

MechoA+

One Scheme to bind them all

Gaspard Levet¹, Franklin J. Bauer¹, James W. Firman², Homa Basiri², Jayne Roberts³,
Bruno Campos³, Paul C. Thomas¹, Mark T.D. Cronin², Geoff Hodges³

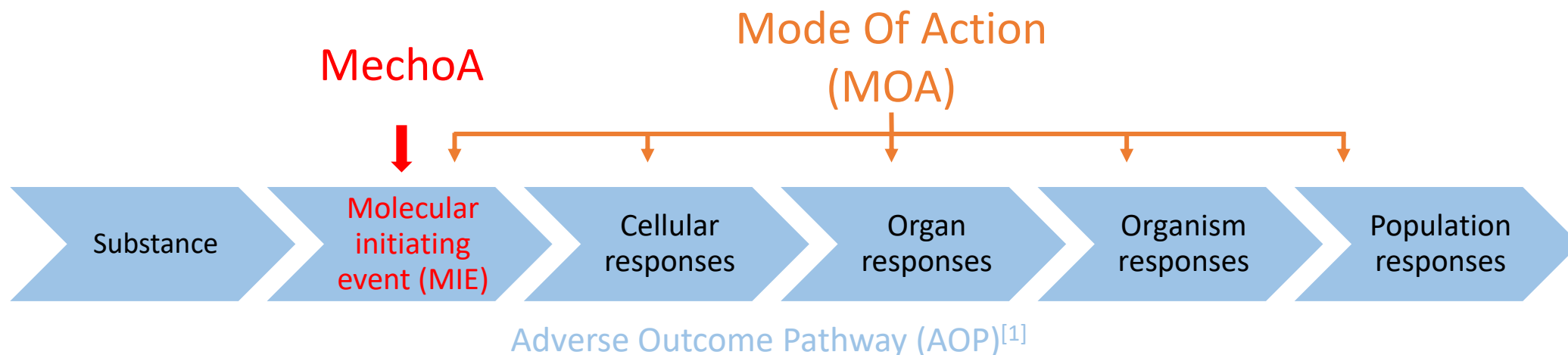
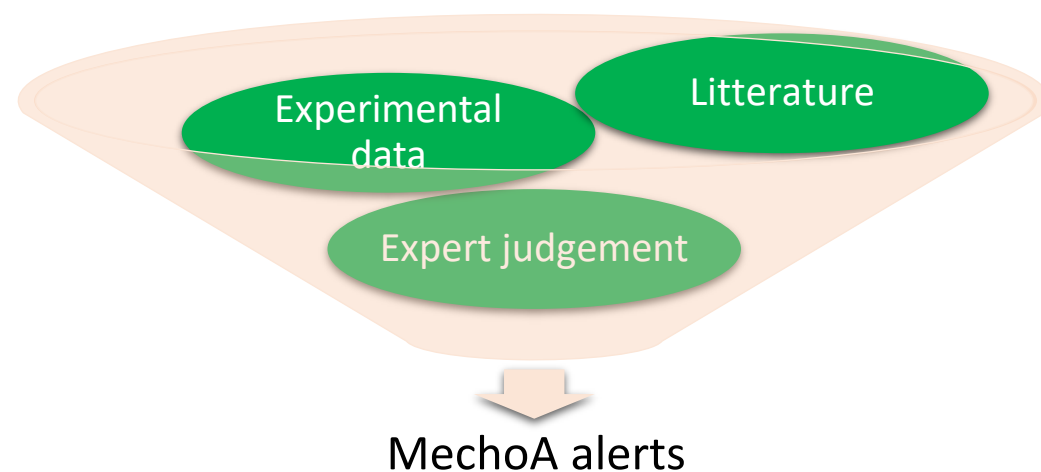
¹KREATiS, 23 rue du Creuzat, 38080 L'Isle d'Abeau, France

²School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool (LJMU), UK

³Safety, Environmental and Regulatory Science (SERS), Unilever, Sharnbrook, UK



- Collaborative work: KREATiS, LMU, Unilever
- Structure-Activity Relationships (SAR) model
- Predict Molecular Initiating Events (MIE)
- For organic substances
- For many species
- Unify ecotoxicologists et human health toxicologists



[1] Adapted from Ankley, G. T. *et al.*, 2010. Environ. Toxicol. Chem. 29, 730–741.



