Toxtree README
(last revision - 05 Aug 2011)

This is the README file for the Toxtree installer distribution. If you're reading this, you've probably just run our installer and installed the Toxtree application on your system.

The present README file could be also accessed at "Start -> All Programs -> Ideaconsult -> Toxtree-vX.YZ -> README").

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INTRODUCTION

Toxtree is a full-featured and flexible user-friendly open source application, which is able to estimate toxic hazard by applying a decision tree approach. Currently it includes the following plugins:


- A decision tree for estimating eye irritation and corrosion potential, based on rules published in "Assessment of the eye irritating properties of chemicals by applying alternatives to the Draize rabbit eye test: the use of QSARs and in vitro tests for the classification of eye irritation," Ingrid Gerner, Manfred Liebsch & Horst Spielmann, Alternatives to Laboratory Animals, 2005, 33, pp. 215-237;


- START (Structural Alerts for Reactivity in Toxtree) biodegradation and persistence plug-in is based on a compilation of structural alerts for environmental persistence and biodegradability. These structural alerts are molecular functional groups or substructures that are known to be linked to the environmental persistence or biodegradability of chemicals. The rulebase utilizes the structural alerts in logical decision trees. If one or more the structural alerts embedded in the molecular structure of the chemical are recognized, the system flags the potential persistence or biodegradability of the chemical. Installation and user manuals available;

- Structure Alerts for the in vivo micronucleus assay in rodents, based on the rules, published in the document "Development of structural alerts for the in vivo micronucleus assay in rodents", by Romualdo Benigni, Cecilia Bossa, Olga Tcheremenskaia and Andrew Worth, European Commission report EUR 23844 EN;

- Cramer rules with extensions: This plug-in is a copy of the original
plug-in, plus minor extensions. Like the Cramer plug-in, this plug-in works by assigning compounds to Class I, II, or III, according to the rules from Cramer, and some extra ones. Several compounds were classified by Munro in 1996 as Class I or Class II compounds according to the Cramer rules, even though Munro reported low NOEL values upon oral administration (indicating relatively high toxicity). To overcome such misclassifications, five rules have been introduced to capture the possible toxicity of these compounds:


- Skin sensitization alerts, as per Enoch SJ, Madden JC, Cronin MT, Identification of mechanisms of toxic action for skin sensitisation using a SMARTS pattern based approach, SAR QSAR Environ Res. 2008; 19(5-6):555-78;


- Modified Verhaar scheme for predicting toxicity mode of actions - rules reordered, according to S.J. Enoch, M. Hewitt, M.T.D. Cronin, S. Azam, J.C.
Madden, Classification of chemicals according to mechanism of aquatic toxicity: An evaluation of the implementation of the Verhaar scheme in Toxtree, Chemosphere 73 (2008) 243-248;


Toxtree could be applied to datasets from various compatible file types. User-defined molecular structures are also supported - they could be entered by SMILES, or by using the built-in 2D structure diagram editor.

The Toxtree application is suitable for a standalone PC. It has been designed with flexible capabilities for future extensions in mind (e.g. other classification schemes that could be developed at a future date). New decision trees with arbitrary rules can be built with the help of graphical user interface or by developing new plug-ins.

SYSTEM REQUIREMENTS & INSTALLATION

Toxtree requires Java(TM) 2 Runtime Environment, Standard Edition 1.6 or newer on the target system and it is platform-independent. It runs under any host operating system, which supports Java(TM) 2 Runtime Environment, Standard Edition.

The Toxtree application is distributed with a fully automated offline installer (Toxtree-vX.Y.Z-setup.exe), compatible with recent versions of the Microsoft Windows (NT, 2000, XP, 2003) operating system. In order to install Toxtree just run the installer and follow its instructions. It contains all the required packages, including the Java(TM) 2 Runtime Environment, Standard Edition 1.6 setup.
If the installer does not detect Java(TM) 2 Runtime Environment, Standard Edition 1.6 or newer on the target system, it will attempt to install it before proceeding with the Toxtree setup. In this case, the user running the installer SHOULD HAVE ADMINISTRATIVE PRIVILEGES on the target system (otherwise the Java(TM) 2 Runtime Environment, Standard Edition setup would be aborted and Toxtree would not be installed).

