In Silico Weight-of-Evidence Assessment of Drug-Induced Liver Injuries to Translate Preclinical Studies to Humans

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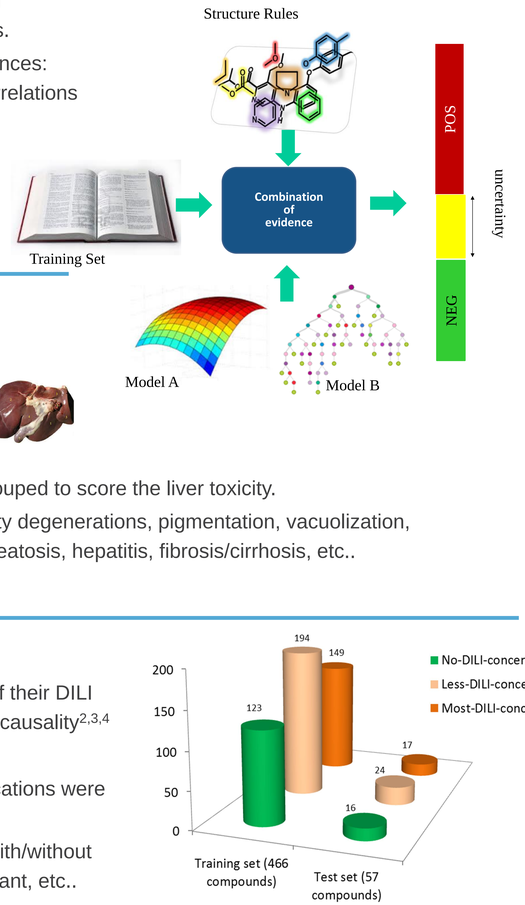
MOTIVATION

- Drug-induced liver injury (DILI) in humans is an adverse effect whose reliable assessment falls short by current in vivo toxicological studies during drug discovery and development.
- For cosmetics or industrial chemicals, repeated dose toxicity of target organs is still not replaced by alternative testing methods.
- A real need exists for a practical and yet reliable alternative.

WEIGHT-OF-EVIDENCE *IN SILICO* APPROACHES

- QSAR (Quantitative Structure Activity Relationship) has not yet been demonstrated to be satisfactory for predictions of target organ effects.
- Multiple *in silico* approaches are employed to leverage various evidences:
  - Structural knowledge – rule-based for positive and negative correlations
  - QSAR method based on partial logistic regression
  - Decision forest partitioning method
- Decision Theory is applied to combine evidence sources to obtain a weight-of-evidence prediction with estimated uncertainty



MAMMALIAN DILI DATASET

- The eTOX project[1] compiled over 1800 Active Pharmaceutical Ingredients (APIs) with detailed pre-clinical toxicity data
- Training set:
  - 600 structures with treatment-related findings
  - 308 structures with no liver findings
- Ontology approach: findings descriptions linked to diseases were grouped to score the liver toxicity.
  - over 400 descriptions (liver enzyme, organ weight changes, fatty degenerations, pigmentation, vacuolization, inflammation, necrosis, etc.) were mapped into categories of steatosis, hepatitis, fibrosis/cirrhosis, etc..

HUMAN DILI DATASET

- US FDA NCTR provides a liver toxicity knowledgebase.
- 1036 drugs administered to humans have been classified in terms of their DILI risk based on FDA drug labels, called DILIRank, after verification for causality[2,3,4]
- A subset of 769 drugs with verified DILIRank were identified.[3,4]
- A data set of 523 orally administered drugs. Ambiguous DILI classifications were not used.
- DILI descriptions: serum enzyme elevations, no jaundice/jaundice, with/without hospitalizations, other severe symptoms, hepatic failure, liver transplant, etc..

REFERENCES

(1) eTOXsys products at http://etoxsys.com/, eTOXsys sampler at https://etoxsys.eu/etoxsys.v3-demo-bk/dashboard/. **(2)** Willyard C. *Nature Medicine*, 22(5), 450-451, 2016. **(3)** Chen M et al. *Toxicol Sci* 136(1), 242-249, 2013. **(4)** Thakkar S, Chen M, Fang H, Liu Z, , Roberts R, Tong W. *Expert Review of Gastroenterology & Hepatology*, 12:1, 31-38, 2017. "The Liver Toxicity Knowledge Base (LKTB) and drug-induced liver injury (DILI) classification for assessment of human liver injury". **(5)** Steger-Hartmann T, Pognan F. *Pharmazeutische Medizin*, Jahrgang 19, Heft 1, März, 2017. **(6)** Yang C et al. *Journal of Chemical Information and Modeling*, 55(3), 510–528, 2015. **(7)** Rathman J, Yang C, Zhou H. *Computational Toxicology*, in press, 2018. "Dempster-Shafer theory for combining *in silico* evidence and estimating uncertainty in chemical risk assessment"

