Overview

The ACD/Labs Acute Toxicity predictor provides three different software components related to acute toxicity:

- The LD$_{50}$ module provides fast and accurate predictions of LD$_{50}$ values for rats and mice according to various routes of administration.
- Hazards - A knowledge-based expert system that identifies and visualizes hazardous structural fragments.
- Categories - Classifies compounds into one of five OECD categories for acute oral toxicity.

This combination of both a probabilistic predictor and a knowledge-based expert system provides two different approaches to the determination of acute toxicity, ensuring greater confidence in results.

Features

- Calculates LD$_{50}$ (mg/kg) for the compound of interest in rats and mice after several routes of administration.
- All predictions are supported by Reliability Index (RI) values that represent a quantitative evaluation of prediction confidence.
- Shows Experimental LD$_{50}$ values for 5 most similar structures from the training set for each of the considered species and administration routes.
- Defines possible “Oral Acute Toxicity Hazard Categories” for a compound and displays experimentally assigned categories for similar compounds.
- Provides a knowledge-based expert system that identifies and visualizes structural fragments potentially involved in hazardous activity, and displays plots illustrating distribution of LD$_{50}$ values among compounds possessing the same fragment and in the entire training set.
- Batch calculation mode allows automatically calculating acute toxicity of hundreds of molecules per minute without user intervention.
- LD$_{50}$ predictors are trainable – increase prediction accuracy with your experimental data.

Technical Information

Experimental Data

The Acute Toxicity predictor was built using critically evaluated experimental data for more than 100,000 compounds extracted from the Registry of Toxic Effects of Chemical Substances (RTECS) and European Survey of Information Society (ESIS) databases.
Quantitative data
A standard measure of acute toxicity is LD$_{50}$ (lethal dose 50), defined as a dose that is lethal to 50% of the treated animals. It can be viewed as a “cumulative potential” to cause various acute effects and death of animals.

In ACD/Percepta, LD$_{50}$ for two rodent species and four different administration route are considered. The sizes of the data sets used for model development are listed in the table below.

**Table 1.** Number of compounds used for development of LD$_{50}$ predictive models.

<table>
<thead>
<tr>
<th>Administration route</th>
<th>Species</th>
<th>Mouse</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td></td>
<td>19571</td>
<td>8631</td>
</tr>
<tr>
<td>Intraperitoneal</td>
<td></td>
<td>36031</td>
<td>5002</td>
</tr>
<tr>
<td>Intravenous</td>
<td></td>
<td>19963</td>
<td>-</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td></td>
<td>8577</td>
<td>-</td>
</tr>
</tbody>
</table>

Modeling details & prediction accuracy
This document only provides a brief summary of the main technical aspects related to LD50 models. Detailed information is available in Sazonovas A. et al. SAR QSAR Environ Res. 2010; 21(1):127-48.

Prior to modeling, the original experimental data were converted to logarithmic form (pLD$_{50}$) in order to maintain linear relationship with used descriptors. The final prediction results returned to the user are converted back to LD$_{50}$ value (mg/kg).

The predictive model for pLD$_{50}$ were derived using GALAS (Global, Adjusted Locally According to Similarity) modeling methodology. A GALAS model consists of two parts:

- **Global** (baseline) statistical model based on PLS with multiple bootstrapping, using a predefined set of fragmental descriptors.
- **Local** correction to baseline prediction based on the analysis of model performance for similar compounds from the training set (the so called Self-training Library).

Reliability Index ($RI$)
Local part of the model provides the basis for estimating reliability of prediction by the means of calculated Reliability Index ($RI$) values. $RI$ is a number ranging from 0 to 1 (0 – unreliable prediction, 1 – idealistic, fully reliable prediction). The following two criteria are applied for reliability estimation:

- Similarity of the analyzed molecule to compounds in the Self-training Library (a reliable prediction cannot be made if no similar compounds have been found in the Library).
- Consistency of model predictions with experimental data for similar compounds (highly variable LD$_{50}$ values for similar molecules lead to lower $RI$ values).

$RI$ can serve as a valuable tool for interpreting prediction results. If a compound obtains $RI$ lower than a certain cut-off value (typically, set at 0.3), it means that this compound falls outside of the Model Applicability Domain, and the respective prediction should be discarded from further analysis regardless of calculated LD$_{50}$ value.
Model Performance

Predictive models of LD\textsubscript{50} in various systems have been validated on external data sets. Validation results show that the accuracy of prediction is proportional to the reliability index (see Table 2). The predictions with a high or moderate reliability index are accurate (average prediction error is about 0.5–0.7 log units). A high/moderate reliability index was reported for 20–50% of compounds in the validation sets.

**Table 2.** Residual Mean Square Error (RMSE) of pLD\textsubscript{50} predictions (mouse, IP route) at various Reliability Index ranges.

<table>
<thead>
<tr>
<th>Reliability Index (RI)</th>
<th>No. of compounds</th>
<th>RMSE</th>
<th>Prediction quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.3</td>
<td>465</td>
<td>0.903</td>
<td>Not reliable</td>
</tr>
<tr>
<td>0.3 – 0.5</td>
<td>1485</td>
<td>0.594</td>
<td>Borderline</td>
</tr>
<tr>
<td>0.5 – 0.75</td>
<td>4543</td>
<td>0.406</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt; 0.75</td>
<td>2534</td>
<td>0.259</td>
<td>High</td>
</tr>
</tbody>
</table>

Improving Prediction Accuracy via Training

GALAS modeling methodology provides the basis of model Trainability. This feature addresses the issue of the chemical space of ‘in-house’ libraries being considerably wider than that of publicly available data which results in limited applicability of most third-party QSARs for analysis of ‘in-house’ data. The ‘Training engine’ makes appropriate corrections for systematic deviations produced by the baseline QSAR model based on analysis of similar compounds from the experimental data library.

Addition of user-defined experimental data to the model Self-training Library leads to an instant improvement of prediction accuracy for the respective compound classes, therefore avoiding the need for time-consuming rebuilding of the models from scratch when reasonably large amounts of experimental data for new compounds become available.
OECD Categories

Chemicals are assigned to one of the five Oral Acute Toxicity Hazard Categories according to the LD50 values after oral administration to rats. Categories were defined by OECD (Organization for Economic Cooperation and Development. A Guide to The Globally Harmonized System of Classification and Labeling of Chemicals (GHS)):

- V – LD50 2000-5000 mg/kg (may be harmful if swallowed)
- IV – 300-2000 mg/kg (harmful if swallowed)
- III – 50-300 mg/kg (toxic if swallowed)
- II – 5-50 mg/kg (fatal if swallowed)
- I < 5 mg/kg (fatal if swallowed).

Predictions are provided as a list of probabilities that the compound's LD50 (rat, oral route) would exceed the cut-off values separating different categories. On the basis of these values, the software selects the most probable OECD Hazard categories for that compound (Fig. 2).

Figure 2. Screenshot of ACD/Percepta Acute Toxicity Categories module
Acute Toxicity Hazards

Hazards is a knowledge-based expert system that identifies and highlights structural elements that may be responsible for high acute toxicity of compounds in rodents. Tox Hazards system contains a list of 86 predefined ‘toxicophores’ compiled after thorough analysis of toxicological literature. Significance of the defined hazardous fragments was verified on the entire acute toxicity data set containing more than 100,000 compounds.

For each hazardous fragment, the software displays additional relevant information, such as distribution of LD50 values for compounds containing the highlighted fragment compared to the entire data set for a specific species/administration route system.

Figure 3. Screenshot of ACD/Percepta Acute Toxicity Hazards module