iSafeRabbit QSAR To Predict Skin And Eye Irritation Potency Of Organic Chemicals

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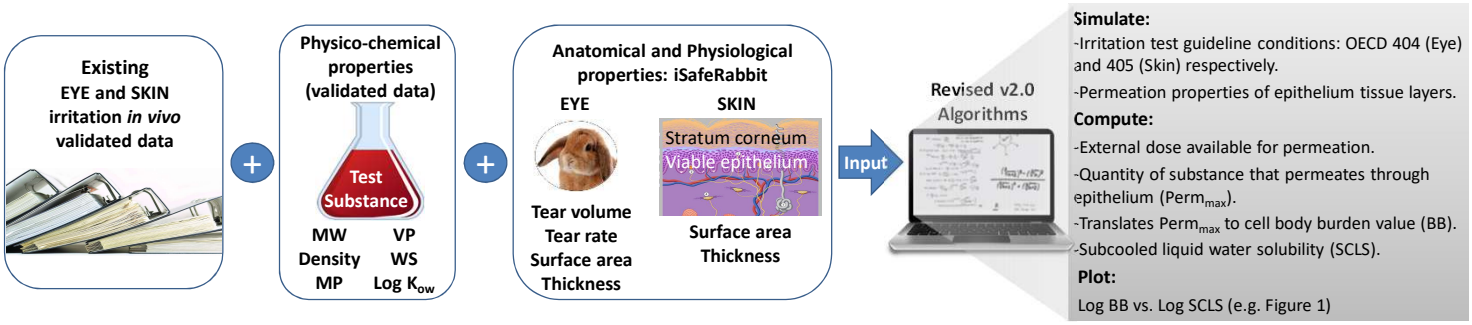
Replacing Experimentation

Introduction

In agreement with the 3Rs commitment (replacement, reduction and refinement of bioassays performed on laboratory animals) iSafeRabbit is an *in silico* model that predicts skin and eye irritation potency of substances aiming to replace animal testing for the substances in its applicability domain. According to CLP and GHS, the clinical signs driving the classification of a substance for irritation are: erythema and/or edema for the skin and corneal opacity and conjunctival redness for the eye. iSafeRabbit prediction models are based on the hypothesis that the clinical signs of irritation/corrosion are the result of skin or eye cytotoxicity, caused by a specific body burden level.

Materials and Methods



Results and Discussion

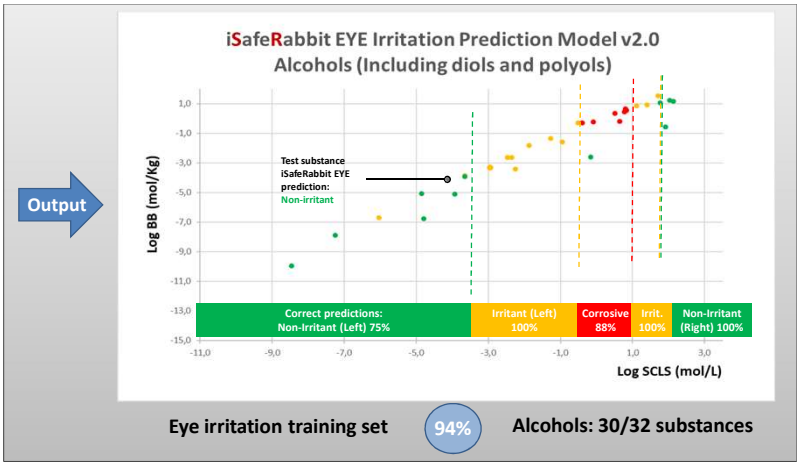


Figure 1: The output of iSafeRabbit eye irritation prediction model is shown for the chemical family of alcohols, including diols and polyols

The decimal logarithm of the cell body burden (**Log BB**) is plotted as a function of the decimal logarithm of the subcooled liquid water solubility (**Log SCLS**) for each substance in the training set. The plot is divided into zones, according to the *in vivo* irritation data colour code: **non-irritant**, **irritant** and **corrosive** for eye (or skin respectively). The coordinates of a given **test substance** within the plot predict the irritation potency of the substance (e.g. Figure 1).

For the alcohol chemical family, the overall percentage of eye irritation correct predictions is of 94% (30/32 substances). The percentage of correct predictions by irritation potency zone is also shown for alcohols in Figure 1.

EYE v2.0	Structural domain	SKIN v1.2
New	KETONES	New
New	NITROS	New
New	TRIAZOLES/PESTICIDES	New
In the pipeline	AMIDES	New
In the pipeline	THIAZOLES	New
In the pipeline	SURFACTANT/AMINES	New
New	NITROPHENOLS	New
New	POLYOLS	In the pipeline
✓	ACIDS	✓
✓	ALCOHOLS	✓
✓	ALDEHYDES	✓
✓	ALKANES	✓
✓	ALKENES	✓
✓	AMINES	✓
✓	ANILINES	✓
✓	AROMATICS	✓
✓	DIOLS	✓
✓	ESTERS	✓
✓	ETHERS	✓
✓	ETHOXYLATED ALCOHOLS	✓
✓	HALIDES	✓
✓	PHENOLS	✓

Table 1: Structural domains covered by iSafeRabbit irritation prediction models

EYE

Since the previous version, the eye models structural domain has grown from 90 to 191 fully validated substances and from 14 to 19 chemical families, with 3 more families in the pipeline.

SKIN

The skin models structural domain has also grown, from 102 to 226 fully validated substances and from 14 to 21 chemical families, with 1 more in the pipeline.

Conclusions and Perspectives

After the v1.1 of iSafeRabbit models, over 100 fully validated substances were added to each model. The eye models algorithms were revised and adapted to take into account Henry's constant as a physico-chemical parameter, tear volume and tear rate as physiological parameters and the available dose was adapted from a constant to a dynamic variable dependent on the newly added parameters. These modifications allowed to expand the applicability domain of iSafeRabbit eye model to cover 4 additional chemical families in its structural domain (Table 1). A similar approach is being implemented to furtherly refine and expand the applicability domain of the iSafeRabbit skin irritation model.

Additional data is being gathered and analyzed to further improve and expand both models: **Physico-chemical descriptors** like pKa (to take into account pH variations), dipole moment and topological polar surface area (as electronic descriptors) and **Mechanism of action (MechoA) data** (to take into account substance reactivity).

In the pipeline: external validation and statistical validation, as well as, the necessary documents for regulatory compliance to go with the models (QPRF and QMRF). Since 2013, *in vitro* data must be used for both skin and eye irritation studies. These studies are under validation and inclusion in the training set of both models.

References

(1) Inspired by Tibaldi et al. (2014) J. Occup. Environ. Hyg. "Dermal Absorption of Chemicals: Estimation by IH SkinPerm", 11, 19-31. (2) OECD (2002). Test No. 404: Acute Dermal Irritation/Corrosion, and Test No. 405: Acute Eye Irritation/Corrosion OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris. (3) MechoA: Bauer, Franklin J., et al. (2018) Computational Toxicology: "A new classification algorithm based on mechanisms of action." 5 : 8-15. (4) Faizan Sahigara, et al. (2016) NC3R Workshop: "A High Accuracy QSAR Based on Rabbit Data to Predict the human Skin (Eye) Irritation Potential of Individual Constituents and Mixtures" London, United Kingdom.

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