Rules model for *in vitro* gene mutation study in bacteria (Ames test) (v1.0)

ProtoICH

ProtoICH is a computational (*in silico*) tool specially focused on **ICH M7 Guideline**, aimed to reduce the potential carcinogenic risk of impurities. ICH M7 Guideline proposes the use of computational methods as an alternative for mutagenicity assays. It requires the prediction by means of two computational metodologies: a **statistical method (QSAR)** and an **expert-rule based method**. Moreover, it requires the detection of aflatoxins, N-nitrosamines and azoxy compounds (carcinogenicity **cohort of concern**).

Endpoint

Human health effects: Mutagenicity. OECD 471: Bacterial reverse mutation test.

Mutagenicity refers to the induction of permanent transmissible changes in the amount or structure of the genetic material of cells or organisms. The Bacterial reverse mutation test evaluates gene mutations. The test uses amino-acid requiring strains of bacteria to detect (reverse) gene mutations (point mutations and frameshifts).

Rules

This model is an expert rule-based system, formed by a set of 48 rules (structural alerts) related to mutagenicity activity in the Ames test adapted from Benigni and Bossa (Benigni R, Bossa C, 2011, Chem Rev 111:2507 and Benigni R, Bossa C, Tcheremenskaia O, 2013, Chem. Rev. 113:2940).

Validation

The external validation set comprises 6492 compounds (of a raw dataset of 6500) extracted from Hansen K et al. J. Chem. Inf. Model. 2009, 49(9):2077-81.

Validation set

Experimental values	QSAR predictions	
	non-mutagenic	**mutagenic**
non-mutagenic	1975	1025
mutagenic	558	2934

Parameters	Validation
Accuracy	0.76
Sensitivity / recall	0.84
Specificity	0.66
Precision	0.74
Negative predictive value	0.78
F-score	0.79
Matthews Correlation Coefficient	0.51
Critical Success Index	0.65
Area under the ROC	0.75