MechoA+: use, versatility, and structural diversity

G. Levet[1], F. J. Bauer[1], J. W. Firman[2], B. Campos3, J. Roberts[3], S. Gutsell[3], Mark Bonnell[4], Paul C. Thomas[1], M.T.D. Cronin[2], Geoff Hodges[3]

[1] KREATiS SAS, 23 rue du Creuzat, ZAC de St-Hubert, 38080 L'Isle d'Abeau, France

[2] School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, UK

[3] Safety and Environmental Assurance Centre, Unilever, Colworth Science Park, Sharnbrook, Bedfordshire MK44 1LQ, UK

[4] Science and Risk Assessment Directorate, Environment & Climate Change Canada, Gatineau, Canada

Contact us : www.kreatis.eu / contact@kreatis.eu

INTRODUCTION

Last year, we presented the most recent advances on the Mechanisms of Toxic Action (MechoA) classification scheme, now called **MechoA+**. This tool was developed in collaboration with Liverpool John Moore University (LJMU) and Unilever. It is a structure-activity relationship (SAR) tool which predicts molecular initiating events (MIE) being the starting point of an adverse outcome pathway. It is the most recent tool for the identification of mechanisms of action now including alerts from Sapounidou et al[2], and Firman et al[3] combined with the existing alerts in MechoA scheme.

We have previously described that MechoA+ has a wider mechanistic, structural and species domain (mammals, fish, daphnids, algae, some bacteria, fungi, etc.) than the previous MechoA scheme[1] and Sapounidou-Firman scheme[2,3]. In this work, the research group explored the coverage of the enhanced scheme throughout various types of chemistry on one hand, and highlighted the usefulness of the tool within a regulatory context or product development stages with a case study on the other hand.

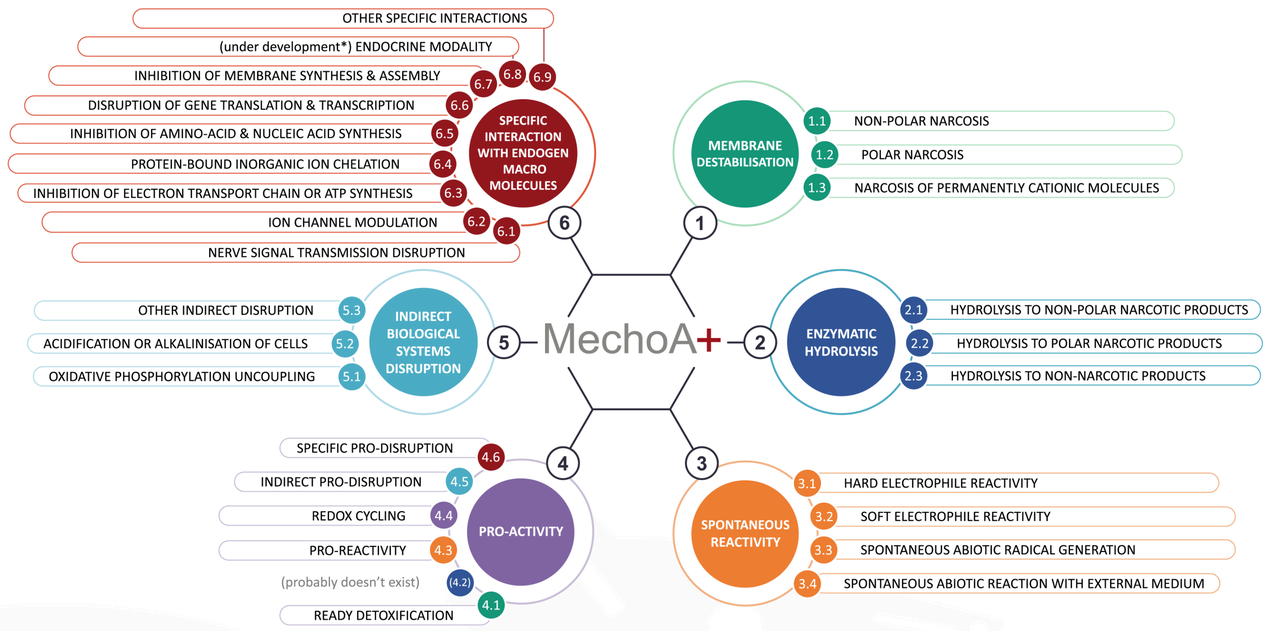


Figure 1: MechoA+ classification scheme

METHODS

Coverage: A dataset of **76120 substances** gathered from various sources[3] that comprises substances used in general chemistry, pharmaceuticals, cosmetic products, pesticides or botanicals, was used in this work to challenge the applicability domain of the tool. Using iSafeRat® Desktop[4] v4.3.19 in batch mode, MechoA+ was run and an analysis of the MechoA results was performed on both the degree of coverage and predictions obtained.

Case study: A case study was envisaged where the goal was to select a **plasticiser** to be integrated into a PVC-based material, with one goal being to select the least hazardous substance in case of potential leakage from the final product. In practice, other properties of plasticisers may be considered key criteria, such as heat resistance or cost, but this case study will focus on the **(eco)toxicological profile** as the principal criterion. 37 diverse plasticisers, among which were phthalates, aliphatic diesters, epoxidized vegetable oils, were profiled with MechoA+ using iSafeRat® Desktop[4].

MechoA+

- A useful classification tool relevant for:
  - ✓ read-across
  - ✓ eco-conception
  - ✓ QSAR development
- Wide structural, mechanistic, and species applicability domain.

