What is new in OASIS TIMES?

v. 2.34.1

I. Modifications in the platform

- Documented Metabolism database version is updated from 3.4.2 to 3.4.3 (compatible with MetaPath version 5.4.3).
- Docking with ***OECD QSAR Toolbox ver.4.8***.

The latest update of IUCLID (May, 2025) includes new features and format changes, including modifications associated with the harmonized templates and inclusion of QAF fields to accommodate results from QSAR predictions. In general, there are 20 new fields associated with the QAF protocol. When a (Q)SAR prediction is done within the QSAR Toolbox (e.g., using the TIMES models), it could be transferred to IUCLID with the relevant QAF-requested information. Due to time constraints, only four data fields (out of all 20 new fields) are currently automatically populated with information from the TIMES models. Still, the full QPRF of the used OASIS model (organized according to the QAF criteria) can be attached to the transferred prediction in IUCLID manually. The information that comes from the OASIS models is now being associated with the other sixteen QAF fields in IUCLID (ongoing process), requiring additional modifications in both Toolbox and OASIS software. The modifications could be included in the next releases of both systems (expected in 2026). This will allow the OASIS predictions done in Toolbox, to be transferred to the custom IUCLID database with automated population of the relevant QAF fields.

II. Modifications in the models, existing and new functionalities

- Modifications in the non-kinetic genotoxicity models:
    - Addition of new documented maps is performed for *in vitro* and *in vivo* metabolism databases.
    - Modifications are done in the *in vitro* S9 and *in vivo* rat metabolic simulators to improve their predictive capabilities.
    - Modifications in DNA binding N-Nitrosamine's alert is performed to address mutagenicity of parents and metabolites simultaneously.

- Modifications in the kinetic genotoxicity models:
    - The modifications done in the non-kinetic models related to the update of alert definition, metabolic transformations and databases with documented metabolism are transferred to the respective kinetic models.
    - In the current version of Ames kinetic model, the kinetic approach for calculating quantities of simulated metabolites is taken into account to resolve some limitations of the probabilistic approach (used in the previous version of the model). It is developed based on the following principles:
        - The first order kinetic is assumed for the kinetic curves describing the metabolic transformations;
        - The functions for calculating quantities of parallel transformations are re-derived from well-known differential equations.
- Modifications in the non-kinetic skin sensitization models:
    - Enzymatic information is provided in the transformation tables of all skin sensitization models.
- Modifications in the kinetic skin sensitization model:
    - Four additional P-Groups are included to resolve some technical problems identified with the model.
- ***Report of metabolites' quantities over the time*** is a new functionality, implemented for all kinetic models available in the TIMES software. It allows to report the quantity of all simulated metabolites as a function of time.
- ***Enzyme report*** button is implemented for models where enzyme information is available.
- ***Exact mass*** calculation of parent molecules and simulated metabolites is provided and could be included in the reports (e.g., full report, QPRF, etc.). It is developed as a new

2D parameter allowing to calculate the exact mass of the chemicals considering the mass of the most stable and longest-lived isotopes.

- ***Improvements of the QPRF***:
  - Filtering the analogues supporting prediction with the profilers available in QSAR Toolbox. Reporting the obtained results.
  - Modifications of the report allowing to omit the empty fields that are not filled in by the user.
- ***Improvements related to QAF protocol***:
  - Transfer TIMES predictions generated in Toolbox to IUCLID.
  - Automatically fulfilled fields in IUCLID (through Toolbox).
  - Transfer QPRF from the TIMES model to IUCLID (as an attachment).

v. 2.33.1

I. Modifications in the platform

- Documented Metabolism database version is updated from 3.4.1 to 3.4.2 (compatible with MetaPath version 5.4.2).
- Calculation of EPI Win *log* K_{OW} and Water solubility is executed directly, not by full EPI report. This increases the speed of calculation when only one of these parameters is needed.
- Docking with ***OECD QSAR Toolbox ver.4.7***.

II. Modifications in the models, existing and new functionalities

- Modifications in the non-kinetic genotoxicity models:

- The training set of *in vitro* Ames mutagenicity S9 model is expanded with additional mutagenicity data collected according to the recommendations in the OECD technical guideline 471.
- Due to the preformed external validation with Ames data available in the EFSA database and after expert evaluation, the following modifications have been done:
  - some of the Ames mutagenicity data from the training set are updated.
  - some of the alerts related to the interactions with DNA are modified.
  - new alerts for DNA binding are implemented.
- Modifications are done in the *in vitro* S9 and *in vivo* rat metabolic simulators to improve their predictive capabilities.
- Enzyme information is implemented for the transformations in the *in vivo* metabolic simulator.

