A High Accuracy QSAR based on rabbit data to predict the human eye irritation potential of individual constituents and mixtures

iSafeRabbit
HIGH ACCURACY QSARs BY KREATiS

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Background & Introduction

An experimental test must be performed following OECD Test Guideline 405 for the assessment of eye irritation/corrosion of a substance[1]. Since 2004, with the EU animal testing ban of finished cosmetic products, REACH coming into force in 2007, however this has not totally avoided animal testing. There has been growing efforts made by the regulatory authorities to minimise the use of animal testing by switching to alternative approaches such as QSARs and Read-Across. The NC3Rs CRACK-IT programme[2] QSARs Mix challenge sponsored by Shell, was initiated early 2015. The scope of the project was to address the well-known 3R principles of animal testing for skin and eye irritation endpoints ultimately also for mixtures to replace the experimental studies. The challenge was completed in March 2016 with the development and validation of the Eye Irritation module of "iSafeRabbit" – the High Accuracy QSAR (HA-QSAR)[3]. This poster briefly outlines the modelling strategy and focusses on the validation of the model for individual substances as well as testing for mixtures. The predictive power of the iSafeRabbit model was compared to those derived from other existing models on a validation set comprising of chemicals across various chemical groups.

Model in a nutshell

I. iSafeRabbit Eye Irritation model for single substances

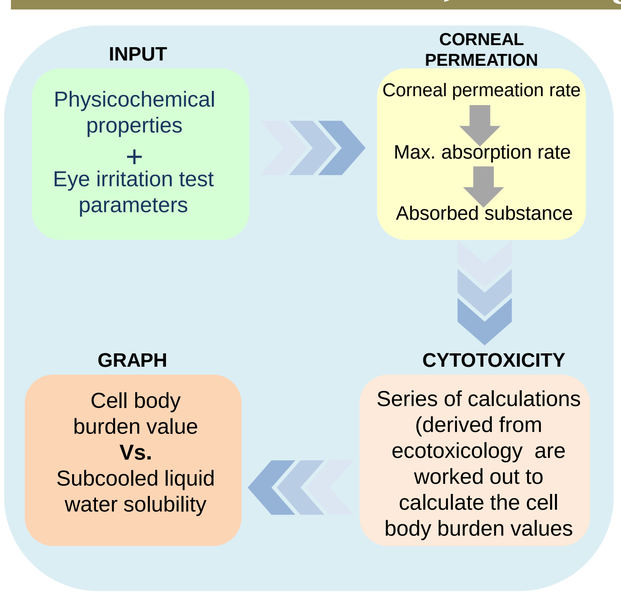
a) Working principle for single substances

Step 1 The model determines whether the instilled dose (0.1 ml) causes cytotoxicity, thereby inducing corneal opacity.

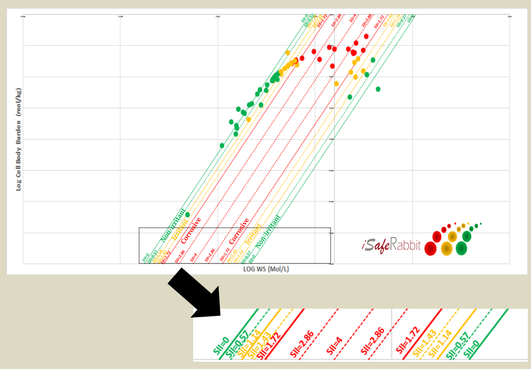
Step 2 The dose is the input to a series of calculations (derived from ecotoxicology) to determine if the concentration in the stroma reaches a cytotoxic concentration. These concentrations are plotted against the water solubility of the substances.

Step 3 The plot is already sub-divided into corrosive, irritant and non-irritant zones. A substance will fall into one of these zones, thereby allowing a classification.

b) Modelling strategy



iSafeRabbit Eye Irritation Model v1.1



So far the iSafeRabbit Eye Irritation model has been validated on 90 substances representing 14 chemical groups. The validation exercise will be extended in the future to cover more chemical groups inside the applicability domain of the model.

c) Simplified Irritation Index for Eye irritation (SII_{EYE})

SII_{SKIN} range	Interpretation
0 - <1.14	Not irritant
1.14 - <1.72	Irritant
1.72 - 4	Corrosive

