irritation; hypotension may develop after large ingestion; epistaxis and sore throat may develop after inhalation. Nausea, vomiting, diarrhea, and abdominal pain are common (R383).
Treatment	In case of oral exposure, administer charcoal as a slurry. Consider after ingestion of a potentially life-threatening amount of poison if it can be performed soon after ingestion. The treatment is symptomatic and supportive. In case of eye exposure, irrigate exposed eyes with copious amounts of room temperature water for at least 15 minutes. In case of dermal exposure, remove contaminated clothing and jewellery. Wash the skin, including hair and nails, vigorously; do repeated soap washings. Discard contaminated clothing. (R383)
	• R383 - Rumack BH (2009). POISINDEX(R) Information System. Englewood, CO: Micromedex, Inc. CCIS Volume 141, edition expires Aug, 2009. • R1010 - Worthing, CR and SB Walker (1987). The Pesticide Manual - A World Compendium. 8th ed. Thornton Heath, UK: The British Crop Protection Council.

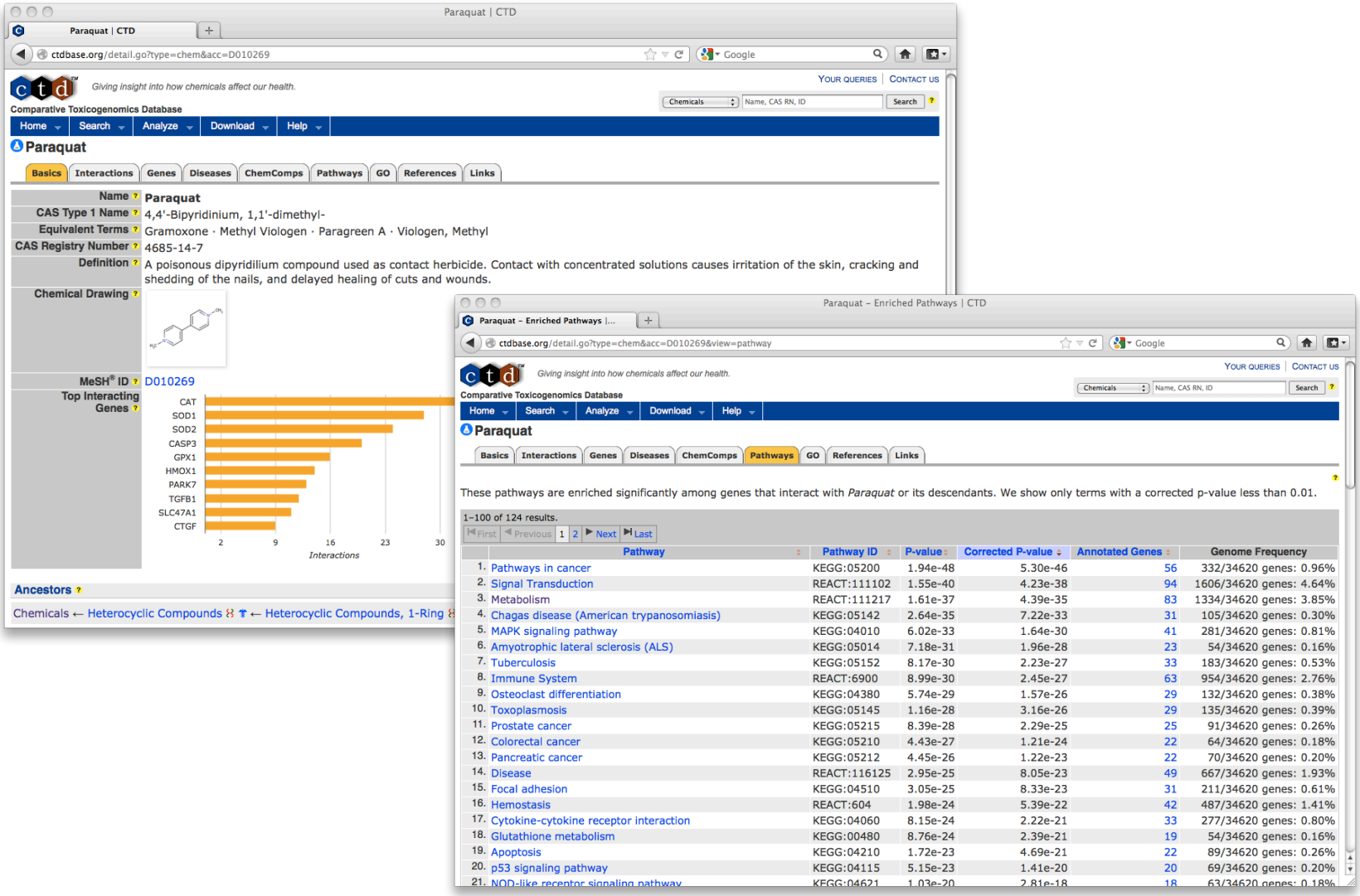
Paraquat via ACToR



Paraquat via SuperToxic



Paraquat via CTD



	Pathway	Pathway ID	P-value	Corrected P-value	Annotated Genes	Genome Frequency
1.	Pathways in cancer	KEGG:05200	1.94e-48	5.30e-46	56	332/34620 genes: 0.96%
2.	Signal Transduction	REACT:111102	1.55e-40	4.23e-38	94	1606/34620 genes: 4.64%
3.	Metabolism	REACT:111217	1.61e-37	4.39e-35	83	1334/34620 genes: 3.85%
4.	Chagas disease (American trypanosomiasis)	KEGG:05142	2.64e-35	7.22e-33	31	105/34620 genes: 0.30%
