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

iSafeRabbit
HIGH ACCURACY QSARs BY KREATiS

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Background & Introduction

To evaluate the skin irritation of a substance, an experimental test must be performed following the OECD Test Guideline 404[1]. Since 2004, with the EU animal testing ban of finished cosmetic products, REACH coming into force in 2007, the use of alternative approaches including *in vitro* and *in silico* methods have seen a noticeable decrease in animal testing. To date QSARs have not been successfully applied to determine skin irritation. 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 Skin 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 Skin Irritation model for single substances

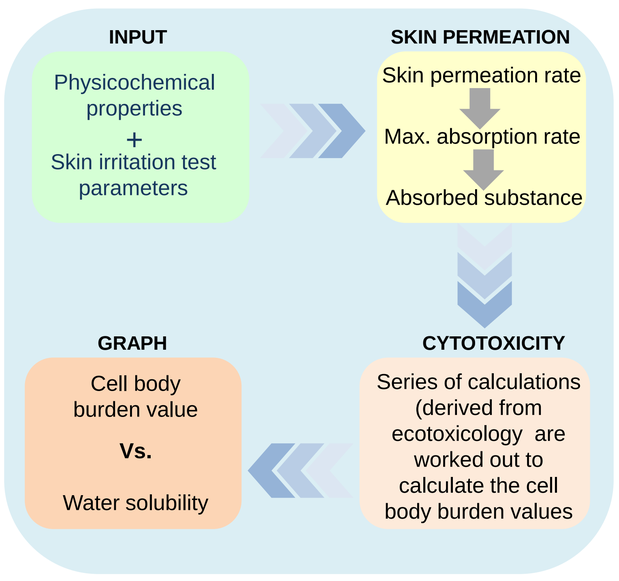
a) Working principle for single substances

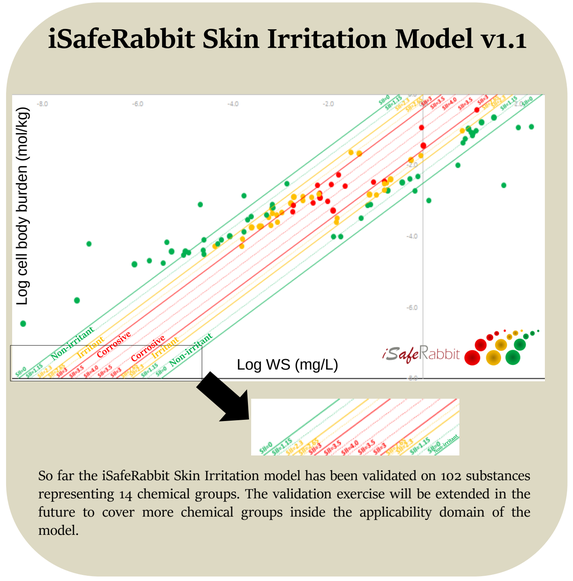
Step 1 The model determines whether the applied dose of a chemical causes cytotoxicity, thereby inducing erythema and/or oedema.

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

Step 3 The plot is 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





So far the iSafeRabbit Skin Irritation model has been validated on 102 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 Skin irritation (SII_{SKIN})

SII_{SKIN} range	Interpretation
0 and <2.3	Not irritant
2.3 and <3	Irritant
3 and 4	Corrosive

One of the commonly used scoring methods to quantify the skin irritation potential of chemicals is to calculate their Primary Irritation Index scores using the grading scale for skin irritation effects (Erythema and Oedema scores)[4-5]. The iSafeRabbit model uses a similar but simplified scoring method to derive the Irritation Index (SII_{SKIN}) to quantify the skin irritation potential of chemicals based only on the erythema scores. There was a significant overlap between SII_{SKIN} 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	Negative	No alert	Mild irritant
2-ethoxyethanol	Non-irritant	Non-irritant	Negative	No alert	Mild irritant
naphthalene	Non-irritant	Non-irritant	Negative	No alert	Non-irritant
cyclohexane	Irritant	Irritant	Positive	No alert	irritant
1-bromohexane	Irritant	Irritant	Positive	No alert	Mild irritant
Butanol	Corrosive	Corrosive	Inconclusive	No alert	Mild irritant
o-tert-butylphenol	Corrosive	Corrosive	Positive	No alert	Irritant

Only **iSafeRabbit** can accurately differentiate between skin irritant and corrosives in this data set. The entries in grey for **Danish QSAR database** indicates that the substances were out of it's applicability domain. Danish QSAR database predictions correspond to a battery of three models for skin irritation: CASE Ultra, LeadScope and SciQSAR. 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 skin irritation/corrosion inclusion rules by BfR; subcategorisation was based on functional groups and structural similarity) .

II. iSafeRabbit Skin Irritation model: Mixtures plug-in inspired by a thermodynamically driven method

a) Working principle for mixtures

Step 1 Determines the minimum applied dose of each constituent required to cause cytotoxicity.

Step 2 The constituent dose is the input to a series of calculations (derived from ecotoxicology) to work out the cell burden values using a thermodynamic approach where the partitioning of substances into each other reduces their bioavailability. The bioavailable fraction of each constituent is then compared to the dose needed to induce skin irritation/corrosion.

Step 3 The plot is already sub-divided into corrosive, irritant and non-irritant zones. Based on where the constituents are projected, classification for mixtures can be determined on a per constituent basis.

b) Case studies: UVCB and mixtures

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

Constituent	Comp.	Adjusted comp. % *(w/w)*	Irritation potential
Benzene	up to 30%	18%	SII_{Pred}=2.6
Toluene	up to 20%	12%	SII_{Pred}=1.7
Ethylbenzene	up to 10%	6%	SII_{Pred}=0
Styrene	up to 15%	9%	SII_{Pred}=1.0
Naphthalene	up to 70%	42%	SII_{Pred}=2.2
Biphenyl	up to 15%	9%	SII_{Pred}=0
Anthracene	up to 5%	3%	SII_{Pred}=0
Exp. result	Borderline Irritant	**iSafeRabbit v1.1**	Irritant/SII_{Pred}=2.6

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

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

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 skin 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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Acknowledgments

The authors would like to thank the NC3Rs CRACK-IT funding programme to provide a platform for this research work.

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This poster was presented on the 28th April 2016 during a one-day workshop at the National Centre for the Replacement Refinement & Reduction of Animals in Research, London, United Kingdom