Classification & Labelling Assessment for Skin Sensitisation (CLASS) update: a mechanistic *in silico* model to predict skin sensitisation potential

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Introduction

The innovative, mechanistic model iSafeRat® CLASS (Classification & Labelling Assessment for Skin Sensitisation) is designed to **predict skin sensitisation** (SS) of organic chemical substances in the mouse local lymph node assay (LLNA). SS is predicted through four sub-models: skin penetration (SkinAbs v1.0), hapten (i.e. protein adduct formation) & pro-hapten detection (Hapt v1.2), pre-hapten detection through autoxidation (Autox v1.0) and expected positivity in the LLNA test only (LLNA+ v1.1). The first version which predicted only the potential for positive or negative sensitisation was developed in 2023. Since then, major improvements have been integrated which **increase confidence in predictions and broaden the applicability domain**. In the meantime, regulatory needs were redefined in the recent publication of the QSAR Assessment Framework (QAF)[1]. This framework was designed to help regulators across the OECD member states to **better assess the prediction capacity of QSARs** by using a reflective check list scheme to arrive at a consensus result. QAF sets 4 new principles for prediction validity, in addition to the 5 OECD principles for model validity.

This poster presents the improvements of iSafeRat® CLASS for SS potential prediction and the related updates in **compliance with the QAF requirements**.

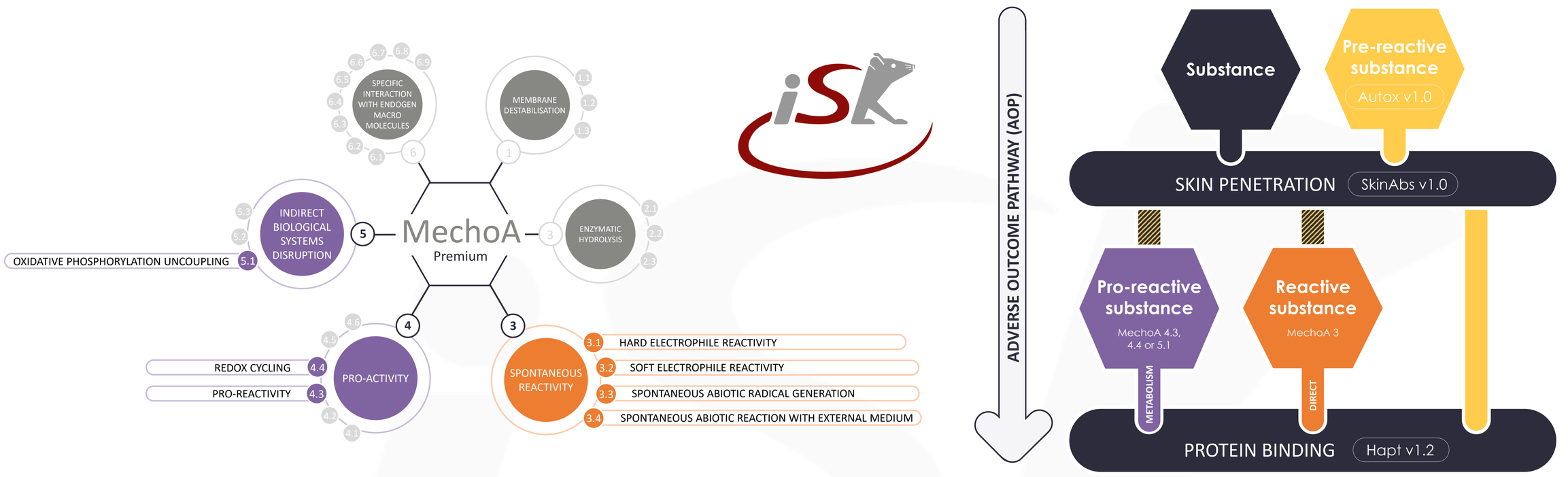

Figure 1. *Classification & Labelling Assessment for Skin Sensitisation (CLASS) model is combining 4 sub-models (Autox v1.0, Skin Abs v1.0, Hapt v1.2 and LLNA+ v1.1 which is not represented here) to assess skin sensitisation through MechoA Premium.*

Methods

Database: LLNA data from NiceATM, CosUE, ECHA dossiers and proprietary data were evaluated for their reliability according to the OECD 429, 442a and 442b guideline requirements, to select only high-quality data. Inorganic substances and multi-constituents were removed from the database. The new database for iSafeRat CLASS v1.4 was composed of validated data on 590 substances (321 sensitisers and 269 non-sensitisers).

Improvement of the model reliability & applicability domain: Following a new splitting method, we (re)defined the structural alerts and exclusion rules for the sub-models based on the addition of new substances in the training set and further literature searches. Furthermore, in order to distinguish positive and negative sensitisers coming from fragment databases, an additional fragmentation approach was implemented. This method improves the automatic structural domain evaluation by iSafeRat® CLASS for both positive and negative predictions.

Improving expert knowledge confidence in the prediction: an automated analogue search now provides mechanistic and structurally similar analogues as part of the iSafeRat® Desktop software output.