- Merging of the most recent MIE schemes
- Built on the advantages of both
- Refine and improve



[© Amazon-MGM studios]

MechoA+ scheme

152 MIE alerts

6 classes

27 sub-classes

MechoA scheme^[2]

69 MIE alerts

6 classes

23 sub-classes

Sapounidou-Firman scheme^[3-4]

183 MIE alerts

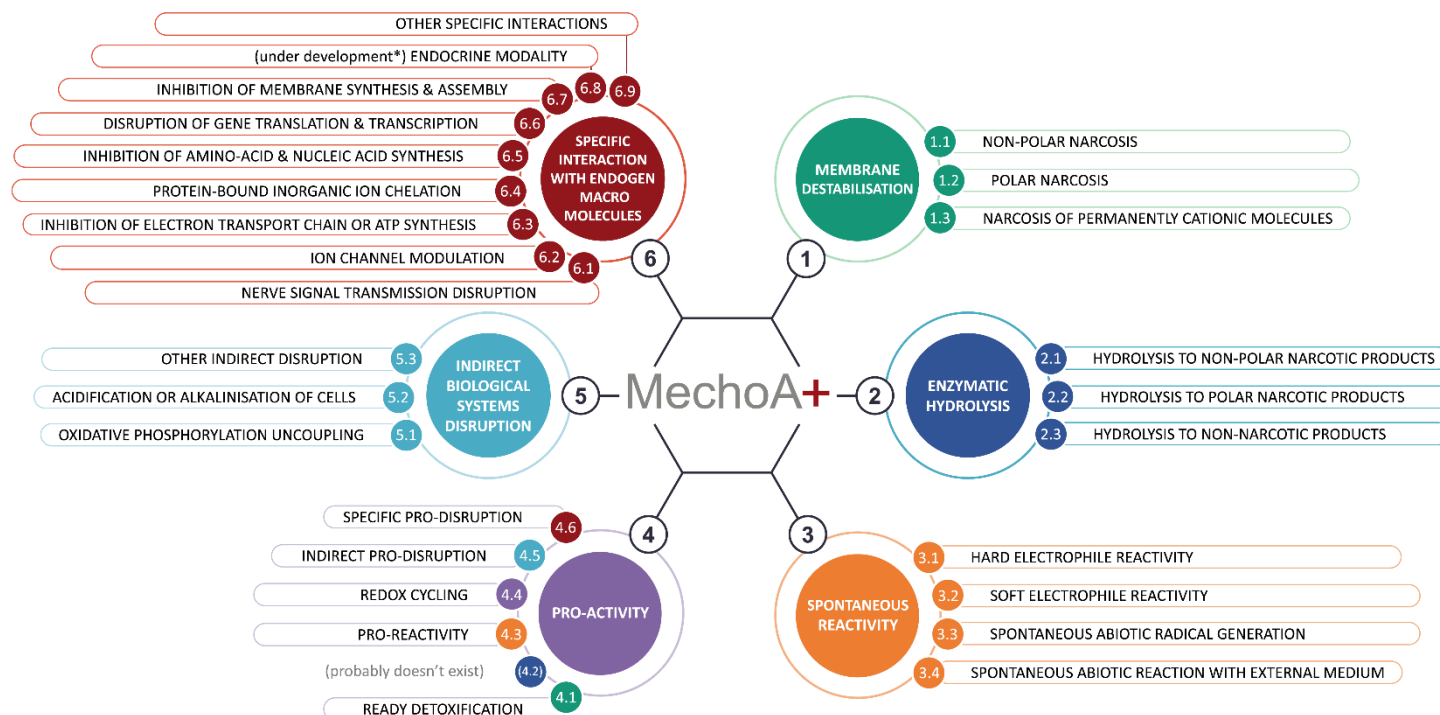
3 classes

25 sub-classes

[2] Bauer FJ, *et al.*, 2018. Comput. Toxicol. 7, 36-45.

[3] Sapounidou M, *et al.*, 2021. Environ. Sci. Technol. 55, 1897-1907.

[4] Firman J.W., *et al.*, 2022. Environ. Sci. Technol. 56,17805–17814.



*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

MechoA xx Y. Z : Brief description of MIE with an indication of the taxa of concern.
 Taxa code class sub-class

MechoA **pl** 6.3 : inhibition of Protein D-1 at photosystem II (QB site), blocking the production of dioxygen and energy, for **plants**.



