SAR Models for Predicting Skin and Eye Acute Toxicity Effects

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ABSTRACT: The purpose of the hazard assessment is to categorize substances according to defined by regulatory authorities classification scheme [1]. The models for skin and eye irritation/corrosion (I/C) implemented in TIMES system predict the reversible (irritation) and irreversible (corrosion) damage of the skin and eye. Sensitivity of both skin I/C and eye I/C models is high - 85% and 94%, respectively. Given the insufficiency of non irritating/corrosive substances in both training sets, the models specificity cannot be estimated adequately. Original skin I/C and eye I/C models developed by BfR and implemented in Toolbox are combination of inclusion rules (IRs) and exclusion rules (ERs). In current versions of the models exclusion rules (physicochemical cut-off values) are removed due to the producing of large number of FNs. The mechanism of skin and eye irritancy are seemingly dependent on the chemical reactivity of the irritant and the metabolites itself. However, experimentally corrosive chemicals can behave as irritating depending on their concentration.

INTRODUCTION

The mechanisms of irritancy and corrosivity are complicated. Irritation could be regarded as chemical and physical dysfunctions. The chemical irritation is considered to be similar with the skin allergy in terms of covalent interaction with the proteins [3]. However, the irritation can also be caused by non-covalent interactions with the macromolecules (ionic, reversible denaturation of proteins, etc). Physical irritation results in dissolution of the lipids. The corrosivity is erosion of the tissues of skin and eye by strong organic acids with pH < 2 and bases with pH > 11.5 (cationic surfactants, quaternary ammonium salts, sulphonium ions, and etc.).

MATERIALS AND METHODS

Training sets

- **Skin I/C** model is based on a training set of 3153 organic chemicals: 2170 skin irritants, 795 skin corrosives and 188 negative substances. The training set was compiled using different sources of data such as the primary skin irritation indices (PII), the risk phrases R34, R35 or R38 (according to the *EU Dangerous Substances Directive*) and health hazard H phrases H314, H315 or H316 (according to *Global Harmonized System*).
- **Eye I/C** model training set consists of 119 organic chemicals. Of them 110 are irritating/corrosive to eye and 9 are non-irritating having experimentally documented data for modified maximum average score (MMAS) [2].

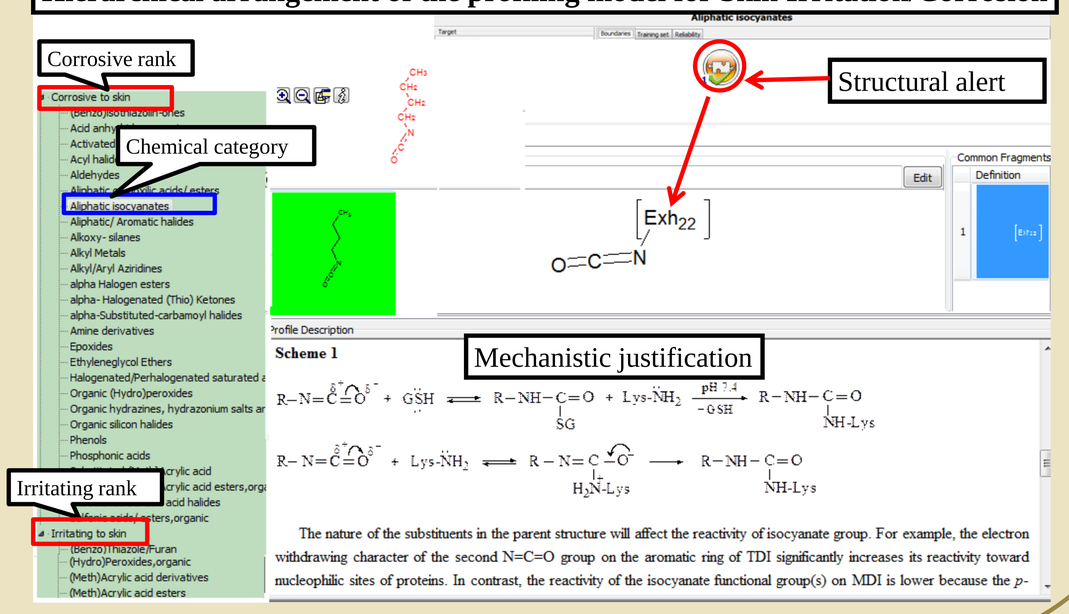
Modeling concept

- **Original skin I/C and eye I/C models** developed by BfR and implemented in Toolbox are combination of inclusion rules (IRs) and exclusion rules (ERs) [4,5]. The IRs (chemical categories) are molecular functionalities which are assumed to trigger molecular initiating event (MIE) resulting to I/C effect. ERs include physicochemical cut-off values for assessment the negative skin and eye irritation/corrosion chemicals. They are used to pre-filter true positives and facilitate the performance of the IRs.
- **OASIS models**

