EPAA Designathon: MechoA system towards a future classification of systemic toxicity in humans

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Introduction

The EPAA Designathon challenged us to propose a methodology that would be capable of classifying substances as potential systemic toxicants in humans. Our proposal is to use MechoA (Mechanisms of toxic Action) Premium structural alert scheme dividing organic substances into 6 Mechanism of toxic Action classes and divided into a total of 28 subclasses as a starting point. A MechoA is similar to an MIE in that it is based on the first event in an AOP chain, but it often informs more than just the MIE and can be used to replace the term MoA, which is often based on a final outcome rather than on the initial molecular interaction of a xenobiotic material with biological material. Although certain subgroups are still being elucidated in this MechoA classification (such as endocrine disruptor mechanisms), the general MechoAs are considered to cover much of the chemical universe for both mammalian and environmental toxicology thereby creating the basis for a single classification approach based on molecular interaction for toxicologists and environmental scientists alike.

Methods

The Mechanisms of toxic Action (MechoA), structural alert scheme originally designed by Bauer et al., (2018), recently updated by KREATiS with data from a collaborative project (Firman et al 2022) to provide a more complete version is an in silico tool that is reliable and fast enough to improve the decision-making process.
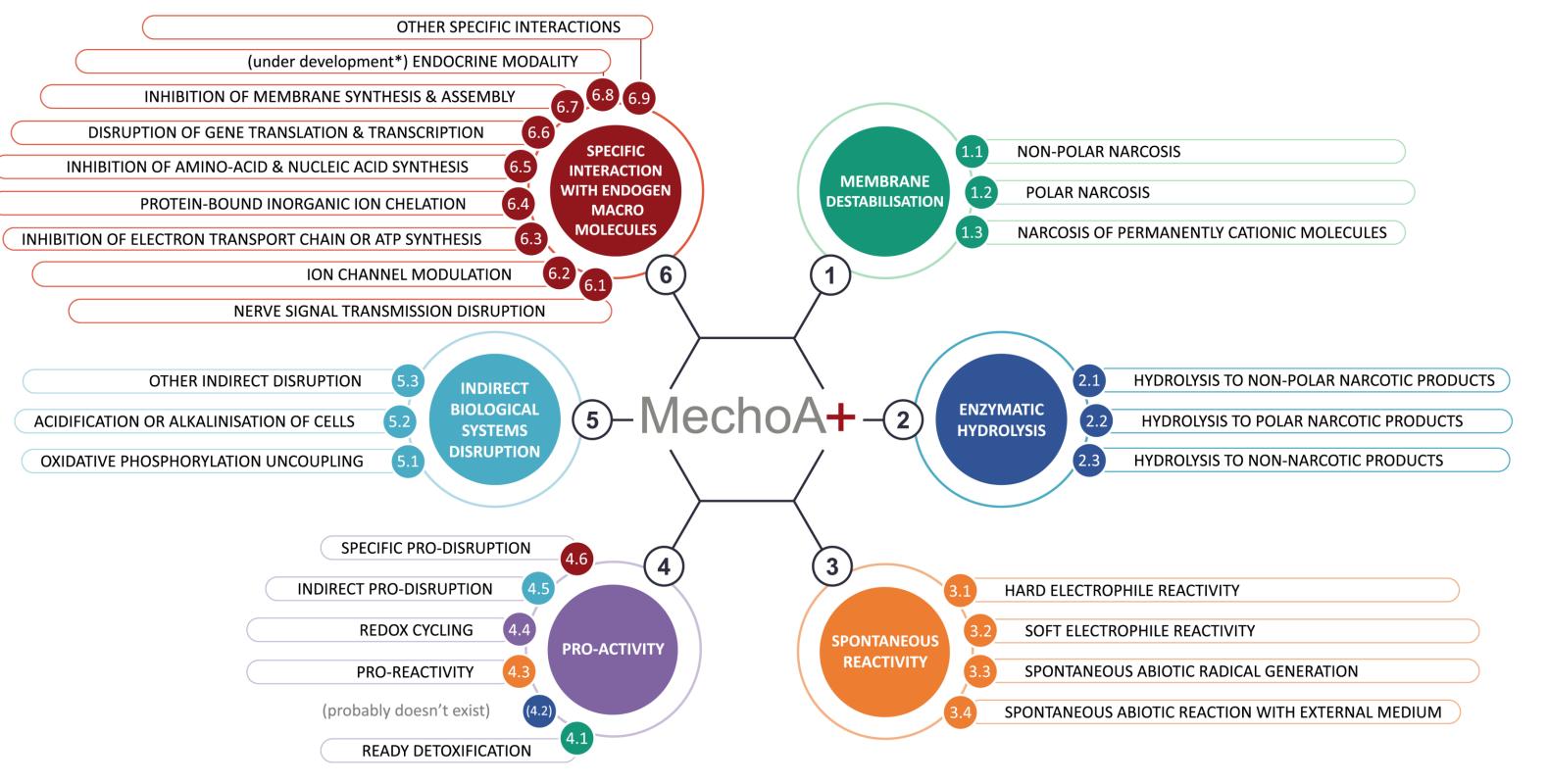
The MechoAs are similar to Molecular Initiating Events (MIEs) but more complete, referring to the MIE, where relevant, and further key events).

