ASSESMENT OF ALERT PERFORMANCE IN OASIS TIMES MODELS

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Introduction

The Tissue Metabolism Simulator (TIMES) is an integrated platform combining metabolic simulators and (Q)SAR models for predicting human health toxicity. The TIMES models are designed to predict different toxicological endpoints and for some of them (e.g. Skin sensitisation) metabolic activation of chemicals is taken into account. The models consist of a set of rules (named alerts) and each rule could be defined by a set of sub-rules (named boundaries). The application of a rules and sub-rule to a chemical structure produces true or false value. In accordance with the OECD Validation Principles [1] it is critical to be assessed the robustness of the structural alerts which are fundamental units of all the TIMES models. The aim of the current work is to introduce a strategy for assessment of the predictive power of toxicity alerts implemented in the OASIS TIMES models.

Alert reliability criteria in TIMES

The methodology proposed in the current work provides assessment of the alert reliability based on three criteria:

- ***Number of chemicals (n)*** in the local training set used to define the alert (i.e. compounds with observed data having the same structural functionality believed to cause the toxic effect);
- ***Alert performance:*** Alert performance is a probabilistic measure of the classification power of an alert. It is estimated as a ratio between the correctly predicted compounds over the total number of compounds in the local training set:

$$Alert\ pertformance = \frac{Number\ of\ correctly\ predicted\ compounds}{Total\ number\ of\ compounds\ in\ Training\ set}$$

  The metabolic activation of the compounds from the alert training sets is taken into account when the alert performance is estimated.
- ***Mechanistic justification*** of toxic endpoint exerted by the alert. Mechanistic justification of the causality-effect relationship is critical for proper definition of the alerts.

Alert reliability states

Based on the above criteria a number of states for alert reliability are defined – high, low, undetermined and undetermined theoretical alerts. Below are presented the thresholds used for descriminating the four reliability states in TIMES Skin sensitisation and *in vitro* AMES mutagenicity models:

1) ***High reliability*** – alert performance higher than 0.6 (for both models), number of chemicals (n) more than 5 in Skin model and more than 10 for Ames model, and available mechanistic justification;
2) ***Low reliability*** – alert performance less than 0.6 (for both models), n > 5 in skin model and n > 10 for Ames model, and available mechanistic justification;
3) ***Undetermined reliability*** - *n > 5* in skin model and n > 10 for Ames model, and available mechanistic justification. The alert performance is not taken into account.
4) ***Undetermined theoretical reliability*** - mechanistic justification of the toxic end-point is available only.

