A Workflow for *In Silico* Assessment of Genetic Toxicity and Application to Pharmaceutical Genotoxic Impurities under ICH M7

TOX NAVIGATION
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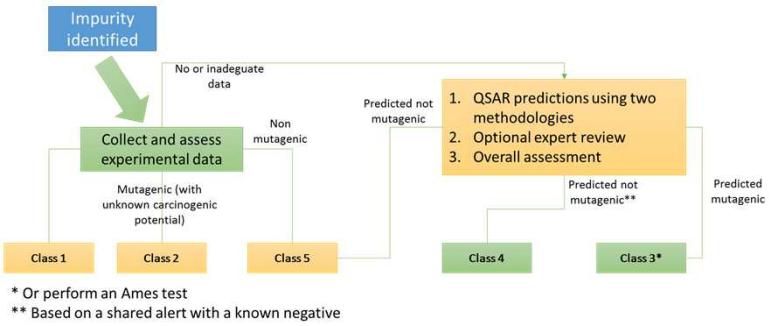
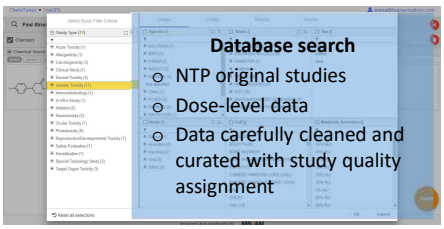
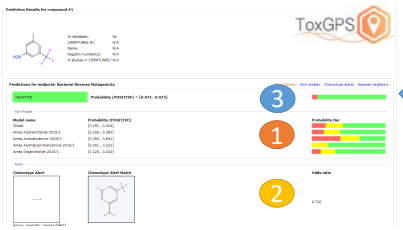
BACKGROUND

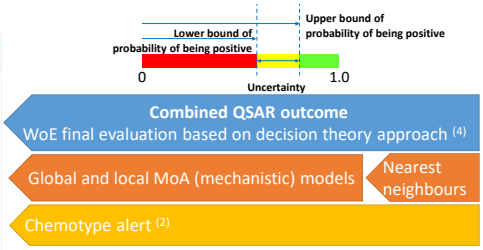
- The ICH M7 guideline provides a framework for assessing and controlling DNA reactive impurities in a pharmaceutical product.
- The guideline describes how actual and potential drug impurities are identified and outlines how a hazard assessment should be performed.
- When no adequate experimental mutagenicity and/or carcinogenicity results are available, an assessment of Structure-Activity Relationships (SAR) that focuses on bacterial mutagenicity predictions should be performed.



Methods







Database search → Statistical-based QSAR result → Expert rule-based QSAR result → Combine with WoE → Final

Models information

Biology	• Salmonella typhimurium (TA98, TA100, TA1535, TA1537) and E-coli (WP2, WP2 uvrA), with and without rat S-9
Data source	• US FDA CFSAN, US FDA Drugs@FDA, US NTP, EU SCCS, REACH (ECHA) database • Published literature papers when reviewed by our experts
Training set	• QSAR training set: 2,814 compounds (33% positive) • Knowledgebase for alerts: over 8,000 structures • OECD 471 or equivalent data quality preferred

Models have been validated at customer sites, FDA CFSAN, and NIHS Japan

Model description

Corina (1) Symphony properties	• Global molecular descriptors • Shape and size descriptors • Semi-empirical QM parameters
ToxPrint Chemotypes	• Public library of chemotypes • Toxicity-related features relevant to human & environment safety • Generic compound classes

Modeling approach

Method	**QSAR Development** • Partial Logistic regression • KNN • Random Forest	**Structural rules development** • Mechanistic design • Chemoinformatics assisted
Training strategy	**QSAR** • Mechanistic MoA neighbours • Chemotype class • Global	**Structural rules** • Mechanistic MoA neighbours • Chemotypes / Fragments
Weight of Evidence	**Final prediction** • Decision theory approach: rigorous approach to handling uncertainty • Final outcome: systematic and quantitative method of combining evidences (QSAR and structural rules)	

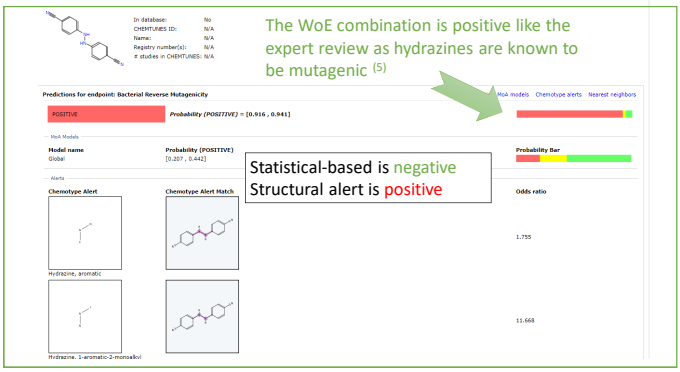
Case studies

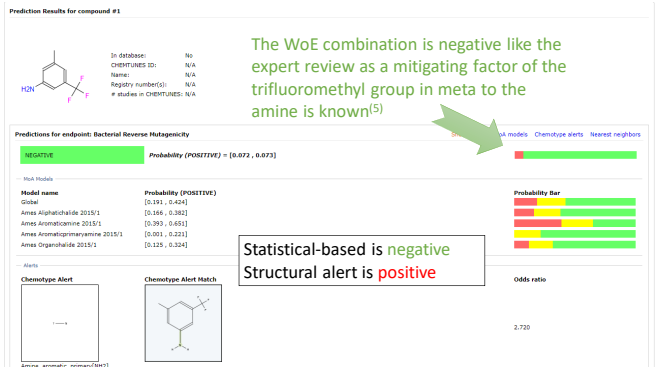
Ames Mutagenicity prediction challenge by NIHS Japan

- Phase 1: Test set with 3,950 compounds 16 participants
- Phase 2: Test set with 3,840 compounds 18 participants
- *Phase 1 results were provided to participants and could be incorporated into models developed for Phase 2*

	Sensitivity		Specificity	
Phase	ToxGPS	Range	ToxGPS	Range
1	66%	39-70%	76%	65-92%
2	57%	42-68%	92%	78-93%

- **Assay Load**: If an impurity is not predicted to be negative, then it must be tested experimentally. False positives unnecessarily increase the assay load.
- **Risk**: Impurities that are genotoxic but predicted to be negative present a product risk.
- The ToxGPSAmes model performs well with respect to these two important metrics:
  - Load Rank (e.g., ranked 4th out of 18 in phase 2)
  - Risk Rank (e.g., ranked 3rd out of 16 in phase 1 in false negatives rate)





SUMMARY AND FUTURE

- QSAR modeling based on biologically meaningful grouping using mechanistically selected chemotypes and molecular descriptors
- Final outcome combines the evidences of QSAR models and chemotype rule-based predictions to provide good prediction performance
- Robust risk assessment system providing rigorous method for quantitative weight-of-evidence
- In two open challenges involving over 8,000 compounds, ToxGPSAmes mutagenicity model ranked highly for GTI relevant statistics
- Include in the workflow the assessment for class 4

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