An In Silico Workflow for Translational Safety Assessment of Drug-Induced Liver Injury

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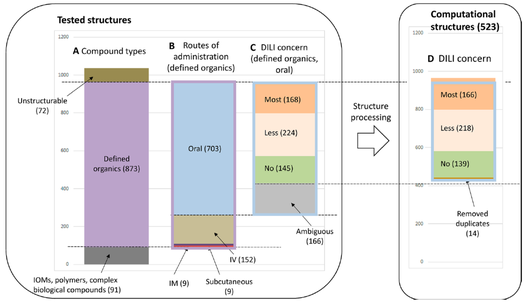
1 INTRODUCTION

- Translational safety assessment has recently become the focal point of many computational approaches.
- Drug-Induced Liver Injury (DILI) is one of the most difficult endpoints in drug discovery and chemical safety assessment, as is relating preclinical animal data to human/clinical findings.
- Using celecoxib as a case study compound, we present in silico workflow utilizing both preclinical and clinical information – leveraging existing preclinical and clinical data along with mechanistic and metabolism knowledge to better translate mammalian to human DILI.

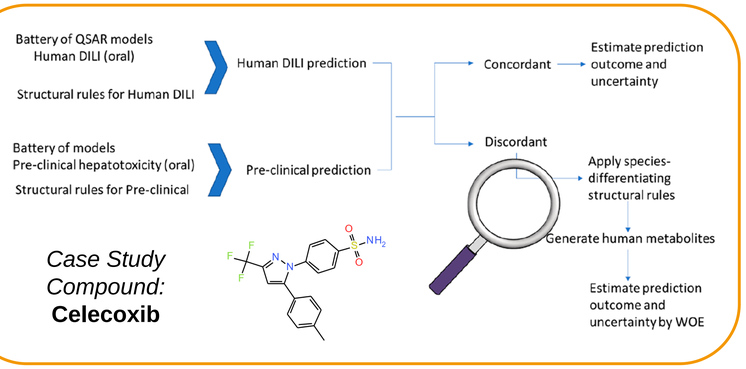
2 HUMAN DILI DATA

- The human DILI (hDILI) dataset was built from US FDA Liver Toxicity Knowledge Base (LTKB)[2].

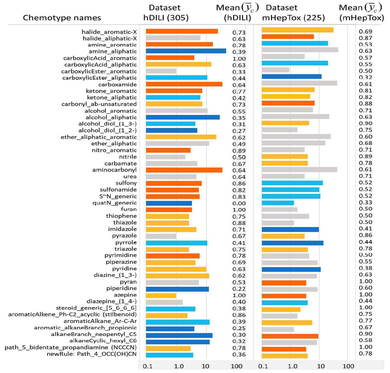


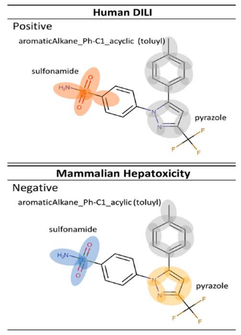
3 MAMMALIAN HEPATOXICITY DATA

- Mammalian Hepatoxicity database contains 1457 records including industrial chemicals (~600), cosmetics and foods (~300), and agrochemicals (~500).
- 225 drugs were used as the training set for preclinical QSAR models.
- The selection criteria included: Oral route of administration; Observed pathology changes of liver and bile duct; Studies providing data on multiple species were available; Detailed dose-level toxicity data covering wide dose ranges, preferably with PBPK and/or toxicokinetic profiles; Drugs with known hDILI data whenever possible.