EASE OF USE / AVAILABILITY

- User-friendly
- Visual: MechoA wheel
- Automated
- Toxicologists and ecotoxicologists share a common language
- MechoA+ Profiler soon in OECD QSAR Toolbox (free to use)
- MechoA Premium in iSafeRat® Desktop (under licence)

APPLICATIONS

- For QSAR modelling
 - Related to mechanistic QSARs (iSafeRat Desktop®)
- For Read-Across
 - justification for regulatory registration
- For eco-conception
 - Development of new chemicals
 - Analogues search

Posters

6.05.P-Tu440 - A Safe & Sustainable by Design R&D pipeline using *in silico* methodology

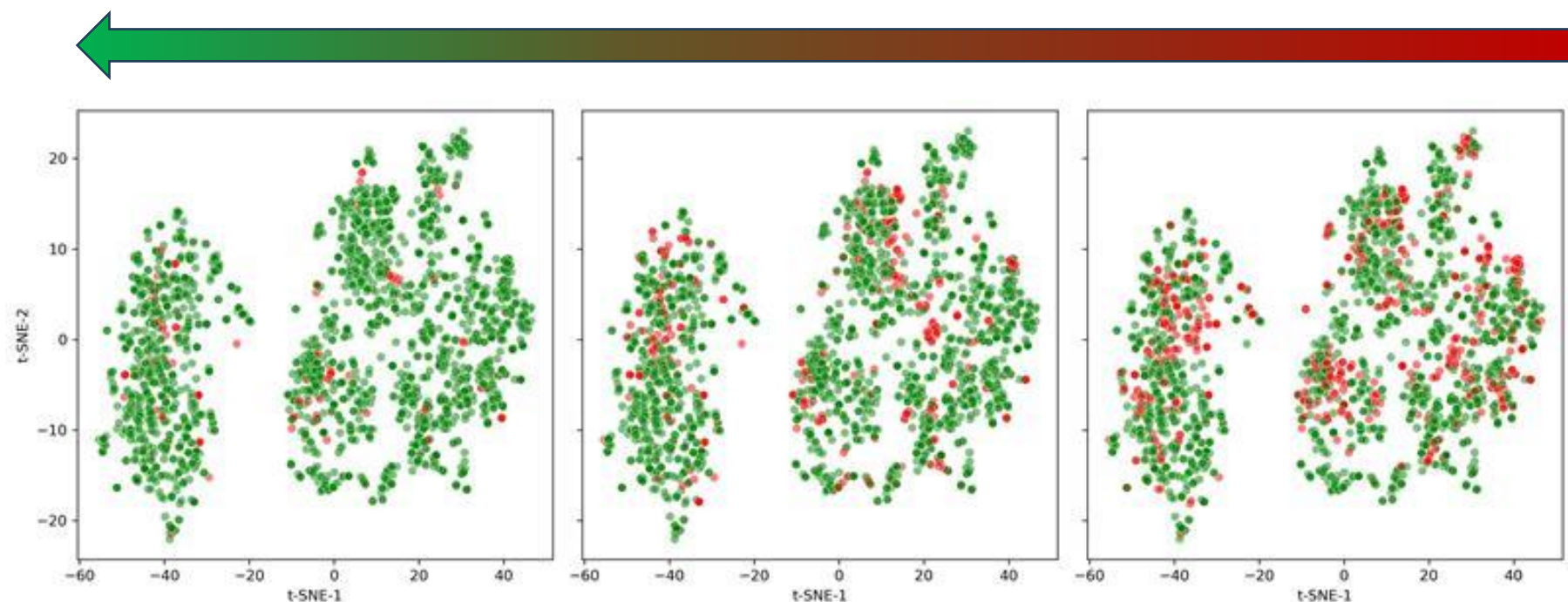
1.08.P-Tu048 - The Many Pros and a Few Cons of Mechanistic *in silico* NAMs

REGULATORY RELEVANCE

- Helps in 3Rs (reduce, refine, replace animal testing)
- Mechanistic insight:
 - OECD 5th principle of QSAR validity; important in the RAAF (*e.g.*, AE 2.2)
- Useful for many endpoints, such as: acute and chronic fish and daphnid toxicity, skin sensitisation, *in vitro* mutagenicity, *etc.*