If the installer detects Java(TM) 2 Runtime Environment, Standard Edition 1.6 or newer already installed on the target system, it will proceed directly with the Toxtree setup. In this case, ADMINISTRATIVE PRIVILEGES ARE RECOMMENDED but not necessarily required.

When the installer is launched by a user with administrative privileges, it will create Toxtree start menu shortcuts for all the users registered in the target system. Otherwise, start menu shortcuts will be created only for the unprivileged user, who launched the installation.

After a successful installation, Toxtree could be launched from the Start Menu ("Start -> All Programs -> Ideaconsult -> Toxtree-vX.Y.Z -> Toxtree-vX.Y.Z").

Each version of Toxtree could be uninstalled either by using the "Control Panel -> Add or Remove Programs" or by clicking the "Uninstall" link located in "Start -> All Programs -> Ideaconsult -> Toxtree-vX.Y.Z -> Uninstall-Toxtree-vX.Y.Z". Any application files which may happen to be locked during the uninstall procedure would be deleted after the next reboot of the system. Java(TM) 2 Runtime Environment, Standard Edition would not be uninstalled by the Toxtree uninstaller. If needed, it could be uninstalled via its own entry in "Control Panel -> Add or Remove Programs".

RELEASE NOTES
Toxtree-v2.5.0 is a stable release including new features and bug fixes.

BUG REPORTS AND FEEDBACK

You should send any comments, inquiries, bug reports, feature requests and other suggestions to Nina Jeliazkova <jeliazkova.nina@gmail.com>

TOXTREE DOCUMENTATION

The complete Toxtree documentation is located in the "doc" application subfolder.

REDISTRIBUTION

Toxtree is distributed under the GNU General Public License (see LICENSE.txt). It is freely distributable.

CHANGE LOG

* Toxtree-v2.5.0 (build date 05 Aug 2011):
  - updated to cdk 1.3.8;
  - updated to ambit-2.4.2;
  - OpenBabel is no longer included in the distribution; in order to use OpenBabel (optionally) from within Toxtree, install OpenBabel separately and set the OBABEL_HOME environment variable to point to the folder where OpenBabel is installed;
  - added metadata for all plugins (explanation, references, vendor, links to datasets);
  - improved display of decision tree details;
  - improved help menus (About / Files info / Help);
  - enabled CAS & EINECS lookup in remote OpenTox service; this new functionality is disabled by default -- check "Method/Decision tree option/Remote Query" menu to enable it;
  - added two new plug-ins: Modified Verhaar scheme, and Structural Alerts for Functional Group Identification (ISSFUNC);
- fixed Cramer rules Q2 (NC#N recognised as functional group associated with enhanced toxicity);
- fixed Cramer rules Q2 (secondary amine highlight);
- fixed Benigni / Bossa rulebase SA31b (biphenyls recognition);
- fixed Benigni / Bossa rulebase SA30 (coumarins recognition);
- fixed Benigni / Bossa rulebase rule (QSAR6,8 applicability domain);
- improved implementation of Verhaar scheme plugin; validated against a published dataset;
- SMARTCyp plug-in - added metabolite generation, based on Site of Metabolism, calculated by SMARTCyp and ambit-SMIRKS package.
- included jre-6u26-windows-i586.exe in Windows installer;
- updated manuals and README;
* Toxtree-v2.2.0 (build date 25 Oct 2010):
  - updated to cdk 1.3.67 (= cdk 1.3.6 + jni-inchi 0.7);
  - updated to jchempaint-3.1.3;
  - fixed not working Edit/Preferences;
  - removed valency labels that were appearing in JChemPaint by default;
  - fixed rendering of disconnected structures (e.g. salts);
  - fixed Cramer rule Q3 - S in aromatic ring is now recognized as divalent;
- included jre-6u22-windows-i586.exe in Windows installer;
- updated manuals and README.
* Toxtree-v2.1.1 (build date 07 Oct 2010):
  - upgraded to Java 1.6;
  - included jre-6u21-windows-i586.exe in Windows installer;
  - upgraded to OpenBabel v2.2.3;
  - fixed SMILES parsing (OpenBabel v2.2.3);
- enabled InChI-to-structure conversion based on jni-inchi-0.7-std;
- enabled name-to-structure conversion based on OPSIN v0.8.0;
- fixed outcome from QSAR8;
- values "true" and "false" in input file will be parsed into 1 or 0;
- fixed batch processing "Non serializable exception" for micronucleus and skin sensitiation plugins;
- added check for phosphates in Q4 of Cramer Extended rules;
- updated manuals and README.

