Assessment of the Confidence of a Novel *In Silico* Classification Scheme for Environmental Toxicology

Mark TD Cronin,[1] Franklin Bauer,[2] David J Ebbrell,[1] James W Firman,[1] Steve Gutsell,[3] Geoff Hodges,[3] Jayne Roberts,[3] Maria Sapounidou,[1] Nicoleta Spinu,[1] Paul Thomas[2]

[1]School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, UK

[2]KREATiS, Lyon, France [3]SEAC, Unilever Research, Sharnbrook, UK

Introduction

- Structural alerts predict toxicity prediction to identify hazard or group chemicals for read-across.[1]
- Approaches to develop structural alerts range from expert opinion to data-mining.
- A recent scheme using structural alerts allows for grouping for environmental toxicology. Click here for details.[2]
- Despite widespread use, there is no systematic approach to describe or evaluate the validity of structural alerts for toxicity prediction or to objectively measure uncertainty (and hence confidence).[3]

Aims of Investigation

- To develop an approach to evaluate the uncertainty of structural alerts.
- To evaluate uncertainty and demonstrate confidence that may be placed in structural alerts for ecotoxicology.

Methods

Criteria were defined relating to the properties of, and uncertainty associated with, structural alerts for toxicity prediction. These are based on:

- Description and domain of the structural alert
- Concordance and consistency of biology e.g. supporting data
- Evidence of causality e.g. mechanisms of action
- Performance of the structural alert

The criteria were applied to structural alerts for mechanistic classification.

Scheme to Evaluate Structural Alerts

Ten Criteria for Uncertainty of Structural Alerts Identified → Characteristics of Low / Moderate / High Uncertainty Defined

Criterion	Characteristics of Low Uncertainty
Purpose	Toxicity prediction or grouping
Structural Description	Unambiguous description
Structural Domain	Molecular environment/ properties
Endpoint	Clear and unambiguous
Species Relevance	Unambiguous identification
Metabolic Domain	Metabolic activation
Mechanistic Interpretation	Defined mechanism / AOP
Mechanistic Causality	Chemistry is associated with the MIE and / or KE
Coverage	Low coverage / few false positives
Performance	Excellent predictive performance
1° Supporting Evidence	Supporting toxicological data
2° Supporting Evidence	NAMs

Case Study Using Uncertainty Criteria

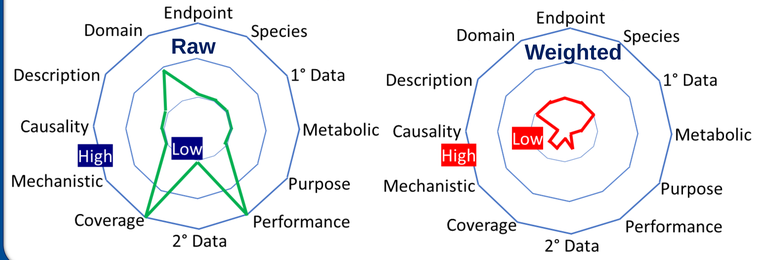
Criteria Applied to  → Uncertainty for Each Criterion → Uncertainty Scores Weighted

Uncertainty Relating to Alert for Aliphatic 1˚ Hydroxy Group	Assigned Uncertainty		Proposed Uncertainty Weighting
Grouping / confirm QSAR domain	Low	x	2
Well defined (1° aliphatic hydroxy)	Low	x	10
Molecular environment known/ limits of phys-chem properties less well defined	Moderate	x	10
Acute toxicity	Low	x	10
Relevant across aquatic taxa	Low	x	10
No requirement for metabolic activation	Low	x	5
Non-polar narcosis	Low	x	5
Unreactive chemistry consistent with membrane accumulation	Low	x	2
Coverage not known	High	x	2
Performance statistics not known	High	x	2
Many acute toxicity data across species	Low	x	10
Many NAMs data	Low	x	2

Quantification and Weighting of Uncertainty Scores

- To facilitate the process of quantifying uncertainty, scores were applied: Low = 1 Moderate = 2 High = 3
- Some criteria are considered more important e.g. full definition of the alert species, supporting information.
- A weighting scheme is proposed for the criteria, as would be applied for grouping.
- The raw and weighted scores for the structural alert are shown in Figure 1.

Fig 1. Raw / weighted uncertainty scores for aliphatic 1˚ hydroxy alert



- Radar plots demonstrate uncertainties of the alert.
- Aliphatic 1˚ hydroxy group (Fig 1) has high confidence / low uncertainty in the weighted scheme.
- The weighting scheme is intended to be flexible and use dependent.
- More work on use cases and the weighting schemes is required.

Discussion

- Structural alerts for classification of environmental toxicity were assessed: alerts for narcosis have low uncertainty, electrophilic and specific MIEs higher uncertainty (data not shown).
- Evaluations of structural alerts in terms of uncertainties allowed for weaknesses to be identified: these can be addressed with further evidence e.g. existing data, NAMs etc.
- Uncertainty criteria may be used to characterise different types of alerts and provide confidence in their use.
- Use cases for structural alerts will emphasise different uncertainty evaluation criteria.

Conclusions

- Criteria to evaluate the uncertainty of structural alerts have been established.
- Application of the criteria demonstrates the overall confidence that can be placed in an alert.

Further information → Mark Cronin: m.t.cronin@ljmu.ac.uk

References

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2. Sapounidou M. et al (2020) Under Review in *Environmental Sciences & Technology*
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LIVERPOOL JOHN MOORES UNIVERSITY

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