- Modifications in the kinetic genotoxicity models:
  - All modifications done in the non-kinetic models related to the update of training sets, improved metabolic transformations and alert definitions are transferred to the respective kinetic models.
  - The quantitative thresholds for the amount of DNA and protein adducts associated with positive effect are also modified.
  - The probabilistic formalism used for calculating the quantities of simulated metabolites is changed with a new kinetic formalism (except for the Ames kinetic model), aiming to improve the predictive capabilities of the models.
- Modifications in the kinetic skin sensitization model:
  - The new kinetic formalism for calculating the quantities of simulated metabolites is also implemented in the Skin sensitization kinetic model.

  - Consideration for the multi dose application of the target chemicals is also implemented aiming to mimic the experimental conditions of the LLNA test.
  - The quantitative threshold discriminating Strong from Weak sensitizers is also modified.

- ***Improvements of the QMRFs and QPRFs*** based on the latest QSAR Assessment Framework (QAF) documentation introduced recently in the OECD TG 386.
- Generation of customized QPRF is also allowed for the metabolic simulators where the tissue specific metabolism is considered only, with no relation to the endpoints.
- In case of simulating the metabolism of chemicals having symmetric functionalities, a new setting to ***Merge the equal metabolic branches*** is considered to prevent the overestimation of calculated metabolic quantity.
- The visualization of transformations names is improved, i.e., the full transformation names are already visible on the simulated 2D map and also reported in the QPRFs.
- ***Color legend*** is implemented in the 2D map with simulated metabolism to support the explanation of different highlighting.
- The ***Clustering*** functionality is expanded with new criteria for grouping of chemicals, based on 2D/3D parameters and custom structural fragment.
- The complex ***Flexible search*** combined with metabolism is already allowed to be explained (so far, flexible search without metabolism was allowed for explain only).
- The simulated metabolic maps could be already filtered based on different criteria and applying the Flexible search functionality (e.g., using the knowledge from Toolbox, 2D/3D parameters, structure similarity, etc.).
- ***New functionality*** showing the quantity distribution of parent/metabolites over the time is implemented in the *Metabolite distribution* window.

III. New models

- New kinetic *in vitro* Half-life model is developed and implemented in the TIMES software, where the half-life is predicted as a function of rate constants and phys-chem parameters calculated for each target chemical individually. The quantity of parent and each metabolite is already estimated as a function of time.

v. 2.32.1

I. Modifications in the platform

- Documented Metabolism database version is updated from 3.4.0 to 3.4.1 (compatible with MetaPath version 5.4.1).
- EPIWin v.4.11 module is used for the calculations of logKow and Water solubility parameters accounted in the parametric layer of the applicability domain. Interface with the package is improved to work in a hidden Windows desktop to avoid unpleasant flashing when starting individual programs.
- Docking with ***OECD QSAR Toolbox ver.4.6***.

II. Modifications in the models, existing and new functionalities

- Modifications in the non-kinetic genotoxicity models:
    - The training set of *in vitro* Ames mutagenicity S9 model is expanded with additional mutagenicity data collected according to the recommendations in the OECD technical guideline 471.
    - Some of the alerts related to the interactions with DNA are modified (e.g., N-nitroso compounds alert).
    - Slight modifications are done in the *in vitro* S9 and *in vivo* rat metabolic simulators to improve their predictive capabilities.
    - Information for the enzymes catalyzing metabolic transformations is implemented in *in vitro* genotoxicity models and *in vitro* S9 simulator.
- Modifications in the kinetic genotoxicity models:

- All modifications done in the non-kinetic models related to the update of training set, improved simulation of metabolism and alert definitions are transferred to the respective kinetic models.
- Categorization of the metabolic transformations names is done for Ames mutagenicity S9 kinetic and Chromosomal Aberration S9 activated kinetic models.
- The quantitative thresholds for the amount of DNA adducts associated with positive effect are also modified.