One of the commonly used scoring methods to quantify the eye irritation of chemicals is Modified Maximum Average Scores (MMAS) dependent on eye irritation effects (namely the corneal opacity, iris lesions, conjunctival redness, chemosis and discharge)[4-5]. iSafeRabbit model uses a similar but simplified scoring method to derive the Irritation Index (SII_{EYE}) to quantify the eye irritation potential of chemicals based only on the corneal opacity and conjunctival redness. There was a significant overlap between SII_{EYE} scores and conclusions made following the CLP criteria[6].

d) iSafeRabbit vs. other existing QSARs

Table 1: Prediction results from iSafeRabbit and other QSARs for a validation set

Substance	Exp. Study results	iSafeRabbit v1.1	Danish QSAR DB	DEREK	OECD QSAR Toolbox v3.3
pentane-1,2-diol	Non-irritant	Non-irritant	N/A	No alert	Non-irritant
naphthalene	Non-irritant	Non-irritant	N/A	No alert	Minimally irritant
cyclohexane	Non-irritant	Non-irritant	N/A	No alert	Minimally irritant
1-bromohexane	Non-irritant	Non-irritant	N/A	No alert	Non-irritant
2-ethoxyethanol	Irritant	Irritant	N/A	No alert	Moderately irritant
Butanol	Corrosive	Corrosive	N/A	No alert	Severely irritant
o-tert-butylphenol	Corrosive	Corrosive	N/A	No alert	Minimally irritant

Only **iSafeRabbit** can accurately differentiate between eye irritant and corrosives in this data set. **Danish QSAR database** doesn't provide predictions for eye irritation. For **DEREK,** 'No alert' indicates that no structural alerts were triggered. **OECD QSAR Toolbox** results were derived performing a Read Across (profiling and category formation was based on eye irritation/corrosion inclusion rules by BfR; subcategorisation was based on functional groups and structural similarity) .

II. iSafeRabbit Eye Irritation model: Mixtures plug-in using the SII weight-fraction approach

a) Working principle for mixtures

Step 1 Composition of each constituent is given as input, otherwise theoretical composition is worked out, provided some information for each constituent is available (e.g. range of % composition or constituent ratio).

Step 2 SII_{Pred} for all the constituents are calculated at 100% dose (0.1 ml as per the OECD TG 405). The SII_{Pred} is then adjusted to the corresponding weight fraction of each constituent in the mixture. The adjusted SII_{Pred} for all the constituents is added together and the final sum represents the SII_{Pred} for the mixture.

Step 3 The mixture is classified as non-irritant, irritant or corrosive based on its SII_{Pred} value.

b) Case studies: UVCB and mixtures

UVCB Case study: CAS: 64742-90-1 Residues (petroleum), steam-cracked

Constituent	Comp.	Adjusted comp. % *(w/w)*	SII_{Pred} score (fraction in mixture)
Benzene	up to 30%	18%	0.32
Toluene	up to 20%	12%	0.17
Ethylbenzene	up to 10%	6%	0.08
Styrene	up to 15%	9%	0.13
Naphthalene	up to 70%	42%	0.24
Biphenyl	up to 15%	9%	0
Anthracene	up to 5%	3%	0
Exp. result	Non-irritant	**iSafeRabbit v1.1**	Non-Irritant SII_{Pred}=0.94

Mixture case study: CAS: 75782-86-4 Alcohols C12-C13

Con fraction stituent	Comp.	Adjusted comp. % *(w/w)*	Irritation potential
Dodecanol	30-50%	40%	SII_{Pred}=0.16
Tridecanol	50-70%	60%	SII_{Pred}=0
Exp. result	Non-irritant	**iSafeRabbit v1.1**	Non-Irritant SII_{Pred}=0.16

Both the case studies hint that the iSafeRabbit predictions were in agreement with the experimental data. The case study of UVCB particularly demonstrates how the composition of each constituent can be adjusted and given as input to the model.

Conclusions

The working principle and modelling strategy for iSafeRabbit models were briefly discussed. The iSafeRabbit eye irritation model for single substances was associated with highest predictive power when compared to other existing QSARs for the results presented on a validation set of 7 substances. The iSafeRabbit results were presented for two case studies – a UVCB and a mixture. The predicted irritation potential with iSafeRabbit was in close agreement or slightly conservative when compared to experimental study results.

References

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