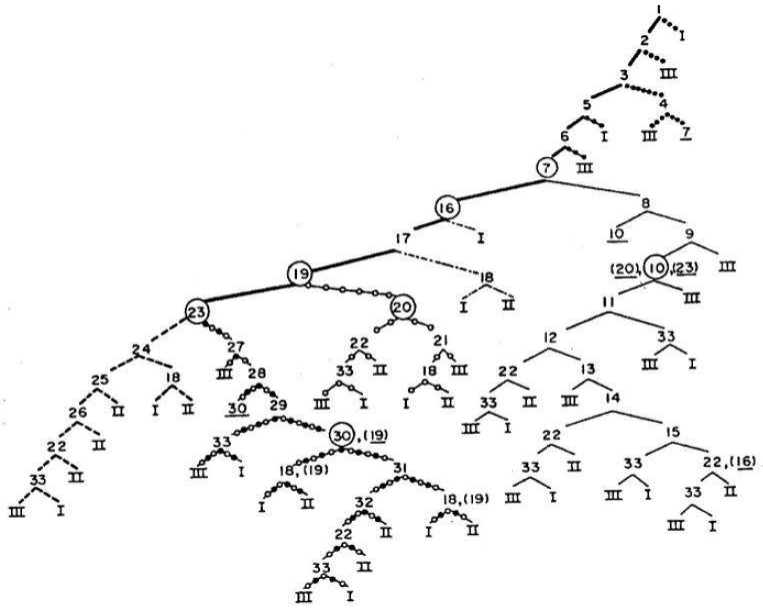
Cramer rules
with extensions

the Cramer rulebase with more
human compounds and structural alerts

User Manual



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Background

Cramer rules

The threshold of toxicological concern (TTC) is an open research topic with significant practical implications. Thresholds based on structural information have typically been developed by the principles established by Cramer. Chemicals are divided into three structural classes based on a decision tree. This tree originally comprises some 33 structural rules and places evaluated compounds into one of three classes:

Class I substances are simple chemical structures with efficient modes of metabolism suggesting a low order of oral toxicity;

Class III substances are those that permit no strong initial presumption of safety, or may even suggest significant toxicity or have reactive functional groups;

and finally, Class II are assigned to intermediate substances.

Much more background information on the methodology and structural rules can be obtained from browsing the Cramer tree as it is implemented in ToxTree (through Method > View decision tree), or from related references [1-3]. The implementation of the Cramer rules via ToxTree [1] ensures an objective and reproducible means for the classification of the TTC of new compounds.

Cramer rules with extensions

The Cramer rules have been published in 1978 and they were originally validated with 82 compounds with NOEL data, and with a large set of carcinogens [1,2]. As noted above, the Cramer tree is set up such that it detects few harmless compounds as Class I (low concern) substances, and virtually all other compounds as Class III (high concern, i.e. no assumptions of safety possible). 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 [3] 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.

Extension details

A plug-in has been built for ToxTree, called 'Cramer tree with extensions'. This plug-in is basically a copy of the original plug-in, plus minor extensions. These extensions are detailed below.

Q40 & Q41 allow natural phosphates

Q3 and Q4 of the Cramer rules ("Does the structure contain elements other than C, H, O, N or divalent S?") detect (amongst others) phosphorus atoms (P) and assigns any compound with it as Class III (high concern). One reason for this is that most insecticides are organophosphates (with uncharged (thio)phosphates) that are also very toxic to humans. However, negatively charged phosphates occur in over half of all human compounds, and it is therefore unlikely that such a feature warrants a high concern label. Q40 therefore recognises harmless phosphates (those with a negative charge) and puts these possibly safe compounds through Q41. Q41 splits harmless phosphates from (natural) compounds and considers each resulting fragment individually in the tree: the most toxic classification of these fragments is then used to classify the compound.

Q42 detects more benzene-like substances as Class III

Q42 recognises benzene-like compounds that possess low NOELs and false class I/II predictions, which were not recognised by Q6. Q42 assigns compounds that consist of a single aromatic ring with zero to six single atom-substituents as High/III. An example of a compound that Q42 recognises is 2,6-dimethylphenol (which has a total of three single (heavy) atom-substituents).

Q43 detects some non-natural divalent sulphurs as Class III

Q3 and Q4 of the Cramer rules ("Does the structure contain elements other than C, H, O, N or divalent S?") possibly miss the toxicity of several compounds that contain a specific divalent sulphur. Given that these moieties do not occur in natural human compounds, we can assume that compounds with such a moiety can pose a toxic risk. Therefore, Q43 recognises non-natural / possibly toxic divalent sulphur moieties and assigns compounds containing them as High/III.

