Development of Chemical and Toxicological Domains to Support a Chemoinformatics Tool to Identify Chemicals Promoting Cholestatic Liver Injury

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INTRODUCTION

- Cholestasis one of the main forms of chronic drug induced liver injury and is brought about by the impairment of normal circulation of bile.
- Cholestasis is described by an Adverse Outcome Pathway and has defined Molecular Initiating Events (MIEs) which can guide *in silico* modelling.
- Structural fragments related to cholestasis have been identified by Firman et al. (2021), but their utility as a functional *in silico* tool has not been demonstrated.

AIMS

- To code structural alerts for cholestasis in Chemical Subgraphs and Reactions Markup Language (CSMRL) to enable implementation in a chemoinformatics tool.
- To investigate the performance of the alerts with regard to predicting liver toxicity.
- To define domains for the alerts with regard to physico-chemical properties.

METHODS

- Rules capturing the structural alerts for cholestasis were coded within CSRML and implemented in the ChemoTyper software.
- The rules were run against a data set of 1,000+ compounds with known liver toxicity, taken from Pizzo et al. (2016) to calculate performance statistics.
- Domains for alerts were calculated from positive compounds using RDK.

Alerts for Cholestasis (Firman et al., 2021)

Alert		
Oestrogenic steroid	Sulfonamide (antimicrobial)	Azole antifungal
Androgenic steroid	Thiazide	Fluoroquinolone
Stilbene derivative	Benzenesulfonylurea	NSAID (-profen)
Phenothiazine	Beta-lactam	ACE inhibitor (peptidic)
Dibenzocycloheptane	Desosamine	Statin

CSMRL Coding of Alerts in the ChemoTyper

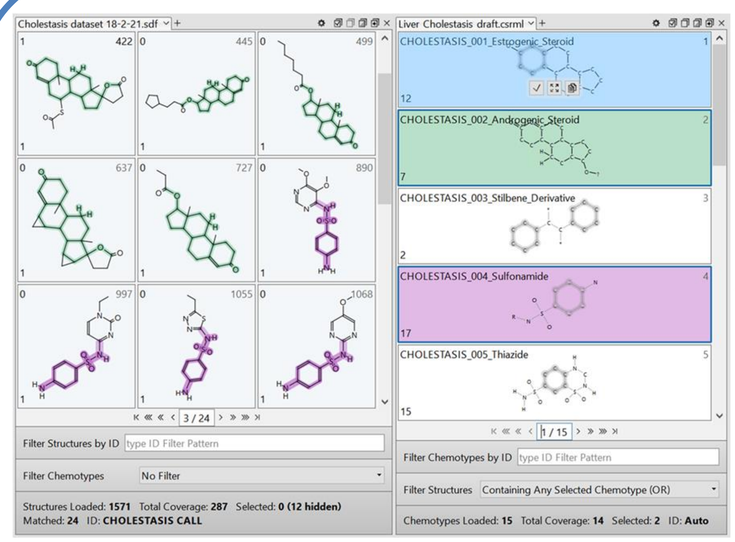


Fig. 1. Screenshot of the ChemoTyper showing implementation of cholestasis alerts

- Alerts were successfully coded into the ChemoTyper, as shown in Fig. 1
- The alerts can be applied to identify possibly cholestatic compounds