Typically, the MechoA sub-Classes are linked to QSAR models. At this stage we have high accuracy QSARs for fish, daphnids, algae and microorganisms for the environment, and for skin sensitization (based on LLNA) for human health. We are working on systemic models (repeated dose study) using this approach. Our approach is:
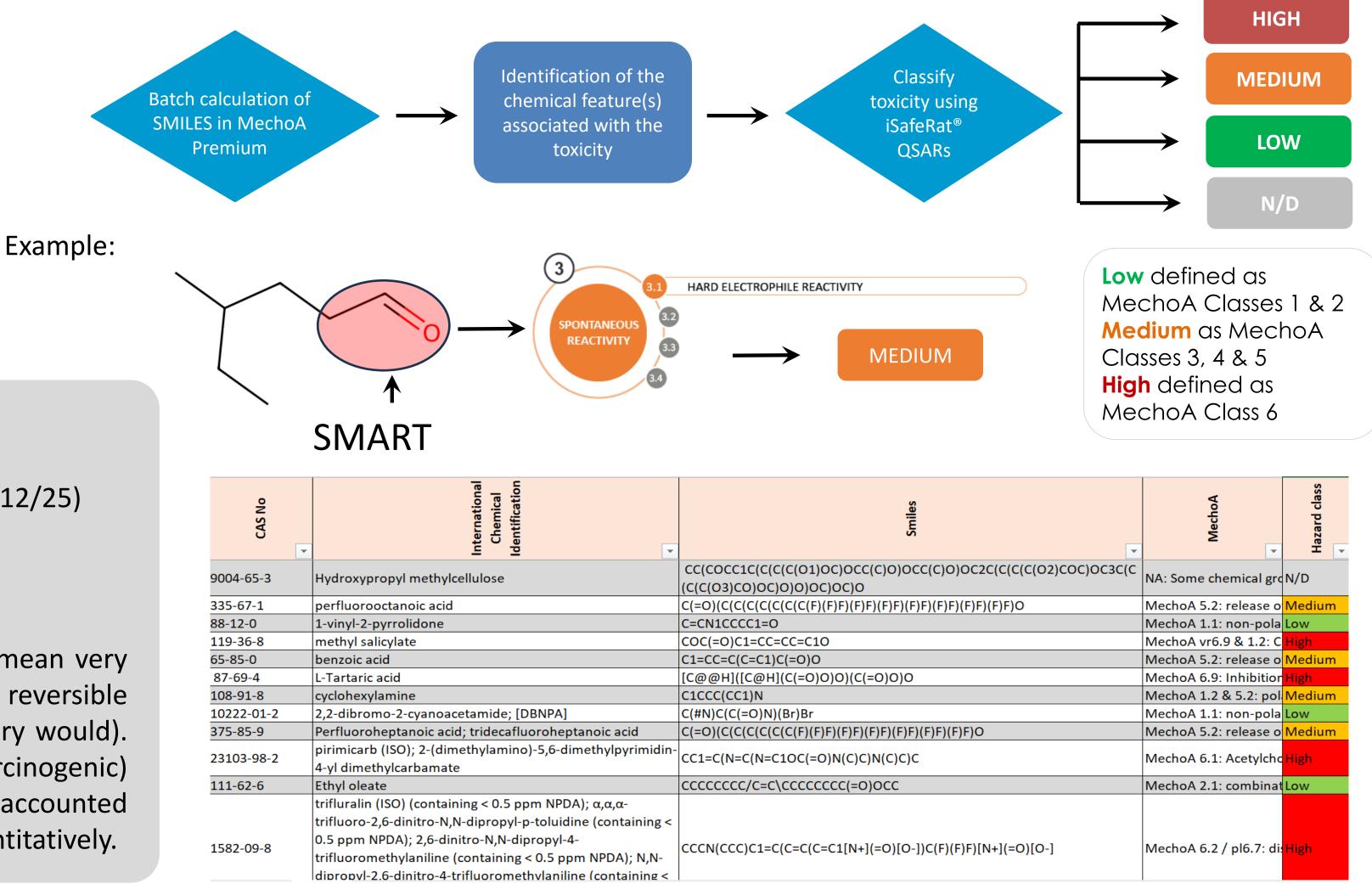
1) SMARTS were related to specific MechoAs (sub-classes) according to the scheme (see figure).