* Toxtree-v2.1.0 (build date 30 Jun 2010):
- added highlighting of structural alerts;
- upgraded Toxtree to JChemPaint 3.0.1 and CDK 1.3.3;
- added 3 new plug-ins (Skin sensitization alerts, SMARTCyp - Cytochrome P450 - Mediated Metabolism & Kroes TTC decision tree);
- implemented several bug fixes;
- updated manuals and README.

* Toxtree-v1.60 (build date 15 Jul 2009):
- added Cramer rules with extensions plugin and updated bodymol.sdf;
- added Structure Alerts for the in vivo micronucleus assay in rodents plugin;
- added START biodegradation and persistence plugin;
- added structural Alerts for identification of Michael Acceptors plugin;
- Skin irritation plugin: fixed bugs in rules Q52 and Q53;
- Cramer rules plugin: fixed bugs in Q8 and Q21;
- Begnini/Bossa rulebase plugin: fixed issue when results for structural alerts (e.g. SA10) are not displayed if the outcome is YES;
- Begnini/Bossa rulebase plugin: QSAR8 question rephrased, to avoid
confusion;
- fixed issue when editing an example in the decision tree editor was not working;
- introduced TOXTREE environment variable, which should be set to point to the Toxtree-<version>.jar and helps locating SDF files and plugins when Toxtree is used by third party software;
- fixed issue when after creating a new tree it could not be saved;
- OpenBabel updated to v2.2.1 (build March 2, 2009);
  - updated documentation;
  - updated README;
* Toxtree-v1.51 (build date 26 Jun 2008):
  - fixed property checking rules bug;
  - updated README;
* Toxtree-v1.50 (build date 30 May 2008):
  - added support for eye irritation/corrosion prediction;
  - updated user manual;
  - updated README;
* Toxtree-v1.40 (build date 24 Mar 2008):
  - improved descriptor calculations (I(An),I(BiBr));
  - updated QSAR6, QSAR8, QSAR13;
  - new decision tree layout based on prefuse library - can be exported as .png, .bmp, .jpg or .gif;
  - new decision tree export options - .html, .pdf or .txt;
  - user preference options (persistent across application instances);
  - updated user manual;
  - updated README;
* Toxtree-v1.36 (build date 17 Feb 2008):
- improved partial molar refractivity, Sterimol and Idist descriptor calculation;

- updated README;

* Toxtree-v1.35 (build date 3 Feb 2008):

- updated the structural alerts for predicting carcinogenicity and mutagenicity;

- updated descriptor computations;

- updated README;

* Toxtree-v1.34 (build date 20 Jan 2008):

- updated CDK library;

- updated the structural alerts for predicting carcinogenicity and mutagenicity;

- updated descriptor computations;

- updated README;

* Toxtree-v1.33 (build date 6 Jan 2008):

- updated to CDK 1.1 release;

- updated the structural alerts for predicting carcinogenicity and mutagenicity to take into account overlaps;

- updated README;

* Toxtree-v1.32 (build date 26 Sep 2007):

- support for assigning multiple labels;

- improved implementation of structural alerts for the decision tree for predicting carcinogenicity and mutagenicity;

- MOPAC call bug fix;

- updated README;

* Toxtree-v1.31 (build date 21 Aug 2007):

- initial implementation of a decision tree for predicting carcinogenicity
and mutagenicity - 35 structural alerts and 3 linear discriminant rules, making use of 11 descriptors;

- new descriptors implemented:

