OASIS software
Predicting Human health hazard endpoints
ADVANCED AGENDA
2023

I. TIMES platform

TIMES system combines on a same modeling platform tissue metabolism simulator (toxicokinetics) and reactivity models (toxicodynamics). The metabolism simulator is based on a heuristic algorithm to generate metabolic maps from a comprehensive library of biotransformations and abiotic reactions. Reactivity models for binding of chemicals with protein, DNA, lipids etc. predict toxicity of generated metabolites and parent chemicals. Toxic metabolites are explicitly simulated and highlighted in generated metabolic maps along with the associated mechanisms of interactions with macromolecules. The ability of TIMES to predict in the same interface metabolism of chemicals and toxicity resulting from their metabolic activation is an important and unique advantage of the system.

Presently, the TIMES platform is used to predict skin sensitization, mutagenicity, chromosomal aberrations and micronucleus formation taking into account the metabolic activation of chemicals. Apart from genotoxicity the system allows prediction of hormonal toxicity including models for predicting ER/AR and AhR binding affinities accounting for the conformational flexibility of chemicals. [1]

Applicability domain is available for each of the models available in the TIMES platform and the approach used to determine and assess the domain is described in the provided reference.

1. Useful functionalities for demonstration and training purposes

a. Searching capabilities:
   i. Simple search
   ii. Flexible search

Searching for parents and/or metabolites in large chemical inventories meeting specific criteria. The search could be based on logical combination of:

- *structural fragments in the parents and/or metabolites;*
- *phys-chem properties;*
- *reactivity mechanisms or OFG using Toolbox profilers*
- *Common metabolite*
- *Common transformation sequence*

[1] All models could be seen in Appendix I at the end of this document

b. Selection of analogues

The approach provides two types of analogues:

- *supporting endpoint prediction – searching for structurally and mechanistically similar analogues with experimental endpoint data*
- *supporting adequacy of simulated metabolism – searching for similar analogues with documented metabolism data; the approach is used to evaluate the adequacy of simulated metabolism.*

c. AD**M**E similarity: Metabolic similarity

Assessing metabolic similarity between different chemicals, in terms of similarity:

- *between transformation pathways,*
- *reactivity or structural similarity of metabolites (using TB profilers),*
- *common metabolites,*
- *justifying the conflict in endpoint data (Ames) of structurally similar chemicals.*

d. Documented metabolism data supporting metabolic transformations

i. Databases with documented metabolism data
ii. Metabolic transformations. Local training sets with documented metabolism data
iii. Access to the treatment groups associated with molecular transformations and generated metabolites

A new functionality of searching in the databases with documented metabolism data was developed. It provides experimental data support for each molecular transformation and allows the metabolic transformations to be associated with the treatment groups and to check their validity. This support is organized as local training set of the respective transformation.

e. Other functionalities:

i. Grouping of chemicals and clustering based on different criteria
ii. Selection of representatives from a list of chemicals (to minimize the testing)

The functionality is a powerful tool for assessment of the UVCB constituents. It allows grouping of the chemicals into small sets (clusters) where the chemicals in each cluster are similar with respect to predefined criteria. In addition, it is possible to select the representative chemical from a cluster for further testing.

f. Reporting functionalities:

i. Full report
ii. Summary report
iii. QPRF

iv. Metabolic maps
v. Export/report metabolic similarity

TIMES platform supports several types of report:

- *Full report – provides information for the phys-chem properties, calculated quantities, observed and predicted endpoint values, alerting functionalities, applicability domain, etc. The results are provided independently for the parent and simulated metabolites.*
- *Summary report – provides the same type of information as full report but here the results are summarized on a single row for the parent and metabolites.*
- *QPRF – QSAR Prediction Reporting Format is a standard report. The template is adopted by OECD and ECHA.*
- *Metabolic maps report – allows export of the metabolic information associated with the simulated maps, such us connectivity between metabolites (predecessor of each metabolite), transformations responsible for generating the metabolites, enzymes, etc.*
- *Metabolic similarity report – provides the results obtained as a result of estimation of metabolic similarity between two or more chemicals.*
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2. Principle/theoretical items for presentation and discussion

a. Differences between *in vitro* and *in vivo* genotoxicity. The role of metabolism

Addresses the issue of predicting in vivo effects using a battery of in vitro tests. The approach demonstrates the role of test duration and enzyme activity on metabolism and explains the differences between in vitro and in vivo genotoxicity.

