An innovative modular *in silico* model to predict skin sensitisation potentiel

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Introduction

iSafeRat® CLASS (Classification & Labelling Assessment for Skin Sensitisation) is an innovative model mostly based on the first key events of the skin sensitisation (SS) adverse outcome pathway (AOP) leading to protein adduct formation. This model is designed to predict SS with high accuracy using a combination of four independent modules organised in an optimised decision tree to generate the final consensus (*i.e.*, skin sensitiser/not skin sensitiser). First, iSafeRat® Mechanism of toxic Action Premium (MechoA Premium) profiler[1], included in the OECD Toolbox 4.6 as MechoA+, is a robust and efficient Structure Activity Relationship (SAR) model which predicts Molecular Initiating Events (MIE)[2]. Among others, it efficiently detects reactive parent compounds (haptens) and pro-reactive substances (pro-haptens). Then, an autoxidation SAR model predicts if substances encompass chemical features susceptible to become reactive after reaction with oxygen (pre-haptens). Thirdly, another SAR informs if positivity is expected in LLNA and believed inconsistent by comparison with results from *in vivo* tests (e.g., GPMT or Buehler). Finally, a skin penetration profiler estimates whether a substance can sufficiently cross the stratum corneum to trigger skin sensitisation.

In this study, the performances of iSafeRat® CLASS were evaluated on the expanded version of the Cosmetics Europe SS Database (CESSD) and compared to the predictions of a previous version of Derek Nexus tested against the CESSD[3]. Finally, the performance of iSafeRat® was evaluated on a larger in-house dataset.

Methods

First, a dataset of reliable LLNA data totalling 374 substances was constituted. LLNA tests had to be performed in accordance with the OECD Guideline 429. Among those, 154 substances were extracted from the extended Cosmetics Europe Skin Sensitisation Database (CESSD). Another 185 substances were gathered from the LLNA NiceATM database after thorough expertise. Lastly, 35 LLNA proprietary data were graciously offered by the private sector.

Together with scientific literature, this dataset was then used to develop and/or train the different modules of iSafeRat® CLASS. MechoA Premium module was a special case as this module was developed starting from previously published MechoA versions[1]. In this case, the development consisted of the edition of new structural alerts or in the refinement of existing alerts when needed (*e.g.*, benzaldehydes). The three other modules were developed *de novo*. For instance, the physico-chemical cut-off limits for skin penetration were based on the R.7C chapter from ECHA agency[4]. Different combinations of key physico-chemical parameters in skin absorption process (*e.g.*, vapour pressure) were tested and the most relevant was selected based on the lowest loss in model sensitivity. An autoxidation module, based on most likely bonds for autoxidation reaction, completed the profilers used.

The performances of iSafeRat® CLASS were estimated on the extended CESSD (159 LLNA data) and compared with those of Derek Nexus v6.0.1 published in the CESSD[3], the *in silico* reference for skin sensitisation. In addition, the performances of iSafeRat® CLASS were calculated for the entire dataset.