Comparison of coverage MechoA+ VS MechoA VS Sapounidou-Firman

t-SNE analysis^[5] of the training set (2091 substances)



MechoA+ scheme

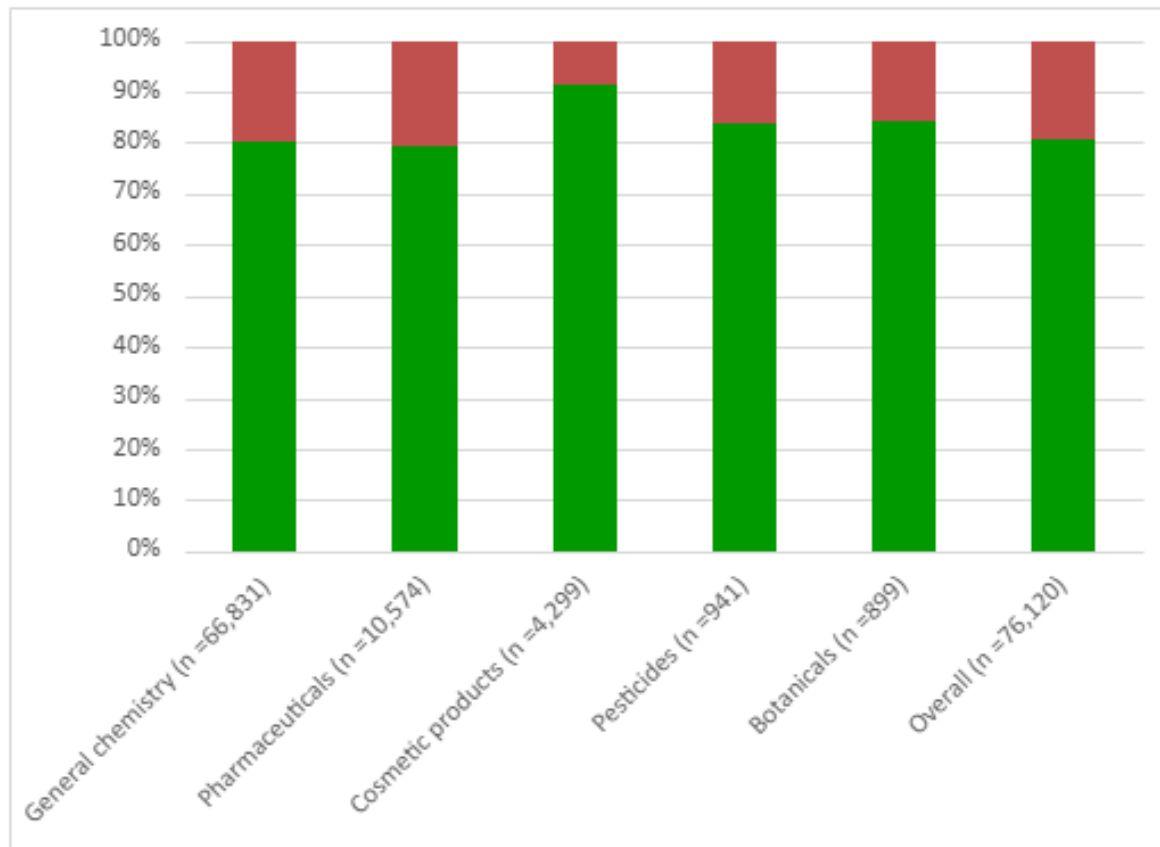
MechoA scheme

Sapounidou-Firman scheme

*green: predicted substances
red: not predicted substances*

[5] van der Maaten L. & Hinton G., 2008. JMLR. 9, 2579–2605.

Percentage of substances predicted in several databases



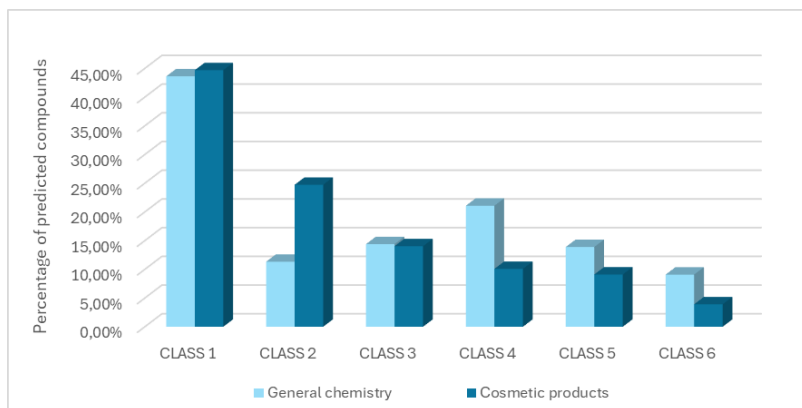
green: predicted substances
red: not predicted substances