5.	MAPK signaling pathway	KEGG:04010	6.02e-33	1.64e-30	41	281/34620 genes: 0.81%
6.	Amyotrophic lateral sclerosis (ALS)	KEGG:05014	7.18e-31	1.96e-28	23	54/34620 genes: 0.16%
7.	Tuberculosis	KEGG:05152	8.17e-30	2.23e-27	33	183/34620 genes: 0.53%
8.	Immune System	REACT:6900	8.99e-30	2.45e-27	63	954/34620 genes: 2.76%
9.	Osteoclast differentiation	KEGG:04380	5.74e-29	1.57e-26	29	132/34620 genes: 0.38%
10.	Toxoplasmosis	KEGG:05145	1.16e-28	3.16e-26	29	135/34620 genes: 0.39%
11.	Prostate cancer	KEGG:05215	8.39e-28	2.29e-25	25	91/34620 genes: 0.26%
12.	Colorectal cancer	KEGG:05210	4.43e-27	1.21e-24	22	64/34620 genes: 0.18%
13.	Pancreatic cancer	KEGG:05212	4.45e-26	1.22e-23	22	70/34620 genes: 0.20%
14.	Disease	REACT:116125	2.95e-25	8.05e-23	49	667/34620 genes: 1.93%
15.	Focal adhesion	KEGG:04510	3.05e-25	8.33e-23	31	211/34620 genes: 0.61%
16.	Hemostasis	REACT:604	1.98e-24	5.39e-22	42	487/34620 genes: 1.41%
17.	Cytokine-cytokine receptor interaction	KEGG:04060	8.15e-24	2.22e-21	33	277/34620 genes: 0.80%
18.	Glutathione metabolism	KEGG:00480	8.76e-24	2.39e-21	19	54/34620 genes: 0.16%
19.	Apoptosis	KEGG:04210	1.72e-23	4.69e-21	22	89/34620 genes: 0.26%
20.	p53 signaling pathway	KEGG:04115	5.15e-23	1.41e-20	20	69/34620 genes: 0.20%
21.	NOD-like receptor signaling pathway	KEGG:04621	1.03e-20	2.81e-18	18	63/34620 genes: 0.18%

Toxicology Databases

Other DBs

- General preference for breadth over depth
- Focus on toxicity, not molecular mechanisms
- Content is fragmented, limited search, not linked to other resources, lightly referenced