- Modifications in the models related to skin sensitization:
  - Training sets of Skin sensitization DST and Skin sensitization kinetic models are updated including data collected according to the recommendations in the OECD technical guideline 429 only.
  - Some of the alerts related to the interactions with skin proteins are modified.
  - Slight modifications are done in the skin metabolism simulator to improve its predictive capabilities.
- ***New functionality*** for searching in the databases with documented metabolism data has been introduced in the software. It:
  - provides experimental data support for each molecular transformation
  - allows the metabolic transformations to be associated with the treatment groups and to check their validity
  - is organized as ***local training set*** of the respective transformation.
- ***Improvements in the QPRF*** of the models – more than one graph with the distribution of metabolites based on different parameters (e.g., quantity, LogKow, etc.) could be reported as an Appendix; comments could be provided for each of the appendices independently; update of the save/load functionalities.

- ***Metabolism similarity report/export*** – new types of reports are introduced allowing to report/export the results after comparison between chemicals and their metabolites based on selected criteria (e.g. similarity in metabolic transformations, mechanistic or structural similarity, etc.).

III. New models

- ***New model*** has been developed to predict the aquatic toxicity of Cyprinidae (LC50 96h).

v. 2.31.2

I. Modifications in the platform

- The TIMES software requires activation of a ***License key*** with an expiration period (depending on the contractual issues) to allow working with the system.
- Optional export SMILES in DayLight format.
- Documented Metabolism database version is updated from 3.1.1 to 3.4.0 (Application (MetaPath) version 5.4.0).
- The list with cache files used for storing of pre-calculated results has been extended to accelerate the work with the system.
- EPIWin v.4.11 module is used for the calculations of logKow, Molecular weight and Water solubility parameters accounted in the parametric layer of the applicability domain.
- In case the calculation from EPIWin v.4.11 cannot be done, the old dll module (Syracuse University) is applied.

- TIMES requires installation of Microsoft.NET.
- Docking with ***OECD QSAR Toolbox ver.4.5***.

II. Modifications in the models, existing and new functionalities

- The prediction workflow has been improved organizing all of the functionalities associated with: explain of the predictions, searching for analogues supporting prediction, analogues supporting simulated metabolism, domain information and reporting.
- New functionalities have been introduced in the software for:
    - ***Evaluating adequacy of simulated metabolism*** by providing:
        - ***Experimental support*** – finding analogues with documented metabolism data based on selected criteria supporting selected sequence of simulated transformations
        - ***Theoretical support*** – mechanistic justification of the transformations simulating metabolism
    - ***Metabolic similarity*** – comparison between chemicals and their metabolites based on selected criteria (e.g. similarity in metabolic transformations, mechanistic or structural similarity, etc.)
    - ***Reporting of metabolic map*** – providing: IDs of parent and all generated metabolites; the level of generation and predecessor of each metabolite; indication for observed metabolite; quantities and prediction results of metabolites; the transformations responsible for generating the metabolites and their probabilities.
    - ***Clustering*** – grouping of chemicals based on selected criteria
    - Entropy – removing less informative chemicals based on selected criteria

- ***Similarity matrix*** – contingency table for the similarity between chemicals based on selected criteria
- ***Selection of representatives*** – prioritization of the chemicals based on their metabolic/structural similarity compared to the other chemicals in the list

- ***Help files*** with more detailed information are provided within the software platform.
- Flexible search functionality has been extended with:
  - Search by list (SMILES, Chemical name)
  - Search by Distance for Parameters
  - Masks could be added if fragment search is used
  - ***Transformation search***
- ***Improvements in the QPRF*** of the models – new organization of generation window, new appendix for analogues supporting metabolism, spell-check included for user-defined sections, save/load functionalities implemented.
- The classification of transformations` names has been improved for in vitro S9 and in vivo rat liver metabolic simulators.
- Skin sensitization kinetic model (pilot version) has been upgraded using the modelling concept of Common Potency Thresholds (CPT) (more details are available in the Description file of the model).
- Information for the tautomers of the parent chemicals and further evaluation of their stability is implemented in the report of Skin *sensitization with autoxidation* and *Skin sensitization based on GHS* models.
- Domain is not applied on hydrolysis products in models accounting for metabolism.

