

Predictive Capacity of the iSafeRat EICM: Eye Irritation/Corrosion Prediction Model (QSAR)

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Introduction

Currently, there are no *in vitro* or *in silico* methods to replace the *in vivo* Draize method^{1,2,3} to classify eye irritation (OECD Category 2, Cat. 2) substances. In the chemical regulatory field, *in vitro* methods (e.g., BOP, ICF) use Cat. 1 (serious eye damage) and chemicals not requiring classification for eye irritation/corrosion (EC) with a "no prediction can be made" (NCP). *In vitro* methods are not able to distinguish Cat. 1 and Cat. 2 (Irritant) EICM, since no product such as irritation and corrosion potential of chemicals aiming to fit the data gap Cat. 1 for chemicals in its applicability domain (AD), resulting in predicting "irritant", we compare iSafeRat EICM predictive capacity to that of *in vitro* methods as stated in the OECD guidelines^{1,2} using the same predictive criteria as used for comparison, and, to that of *in silico* methods through a comparative study.

Method

iSafeRat EICM is a mechanistic model, for which the predictions are the result of quantitative predictions (QP) of the test substance absorbed to be assimilated to the eye tissue. These cell kinetics depend exclusively upon the intrinsic physico-chemical properties of the test substance.



The predictive capacity of iSafeRat EICM and other existing alternative methods for eye irritation, such as, *in vitro* and *in silico* methods were then compared to *in vivo* data following the Draize method (TS-028) and classified according to the OECD TG001.

Results

***In vitro* / *in silico* methods vs. iSafeRat EICM**
In the OECD TG, the predictive capacity for *in vitro* method^{1,2,3} (Draze) is reported as the capacity to predict categories (NC) chemicals and the capacity to predict just Cat. 1 and Cat. 2 chemicals. Therefore, the results obtained with iSafeRat EICM were tested using the same criteria for comparison with the *in vitro* methods. The results for iSafeRat EICM in Table 1 represent the full data set (= 242 (training & external validation set)) as the mean value comprising 13 local models. *In vitro* looks other than iSafeRat EICM are QSAR Toxins and Toxins. Both are based on the rules developed by BR for eye irritation/corrosion⁵. The predictive capacity of the BR evaluation rules is reported as regular prediction score (RPS + BR, iSafeRat EICM) which by definition corresponds to the capacity to predict NC substances. For the inclusion rules by BR, the authors report the positive probability for NC (Cat. 2) as 62% (320% for iSafeRat EICM) and for RM (Cat. 1) as 102% (82% for iSafeRat EICM).

Toxins & QSAR Toxins vs. iSafeRat EICM
Eye irritation/corrosion evaluation and/or inclusion rules by BR^{5,6} as implemented in Toxins and QSAR Toxins were used to predict eye irritation for the same 242 substances with fully validated *in vitro* studies from the iSafeRat EICM data set. The outputs obtained are listed in Table 2 and 3 respectively.

Table 1. Toxins eye irritation and corrosion prediction on 242 (full) substances.

Substances	Number of substances	Eye irritation/corrosion prediction			Total
		NC	Cat. 1	Cat. 2	
242 (full)	242	17	16	109	
QSAR Toxins	242	17	16	109	
Toxins	242	17	16	109	

Using Toxins a clear prediction in the form of the phrases related to eye irritation could be obtained for 40 out of 242 substances. For 11 substances a skin irritation/corrosion the phrase was given as output and for 273 substances an unknown (unable to predict) output was obtained. For this model, the authors reported that within the validation set, 276/297 substances showed no prediction, which is in agreement with our results using this software (277/242 with no prediction). Out of the 40 predictions that could be obtained 17 substances were over-predicted (43%) and 1 was under-predicted (2%).

Table 2. Predictive capacity of iSafeRat EICM vs. *in vitro* & *in silico* eye irritation/corrosion methods.

Substances	Number of substances	Eye irritation/corrosion prediction		Total
		NC	Cat. 1	
242 (full)	242	17	16	
BR	242	17	16	
QSAR Toxins	242	17	16	
Toxins	242	17	16	

Table 3. QSAR Toxins eye irritation and corrosion prediction on 242 (full) substances.

Substances	Number of substances	Eye irritation/corrosion prediction		Total
		NC	Cat. 1	
242 (full)	242	17	16	
BR	242	17	16	
QSAR Toxins	242	17	16	
Toxins	242	17	16	

Using QSAR Toxins inclusion rules by BR resulted in 2 types of output messages: "Inclusion rules not met" which is interpreted as non-irritant to eyes or "Inclusion rules met", meaning a structural alert by that name was detected for these substances. To check whether these alerts corresponded to an irritant or corrosive classification, the rules detailed by the authors⁵ were applied and listed in Table 3 according to inclusion rules by BR correctly predicted 130/142 (92%) substances, while over-predicting 12 substances (8%) and under-predicting 19 substances (13%). Inclusion rules by BR, resulted for 241/242 substances in an "undefined" output (i = 10) as e.g., "Missing C-Matching point + 08 0; undefined" output message (i = 10), the latter meaning that at least one of the physicochemical inclusion rules were undefined, in QSAR Toxins these input parameters are extracted from the internal database of the software and if one parameter is missing the prediction cannot be made.

Conclusion

iSafeRat EICM's predictive capacity is comparable to the highest performing alternative models *in vitro* and *in silico* within its AD, with the advantage that it can accurately predict Cat. 2, which cannot be identified at all using *in vitro* methods and which was often under- or over-predicted using BR rules for eye irritation and corrosion (QSAR Toxins and Toxins). Furthermore, iSafeRat EICM has the advantage of providing a clear output format for eye irritation/corrosion prediction in the form of a specific, OECD-like classification category for the test substance, in comparison to the ones currently provided by other *in vitro* models, e.g., outputs referring to skin irritation (no phrase) (Toxins) when the model predicts eye irritation, or a structural alert stating the name of the chemical class (e.g. monocyclic aromatic, QSAR Toxins, inclusion rules) which requires knowledge of the functioning of the model to obtain a clear classification category. It is important to stress that the applicability domains of iSafeRat EICM and the tests presented in this *in vitro* models are not identical. Therefore, the methods presented herein are complementary in terms of their AD, e.g. while Toxins eye irritation and corrosion module could only give a prediction for 40/242 substances tested in this study, QSAR Toxins provided predictions to all 242 (inclusion rules) or 241/242 (with no prediction possible (inclusion rules)) due to lack of physicochemical data needed to run the model (e.g. 50% undefined). Of the *in vitro* methods BOP, ICF and iSafeRat EICM have a good capacity to predict non-classified chemicals, but they have a tendency to under-predict classification (especially BOP). Substances on the other hand had a good capacity to predict classified (Cat. 1 + Cat. 2) chemicals without distinction but had a tendency to over-predict non-irritant substances.

Bibliography

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