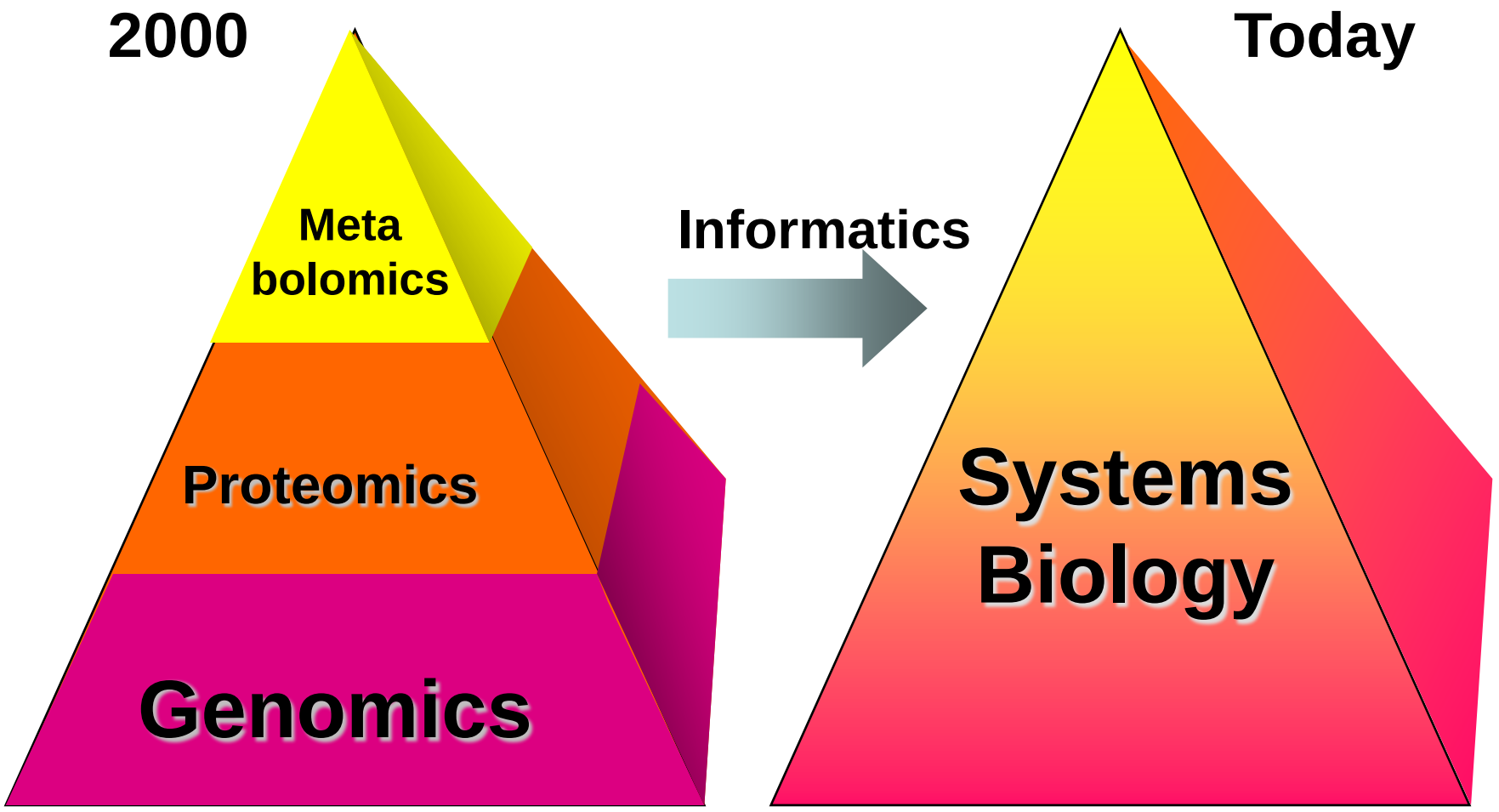
T3DB

- General reference for depth over breadth
- Focus on toxicity AND molecular mechanisms
- Content is uniform, extensive search offerings, linked to 15 other DBs, heavily referenced