III. New models

- ***New models*** have been developed based on a new QSAR modelling concept accounting for the kinetics of metabolism and adduct formation:
  - ***In vitro* Ames mutagenicity kinetic model**
  - ***In vitro* Chromosomal aberrations kinetic model**
  - ***In vivo* TGR kinetic model**
  - ***In vivo* Micronucleus kinetic model**

v. 2.30.1

- New *in vivo* Skin sensitization kinetic model (pilot version) has been developed
- New functionality for evaluating metabolism similarity accounting for different criteria is implemented by comparing:
  - generated metabolic maps of selected chemicals based on the same metabolic simulator
  - generated metabolic maps of a single chemical based on two different metabolic simulators
- Estimation of Alert performance (AP) is implemented along with its confidence interval, p-value and visualization graph
- Documented Metabolism database version is updated from 3.1.0 to 3.1.1
- Cache files with pre-caching results of generated metabolites, prediction results, etc. for the training sets of the models
- Highlighting of the structures (parent and/or metabolites) bringing the positive effect on the generated 2D metabolic map automatically
- Highlighting of the local training set chemicals corresponding to a specific alert query Improved visualization of the 2D depictions in the metabolic map for QPRF
- Flexible search improvements

- Improvements in the QMRF and QPRF files
- Additional supporting information – possibility to see metadata, new help buttons
- Docking to QSAR Toolbox v.4.4

v. 2.29.1

- Compiled with Delphi 10.2 Version 25.0 (previous was Delphi® XE3 Version 17.0)
- Database (ODB) version is changed from 4.6.6 to 4.6.7 associated with verification of existing unhandled 5AAR
- Toxic models are refactored to work on in memory structures instead of representation in on disc database
- Multi-threaded metabolization
- Ability to add custom (external) analogues in QPRF
- Implementation of distributed cache
- Workflow acceleration

v.2.28.1

- In the previous versions of TIMES software was not allowed to load more than one model with metabolic activation. Currently, this issue is resolved and the user could load more metabolic models simultaneously.
- One could change the options for:
    - filtering metabolites in 2D metabolic map
    - filtering metabolites in full report

- metabolization

Now buttons for the default options are provided.

- Improvements have been done for QPRF generation:
  - Searching for analogues (in the training set of the model) based on the measured (observed) data is now possible along with searching based on the predicted values
  - Metabolites in the 2D metabolic map are now numbered; these numbers correspond to the numbering of metabolites listed in Appendix 3.

v. 2.27.19

- Database (ODB) version is changed from 4.6.5 to 4.6.6. This will perform one-time update of the existing ODB files. Some structures containing cis-trans stereo information may need to be recalculated.
- Added new functionalities and improvements in QPRF generation:
  - Added new functionality allowing automatic report creation for more than one prediction,
  - Added new QPRF report options allowing customization of system behavior during reports generation,
  - Content of report item related to model goodness-of-fit and external validation are populated automatically.

v. 2.27.18

- Model parameters in ODB files were transformed to multi parameters. These are parameters having more than one value described with metadata. The metadata contains information for source, author name, experimental conditions etc.

- Added features to transformations that allow:
    - To be defined levels for generation of some metabolites in order to avoid an excessive generation of “false positives” by the simulator
    - Activity of protein binding alerts to be reduced if they are activated by consecutive transformation steps
    - Boundaries of physicochemical properties to be defined to the transformations allowing their implementation
- Added new feature to Report that allow to be reported observed data or calculated MOPAC parameters

v. 2.27.17

- New domain extraction mechanics. The domain is now extracted using the whole aromatic ring as a center atom.
- Added search by a predicted by metabolic model value to the Flexible search functionality.

v. 2.27.16

- User interface was redesigned using the Windows Ribbon Framework.
- QPRF report is now available for all models. Added features for flexible searching for analogues to be added to QPRF.
- Added feature to 2D map filter that allow filtering by individual (node) and aggregate quantity for a metabolite. 2.27.15
- 3D calculations were made multi-threaded to speed up local calculations on multi-core CPUs.
- New ODB file version combining functionalities of previous ODB, A01, SDB and FDB files.

- Sub-fragment search has been extended to use stereo information (in previous version tetrahedral and stereo configuration has been ignored). Now if query molecule has defined stereo information the target should also contains same stereo configuration. To implement this feature also there is a change in SMILES notation.

v. 2.27.14

- The module for SMILES canonization is updated to correct known cases of non-unique canonization. The existing ODB files will be updated automatically upon first opening.