A mechanistically driven One Health application of Quantitative Mechanism-Activity Relationships (QMARs) in ecotoxicity and mammalian toxicology

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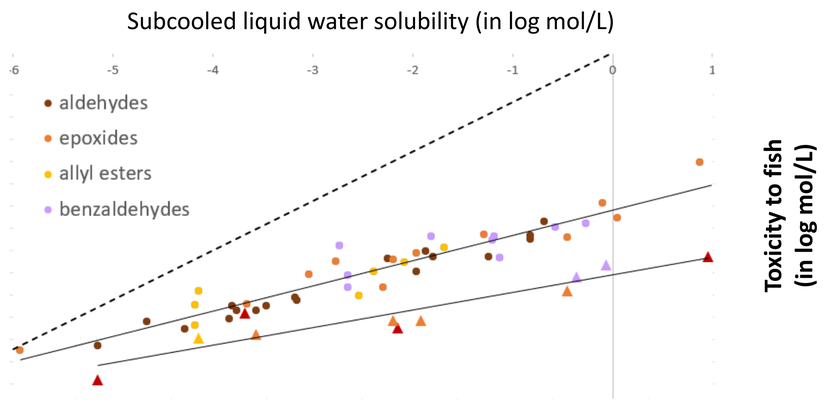
Introduction

All NAMs have both advantages and disadvantages. One advantage of *in silico* NAMs over *in vitro* NAMs, is that they directly predict *in vivo* regulatory endpoints as their dataset is comprised of these studies. Furthermore, mechanistic QSARs or "QMARs" (*i.e.,* quantitative relationships between molecular initiating events (MIE) of specific chemical moieties and effects on biological organisms) can link impacts on both human health and environmental endpoints simultaneously via the same mechanism of toxic action (MechoA).

Concept of our mechanistic approach

MechoA (Bauer *et al.* 2019, Firman *et al.* 2025, Levet *et al.* (submitted)), a structural alert (SAR) scheme, was developed to provide mechanistic insight as a necessary first step to produce reliable QSARs predicting ecotoxicological and human health endpoints, with well-defined applicability domains. It provides an understanding of the interactions between the test substance and the biological matrix explaining the observed toxicity and linking it to chemical structure.

As *in silico* expert-knowledge-based models, our mechanistic QSARs are linked to two keystones: 1) structural features and 2) quantified biological matrix interactions via a mechanism of toxic action (or MechoA, which is an extension of MIEs). The inclusion of a mechanistic interpretation which is underlined by the principles of (bio)chemistry, increases confidence in the outcome by providing a scientific justification for the predicted toxicity. The primary toxicophore within a chemical family defines the MechoA although all the molecules having the same MechoA will not have the same (or even any) toxicity. MechoAs may be different for different organisms (*e.g.,* a substance which is a neurotoxic to fish or rats/humans may be a "baseline" toxicant to algae). It prioritises identified MechoA sub-classes, provides an understanding of the interactions between the test substance and the biological matrix and explains observed toxicity (as extracted from the literature and incorporated in the model via >160 structural alerts). It links toxicity to structurally similar moieties (or toxicophores) within a structure that will impact the biota at different trophic levels. Any endpoint can ultimately be related to a MechoA, by combining with a QSAR related to the endpoint for a quantitative prediction. This approach is relevant for both ecotoxicological and human health endpoints, *e.g.,* 35d EC10 chronic toxicity to fish following OECD 210 Guideline or a Local Lymph Node Assay (LLNA) following OECD Guideline 429. Unlike read-across methods, mechanistic QSARs may contain more than one structural group with the same mechanism of action (thus, the same toxic impact at the same molar concentration).



MechoA 3.1 compounds (96h-LC50) – training set; N = 47; R^2 = 0.79; RMSE = 0.25

MechoA 3.1 compounds (32d-EC10) – training set; N = 12; R^2 = 0.87; RMSE = 0.34

Figure 1. *MechoA 3.1 training set regression for the fish 96h-LC50 (circles) and the fish 32d-EC10 (triangles). Dotted line = water solubility limit. Structurally different but mechanistically similar substances fall on the same regression lines. Goodness-of-fit statistics are shown for both acute and chronic toxicity QSARs.*

