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1

IDEACONSULT

Toxtree Installation Manual

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Table of Contents

Introduction 1
Prerequisites 3
Toxtree distributions 4
Windows™ Toxtree setup 4
Toxtree setup for other OS 5
Uninstalling Toxtree 5

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 plug-ins:

- Cramer rules (Cramer G. M., R. A. Ford, R. L. Hall, Estimation of Toxic Hazard - A Decision Tree Approach, J. Cosmet. Toxicol., Vol.16, pp. 255-276, Pergamon Press, 1978);

- Verhaar scheme for predicting toxicity mode of actions (Verhaar HJM, van Leeuwen CJ and Hermens JLM (1992) Classifying environmental pollutants. 1. Structure-activity relationships for prediction of aquatic toxicity. Chemosphere 25, 471-491);

- A decision tree for estimating skin irritation and corrosion potential, based on rules published in "The Skin Irritation Corrosion Rules Estimation Tool (SICRET), John D. Walker, Ingrid Gerner, Etje Hulzebos, Kerstin Schlegel, QSAR Comb. Sci. 2005, 24, pp. 378-384";

- 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";

- A decision tree for estimating carcinogenicity and mutagenicity, based on the rules published in the document: "The Benigni / Bossa rulebase for mutagenicity and carcinogenicity – a module of Toxtree", by R. Benigni, C. Bossa, N. Jeliazkova, T. Netzeva, and A. Worth. European Commission report EUR 23241 EN[1];

- 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

[1] http://ihcp.jrc.ec.europa.eu/our_labs/computational_toxicology/doc/EUR_23241_EN.pdf

recognized, the system flags the potential persistence or biodegradability of the chemical. Installation and user manual is available online[2];

- 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[3], 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[4] 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;

- Structure Alerts for identification of Michael Acceptors: This plug-in contains structural alerts, able to identify Michael Acceptors, as defined in T. Wayne Schultz, Jason W. Yarbrough, Robert S. Hunter, Aynur O. Aptula (2007) Verification of the Structural Alerts for Michael Acceptors. Chem. Res. Toxicol. 20, 1359–1363;

- 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;

- SMARTCyp - Cytochrome P450 - Mediated Metabolism, implementation of Patrik Rydberg, David E. Gloriam, Jed Zaretzki, Curt Breneman, Lars Olsen, SMARTCyp: A 2D Method for Prediction of Cytochrome P450-Mediated Drug Metabolism, ACS Med. Chem. Lett., 2010, 1 (3), pp 96–100;

- Kroes TTC decision tree - Kroes, R., Renwick, A.G., Cheeseman, M., Kleiner, J., Mangelsdorf, I., Piersma, A., Schilter, B., Schlatter, J., van Schothorst, F., Vos, J.G., Würtzen, G. (2004). Structure based thresholds of toxicological

[2] http://ihcp.jrc.ec.europa.eu/our_labs/computational_toxicology/doc/Toxtree_start_manual.pdf

[3] http://ihcp.jrc.ec.europa.eu/our_labs/computational_toxicology/doc/EUR_23844_EN.pdf

[4] I.C. Munro, R.A. Ford, E. Kennepohl, and J.G. Sprenger, Correlation of structural class with No-Observed-Effect Levels: A proposal for establishing a threshold of concern, Food Chem. Toxicol.34 (1996), pp. 829–867.

concern (TTC): guidance for application to substances present at low levels in the diet. Food Chem. Toxicol. 42, 65–83;

- 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;

- Structural Alerts for Functional Group Identification ISSFUNC (DOI: 10.2788/33281, Catalogue Number: LB-NA-24871-EN-N), Benigni R., O. Tcheremenskaia, and A. Worth, Computational Characterisation of Chemicals and Datasets in Terms of Organic Functional Groups - a New Toxtree Rulebase;

- Protein binding - S. J. Enoch, C. M. Ellison, T. W. Schultz & M. T. D. Cronin, A review of the electrophilic reaction chemistry involved in covalent protein binding relevant to toxicity, Critical Reviews in Toxicology, 2011, 1-20;

- Structural alerts associated with covalent DNA binding. - S. J. Enoch and M. T. D. Cronin, A review of the electrophilic reaction chemistry involved in covalent DNA binding, Critical Reviews in Toxicology,2010;40(8):728-748;

- A decision tree for estimating in vitro mutagenicity (Ames test). Benigni, R., Bossa C., Tcheremenskaia O. (2013) In vitro cell transformation assays for an integrated, alternative assessment of carcinogenicity: a data-based analysis. Mutagenesis 2013;28(1):107-16.

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.

Prerequisites

Toxtree requires Java™ 2 Runtime Environment, Standard Edition 1.7 or newer on the target system and it is platform-independent. It runs under any host operating system, which supports Java™ 2 Runtime Environment, Standard Edition.

Toxtree distributions

Toxtree is distributed in two different ways:

- ZIP archive, containing the complete documented Java™ source code, binaries, example lists of compounds, installation manual and user manual;
- Windows™ (NT, 2000, XP or 2003) standalone (offline) automated installer with integrated Java™ 2 Runtime Environment, Standard Edition 1.7 setup;

The ZIP archive is suitable for use on any operating system with Java™ 2 Runtime Environment, Standard Edition 1.7 already installed. It might be useful also for studying the application source code.

The Windows™ installer includes all the contents of the ZIP archive, as well as the ability to check for the presence of Java™ 2 Runtime Environment, Standard Edition 1.7 on the target system. If the installer does not detect Java™ 2 Runtime Environment, Standard Edition 1.7 already installed on the target system, it would attempt to install it, prior to Toxtree setup.

Windows™ Toxtree setup

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, 7, 2008) operating system. In order to install Toxtree just run the installer and follow its instructions. The installer contains all the required packages, including the Java™ 2 Runtime Environment, Standard Edition 1.7 setup.

If the installer does not detect Java™ 2 Runtime Environment, Standard Edition 1.7 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™ 2 Runtime Environment, Standard Edition 1.7 setup would be aborted and Toxtree would not be installed).

If the installer detects Java™ 2 Runtime Environment, Standard Edition 1.7 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").

Toxtree setup for other OS

Toxtree runs under any host operating system, which supports Java™ 2 Runtime Environment, Standard Edition (e.g. Linux, FreeBSD, Solaris, Mac OS, etc...). If you're running such operating system, you should download and use the ZIP archive distribution of Toxtree.

> *Please, note that before attempting to run Toxtree, you should check that Java™ 2 Runtime Environment, Standard Edition 1.7 (or newer) is installed on your system. If Java™ 2 Runtime Environment, Standard Edition is missing (or an older version is present), please obtain (from http://java.sun.com) and run the appropriate Java™ 2 Runtime Environment, Standard Edition installer for your system.*

Uninstalling Toxtree

Each version of Toxtree could be uninstalled from Windows™ 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.

> *Please, note that Java™ 2 Runtime Environment, Standard Edition would not be uninstalled from Windows™ by the Toxtree uninstaller. If needed, it could be uninstalled via its own entry in "Control Panel►Add or Remove Programs".*

Users of other operating systems, who want to uninstall Toxtree, could safely remove the files and folders, which were created by extracting the ZIP archive distribution of Toxtree.