Implementation in TIMES

Figure 1. Alert performance functionalities implemented in the TIMES SS model

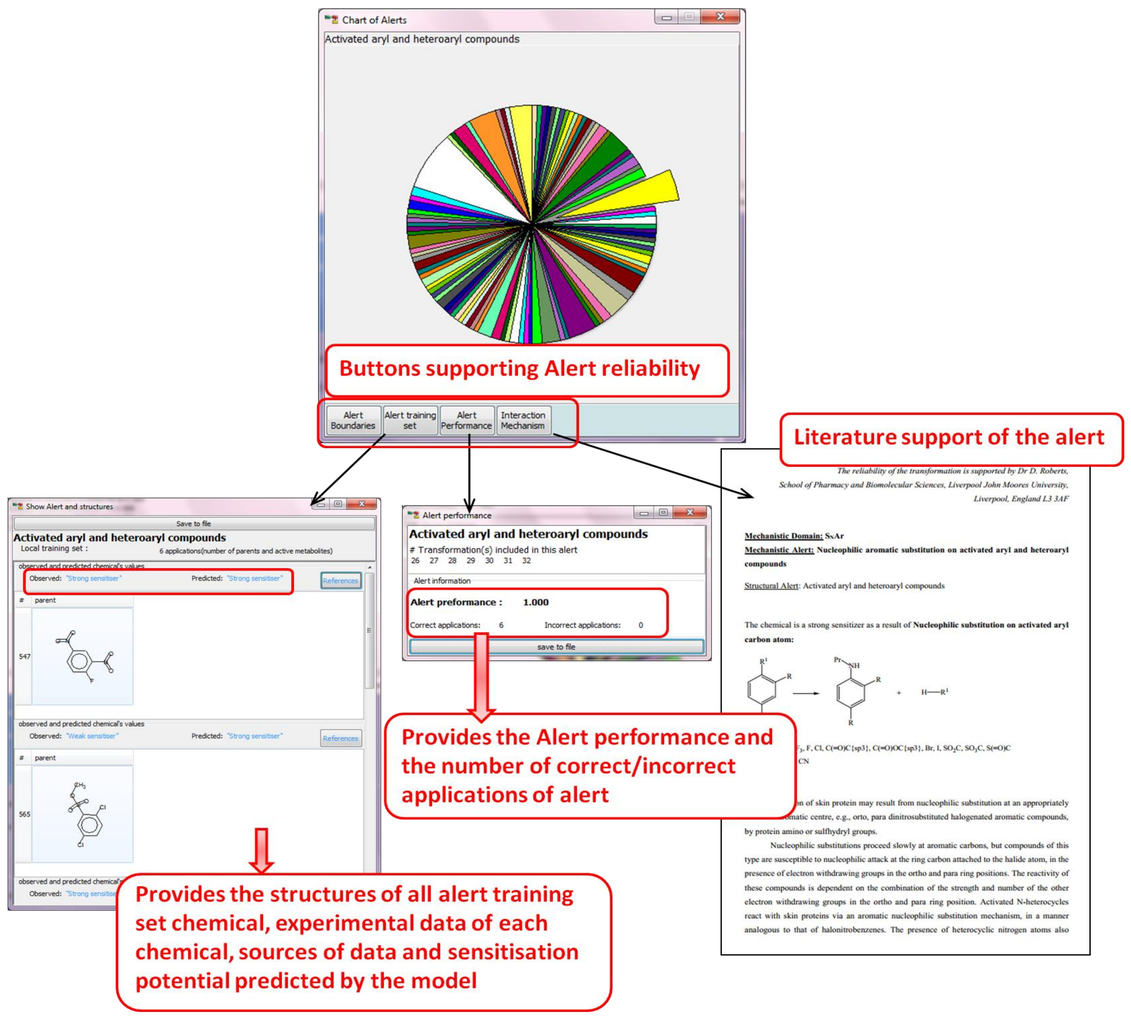
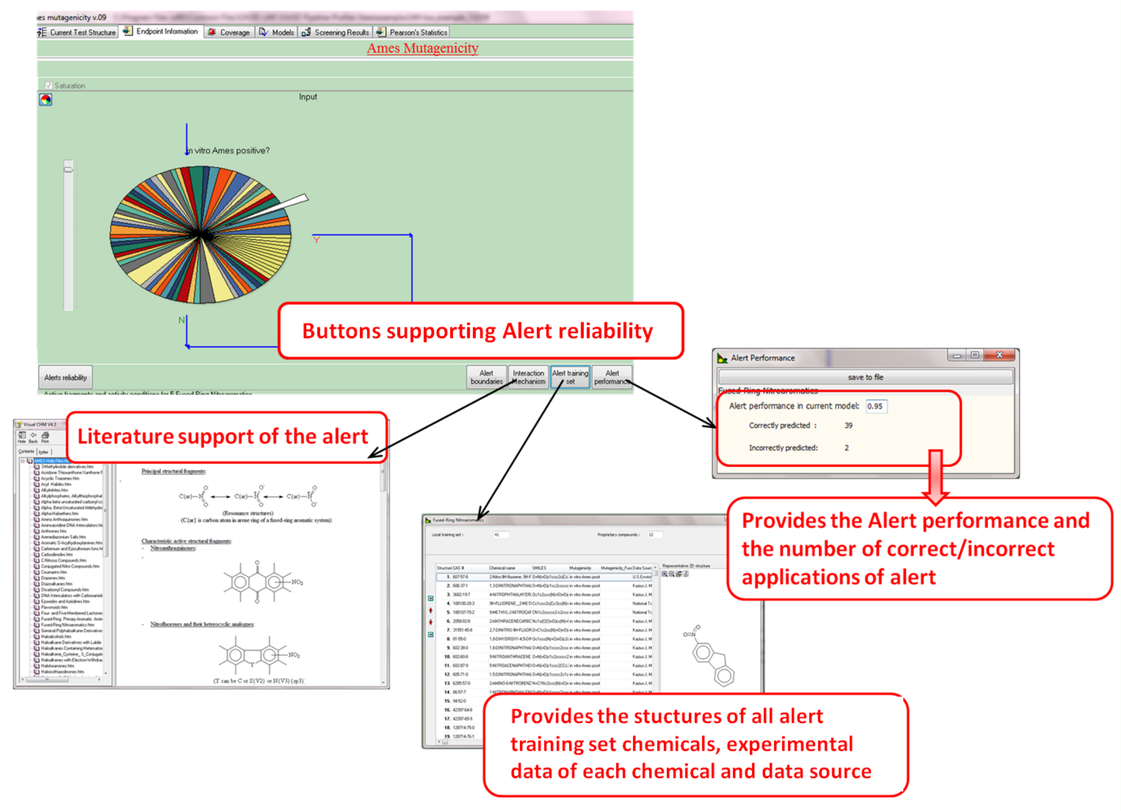


Figure 2. Alert performance functionalities implemented in the TIMES Ames model



Conclusion

The implementation of the criteria for assessing the alerts reliability in TIMES models allows better interpretation of prediction and distinguishing the reliable from the less reliable predictions.

Reference

1. OECD (2004) OECD Principles for the Validation, for Regulatory Purposes, of (Quantitative) Structure-Activity Relationship Models. http://www.oecd.org/chemicalsafety/risk-assessment/37849783.pdf (accessed 14 Nov, 2013).

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