Outline

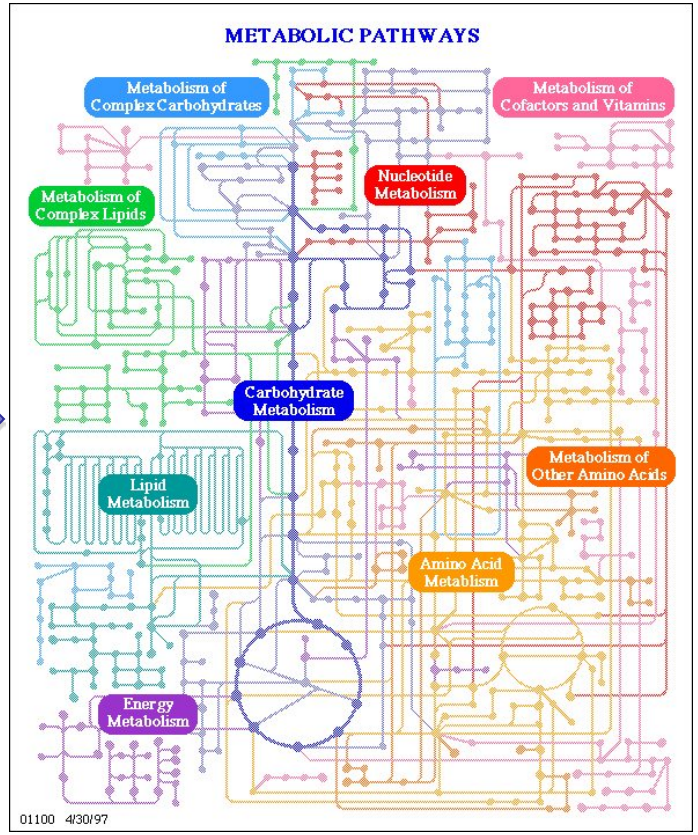
- Brief review of toxicology databases
- Metabolomics and toxicology
- Introducing the toxin, toxin-target database – T3DB
- Systems biology, pathway databases and the small molecule database - SMPDB
- Conclusions & Future Directions

