Genotox-iS™

Artificial intelligence and advanced machine learning algorithms for mutagenicity assessment

Software to support CTD Manual and ICH M7 compliance from Active Pharmaceutical Ingredients (API) suppliers

Altox

ALTERNATIVETOXICOLOGY

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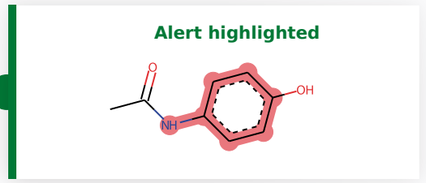
Genotox-iS™

Genotox-iS is a computational tool for prediction of genotoxicity by alerts, statistical and machine learning-based models, designed to meet the requirements of ICH M7 and RDC53/2015, cited in the CTD Manual and RDC nº 57/2009 (ANVISA, Brazil).

The models were validated in accordance with OECD (Organisation for Economic Co-operation and Development) Principles for the Validation for Regulatory Purposes of (Q)SAR Models and datasets were rigorously curated to ensure that results are consistently documented, transparent, and complete.

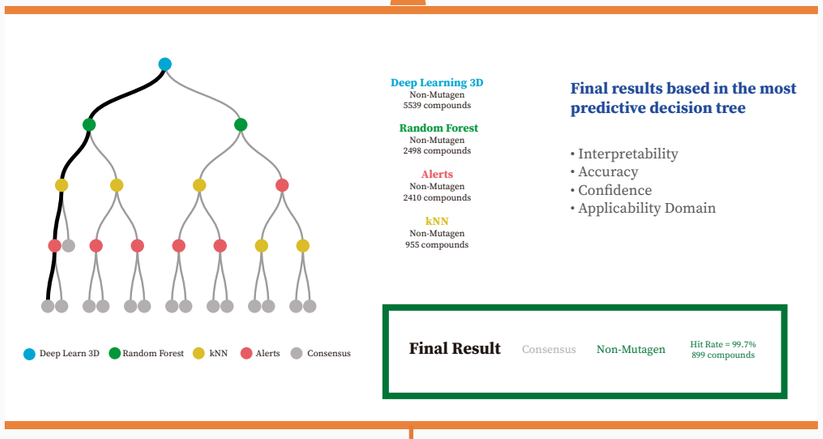
Alert analysis

Analysis of structural alerts rigorously curated by our team to prioritize multiple arguments for and against the toxicity of a chemical weighed up by the evidence.



Final conclusion and Report

A final conclusion is provided by the Consensus Prediction Path®, combining the most predictive individual models in a visual decision tree.



Statistical and artificial intelligence modelling

Modelling by three statistical and artificial intelligence algorithms: random forest model (RF), k-nearestneighbors algorithm (k-NN) and Deep Learning models, using a dataset containing 6,931 rigorously curated structures.

Supporting the expert workflow

STEP 1

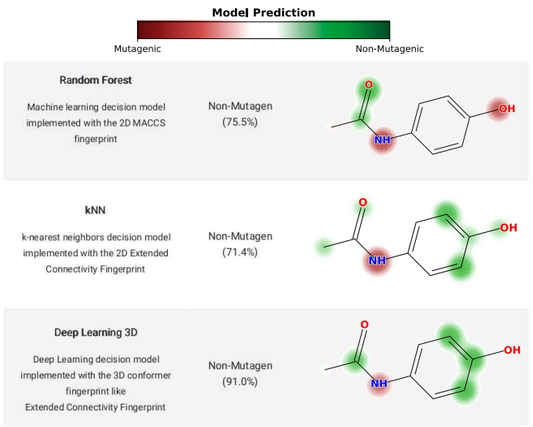
STEP 2

STEP 3

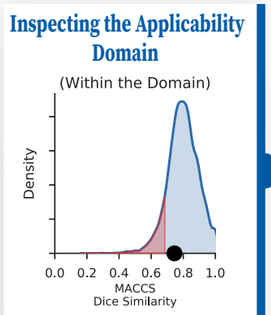
STEP 4

The interactive visualization tools help you to know when to apply to expert knowledge that could potentially refute a (Q)SAR prediction and how to do that for each step.

Visual representation of the structure fragments predicted to contribute to toxicity (red) or non-toxicity (green)



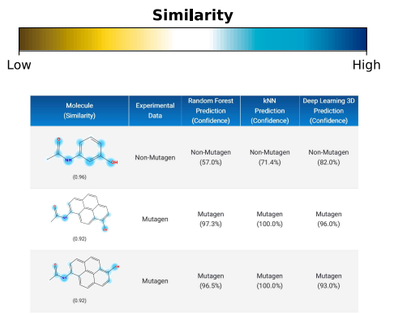
Inspecting the Applicability Domain



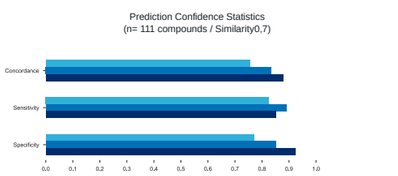
Applicability Domain (AD) inspection

Our visual AD Inspection® is used to establish the AD and limitations of the models, which are represented by a density plot of the average fingerprint-dice similarity for the k-nearest neighbors of each compound during the 5-Fold external model's validation.

Looking at the training set and predictions for the most similar compounds



Looking at the Confidence Statistics for each model



A standardized report is generated to ensure that results are transparent, complete, and consistently documented

What are the requirements?