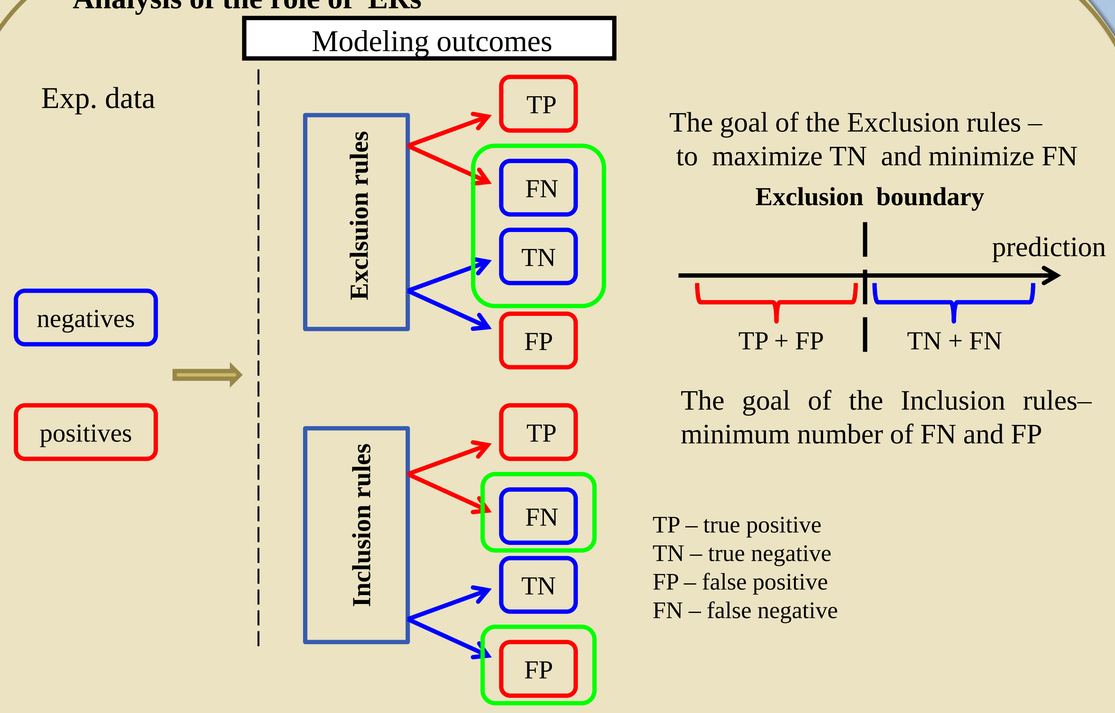
❑Skin I/C model used **category approach** for deriving structural alerts based on the functionally identical chemicals accounting their irritating or corrosive effects. The alerts were grouped into 82 irritating and corrosive categories (IRs). They are hierarchically ordered and the chemicals are classified as irritating, corrosive or not irritating/corrosive (if no alert has been found) to the skin.

❑Eye I/C model was used the **same methodology**. The structural alerts of eye irritation/corrosion model were grouped into 32 categories which classified chemicals as irritating/corrosive to the eye. The model includes also an extrapolation step checking for the presence of skin irritation and corrosion structural alerts in case no eye irritation/corrosion alerts are identified.

