PREDICTING BIODEGRADATION KINETICS ACCORDING TO OECD 301B PROTOCOL

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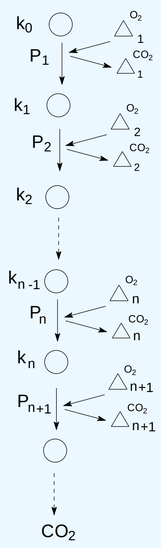
INTRODUCTION

A kinetic model for predicting ready biodegradability of chemicals under OECD 301B test conditions has been developed as part of the CATALOGIC suite [Dimitrov, S.; Pavlov, T, Veith, G, Mekenyan, O *SAR and QSAR in Environ Res*, 22, 2011, 699-718]. The model includes a microbial metabolism simulator predicting biodegradation pathways and allows estimation of biodegradation kinetics of parent chemicals and biodegradation products.

MATERIALS AND METHODS

The model is based on experimental biodegradability data – biodegradation kinetics expressed as the ratio of released CO_2 ($CO_2^{released}$) and theoretical CO_2 ($ThCO_2$) - for a set of 230 proprietary chemicals. The associated kinetic curves include 2565 points. The development of the model consists of: (i) generation of metabolic maps for the training set chemicals using the microbial metabolism simulator; (ii) estimation of kinetic constants and probabilities of occurrence of the simulator transformations. A three-level applicability domain consisting of parametric, structural and metabolism boundaries has been extracted.

Generation of metabolic maps



◯ - parent chemical or metabolite

k_i – number of carbon atoms

P_i – probability of the *i*-th transformation

$\Delta_i^{O_2}$ - oxygen demand of the *i*-th transformation

$\Delta_i^{CO_2}$ - CO_2 released by the *i*-th transformation

Mathematical formalism

Modeled endpoint

% Biodegradation:
$$\%ThCO_2^{Calc} = \frac{\sum_n \Delta_n^{CO_2} \prod_{m=1}^{n} P_m}{\sum_n \Delta_n^{CO_2}} 100,\%$$

Released CO_2:
$$CO_2^{released} = \sum_n \Delta_n^{CO_2} \prod_{m=1}^{n} P_m$$

Theoretical CO_2:
$$ThCO_2 = \sum_n \Delta_n^{CO_2}$$

Estimation of kinetic constants and probabilities of occurrence of coded transformations

The kinetic constants and probabilities of occurrence are estimated by non-linear least square fitting of the experimental data assuming first order kinetics.

$$\min_k RSS = \sum_{n=1}^{N} (\%ThCO_2{}^{Obs.}{}_n - \%ThCO_2{}^{Calc.}(k)_n)^2$$

$\%ThCO_2{}^{Obs.}$ - observed % biodegradation

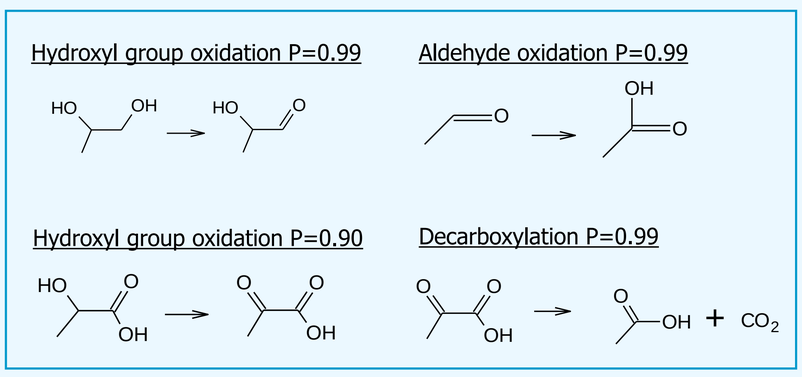
$\%ThCO_2{}^{Calc.}$ - calculated % biodegradation