  +Partial Molar Refractivity of substituents, according to a lookup table
  +Sterimol L & B5 descriptors, according to a lookup table
  +Descriptors for structure presence of aniline, NO2 & bridged biphenyls
  +EHOMO, ELUMO and other electronic descriptors calculated by launching MOPAC 7.1 (http://openmopac.net) with fixed options (AM1)
  - added substituents.sdf file (substituents lookup table);
  - added helper directory, containing MOPAC_7.1.exe;
  - updated README;

* Toxtree-v1.30 (build date 19 Jun 2007):
  - updated to CDK 1.0 release;
  - updated to jre-1_5_0_12;
  - prototype implementation of a decision tree for predicting carcinogenicity and mutagenicity;
  - updated README;

* Toxtree-v1.20 (build date 11 Mar 2007):
  - added global options for skin irritation rules (in addition to rule specific options);
  - added "Silent" option for skin irritation property rules (the answer of the property rule will always be "No" if a property is missing);
  - improved implementation of Verhaar scheme Class 4;
- fixed error when writing SMARTS rule to .tree file;
- updated installation manual;
- updated user manual;
- updated README;

* Toxtree-v1.12 (build date 18 Jan 2007):
- added new rule type based on SMARTS;
- redesigned decision tree editor;
- added Verhaar scheme plugin (Toxicity mode of action prediction);
- added BfR rules plugin (skin irritation/corrosion prediction);
- updated CDK library;
- updated README.

* Toxtree-v1.00 (build date 23 Oct 2005):
  - added complete application documentation, including installation
    manual, user manual, updated README, documentation of the source code;
  - improvements of the decision tree editor.

* Toxtree-v0.05 (build date 14 Oct 2005):
  - user defined decision tree concept introduced;
  - decision trees can be saved to and loaded from a file (a custom
    "tree" file type is used);
  - added graphical user interface for building decision trees;
  - the structure diagram editor (JChemPaint) is now launched as a nonmodal
    dialog. This resolves the issue of some JChemPaint windows
    being inaccessible if the editor is launched as a modal dialog;
  - after structure is edited in JChemPaint, SMILES is created and other
    properties are retained;
  - new command line options are introduced:
    java -jar Toxtree.jar -f <input file for normal open>
java -jar Toxtree.jar -b <input file for batch processing>

- improved recognition of carbohydrates;
- several nucleotides added to bodymol.sdf according to an expert advice;
- better recognition of some ionic groups (note that [Ca++] is recognised only as [Ca+]. For correct representation use [Ca+2] in SMILES);
- batch processing can not be started anymore when input and output files are the same;
- Q11: when a heterocyclic ring substituents are analysed, only heteroatoms in the ring analysed are disregarded (as specified in the Cramer et al, 1976) but not the heteroatoms in other rings. This behaviour is the one of v0.03. In the v0.04 release the behaviour was changed to disregard all heteroatoms, which doesn't follow the specification of Q11 to analyze each ring separately, with the remainder of the structure as substituents of that heteroring;
- added the application source code in the installers;

* Toxtree-v0.04 (build date 04 Oct 2005):
- Q5: better heuristics for carbohydrates;
- Q6: return "yes" only if the a)- and b)-substituents are present simultaneously;
- Q9: if it is a lactone from this point on treat the structure as if it were the hydroxy acid;
- Q11: ketone changed to R-C(=O)-R where R is not (O or H);
- checked the search path for bodymol.sdf and foodmol.sdf, when the application is run from the installer;
- checked that compounds are assigned always the highest (most hazardous) class of their constituents/hydrolysis products;
- optimized searching in foodmol.sdf and bodymol.sdf;
- updated foodmol.sdf and bodymol.sdf according to an expert advice;
- added Back/Forward buttons for easier navigation in the history of the SMILES drop down list;
- made the SMILES entry panel inaccessible for user input, when there is an open file. The name of the file is displayed instead of the SMILES entry panel. If changes are made in the file contents in memory, an asterisk (*) is displayed after the file name. The asterisk is removed after saving the file. Access to the SMILES entry panel is restored after File/New.
- added keyboard shortcut (hotkey CTRL+SHIFT+T) for application launching;
- added Start Menu tool tips;
- minor enhancements of the installers;
- updated README.