Dataset	Size (N)	Out of domain (N)	Accuracy (%)	Balanced accuracy (%)	Sensitivity (%)	Specificity (%)
Training	467	0	78.6	78.3	**84.0**	**72.6**
OECD data set	157	11	91.7	92.5	**91.2**	**93.8**

Table 1. *Statistics of iSafeRat® CLASS v1.4 implemented in iSafeRat® Desktop v4.3.14 and performance metrics calculated using OECD Annex 2 datasheet in GL 497.*

Results and discussion

The update of the model improved the QAF compliancy and gives greater insight into the confidence of the predictions using iSafeRat® CLASS. Statistics of the v1.4 of the model are available in **Table 1**. It should be noted that OECD data are, for the majority, in the data set of CLASS v1.4.

In order to fit QAF requirements[1], the model was developed to comply with the 4 principles, as described in **Figure 2**.

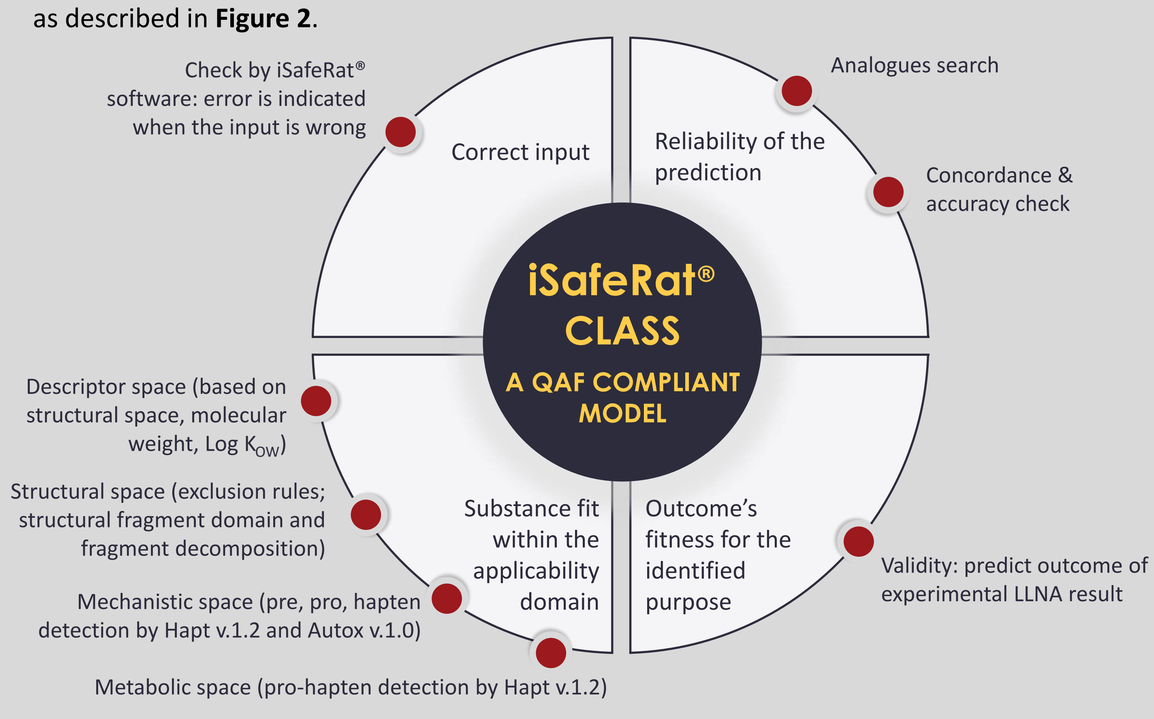

Figure 2. *QAF compliancy of CLASS*

To fit QAF requirements[1], analogues are searched based on both structure similarity and MechoA[2]. Analogue searches are therefore not based exclusively on mathematical and chemical methodology, but also through toxicological similarity. Furthermore, predictions and experimental results of the **analogues are provided in order to assess the reliability of the prediction**. This expert knowledge tool gives more insight into the prediction decision and can therefore be used as a way to validate the relevance of analogues located in the training set of the model for both negative and positive predictions, as requested by the QAF[1].

CLASS provides an in-depth automated analysis of the model applicability domain for a given prediction through a **fragmentation approach** which reinforces and maximises the reliability of the predictions to fit QAF requirements[1]. This information is essential when evaluating a prediction for **regulatory purposes** since it is required in QPRF documents.

Conclusion

This new version of CLASS provides a **better insight into the applicability domain** through a **fragmentation approach**. A tool was also developed to **search for relevant analogues**. This was developed in order to be **fully compliant with the QAF and ECHA guidance** and therefore better fill in the QPRF regulatory document requested in the case of an upcoming registration of a substance. Furthermore, sensitisation potency through EC3 prediction will be implemented in the next version of the model. The analogue seeking will also be improved, with EC3 predictions for analogues given by the software in order to assess reliability of the EC3 prediction. Furthermore, iSafeRat® CLASS is now included in the "me too" process for inclusion in the next version of the OECD guidance of Defined Approaches for Skin Sensitisation (OECD 497).

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[1] OECD. *(Q)SAR assessment framework: Guidance for the regulatory assessment of (quantitative) structure activity relationship models and predictions*. Paris: OECD Publishing. 2023;386.
[2] Bauer FJ *et al. . A new classification algorithm based on mechanisms of action.* Comput Toxicol. 2018;5:8–15.