b. Implementing kinetic factor in the simulation of metabolism and predicting potency

A new QSAR modelling concept was introduced by LMC where the potency is related to the amount of protein/DNA adducts. The presence/absence of alert is necessary but not sufficient reason for predicting positive effect. So far, kinetic models have been developed for SS and in vitro/in vivo mutagenicity endpoints.

c. Search of kinetic metabolism data

A procedure of searching for experimental rate constants of metabolic transformations has been initiated by LMC. The aim is to expand the domain of kinetic models and to increase their usefulness and predictive capabilities.

d. Criteria for reliability of prediction:

i. Ames mutagenicity
ii. Skin sensitization

LMC defines a list of criteria that can be used for justification of the prediction results obtained from QSAR model available in OASIS software. The approach is already published.

II. Pipeline Profiler platform

1. IATA for predicting human health hazard

OASIS Pipeline Profiler is a software platform based on a pipeline technology for predicting toxicity of chemicals. The Pipeline software allows coding and execution of user-defined logical flows for hazard assessment and prioritization of chemicals.

The hazard classification schemes are developed as a simplified Integrated Approach to Testing and Assessment (IATA). They integrate and interpret nonstandard information generated for key events in a manner that can be practically useful for making decision for testing and assessment. IATA could be very helpful in validating the negative predictions to ensure that meaningful weight of evidences (WoE) is collected. Pipeline stages (nodes) include:

- *Profiling of chemicals according to their possible mechanisms of reactivity*
- *Simulated metabolic activation of chemicals*
- *Physicochemical property calculators*
- *Use of experimental data from OECD QSAR Toolbox*
- *Use of (Q)SAR models*

Appendix I. Models and metabolic simulators available in OASIS TIMES

1. Endpoints without metabolic activation

- Acute oral toxicity
- Skin and Eye irritation/corrosion
- AhR /Aryl Hydrocarbon Receptor/ binding
- ER/AR Receptor/ Binding
- Aromatase inhibition
- Photoinduced toxicity
- Acute aquatic toxicity – on 17 aquatic species*

2. Metabolism simulators

- Autoxidation simulator
- *in vitro* rat liver S9
- *in vivo* rat
- Skin metabolism simulator
- Kinetic skin metabolism simulator
- Kinetic rat S9 metabolism simulator
- Lung metabolism simulator
- Gut metabolism simulator

3. Endpoints with metabolic activation

- Peptide reactivity based on DPRA (-Cys and -Lys) - activated by autoxidation
- *In vitro* genotoxicity - activation by rat liver S9 metabolism is simulated
    i. AMES mutagenicity
    ii. Chromosomal aberrations
    iii. MLA
- *In vivo* genotoxicity - activation by rat *in vivo* metabolism is simulated
    i. Comet Genotoxicity
    ii. Liver TGR
    iii. Liver Clastogenicity
    iv. MNT in bone marrow

- ER Receptor Binding – activation by rat liver S9 metabolism is simulated
- Skin sensitization – accounting for skin metabolism and autoxidation for:
    i. GSH classification
    ii. DST classification
    iii. OASIS classification

4. Endpoints with metabolic activation (accounting for kinetics)

- Kinetic model for skin sensitization – accounting for skin metabolism and autoxidation:
    i. For OASIS classification
- Kinetic models for i*n vitro* genotoxicity - activation by rat liver S9 metabolism
    i. AMES mutagenicity
    ii. Chromosomal aberrations
- Kinetic models for i*n vivo* genotoxicity - activation by rat *in vivo* metabolism
    i. Liver TGR
    ii. MNT in bone marrow

*Aquatic species for which toxicity models are available in TIMES:

1) Bacillius_subtilis
2) Carassius_auratus
3) Cerodaphnia_dubia
4) Culex_tarzalis
5) Daphnia_magna_24h_EC50
6) Daphnia_magna_24h_LC50
7) Daphnia_magna_48h_EC50
8) Daphnia_magna_48h_LC50
9) Daphnia_pulex_48h
10) Daphnia_pulex_96h
11) Escherichia_coli
12) Hydractinia_echinata
13) Interspecies_model
14) Lepomis_macrochirus
15) Leuciscus_idus
16) Lymnaea_stagnalis
17) Oryzias_latipes
18) Pimephales_promelas
19) Poecilia_reticulate
20) Rana_japonica
21) Tetrahymena_pyriformis
22) Vibrio_fischeri_5min
23) Vibrio_fischeri_15min
24) Vibrio_fischeri_30min