* Toxtree-v0.03 (build date 30 Sep 2005):
  - included a 2D molecular structure editor based on JChemPaint. It could be accessed via the Compound/Edit menu;
  - processes correctly SDF, CSV and TXT files with empty molecules;
  - fixed incorrect perception of a specific functional groups configuration;
  - bodymol.sdf and foodmol.sdf updated according to an expert advice;
  - minor enhancements of the user interface;
  - updated README.

* Toxtree-v0.02 (build date 25 Sep 2005):
  - Q1 and Q22: implemented to look up for "normal constituent of the body" and "common component of food" in bodymol.sdf and foodmol.sdf respectively. Only a very limited number of molecules are listed currently in these files. The user can replace these files with his own files, provided the
names are the same. The files are expected to be in the same directory as Toxtree.jar (the executable file of the Toxtree application). If the files are not found there, the corresponding rules behave as "NOT IMPLEMENTED" and answer "NO" for every compound;

- Q4: treat the compound as free acid, amine, unsulphonated or unsulphated compound except for the purposes of Q24 and Q33 (as specified in Q4 of Cramer rules);

- Q15, Q17, Q29, Q30, Q31: hydrolysis products (if any) are processed separately, as required by these rules. If the products are assigned different classes, the entire compound will be assigned the most hazardous class (i.e. - if one product is of class I and another of class III, the entire compound is considered of class III);

- ionic representation of compounds is processed correctly now (please, report any exceptions);

- checked that the following input file types are processed correctly (File/Open):
  
  CML
  CSV - comma delimited, has a header;
  HIN
  ICHI
  INCHI
  MDL MOL
  MDL SDF
  MOL2
  PDB
  SMI - each line starts with a SMILES, optional name delimited by single space, no header);
  TXT - tab delimited;
  XYZ

- input/output of CSV and TXT: a column with "SMILES" heading is mandatory in order the structure to be read. All other fields are optional, will be read as molecule properties and displayed as such;

- all the properties from SDF files are read;
- output (File/Save): molecules can be written to SDF, CSV or TXT files,
  together with their Cramer classification data (class & path);
- decision tree results are written as SDF properties or CSV/TXT columns.
  The class assignment is stored in a property "toxTree.tree.cramer.CramerRules". The tree path is stored in a property "toxTree.tree.cramer.CramerTreeResult";
- added a batch processing facility. It allows faster processing without
  loading simultaneously all the compounds into memory. Please, use batch
  processing if the file has more than thousand compounds. A batch could be
  paused, continued after pause or cancelled. Batch configuration (i.e.
  input/output file and processed records) could be saved in a file, loaded
  and continued in a later moment, even after the application has been closed
  and started again later. Batch configuration is saved in a temporary file
  by default. This file is deleted if the batch completes successfully. If
  the batch configuration is saved into a user defined file, it will persist
  even after the batch completes;
- moved the SMILES entry panel from the left to the top of the
  application window;
- history of entered SMILES' is kept in a drop down list;
- the left panel now displays all the properties defined for a molecule
  (not only CAS, SMILES and NAME as in the previous version). The properties
  are read from a file (e.g. CSV columns, SDF fields) or set when decision
  tree estimation is performed. When the compound is created from SMILES
  (using the SMILES entry panel at the top) the property SMILES is set as
  well as a remark "Created from SMILES";
- compounds, consisting of more than one disconnected moiety, are now displayed;
- removed the "Explain" button on the right panel, since the result is automatically explained on estimation. A check box "Verbose explanation" is added instead. It affects the way results are explained;

- since there can be more than one hydrolysis product, the results for each product are displayed in brackets ();

- the application can be configured to output a lot of information on its behaviour. This could be useful for debugging as well as for detailed study of decision tree results. In order to start the application and output debugging messages to the console, type on a command line the following command:

  java -DtoxTree.debugging=true -jar toxTree.jar

To store log in a file use:

  java -DtoxTree.debugging=true -jar toxTree.jar > toxTree.log

- minor enhancements of the installer;

- updated README.

* Toxtree-v0.01 (build date 24 Aug 2005):

- first public beta-release of the Toxtree application.

TO DO

* this section is empty.

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Developed (2010) by Ideaconsult Ltd., 4 Angel Kanchev St., 1000 Sofia, Bulgaria