

ChemTunes • ToxGPS

Database and Knowledgebase for
Safety Evaluation and Risk Assessment



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ChemTunes

- Cheminformatics platform providing toxicity, safety evaluation and metabolism information
- Nearly 100,000 compounds over 30,000 studies covering > 70 endpoints



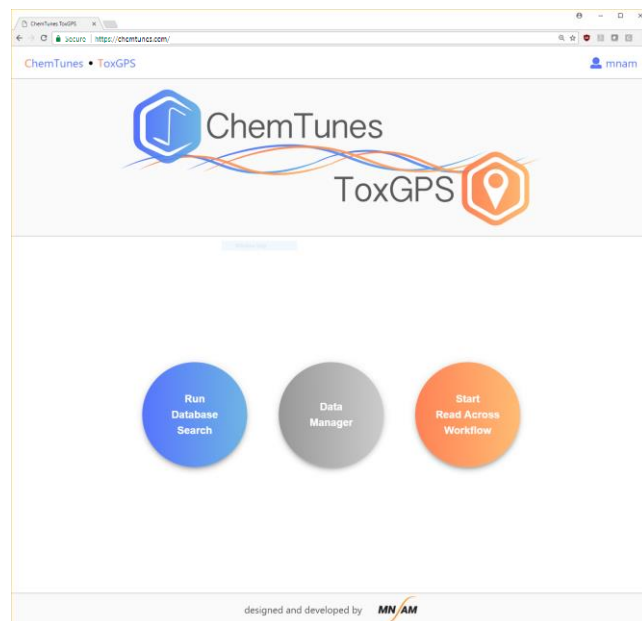
Data on Toxicity, Safety & Metabolism



Analogues & Profiles



Prediction, Workflows & Assessment



Human Health Endpoints

Genetic toxicity

- Bacterial reverse mutagenesis
- In vitro* chromosome aberration
- In vivo* micronucleus

Carcinogenicity

- Mouse tumorigenicity
- Rat tumorigenicity

DART

- Pregnancy loss (rat, mouse, rabbit)
- Cleft palate (rat, mouse, rabbit)

**ChemTunes
•
ToxGPS**

Safety Evaluation...

- NOAEL/LOAEL, MOS, MOE, TDI, ADI, etc.

Dermal toxicity

- Skin irritation
- Skin sensitization (hazard, potency)

Hepatotoxicity

- Steatosis
- Mitochondrial toxicity
- Human DILI

Liver BioPath

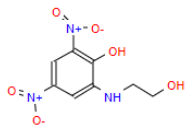
- Metabolic reaction pathways
- Prioritized metabolites

ToxGPS – Prediction

- Knowledgebase offering compound location service, prediction of toxicity and metabolic information, and workflows for *in silico* assessment including MoA QSAR and rule-based predictions, Read-Across, and Threshold of Toxicological Concern






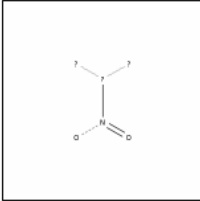
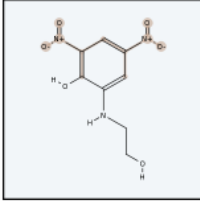
Bacterial Reverse Mutagenesis

Prediction Results for compound #1



In database: Yes
 CHEMTUNES ID: CMS-62110
 Name: 2-HYDROXYETHYL PICRAMIC ACID
 Registry number(s): 99610-72-7
 # studies in CHEMTUNES: 9

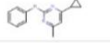
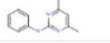
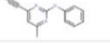
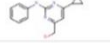




- Combined outcome**
 QSAR (global and MoA) as well as rule-based results are combined into one final outcome by a rigorous decision theory approach¹


Overall prediction	Positive probability 0.99	
QSAR Model Global	Positive probability 0.58-0.85	
MoA Models Aromatic amine	0.39-0.65	
Aromatic nitro	0.38-0.61	
Phenol	0.54-0.84	
Chemotype Alert	Chemotype Alert Match	Alert name Aromatic nitro
		Odds ratio 6.02

ToxGPS – Read-Across

- Chemical speciation – metabolites and tautomers
- Generate analogues (structure, properties, biological)
- Line up evidence
- Combine evidence for outcome and uncertainty estimation