ICH M7 emphasizes considerations of both safety and quality risk management in estabilishing levels of mutagenic impurities that are expected to pose negligible carcinogenic risk. It outlines recommendations for assessment and control of mutagenic umpurities that reside on are reasonably expected to reside in final drug substance or product, taking into consideration the intended conditions of human use.

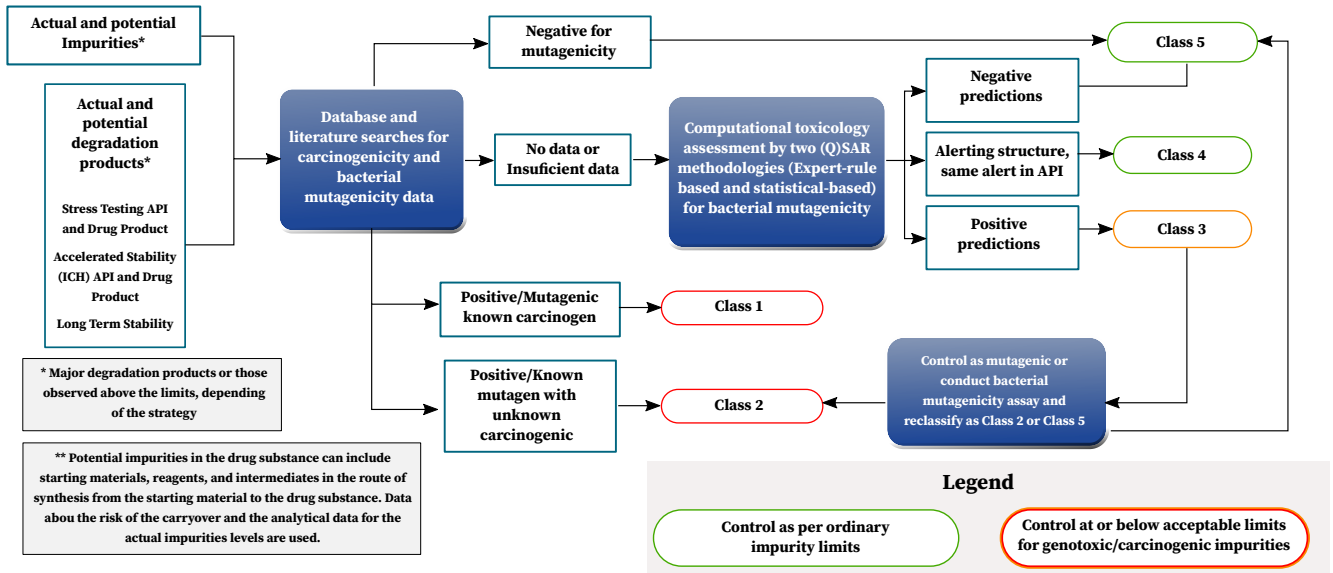
When no experimental mutagenicity and/or carcinogenicity results are available, a computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay. Two (Q)SAR prediction with methodologies that complement each other (expert rule-based and statistical-based methodologies) should be applied. These models should follow the general validation principles set forth by the Organisation for Economic Co-operation and Development (OECD).

The requirements by ANVISA for conducting forced degradation studies and developing a stability-indicating analytical method are described in RDC 53/15, and guidelines for meeting these requirements are published in the revised CP68. Mutagenic impurities (MI) and/or potentially mutagenic impurities (PMIs) formation is a concern during forced degradation studies and strategies for mapping these impurities can be adopted after theoretical studies of degradation and stress studies, using in silico models and extensive literature review.

What makes Genotox-iS special?

- ✓ Fulfills the requirements of the prediction methodologies under ICH M7 and the validation principles set by the Organisation for Economic Co-operation and Development (OECD)
- ✓ An overall **visual** assessment of the results from the two (Q)SAR methodologies, which individually generate positive, negative, or inconclusive predictions, provides an easy to understand, user-friendly interface
- ✓ The interactive visualization tools help you to know when to apply expert knowledge that could potentially refute a (Q)SAR prediction and how to do that;
- ✓ The workflow supports a rationale that may be considered for use in a robust expert review
- ✓ A standardized report is generated to ensure that results are consistently documented, transparent and complete;
- ✓ You have direct support with our scientists and developers!

ICH M7 Workflow



About our company

Altox Ltda is an alternative toxicology services company located in Brazil, with resources focused on toxicity assessment for regulatory purposes. Our team includes experts in software development, data science, predictive toxicology, safety assessment and regulatory toxicology.

Our team experts utilize advances in toxicology utilize advances in toxicology and in silico methodologies for assessment of new molecules, drug substances, biocides, cosmetics ingredients, food ingredients of contact-materials, degradation products, impurities, residue, and contaminants. The company now also provides advanced machine learning services for pharmaceutical, skin care, food, biocidal and fine chemistry companies.

Our tools and models

- Selection of the regulatory endpoints
- Relevant data search and curation steps of the datasets
- Development of (Q)STR models using different approaches like rule-based, statistical and/or Machine Learning-based
- Validation of the models following the OECD Principles and reviews
- Reporting the (Q)STR models employing the standard Reporting Format Files (QMRF) and document process
- Implementation of real-time interface with experts for each endpoint

iS-Ocular™

Pred-CYP2D™

Pred-Oral™

DevTox-iS™

i-Sens™

IrriTest™

iS-Liver™

Acute-Tox™

BCF-Test™

Pred-Ecotox™

i-Sens™

Genotox-iS™

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