A Mechanism of Action classification method unifying toxicology and ecotoxicology

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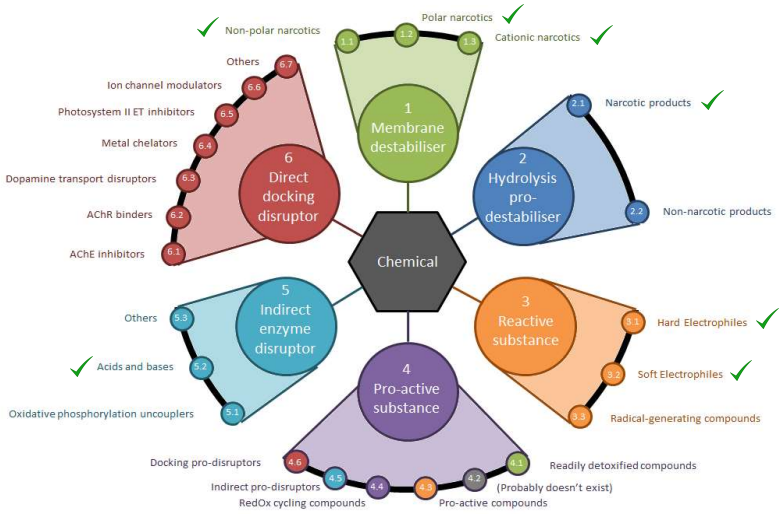
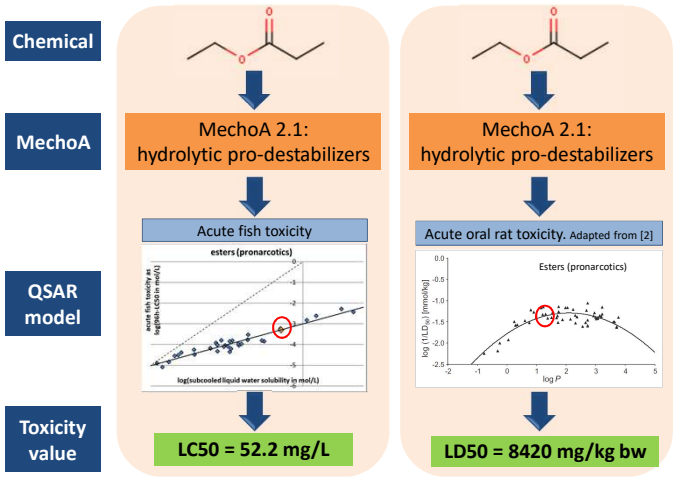
Replacing Experimentation

What are Mechanisms of Action and why use them?

- ❖ Mechanisms of Action (MechoAs) are designed to replace Modes of Action (MoAs).
- ❖ MechoAs are based on molecular initiating events in the AOP framework [1] while MoAs tend to be based on outcomes but mostly lack detail.
- ❖ Depending on the substance, the MechoA can be the same or may vary across species according to the availability of target tissue (e.g. rat ≠ algae).
- ❖ QSARs for any endpoint in any species can be linked directly to each MechoA subclass. A mechanistic understanding of the QSAR can be obtained. To date 7 MechoAs with 3 trophic levels in ecotoxicity (algae, daphnids, fish) have been elucidated (marked with a ✓ below).



Examples of a MechoA/QSAR fish and rat acute toxicity pathway

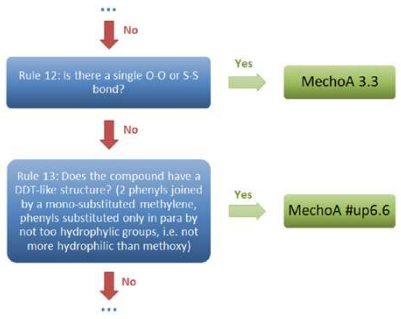


- ❖ Limited to 6 MechoA classes to aid memorisation. 23 MechoA subclasses currently defined. Any future subclasses should fit within the 6 existing classes.
- ❖ MechoAs can be predicted directly from the structure in most cases.
- ❖ A 1st method using quantum calculations was developed [1]. A 2nd method allowing simpler classification of MechoA using structural alerts has been recently published [3].

How are MechoAs predicted?

- ❖ Decision tree classifies substances using structural alerts organised into 63 decision rules.
- ❖ When applicable, different MechoAs are predicted for different species (notation: m = mammals, p = plants, u = unicellular, # = for all species except the following, *etc.*).
- ❖ This scheme has been automated and is freely available online [4]:
  - ❖ For all chemicals, the scheme needs structural formula input (SMILES code).
  - ❖ To improve prediction accuracy of subclass prediction for some structures, pKa input is useful.
  - ❖ For other chemicals (e.g. Direct docking disruptors), optimised 3D structure is required.
  - ❖ The online scheme provides a MechoA for the parent compound and the subclass indicates likely reactions. Further to identification by the user, the model can be rerun on the metabolite.

Example of a MechoA subclass rule designation



Results and Discussion

Classification result	Verhaar scheme	Russom method *	Russom method **	KREATiS method
Correctly classified	54.0	82.5	70.3	92.2
Slightly different	NA	6.3	6.3	3.5
Misclassified	13.4	11.2	10.0	4.3
Unclassified	32.6	0.0	13.4	0.0

* Unclassified = baseline narcotic ** unclassified separated out

- ❖ Performance of our model on training set (301 molecules) and validation set (491 molecules) on organisms from ecotoxicity and mammalian toxicity tests was almost identical (92.0% and 92.2% correct classifications respectively).
- ❖ Our classification method has been compared with other classification schemes [5,6] using the validation set (N=491) and has a better predictive power. Furthermore, to date, mammalian schemes identifying MoA or MechoA from structure have limited applicability.

Conclusion

- ❖ This is the first universal scheme elucidating ecotoxicological and toxicological structural alerts under the same umbrella.
- ❖ Chemicals are organised into just 6 MechoA classes allowing rapid memorisation and simplified use and 23 subclasses which can be extended.
- ❖ The scheme covers the vast majority of the organic chemical universe (excluding nanoforms and polymers).
- ❖ QSARs can be readily associated with MechoA subclasses (Ongoing research).
- ❖ This scheme has been automated and is available for free online [4].

References

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Poster ID: P05-15