- Large spectrum of chemical compounds predicted and variety of uses

Predictivity for each chemical uses

- Percentage of substances predicted in each class

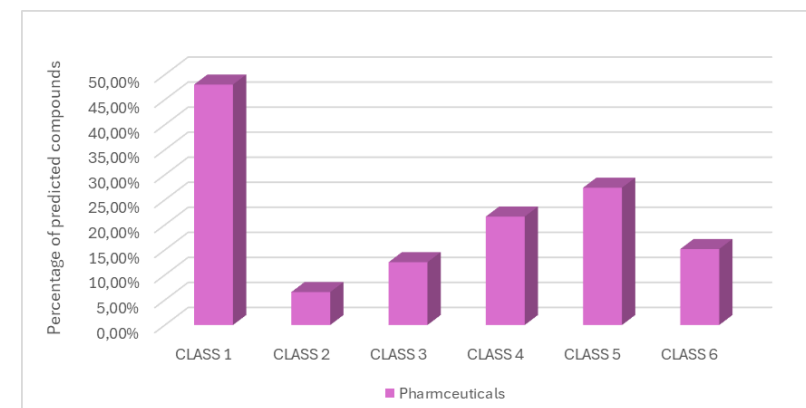
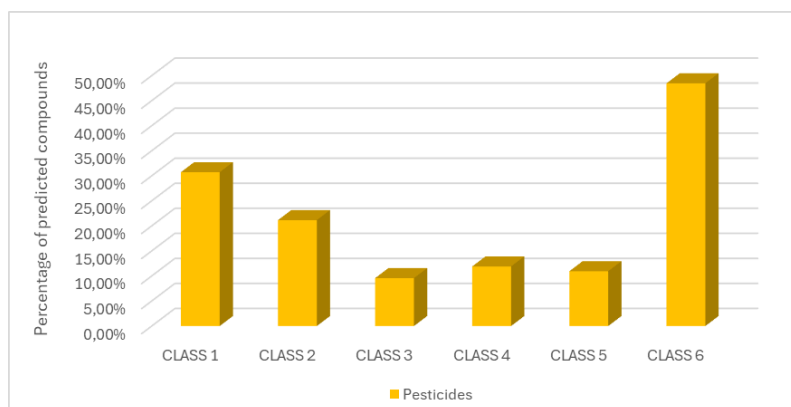
Comment: several MIEs can be detected for each substance, e.g. depending on the target species



General chemicals (66,831 substances) and cosmetics (4,299 substances)

Majority are assigned to be narcotics

Pesticides (941 substances)
Majority are assigned in class 6



Based on Drug bank mostly (10547 substances)

- Majority assigned class 1 → additional mechanism ? formulation ingredients in the database ?
- Many class 4 (pro-active substance) and 5.2 (acids and bases)
- Identify a knowledge gap for class 6 in MechoA+

- Refine alerts for pharmaceutical substances: Involved in PharmERA project (**P4.14.P-Tu374**)
- Inclusion of endocrine modality alerts (MechoA 6.8) soon to come (Cronin *et al.*, **P1.07.P-Mo005**)
- MechoA+ publication in preparation
- Involved in EPAA designathon to help classify human systemic toxicity
- **Ecotoxicology and human health QSARs** developed using MechoA+/Premium scheme

Integrating MechoA+ in SSbD approach can contribute to:

-  **Mechanistic insight** to guide safer alternatives
-  **Early hazard identification** to avoid substances of concern (through MIE)
-  **Reduction of animal testing: read-across and mechanistic QSARs**
-  **Regulatory relevance** to anticipate compliance and reduce late-stage redesign
-  Support for **eco-design and innovation**
-  Unify them all: **human and environmental toxicology**

Thank you for your attention

Find us: booth 65

KREATiS, 23 rue du Creuzat, 38080 L'Isle d'Abeau, France | Email: contact@kreatis.eu