See full MechoA scheme below poster

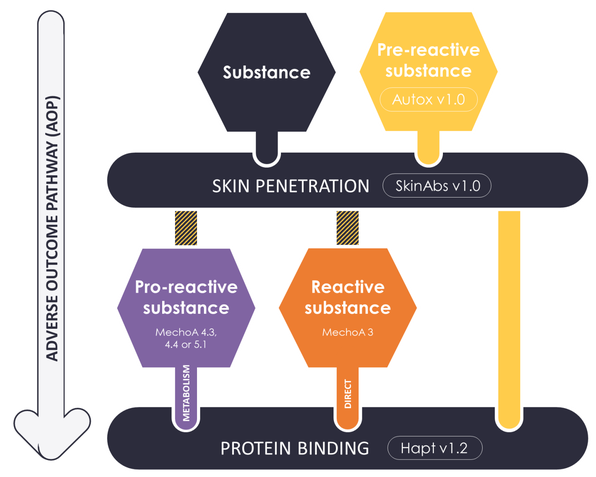


Figure 2. *Skin sensitisation prediction model taking into account potential for skin absorption, autoxidation model transforming non-haptens into pro-haptens, and finally MechoA based protein binding alerts. EC3 values are determined by nearest neighbour analogues.*

Ecotoxicity QMAR

Combining MechoA with internally validated descriptor and toxicity data, we create what we term "High Accuracy QSARs" or "QMARs" which we consider accurate enough within their applicability domain, based on their goodness of fit, to be able to substitute for experimental studies. For MechoA 3.1, in Fig. 1, an acute and chronic fish toxicity QSAR is an example which contains multiple structural groups with the same mechanism of action. The groups are not structural similar but mechanistically all share the same MechoA, fall on the same toxicity regression lines for both acute and chronic fish, daphnids and algae.

To get full details on MechoA functionality just follow the link: KREATiS - MechoApedia
MechoA+ is now available for OECD Toolbox users as an addin here: https://repository.qsartoolbox.org/Tools/Details/70f75627-446c-45b0-8683-52ebd7a2bae7
For non-OECD TB users, a web version of MechoA+ and a new far more complete version of MechoApedia is underway and is expected to be released in June 2026.

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Statistical validation

Any hypothesis is only speculation until its validity stand up to scrutiny using external datasets. Both the skin sensitisation and ecotoxicity methods have proved robust under statistical validation as demonstrated at the bottom of Figure 1 and in Table 1. The latter compares **best** and **worst** case statistical values across a range of NAMs recognised for skin sensitisation assessment

		Predictive parameters compared to LLNA outcome (%)				
		Sensitivity	Specificity	Balanced accuracy	Precision (negative) (NPV)	Precision (positive) (PPV)
in vitro	DPRA (n = 156)	**67.0**	53.2	**60.1**	**41.0**	**76.8**
	PPRA (n = 165)	80.2	46.9	63.6	50.0	78.2
	KeratinoSens™ (n=169)	66.9	56.0	61.5	41.8	78.2
	h-CLAT (n = 168)	88.0	39.2	63.6	58.8	76.9
	U-SENS™ (n = 167)	**91.5**	**36.0**	63.7	64.3	77.0
	SENS-IS (n = 167)	88.9	52.0	70.4	**66.7**	81.3
in silico	DEREK v6.01 (Nexus 2.2.2) (n = 157)	81.7	50.0	65.8	54.5	78.8
	CLASS v1.5 (iSafeRat 5.2.10) (n = 146)	**81.0**	**69.6**	**75.3**	**62.7**	**85.3**

Table 1. *Statistical evaluation of skin sensitisation for recognised NAMs. **Green** boxes = best in class; **red** boxes = worst in class. n = number of substances; positive = skin sensitiser; negative = not skin sensitiser.*

Mechanistic model advantages

Any mechanistically driven toxicity endpoint (*i.e.,* mammalian toxicity or ecotoxicity) can be related to a MechoA alert but each QMAR is based upon the species, biology, study duration, and apical endpoint of interest (*e.g.,* chronic toxicity to fish following OECD 210 Guideline or skin sensitisation in mice following the LLNA study OECD 429).

Mechanistic *in silico* NAMs provide advantages that rarely exist in empirical tests: They provide an ethical solution to avoid testing and a rational explanation for observed toxicity within the context of Adverse Outcome Pathways and quantitatively indicate the degree of toxicity for classification or risk assessment purposes. These methods are increasingly recognised by regulators (as they are rigorously developed following the OECD guidance, such as the QSAR Assessment Framework, for model validation) and industry alike, as alternatives to avoid performing experiments, and particularly importantly animal testing for regulatory submissions.

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References

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