Hierarchical arrangement of the profiling model for Skin Irritation/Corrosion



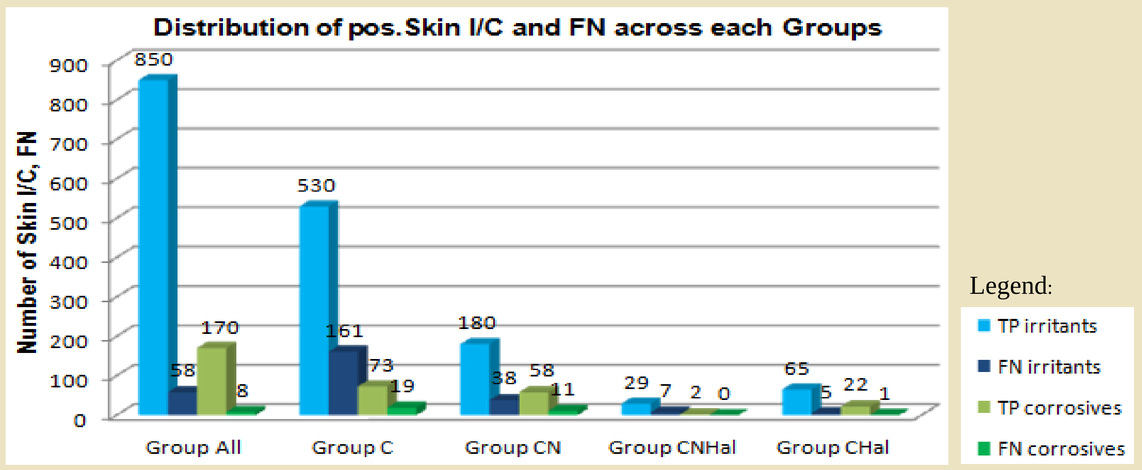
Analysis of the role of ERs



Example illustrating the role of the Exclusion rules

The analysis was based on 1200 chemicals having skin irritation/corrosion exp. data. Of them 1020 were positive and 180 were negative. Of 1020 positive skin irritating/corrosive chemicals 283 (28%) were predicted as FNs.

Distribution of the chemicals across the exclusion groups are summarized in the chart:



Summary

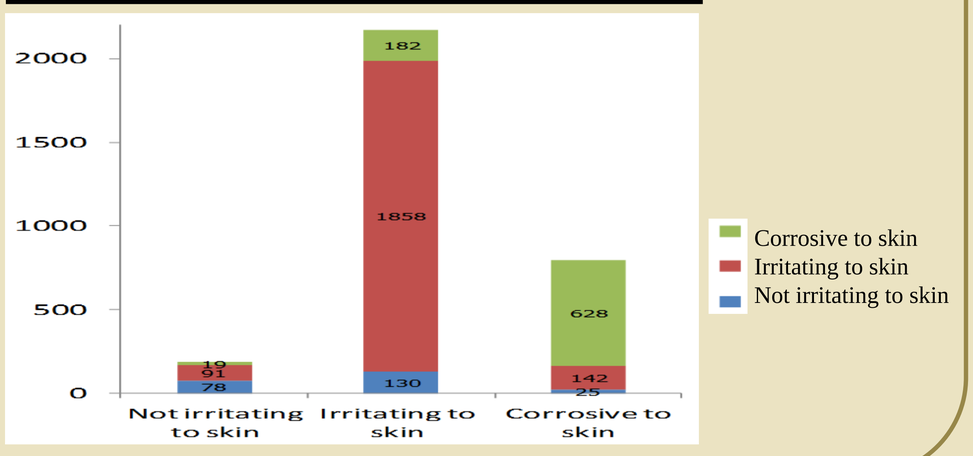
- ERs were found to the eliminate significant number of positive skin irritating/corrosive chemicals.
- The exhaustive collection of mechanistically transparent IRs is enough to explain the variation of experimental data and there is **NO** need of using ERs

Model performance

The skin I/C model performance, evaluated by the percent of correctly predicted (sensitivity) irritants and corrosives, is 85%.

		OBSERVED		
		Non Irritating/Corrosive to s	Irritating to skin	Corrosive to skin
PREDICT	Non Irritating/Corrosive to s	78	130	25
	Irritating to skin	91	1858	142
	Corrosive to skin	19	182	628

Distribution of the observed vs. predicted skin I/C data



CONCLUSIONS

- A model for predicting Skin Irritation/Corrosion has been developed based on category approach. The training set consists of 3200 chemicals.
- The analysis showed that the developed battery of Inclusion rules is good enough for adequate classification of chemicals and no need of using Exclusion rules.
- The model is characterized with high sensitivity (85%); however, the specificity needs to be further improved which required collection of more negative chemicals in training set.
- A large database with documented Eye Irritating/Corrosive data has been developed which will be used for developing the respective model.

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