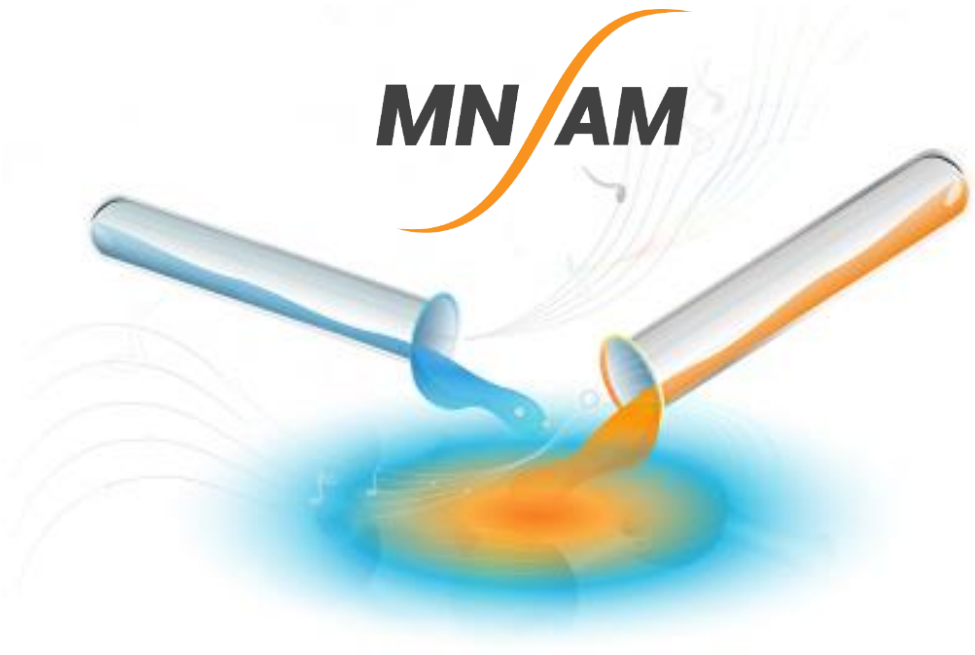
ChemTunes • ToxGPS

Database and Knowledgebase for
Safety Evaluation and Risk Assessment



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Data Mining & Retrieval

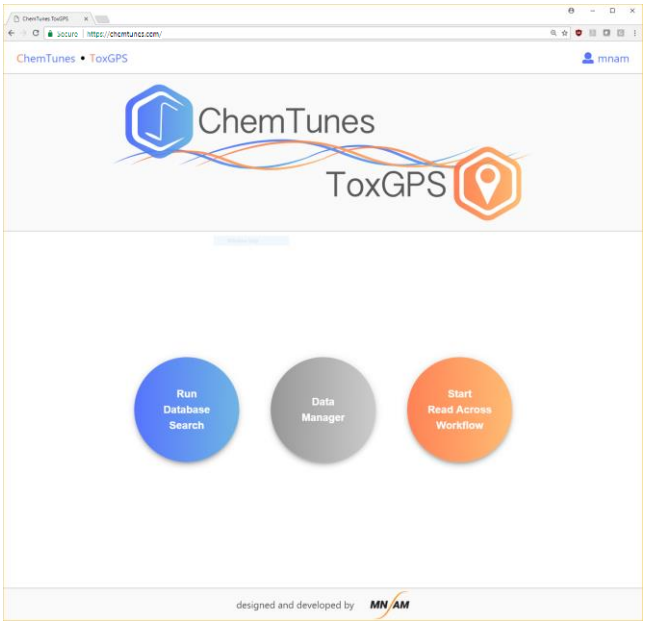
ChemTunes

- 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)

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Dermal toxicity

- Skin irritation
- Skin sensitization (hazard, potency)