Q44 detects some unsaturated heteroatom moieties as Class III

Q44 recognises a small moiety that correlates with low NOELs and false class I/II predictions (an a,b-unsaturated heteroatom moiety) and assigns such compounds (e.g. allyl alcohol) as High/III.

Q1 recognises more natural constituents as Class I

In 2008, the number of natural, human compounds in the Cramer plug-in for ToxTree was limited to 67. These compounds are important for Q1 of the Cramer rules ("Is the substance a normal constituent of the body, or an optical isomer of such?" If so, assign the substance to Class I.). Currently, the number of normal constituents in the body has been increased to over 400 unique compounds and contains no hormones. Cramer's assumption is that such compounds pose a minor threat at most (i.e., no low NOELs). This addition causes the Cramer plug-in to assign more compounds to Class I.

The Toxtree plug-in: Cramer rules, with extensions

Toxtree is a Java based decision tree software with a plug-in interface. This plug-in for Toxtree is basically a copy of the Java based Cramer plug-in, but with some extra structural rules. The following two sections describe the installation and the usage of the plug-in "Cramer rules, with extensions". *This plug-in will only work for Toxtree v1.60 or higher.*

Installation

The implementation of the plug-in follows the standard plug-in mechanism of Toxtree as used in the existing decision tree methods (Verhaar scheme, Eye irritation, etc.). The functionality of the extended plug-in is encoded in the "CramerRulesWithExtensions.jar" library file which has to be copied into the plug-in directory of the Toxtree installation as shown in Figure 1.

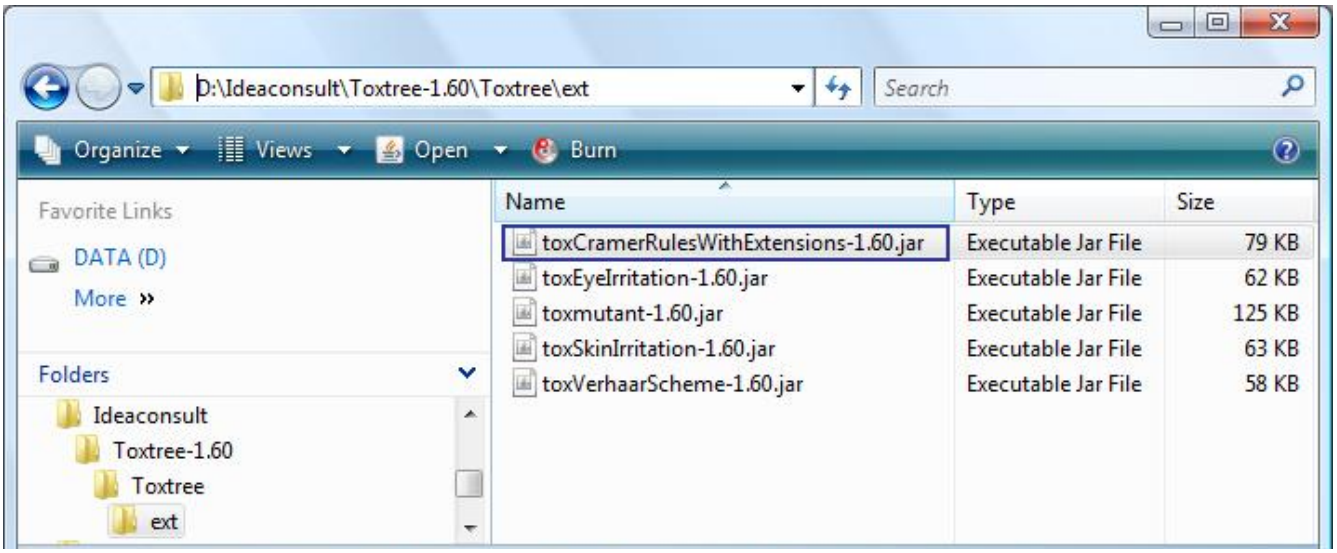

Figure 1 Installation of the plug-in 'Cramer Rules, with extensions' for Toxtree. The library file "CramerRulesWithExtensions .jar" has to be copied into the plug-in directory of the Toxtree installation.

Usage

Once the plug-in has been installed into Toxtree, it has to be activated. This can be done in the menu bar of Toxtree as shown in Figure 2.