Relevant
Reliable
Consistent
Reproducible

Search Results	Analog Structures	Analog Structures	Toxicity Data	Toxicity Prediction	Summary	Actions
	T	A1-T	A2-T	M1-T		
Structure						search Analog Structures
CMS-ID	CMS-6736	CMS-7253	CMS-9416	CMS-6736		generate Metabolites
Name	Cyprodinil	Pyrimethanil	Mepanipyrim	(2-anilino-6-cyclopropylpyrimidin-4-yl)methanol		generate Tautomers
Analog similarity						predict Toxicity
structure-based	1.00	0.82	0.75	0.79		export PDF File
skyline plot correlation	1.00	0.86	0.87	0.85		export XLS File
Analog profile						
In vivo Experimental Data						
Repro Tox reliability	Have data, but not used	No effects	Fertility index dec	No Data		
Dev Tox – maternal reliability	NA	Klimisch 2	Klimisch 2	NA		
Dev Tox – offspring reliability	Have data, but not used	No effects	Pregnancy loss	No Data		
Dev Tox – Teratogenicity reliability	NA	Klimisch 2	Klimisch 2	NA		
In Silico Data						
Repro Tox QSAR reliability	Neg prob = 0.050	predictions not used for analogs	predictions not used for analogs	predictions not used for analogs		
Terat QSAR–Cleft Palate reliability	0.09	NA	NA	NA		
	Neg prob = 0.019	predictions not used for analogs	predictions not used for analogs	predictions not used for analogs		
	0.02	NA	NA	NA		

System designed and developed by 

- [3] Leist M, Yang C, *et al.* Novel Technologies and an Overall Strategy to Allow Hazard Assessment and Risk Prediction of Chemicals, Cosmetics, and Drugs with Animal-Free Methods. *Altex* **2012**, *29*, 4/12, 373-388
- [4] Yang C, *et al.* Computational Toxicology Approaches at the US Food and Drug Administration. *ATLA* **2009**, *37*, 523-531

Marquee Features



- Mechanism-based (MoA) QSAR models
- Rule-based and endpoint specific alerts^{2,3}



- Proven approach used at US FDA for risk assessment^{3,4}



- Data- and knowledge-based system
- Established cheminformatics methods

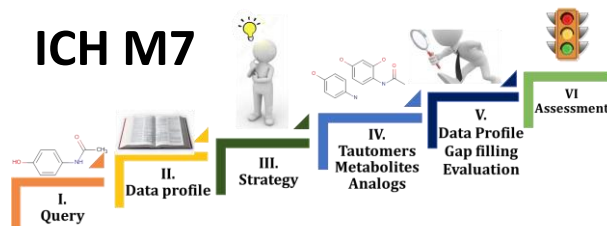


- Decision theory approach Weight-of-evidence (WoE) outcome and uncertainty

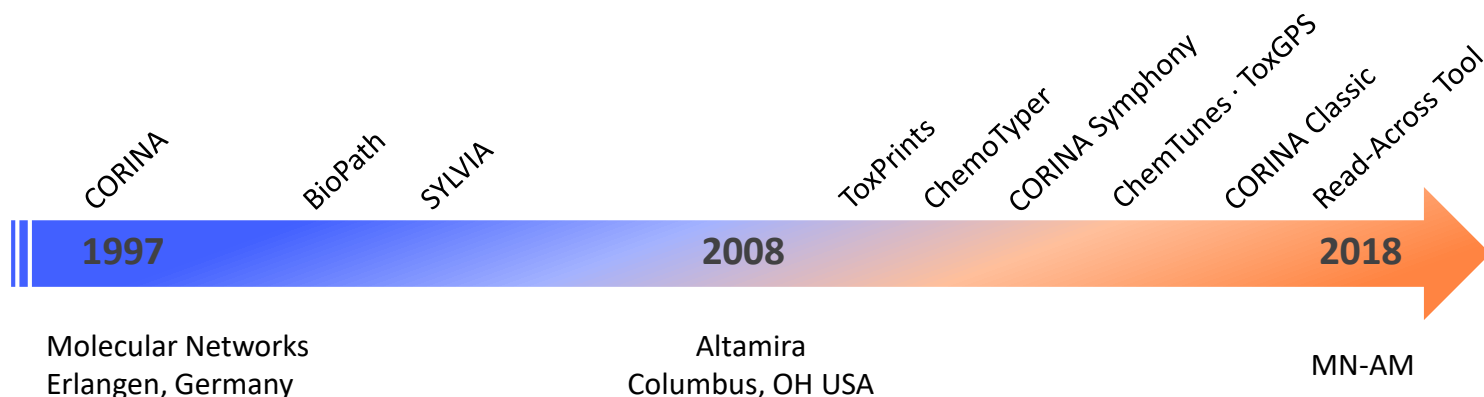
Applications

- Compound location service
- Platform for *in silico* safety assessment
- Read-Across workflow
- ICH M7 Genotoxic impurities in drug products

ICH M7



MN-AM at a Glance



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