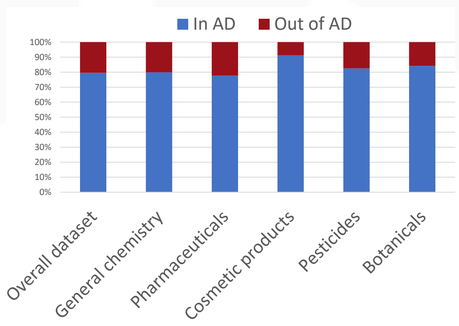


Figure 2: Applicability of MechoA+ for this dataset

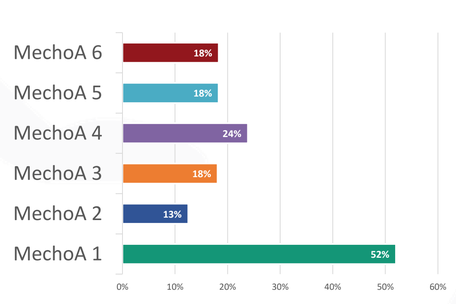


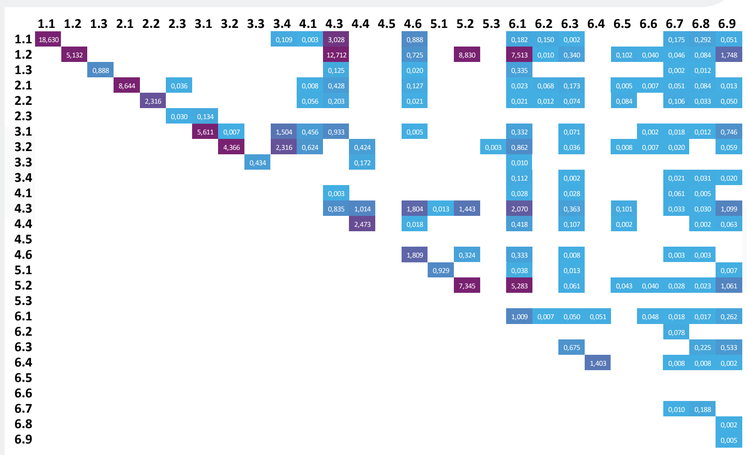
Figure 3: Occurrences of MechoA classes in tested dataset

RESULTS: COVERAGE OF THE SCHEME

Using the 76120 substance dataset, the MechoA+ scheme made predictions for almost **80%** of compounds regardless of the type of chemistry (**Figure 2**). Among the 20% not predicted were inorganics, organometals and mixtures (almost 2000). This is because the software has been developed for organic mono-constituent substances only.

On this large dataset, **478 different MechoA predictions** were obtained. Indeed, several mechanisms can occur at the same time for a single substance, either within the same species or for different species. On another note, it appears in the dataset that narcosis is the most frequent mechanism (**Figure 3**), especially MechoA 1.1 and 1.2 (**Figure 4**), then MechoA 4 followed by other classes.

When looking at the sub-classes, this study showed that MechoA 6.1 frequently occurs, but this is just due to the high number of pharmaceuticals and pesticides in the dataset. Furthermore, some MechoA (e.g. MechoA 5.3) are rarely observed, are not triggered (MechoA 4.5), or not triggered solitarily (e.g. MechoA 6.5). This could be linked to how specific the MechoA is (e.g. species & targets specific) or the absence of a representative chemical feature in the dataset.



Legend: From white to blue to purple, an increase in representativity is observed

Figure 4: Occurrences of MechoA sub-classes in tested dataset

RESULTS: CASE STUDY

As detailed in the **Table 1** below, the results from MechoA+ indicate that **terephthalates**, **aliphatic polyesters** and **benzoates** plasticisers are likely to have a **more favourable environmental and toxicological profile** and could be a preferred alternative provided they meet other decision criteria.

Table 1: Predicted MechoAs of plasticisers

MechoA class (least to most hazardous)	Predicted for the following substances
MechoA 2.1: combination of enzymatic hydrolysis to corresponding acids and alcohols, generating acidity and narcosis of the parent molecule, for all species.	**terephthalates**: DOTP, DBT **aliphatic polyesters**: DC9CH, DOA, DINA, DIDA, DTDA, DMS, DBS, DIDAz, ATBC **benzoates**: ODEDB, OXPDB, INB, IDB
MechoA **3.1**: reaction as a hard electrophile with proteins and DNA, leading to **adducts** formation, for all species.	**o-phthalates**: BBP **epoxidised vegetable oils**: ELO, ESBO, EACO
MechoA 2.1 & **maC2.3**: digestive hydolysis of one ester for all species, monoester product induces PPARalpha (precursor of **liver cancer** development) in chronic timeframe and **binds to FSH receptors**, for mammals.	**o-phthalates**: DEHP, DBP, DIBP, DPP, DIPP, PIPP, DIHP, 711P, DMeP, DnHxP, DCHP, DINP, DIDP, DPHP, DIUP, DTDP **trimellitates**: TOTM
MechoA 6.1: **Acetylcholinesterase inhibition** for animals & probably other esterases inhibition for all species.	**phosphates**: TPP

CONCLUSION

- MechoA+ has a wide applicability domain, thus being helpful in all sectors of organic chemistry (general chemistry, pharmaceuticals, cosmetic products, pesticides or botanicals)
- It can be used for high throughput analysis of big datasets, e.g. for eco-conception purposes, as shown with the case study on plasticisers

PESPECTIVES

- An extended analysis of the results for each database and MechoA prediction
- A comparison of older schemes with MechoA+
- Validation of the predictions to quantify, if possible, the amount of true or false positives
- Comparison with the extended scheme MechoA Premium

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(4) iSafeRat® Desktop v4.3.20, 2024 for High Accuracy QSAR prediction by KREATiS SAS (https://isaferat.kreatis.eu/)
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