4 STRUCTURAL FEATURES





- Differentiation of human DILI vs mammalian liver toxicity based on *in vivo* studies
- Fragment-based Toxprint fingerprints were generated using the public **ChemoTyper**[3,4] application.
- Statistical analysis based on z-scores was applied to identify relevant chemotypes

$$z_c = (\bar{y}_c - \bar{y}) / \sqrt{(n_0/n_c)(S^2/N)}$$

5 QSAR MODELS

- Toxprints, Molecular and Quantum Mechanical Properties calculated using **CORINA Symphony**[5] were used to create the models.
- Partial Least Square Regression used for descriptor selection

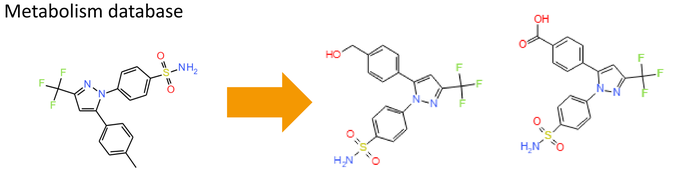
Model	Accuracy	Sensitivity	Specificity	PPV	NPV	MCC	Balance Accuracy
MN-AM hDILI model (MN-AM)	0.82	0.86	0.77	0.82	0.83	0.64	0.82
mHepTox model (MN-AM)	0.71	0.71	0.71	0.81	0.60	0.41	0.71
eTRANSAFE Cholestasis model	0.64	0.60	0.69	0.72	0.57	0.29	0.65

* Available from the eTRANSAFE project. https://etransafe.eu/

- Multiple machine learning methods (Artificial Neural Networks, Random Forest Classifier, Support Vector Classifier, K Nearest Neighbors Classifier and Logistic Regression) were trained and combined into final model

6 METABOLISM

- **ChemTunes BioPath Metabolism Database**[6]: data on human hepatic metabolism consisting mostly of drug and drug-like molecules for a total of 439 parents. These molecules are involved in 2858 phase I and II reactions, resulting in 2927 metabolites.
- **ToxGPS LiverBioPath Metabolizer**[6]**:** A module within ChemTunes·ToxGPS was used to generate potential metabolites of drugs when experimental data were not available from the ChemTunes BioPath Metabolism database



celecoxib | **M1: hyroxymethyl-celecoxib** | **M2: carboxylic acid-celecoxib**

- Celecoxib is extensively metabolized by a single metabolic pathway in all species (via CYP2C9, CYP3A, CYP2C19, CYP2B, CYP3A, CYP2D15) including humans.

7 WEIGHT OF EVIDENCE

- A weight-of-evidence outcome was obtained by combining[7] each of in silico predictions (QSAR and structural rules) for parent and metabolite. The percentages of each test substance found in the plasma were also considered when applying the decision theory rule.

Structure	Evidence sources combined	prob(POS) lower bound	prob(POS) upper bound	uncertainty	DST probability bar
celecoxib	QSAR: hDILI Rule: sulfonamide QSAR: Cholestasis (eTRANSAFE)	0.928	0.987	0.060	
M1: hyroxymethyl-celecoxib	QSAR: hDILI Rule: sulfonamide Rule: alcohol_aliphatic QSAR: Cholestasis (eTRANSAFE)	0.599	0.956	0.357	
M2: carboxylic acid-celecoxib	QSAR: hDILI Rule: sulfonamide Rule: carboxylicAcid_aromatic QSAR: Cholestasis (eTRANSAFE)	0.975	1.000	0.025	
Combined Outcome		0.971	1.000	0.0285	

8 CONCLUSIONS

- The proposed workflow uses structural features, QSAR models, and metabolism knowledge to bridge the gap between human and mammalian pre-clinical information.
- This workflow is logical, transparent, and actionable for implementation as a robust in silico prediction tool.

Citations

1. Rathman et al., Chem Res Toxicol 2021, 34 (2), 601-615
2. https://www..fda.gov/science-research/bioinformatics-tools/liver-toxicityknowledge-base-ltkb
3. Yang, et al. J. Chem. Inf. Model. 55, 510−528.
4. https://chemotyper.org/
5. https://www.mn-am.com/products/corinasymphony
6. https://www.mn-am.com/products/chemtunestoxgps
7. Rathman et al., Computational Toxicology 2018, 6, 16-31

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