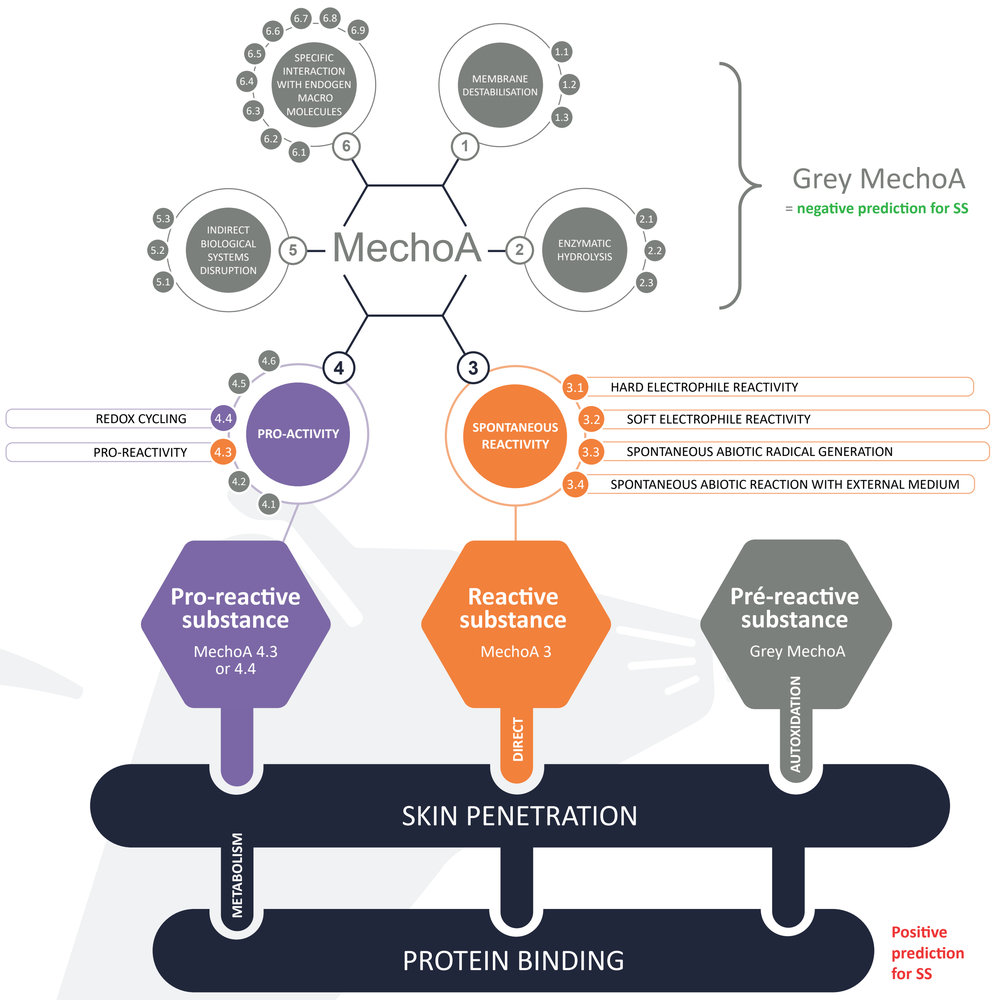

Fig.1 *Positive or negative predictions for SS depending on MechoA of parent substance, autoxidation product(s) or metabolites.*

In Silico CLASSIFICATION and LABELLING ASSESSMENT for SKIN SENSITISATION (iSafeRat® CLASS) COMBINING 3 CONCEPTS:

1) iSafeRat® MechoA 2) Autoxidation profiler 3) Skin penetration predictions

Results

The performances were conveyed in terms of **data coverage** (*i.e.*, percentage of substances of a dataset that are within the applicability domain of a model), **accuracy** (*i.e.*, percentage of accurate prediction of model), **sensitivity** (*i.e.*, percentage of sensitisers that are predicted as such by a model) and **specificity** (*i.e.*, percentage of non-sensitisers predicted as such by a model).

The first milestone of this work was the comparison of iSafeRat® CLASS with Derek Nexus, widely considered as the reference model for skin sensitisation, on the CESSD database (Fig.1 and Table 1). Globally, the performances of the two models were comparable. The **data coverage**, **accuracy** and **specificity** of both models were clearly in the same range of values. However, the **specificity** of iSafeRat® CLASS was 13% higher compared to Derek Nexus.

Then, we established the performances of iSafeRat® CLASS for the full training set. When applied to a greater diversity of chemical structures, the **accuracy** and the **specificity** of iSafeRat were subjected to a limited decrease of 5% and 7%, respectively. By contrast, the capacity of iSafeRat® CLASS to detect skin sensitisers (*i.e.*, **sensitivity**) remained intact despite the inclusion of complex substances. Altogether, this work demonstrated the stability of the performances of iSafeRat® CLASS over two different datasets.

Fig.2 *Data coverage, accuracy, sensitivity and specificity of Derek Nexus v6.0.1 and iSafeRat® CLASS v4.2.1 for the extended CESSD.*

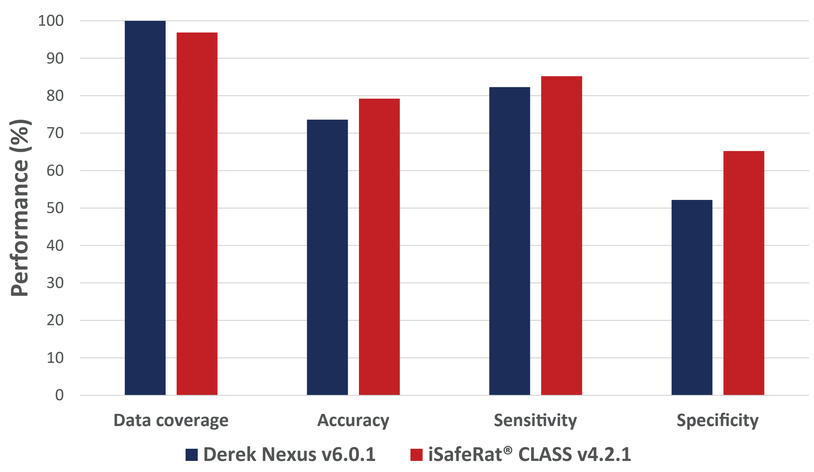

Table 1 *Performances of Derek Nexus v6.0.1 and iSafeRat® CLASS v4.1.11 for the extended CESSD, and preliminary performances of iSafeRat® CLASS v4.1.11 for the training set.*

Model	BDD	N in dataset	Inside AD (N)	Accuracy (%)	Sensitivity (%)	Specificity (%)
Derek Nexus v6.0.1	CESSD	159	159	73,6	82,3	52,2
iSafeRat® CLASS v4.2.1	CESSD	159	154	79,2	85,2	65,2
iSafeRat® CLASS v4.2.1	in-house	374	374	**74,6**	**81,9**	**57,9**

Conclusion

This poster describes the performances of a new conceptual model, **iSafeRat® CLASS**, combining three different SARs to elucidate the ability of a substance to trigger the first key events leading to skin sensitisation in the AOP. In addition, Another SAR was developed to highlight the cases where LLNA results diverge from the other in vivo tests (*e.g.,* Buehler, GPMT).

The model was highly predictive of LLNA outcomes for organic substances including some organo-halogens, with accuracy and sensitivity reaching over 70%. The specificity of the model was around 60%, which is strictly comparable with Derek Nexus. Future enhancements will aim to extend the applicability domain of our model and the prediction of EC_3 values.

Our efforts are currently focused on the recognition of our model as a validated alternative to in vivo experiments for regulatory requirements especially in combination with *in vitro* studies as recommended in the OECD Defined Approach 497.

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References

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