Hepatotoxicity

- Steatosis
- Mitochondrial toxicity
- Human DILI

Liver BioPath

- Metabolic reaction pathways
- Prioritized metabolites

Safety Evaluation…

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

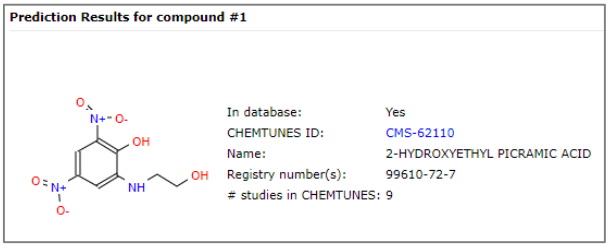
[1] Rathman JF, *et al.* Uncertainty Estimation and Quantitative Combination-of-Evidence using Dempster-Shafer Theory. *Comp. Tox.* ***2018*** in press

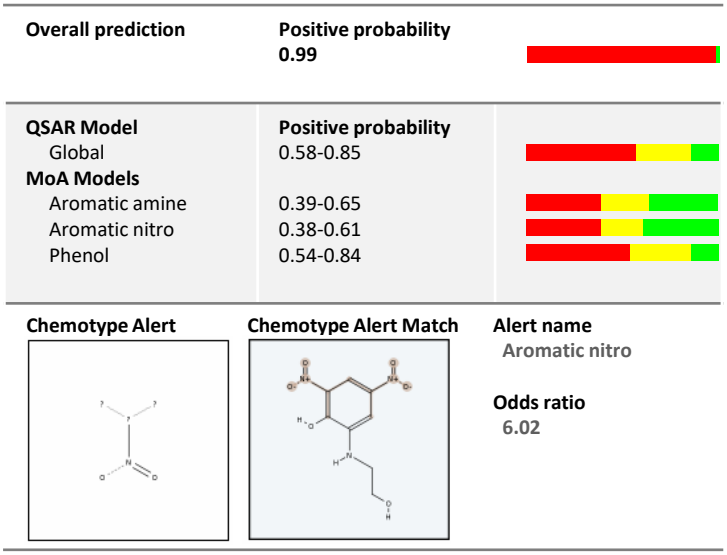
[2] Cherkasov A, *et al.* QSAR modeling: where have you been? Where are you going to? *J. Med. Chem.* **2014**, *57(12)*, 4977-5010