Blurring the Boarders



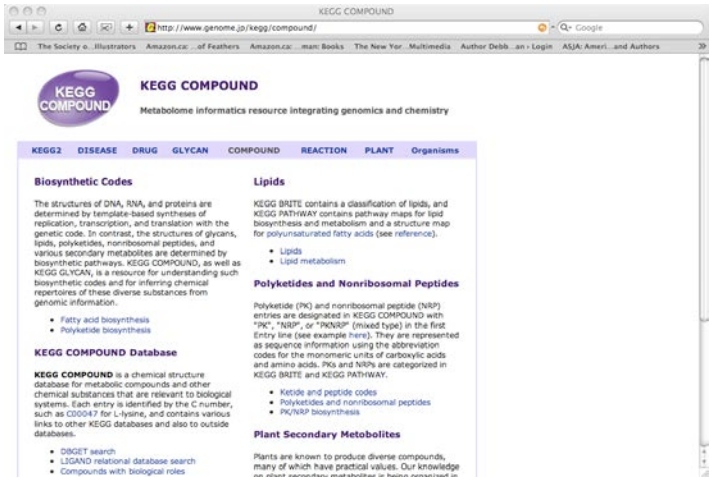
From Lists to Pathways

Compound	Retention Time (min)	Conc. in Urine (µM)	Compound	Retention Time (min)	Conc. in Urine (µM)
Dns-o-phospho -L-serine	0.92	<D.L. *	**Dns-Ile**	6.35	25
Dns-o-phospho -L-tyrosine	0.95	<D.L.	**Dns-3-aminosalicylic acid**	6.44	0.5
Dns-adnosine monophosphate	0.99	<D.L.	**Dns-pipecolic acid**	6.50	0.5
Dns-o-phosphoethanolamine	1.06	16	**Dns-Leu**	6.54	54
Dns-glucosamine	1.06	22	**Dns-cystathionine**	6.54	0.3
Dns-o-phospho -L-threonine	1.09	<D.L.	**Dns-Leu-Pro**	6.60	0.4
Dns-6-dimet hylamine purine	1.20	<D.L.	**Dns-5-hydroxylysine**	6.65	1.6
Dns-3-methyl -histidine	1.22	80	**Dns-Cystine**	6.73	160
Dns-taurine	1.25	834	**Dns-N-norleucine**	6.81	0.1
Dns-carnosine	1.34	28	Dns-5-hydroxydopamine	7.17	<D.L.
Dns-Arg	1.53	36	**Dns-dimethylamine**	7.33	293
Dns-Asn	1.55	133	**Dns-5-HIAA**	7.46	18
Dns-hypotaurine	1.58	10	**Dns-umbelliferone**	7.47	1.9
Dns-homocarnosine	1.61	3.9	Dns-2,3-diaminoproprionic acid	7.63	<D.L.
Dns-guanidine	1.62	<D.L.	**Dns-L-ornithine**	7.70	15
Dns-Gln	1.72	633	**Dns-4-acetyamidophenol**	7.73	51
Dns-allantoin	1.83	3.8	**Dns-procaine**	7.73	8.9
Dns-L-citrulline	1.87	2.9	**Dns-homocystine**	7.76	3.3
Dns-1 (or 3 -)-methylhistamine	1.94	1.9	**Dns-acetaminophen**	7.97	82
Dns-adenosine	2.06	2.6	**Dns-Phe-Phe**	8.03	0.4
Dns-methylguanidine	2.20	<D.L.	**Dns-5-methyo xysalicylic acid**	8.04	2.1
Dns-Ser	2.24	511	**Dns-Lys**	8.16	184
Dns-aspartic acid amide	2.44	26	Dns-aniline	8.17	<D.L.
Dns-4-hydroxy -proline	2.56	2.3	**Dns-leu-Phe**	8.22	0.3
Dns-Glu	2.57	21	**Dns-His**	8.35	1550
Dns-Asp	2.60	90	Dns-4-thialysine	8.37	<D.L.
Dns-Thr	3.03	157	Dns-benzylamine	8.38	<D.L.
Dns-epinephrine	3.05	<D.L.	**Dns-1-ephedrine**	8.50	0.6
Dns-ethanolamine	3.11	471	**Dns-tryptamine**	8.63	0.4
Dns-aminoadipic acid	3.17	70	Dns-pyrydoxamine	8.94	<D.L.
Dns-Gly	3.43	2510	Dns-2-methyl -benzylamine	9.24	<D.L.
Dns-Ala	3.88	593	**Dns-5-hydroxytrptophan**	9.25	0.12
Dns-aminolevulinic acid	3.97	30	**Dns-1,3-diaminopropane**	9.44	0.23
Dns-r-amino-butyric acid	3.98	4.6	**Dns-putrescine**	9.60	0.5
Dns-p-amino-hippuric acid	3.98	2.9	**Dns-1,2-diaminopropane**	9.66	0.1
Dns-5-hydro xymethyluricil	4.58	1.9	**Dns-tyrosinamide**	9.79	29
Dns-tryptophanamide	4.70	5.5	**Dns-dopamine**	10.08	140
Dns-isoguanine	4.75	<D.L.	**Dns-cadaverine**	10.08	0.08
Dns-5-aminopentanoic acid	4.79	1.6	**Dns-histamine**	10.19	0.4
Dns-sarcosine	4.81	7.2	**Dns-3-methoxy -tyramine**	10.19	9.2
Dns-3-amino -isobutyrate	4.81	85	**Dns-Tyr**	10.28	321
Dns-2-aminobutyric acid	4.91	17	Dns-cysteamine	10.44	<D.L.

