ADMET Predictor® release 10.2

By Simulations Plus, Inc. April 2021

Dear ADMET Predictor User,

This new release of ADMET Predictor includes significant enhancements throughout the program. A brief overview of the changes is provided in this document. For detailed descriptions of all changes, please consult the relevant sections of the ADMET Predictor user manual.

Important Notes

If you have previously installed a beta version of ADMET Predictor 10.2, you should uninstall it prior to installing this final release version. After following the normal Windows protocol for software uninstallation, you should completely remove the three installation folders. In most cases these folders are:

- C:\Program Files\Simulations Plus, Inc\ADMET_Predictor10.2
- C:\ProgramData\Simulations Plus, Inc\ADMET_Predictor10.2
- C:\Users\<user_name>\AppData\Local\Simulations Plus, Inc\ADMET_Predictor10.2
  where <user_name> is your specific username

HTPK Module

Several enhancements to the HTPK module have been made through collaboration with a large pharmaceutical company.

- All HTPK workflows now support an option to specify the dosage form, which can be either immediate-release tablet (default) or IV bolus.
- The dose-optimization workflow supports two new options to control how the target plasma concentration is interpreted. The first controls whether the concentration is an average, minimum or maximum, while the second controls whether it represents a total (bound + unbound) concentration or an unbound concentration.
- The dose-optimization workflow can now be run from MedChem Designer.
- There is a new option to control how the intrinsic clearance is corrected to account for non-specific binding to the *in vitro* system. In addition to the previous options for no

correction and for an automatic correction based on Fumic (microsomes) and the Austin equation (hepatocytes), users can now directly specify a percent unbound value.

- AUC from zero to infinity is now estimated and returned as a result value. Note that both the reported clearance and half-life parameters are now derived from this AUC estimate, so are missing in the case that it cannot be estimated.
- The default human volume of distribution parameter has been changed to the mechanistic estimate based on the Lukacova extension of the Rogers method. Users can optionally revert back to ADMET Predictor's statistical Vd model either using the graphical interface or by modifying the relevant HIA parameter files (SimHIA.hia and SimDOSE.hia).
- There is a new option to adjust the fraction unbound in plasma (fup) to account for non-specific binding to lipids, mirroring the equivalent option in our GastroPlus® software. Note that this setting does not affect the mechanistic volume of distribution, which always uses the adjusted fup. Note also that renal clearance (fup * GFR) is always computed using the non-adjusted fup.
- There is a new option to turn on and off the renal component (fup*GFR) of the calculated plasma clearance.
- Cp-time profiles can be generated for up to 16 compounds simultaneously.
- Cp-time profiles can be appended to a previously generated one. This is useful for visualizing the effects of parameter changes.
- Users have more control over display settings in the Cp-time profile window.
- Several physiological parameters have been modified to match those used in GastroPlus® 9.81.
- The algorithm used for computing the number of dosing intervals required to reach steady state in the dose-optimization workflow has been substantially improved.

New Risk Model for Ames Mutagenicity

Recent literature and findings from proceedings of an International Workshop on Genotypic Testing prompted us to add a new model for mutagenic risk, MUTx_Risk, that complements the existing MUT_Risk. The risk weights in the new model have been precisely calibrated to reflect the relative importance of the TA98, TA100 and TA1535 strains, and the model incorporates new rules to better capture the interactions between them. These changes have enhanced both sensitivity and specificity on the benchmark Hansen data set.

Enhanced Parallelization

Several features were made significantly faster by exploiting multi-core CPUs.

- Substructure search

- Compound transformations (standardization, etc.)
- Adding compound attributes
- Class generation using Frameworks or user-defined scaffolds
- Appending new classes using queries

Note that by default, ADMET Predictor utilizes all but one of the available cores for calculations, though this can be changed using the advanced settings dialog.

Command Line

Several new command-line capabilities have been added. These all use the script-file workflow mechanism, where ADMET Predictor is invoked by passing it a user-modifiable text file containing the parameters that control the run. The new workflows are listed below. More information about each is included in the relevant script file and in the user manual.