STRUCTURAL RULES AND QSAR MODELS

- Structural rules derived from ToxPrint chemotypes[6] (https://chemotyper.org/)
- Data sources of knowledgebase
  - Human drug structure set of 769 (originally from FDA NCTR LiverTox Knowledgebase)
  - Mammalian API dataset of 908 from eTOXsys[1]
- Potency-aware rules by correlating with LO(A)EL
- QSAR models: ordinal partial logistic regression
  - Structural features: ToxPrint chemotypes[6]
  - Quantum mechanical properties: HOMO/LUMO, heat of formation; physicochemical properties: logP, logS, TPSA, HBA, dipole moment, shape descriptors, etc.
- Decision theory approach based on Dempster-Shafer theory used to combine multiple results to arrive at a weight-of-evidence outcome with associated estimation of uncertainty.[7]

CHEMOTYPES DIFFERENTIATING SPECIES

Chemotypes	Z-scores Human DILI (523)	Z-scores Mammal DILI (506)
Halide any	3.57 (152)	12.8 (264)
Halide aromatic	3.14 (122)	3.25 (223)
Halide alkyl	0.72 (33)	2.21 (66)
Carboxylic acid	3.10 (108)	0.57 (72)
Amine tertiary	-3.75 (156)	2.30 (191)
Amine aromatic primary	1.95 (28)	0.48 (26)
Amine alicyclic	-2.51 (108)	2.70 (159)
Furan	2.20 (13)	-1.00 (15)
Imidazole / Benzimidazole	2.18 (36)	-1.20 (34)
Nitro	1.96 (17)	-1.25 (10)
Piperazine	1.43 (27)	4.23 (59)
Pyrimidine	1.42 (27)	2.03 (54)
Benzyl alcohol	-4.29 (23)	1.78 (13)

Number in () represents frequency of each class.

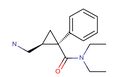
$$z_c = \frac{\bar{y}_c - \bar{y}}{\sqrt{\left(\frac{n_0}{n_c}\right)\frac{S^2}{N}}}$$

Dark orange: most potent (Z ≥ 2)
Light orange: above average (1 ≤ Z <2)
Grey: average (-1 < Z < 1)
Light blue: below average (-2 < Z ≤ -1)
Dark Navy blue: least potent (Z ≤ -2)

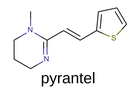
- Chemotypes differentiating humans and mammals (especially rodent), and routes of administration (oral vs. injection) have been identified.

RESULTS

Alerts


milnacipran

Carboxamides (NR2) are positive alerts although primary aliphatic amines are more associated with negative rules in human liver.


pyrantel

Aliphatic tertiary amines and thiophenes are associated strongly with negative rules in human liver.

QSAR **False Negative** → WoE **Positive** → Dempster-Shafer combination of evidence → QSAR **False Positive** → WoE **Negative**

Training and cross validation performance for ordinal (3-level) classification QSAR models

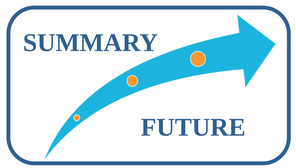
DILI Concern	Global 1 *N* = 295			Global 2 *N* = 294			Alcohol *N* = 149		
	0	1	2	0	1	2	0	1	2
none (0)	106	15	2	105	15	3	48	5	1
less (1)	22	48	27	26	42	29	6	30	18
most (2)	13	35	27	10	28	36	3	20	18

Dempster-Shafer combination of evidence

WoE predictions for test set

DILI Concern	WoE prediction on test set (*N* = 57)		
	0	1	2
none (0)	12	4	0
less (1)	4	11	9
most (2)	3	10	4

diagonal-plus-one concordance = 95%



- A liver knowledgebase prediction system has been developed. and is available from ChemTunes•ToxGPS and eTOXsys
  - Structural rule-base system based on ontology-driven mechanistic data mining and chemoinformatics
  - Structural alerts for specific phenotypes, e.g., steatosis, hepatitis, steatohepatitis, and fibrosis
- Weight of evidence-based approach used to systematically combine different information.
- Next steps: systematic validation and extension of this knowledgebase and approach to cosmetics and industrial chemicals.

CHEMTUNES
TOXGPS

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