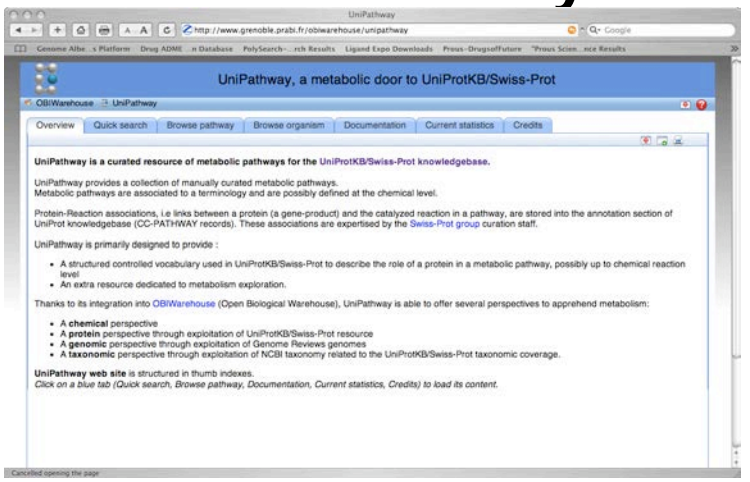


Pathway DBs

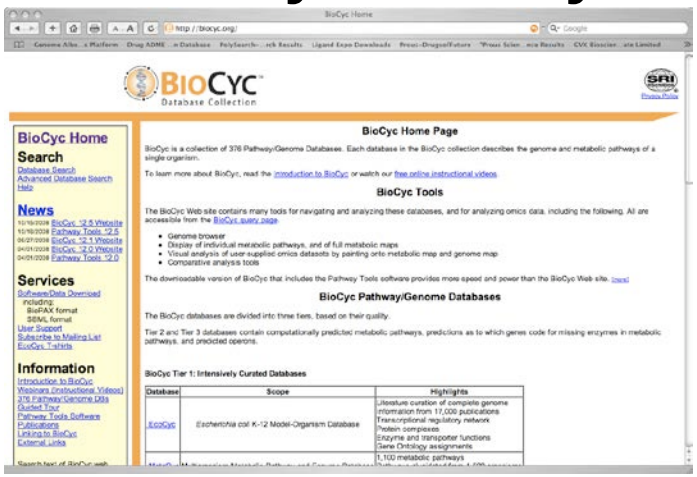
KEGG



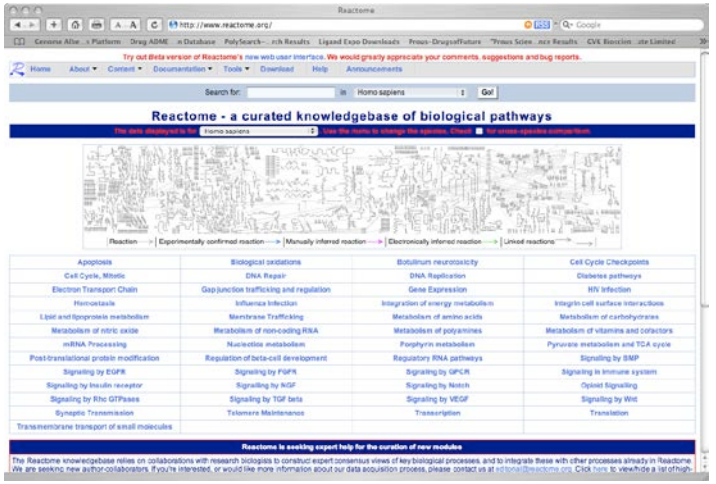
UniPathway



BioCyc/MetaCyc



Reactome



Current Pathway DBs

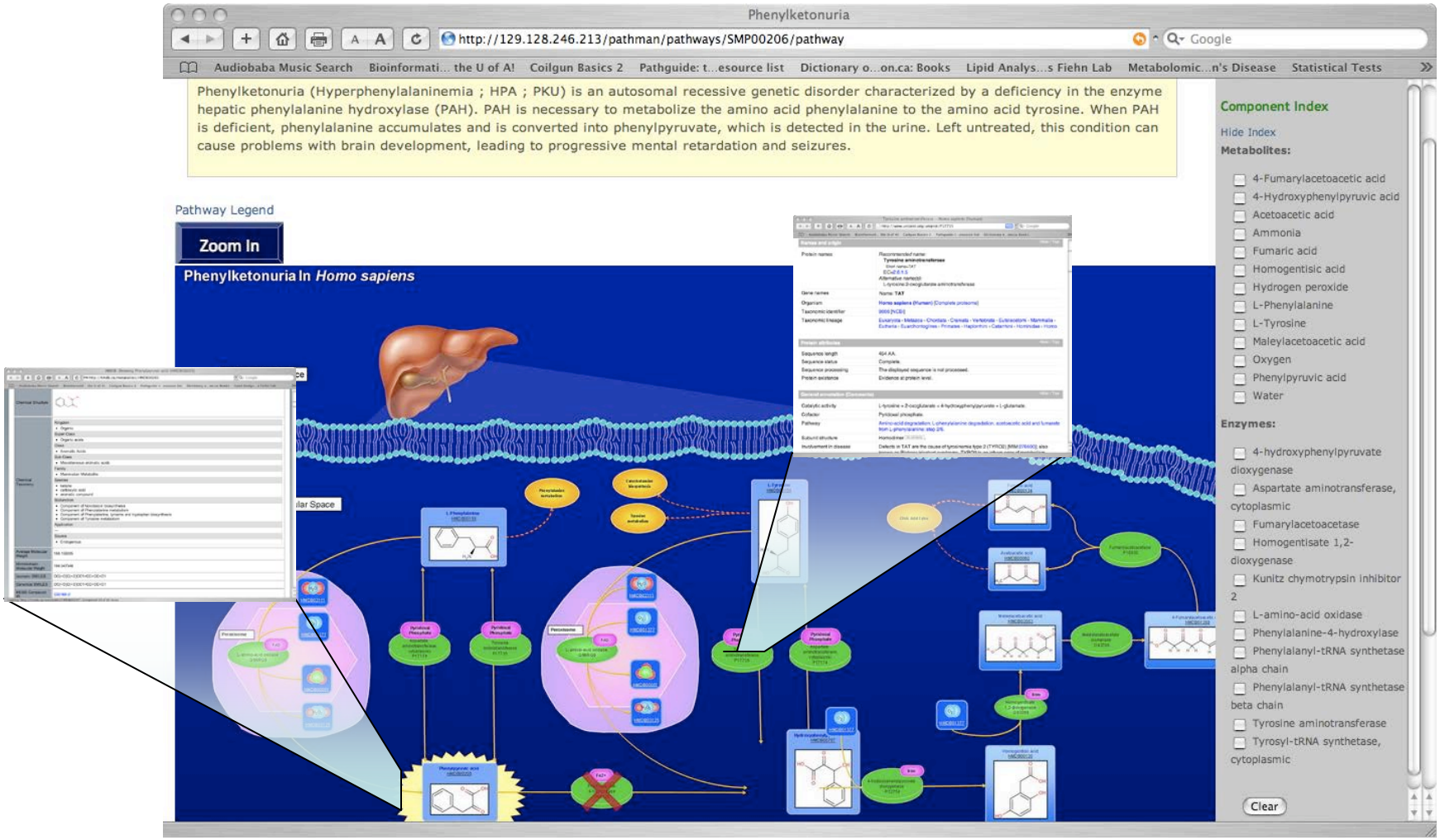
- Most are multi-organism in nature without emphasis on humans
- Most have very simple diagrams with no visible indication of cellular compartments or visible protein/chemical structure
- Most focus on regular metabolism, not diseases, drugs, toxins or poisons
- Most focus on cellular processes, not whole organisms or multi-organ processes