- Generate Metabolites (ms_generate_metabolites.txt). Predicts CYP or UGT metabolites for a set of input compounds.
- Transform Compounds (ms_transform_compounds.txt). Transforms compounds using user-defined transform rules. A new example transform file called Standardize.crf has been included in the ADMET Predictor installation folder.
- Solubility Profile (ms_solubility_profile.txt). For each compound in an input file, generates a text file containing predicted solubilities at pH values ranging from 0 to 14.
- LogD Profile (ms_logd_profile.txt). For each compound in an input file, generates a text file containing predicted logD values at pH values ranging from 0 to 14.
- Generate Tautomers (ms_generate_tautomers.txt). Generates tautomers from a set of input compounds.

These and other script-file workflows now support specifying arguments on the command line. For example, the *structureFile* parameter in ms_generate_metabolites.txt can be overridden on the command line using, for example:

ADMET_Predictor.exe ms_generate_metabolites.txt -structureFile MyFile.sdf

This allows you to specify on the command line those parameters that tend to change from run to run, while leaving the other parameters defined in the file.

Additional Changes

- Users can now modify the rules for standardizing tautomers by adding substructure queries to the new file called TautomerStandardizationQueries.txt, included in the ADMET Predictor installation folder. See the notes in this file, and the user manual, for additional information.

- A new significant-figures option on the Settings >> Format tab was added for improved display of small numbers in the spreadsheet.
- Tooltips have been added for attribute names too long to be fully displayed in dialog list boxes (e.g., for charts and export).
- The Settings >> Advanced tab includes a new option to auto compute user-defined attributes after HTPK calculations. This complements the existing option for ADMET calculations.
- There are new View >> Resize Columns menu options to change all spreadsheet column widths to allow full display of column headers or data.
- The transform rules used for metabolite prediction were modified so that products of spontaneous dehydration are considered observable rather than non-observable.
- Query files (*.cqf) now support optional tooltips through a new QUERYTIP keyword. An example is provided in the installation file AttributeExamples.cqf, which can be used to add attributes to the spreadsheet using the Data >> Add Compound Attributes >> Query menu option.
- Standard valences were added for several less-common elements, primarily metals. This results in improved implicit hydrogen assignments, particularly in MedChem Designer.
- Auxiliary windows such as pKa Microstates and Atomic Properties remember their previous display size during a session.
- The Linear Fit feature of the 2D scatter chart now has an option to display an identity line in addition to the regression line.
- The menu option EDIT >> Select Using File now allows the choice of compound attribute against which to perform the text comparison. Previously only compound identifier was allowed.

Bug fixes

The most significant bug fixes are described below.

- On certain machines ADMET Predictor could crash sporadically due to problems communicating with the license server.
- The model for rat hepatic clearance, HEP_rCLint, was yielding incorrect predictions due to an internal error.
- AIDD error files were not being generated correctly when running in a single thread.
- When multiple seed molecules were submitted to AIDD, only the first one was being considered in generating analogs for the first generation.
- AIDD could produce compounds with invalid wedge bonds.

- Charts did not always display correctly if they were pinned at the time a new data set was opened.
- Model uncertainty estimates were not displayed properly when exported to Excel.
- The Open Query File option in the Structure Sensitivity Analysis window did not work properly if launched from MedChem Designer using more than one compound.
- Automatic scrolling to selected spreadsheet compounds could fail when a large number of spreadsheet rows were hidden.
- The feature to select Pareto optimal compounds in the spreadsheet was incorrectly including hidden compounds.
- Histogram columns in the Classes tab lost format settings after switching to another tab.
- The option to retain registry settings from a previous version of ADMET Predictor was not working properly.
- pKa values could be unrealistic in rare situations as a result of large negative atomic superdelocalizabilities. Atomic superdelocalizabilities are now capped at zero at the lower end, resulting in improved pKa predictions for such molecules.
- KPLS models run in ADMET Predictor could yield invalid results when using multiple threads.
- SVM models produced by Modeler 10.x could not be read by ADMET Predictor.
- Calculations of fractions ionized could result in numerical overflow in rare situations.