2) Narcosis (reversible or « baseline » toxicity) or enzymatic hydrolysis-based toxicity were considered least worrying (Low); Reactive/Proactive toxicity (e.g., aldehydes; acrylates) and indirect biological interaction (e.g., acids) were considered as Medium; Specific interaction toxicity was considered as most hazardous (e.g., biocides, pesticides, pharmaceuticals are typically in this class) (High).

3) The substance SMILES were run as Batch calculations in iSafeRat® Desktop v4.2.21.

4) The results were classified as High, Medium or Low toxicity or out of domain (N/D) and added to the table with a colour code.

A structural alert scheme to predict toxic mechanisms for environment and human health

- MechoA = Most recent and complete tool in the identification of Mechanism of Toxic Action
- Defines structural alerts from literature and (eco)toxicology data observed for many species
- MechoA Premium (>160 alerts) or MechoA+ scheme (150 alerts)
  - Wide mechanistic domain
  - Wide structural domain
  - Wide species domain (mammals, fish, daphnids, algae, some bacteria, fungi, others…)

*The prediction of endocrine modality, apart from a few examples, is not available within this tool, but we provide it as an expert service. Contact us at contact@kreatis.eu

Example:

Low defined as MechoA Classes 1 & 2
Medium as MechoA Classes 3, 4 & 5
High defined as MechoA Class 6

Results

The results were collected in the table (see sample):
25 / 150 N/D (all inorganics and metals are out of domain = 12/25)
38 / 150 LOW
43 / 150 MEDIUM
44 / 150 HIGH

A substance in a "LOW" category does not automatically mean very low toxicity per se but of less concern as typically it will be reversible and not specifically attacking a target (as the HIGH category would). MEDIUM contains reactive (potentially sensitising or carcinogenic) compounds like aldehydes. As an alert scheme, ADME is accounted for and would be a complement to assess hazard more quantitatively.

CAS No	International Chemical Identification	Smiles	MechoA	Hazard class
9004-65-3	Hydroxypropyl methylcellulose	CC(COCC1C(C(C(C(O1)OC)OCC(C)O)OC)OCC(C)O)OC2C(C(C(C(O2)COC)OC3C(C(C(C(O3)CO)OC)O)O)OC)OC)O	NA: Some chemical gro	N/D
335-67-1	perfluorooctanoic acid	C(=O)(C(C(C(C(C(C(F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)O	MechoA 5.2: release o	Medium
88-12-0	1-vinyl-2-pyrrolidone	C=CN1CCCC1=O	MechoA 1.1: non-pola	Low
119-36-8	methyl salicylate	COC(=O)C1=CC=CC=C1O	MechoA vr6.9 & 1.2: C	High
65-85-0	benzoic acid	C1=CC=C(C=C1)C(=O)O	MechoA 5.2: release o	Medium
87-69-4	L-Tartaric acid	[C@@H]([C@H]([C(=O)O)O)([C(=O)O)O	MechoA 6.9: Inhibition	High
108-91-8	cyclohexylamine	C1CCC(CC1)N	MechoA 1.2 & 5.2: pol	Medium
10222-01-2	2,2-dibromo-2-cyanoacetamide; [DBNPA]	C(#N)C(C(=O)N)(Br)Br	MechoA 1.1: non-pola	Low
375-85-9	Perfluoroheptanoic acid; tridecafluoroheptanoic acid	C(=O)(C(C(C(C(C(F)(F)F)(F)F)(F)F)(F)F)(F)F)(F)F)O	MechoA 5.2: release o	Medium
23210-98-2	pirimicarb (ISO); 2-(dimethylamino)-5,6-dimethylpyrimidin-4-yl dimethylcarbamate	CC1=CC(=N C(=N1OC(=O)N(C)C)N(C)C)C	MechoA 6.1: Acetylchol	High
111-62-6	Ethyl oleate	CCCCCCCC/C=C\CCCCCCCC(=O)OCC	MechoA 2.1: combinat	Low
1582-09-8	trifluralin (ISO) (containing < 0.5 ppm NPDA); α,α,α-trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine (containing < 0.5 ppm NPDA); 2,6-dinitro-N,N-dipropyl-4-trifluoromethylaniline (containing < 0.5 ppm NPDA); N,N-dipropyl-2,6-dinitro-4-trifluoromethylaniline (containing <	CCCN(CCC)C1=C(C=C(C=C1[N+](=O)[O-])C(F)(F)F)[N+](=O)[O-]	MechoA 6.2 / pl6.7: dis	High

Conclusion

This poster describes a rapid Mechanistic and structural alert scheme for the screening of potential environmental and human health systemic toxicants using the iSafeRat® MechoA profiler refined to predict the degree of toxic hazard from parent substances or substances that may undergo metabolism

References

1. Bauer, F.J et al. (2018). High-accuracy prediction of Mechanisms of Action using structural alerts. Comput. Toxicol., 7, 36–45.
2. MechoApedia: https://www.kreatis.eu/MechoA/.

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