The Small Molecule Pathway Database (SMPDB)

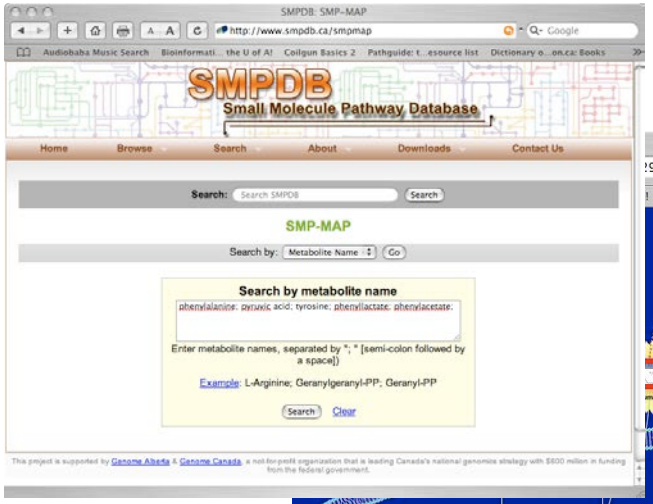
http://www.smpdb.ca

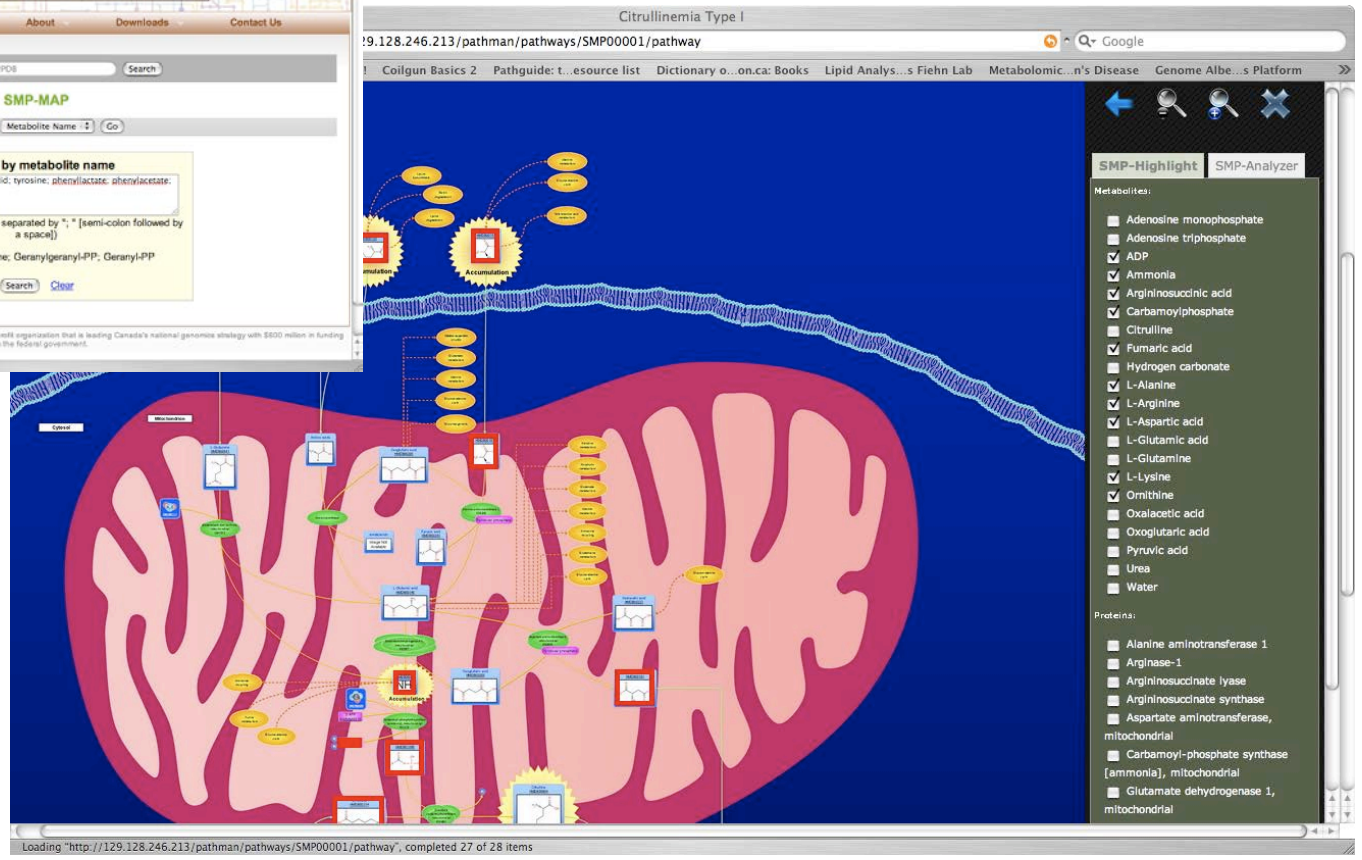
- >450 small molecule pathways for Humans ONLY
- 223 drug/toxin pathways
- 116 disease pathways
- 13 signalling pathways
- 90 metabolic pathways
- Depicts cell compartments, organelles, protein locations, 4º structures
- Maps genechip & metabolomic data
- Converts gene, protein or chemical lists to pathways or disease diagnoses

Inside SMPDB



Mapping Metabolites with SMPDB





SMPDB

- Original SMPDB images were hand-drawn and not easily manipulated or updated, pathways were non-computable and not stored in ML compliant file structure
- Now going through a major update to save all files in BioPax format (which can be converted to SBML)
- Also creating a drawing widget that allows everyone to quickly create nicely colored, BioPax compatible SMPDB pathways
- Still hundreds of pathways to add….

Conclusion

- Current toxicology/toxicity databases are not yet oriented to systems or predictive toxicology
- Emerging resources (ToxcastDB, ToxBank Wiki, T3DB) are starting to change this
- T3DB is still a work in progress
- Current pathway databases still not oriented to toxicology, they are still missing key information
- SMPDB is a step in the right direction, but not yet “finished”
- Still plenty of work to do and plenty of opportunities to share/exchange data

Thanks To

- **Staff - Rupasri Mandal, Ram Krishnamurthy, Farid Aziat, Edison Dong, Igor Sinelnikov, Jeff Xia, Kruti Chaudhary, Souhaila Bouatra, Nick Psychogios, Trent Bjorndahl, Rolando Perez-Pinero, Mike Wilson, Craig Knox, Zerihun Dame, Philip Liu, Faizath Yallou, An Chi Guo, Yifeng Liu, You Zhou, Tim Jewison, Vanessa Neveu, Yannick Djoumbou, David Arndt**
- **Past Staff – Emilia Lim, Alison Pon**
- **Collaborators - Liang Li, Christoph Borchers, Russ Greiner, Augustin Scalbert**
- **Funders - CIHR, Genome Canada, AIBS, NSERC**