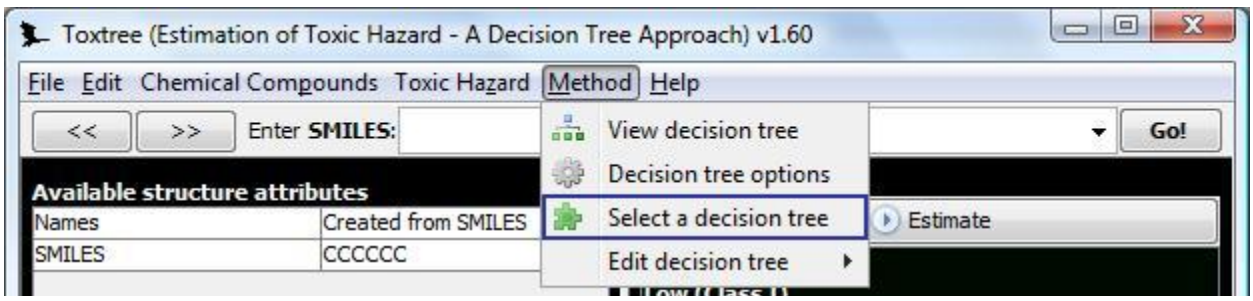

Figure 2 The "Select a decision tree" option in the Toxtree menu bar.

In the "Select a tree" dialogue window the plug-in can be selected from the list of available decision trees ("Cramer rules, with extensions") like any other Toxtree plug-in as illustrated in Figure 3. After clicking OK, the Toxtree plug-in is now ready for use.

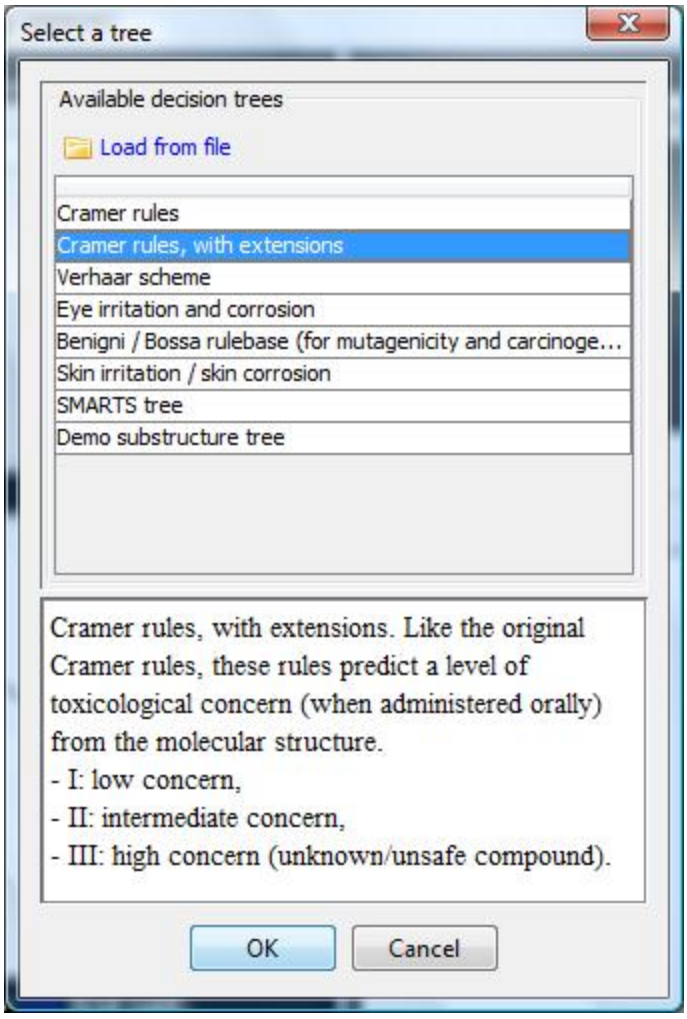

Figure 3 Decision tree selection in the "Select a tree" dialogue window of Toxtree.

References

[1] G. Patlewicz, N. Jeliazkova, R.J. Safford, A.P. Worth and B. Aleksiev, An evaluation of the implementation of the Cramer classification scheme in the Toxtree software, SAR QSAR Environ. Res., 19 (2008), pp. 495–524.

[2] G.M. Cramer, R.A. Ford, and R.A. Hall, Estimation of toxic hazard – a decision tree approach, Food Chem. Toxicol. 16 (1978), pp. 255–276.

[3] 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.