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



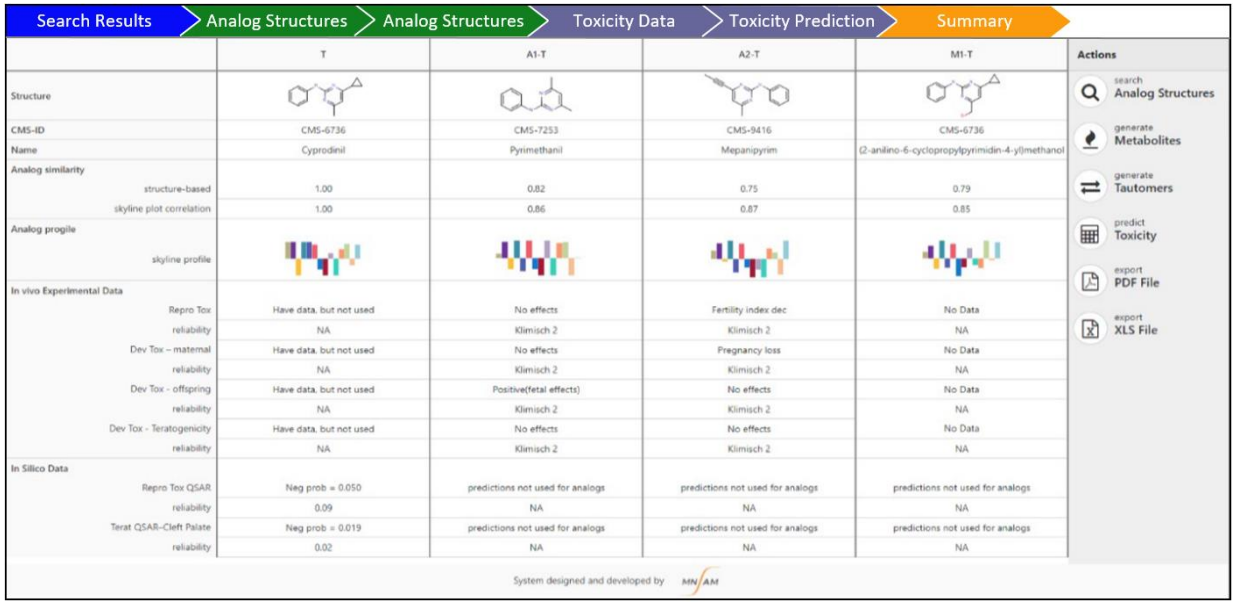


- **Combined outcome**
  QSAR (global and MoA) as well as rule-based results are combined into one final outcome by a rigorous decision theory approach[1]

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



[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

Inspiring Chemical Discovery

Marquee Features

- Mechanism-based (MoA) QSAR models
- Rule-based and endpoint specific alerts[2,3]

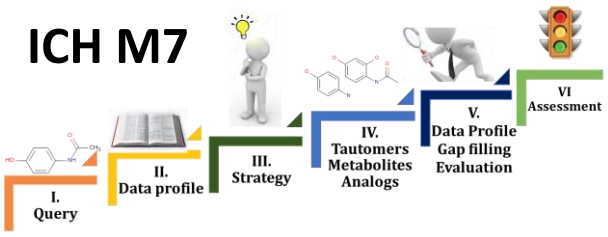
- Proven approach used at US FDA for risk assessment[3,4]

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

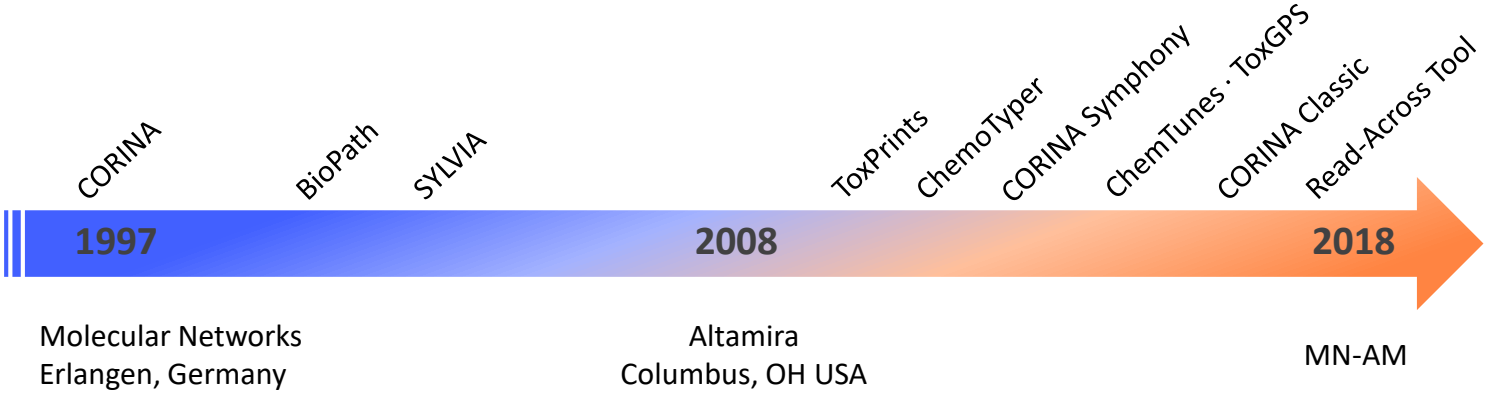
- Decision theory approach Weight-of-evidence (WoE) outcome and uncertainty

Applications

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



MN-AM at a Glance



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