Performance

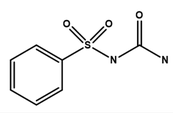
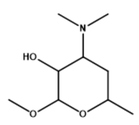
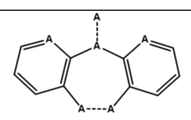
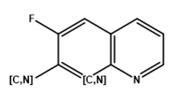
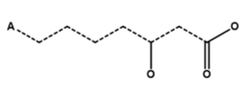
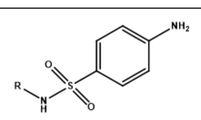
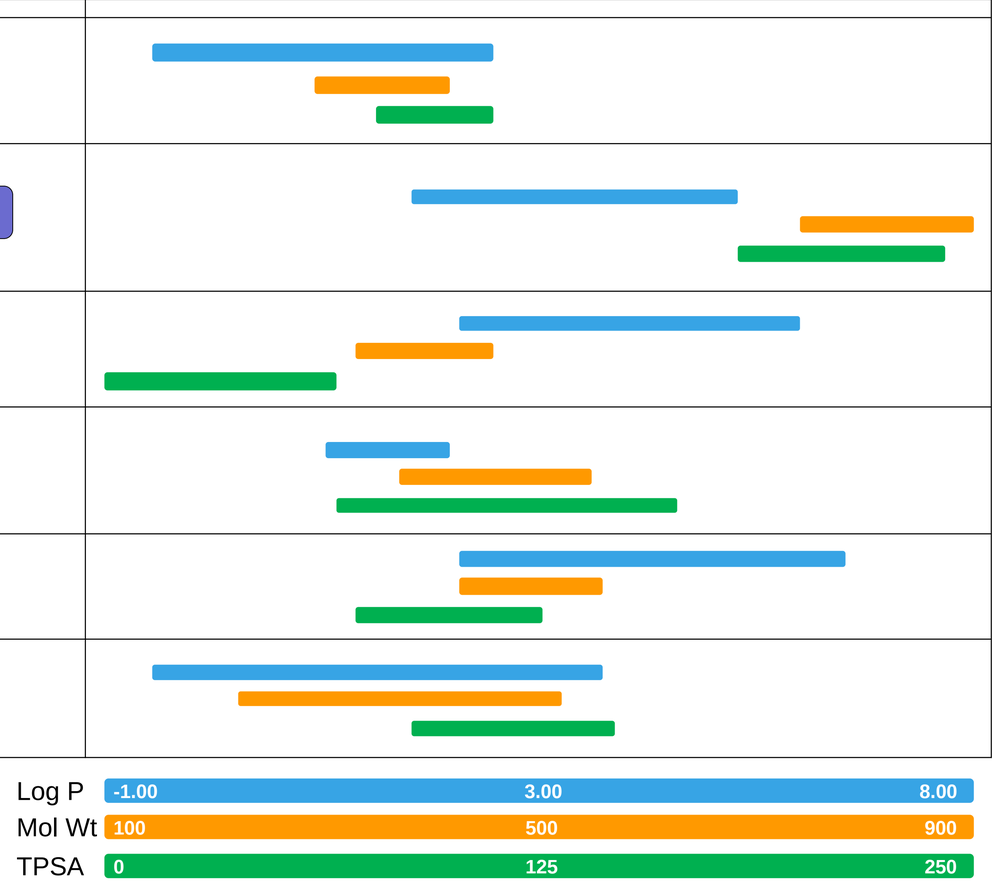
Alert	Chemotype	Sensitivity
Benzenesulfonyl urea		66%
Desosamine		90%
Dibenzocycloheptane		73%
Fluoroquinolone		75%
Statin		80%
Sulfonamide		77%

Fig. 2. Predictive performance and domains of a selection of cholestasis alerts against the liver toxicity dataset

Domains of Alerts



- Alerts were evaluated against the liver toxicity dataset.
- The performance of the alerts varied, with a selection of alerts shown in Fig 2.
- Whilst some alerts showed sensitivity, others may require more evidence e.g. from New Approach Methodologies (NAMs) to allow for acceptable confidence.
- Alerts show a wide variation in their property domains

DISCUSSION

- The MIE provides an information rich source for *in silico* models.
- Structural alerts were developed and coded for cholestasis.
- Approaches to apply structural alerts go beyond its presence / absence in a molecule to consideration of its performance, confidence in domain etc.
- Confidence of rules is increased by the measures related to their “likelihood” of accurate toxicity prediction and the “reliability” of their use.

CONCLUSIONS

- MIE-based structural alerts for cholestasis are defined with physico-chemical domains.
- Extending lines of evidence of alerts increases confidence e.g. for grouping and read-across.
- Incorporation of alerts into chemoinformatics tools, along with NAM data improves confidence in the prediction of complex, chronic adverse effects.

CRITERIA FOR CONFIDENCE IN STRUCTURAL ALERTS

- A full list assessment of criteria to assign confidence in structural alerts was provided by Cronin et al (2022).
- This analysis demonstrates how confidence can be assigned for alerts for cholestasis.
- Where there is high uncertainty / low confidence, more lines of evidence, including NAMs, may be included.

REFERENCES

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