$$P_i = 1 - \exp(-k_i t)$$

k_i - kinetic constants of specific transformations

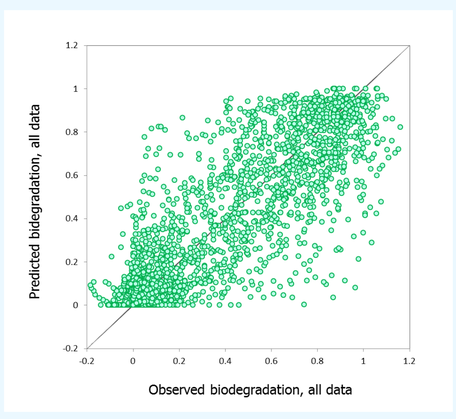
Simulation of microbial metabolism

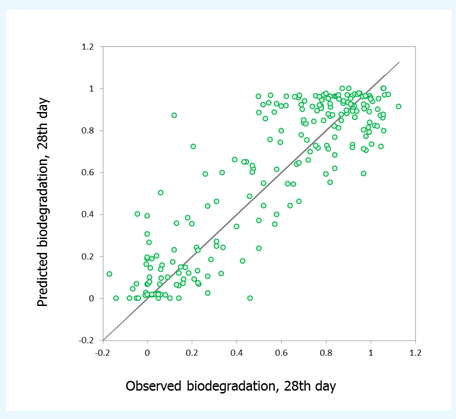
The microbial metabolism simulator included in the model consists of a set of transformations and a system of rules that controls their application. Each transformation consists of source and product fragments describing a microbial biotransformation step. The application of a transformation is inhibited if specific fragments are present in the source structure.



RESULTS AND DISCUSSION

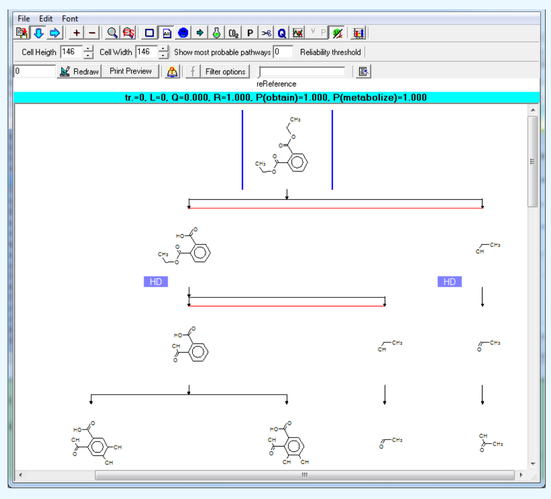
The goodness of fit for the training set chemicals evaluated by the squared coefficient of correlation for all biodegradation data points is R^2=0.74; for biodegradation at the 28th day - R^2=0.77.



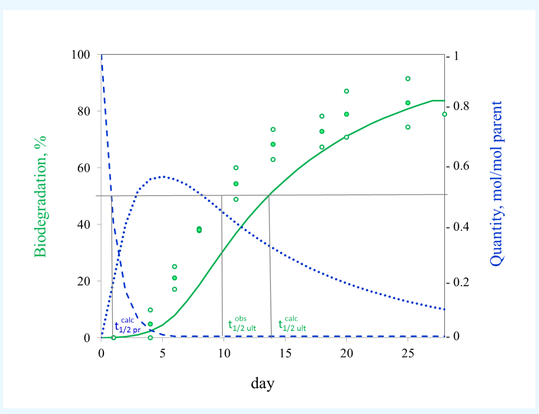


- Correctly classified readily/not-readily biodegradable chemicals of the training set (%):
  - % biodegradability ≥ 0.6 - 94%
  - % biodegradability < 0.6 - 80%
- Correctly classified chemicals of the training set (%) with respect to selected thresholds:
  - % biodegradability < 0.2 - 82%
  - 0.2 % ≤ % biodegradability < 0.4 - 40%
  - % biodegradability ≥ 0.4 - 95%

The model provides comprehensive results for biodegradation of a target chemical: a microbial metabolic map, a biodegradation curve consisting of the estimated biodegradation for each day of the 28-day period of the test, primary and ultimate half-lives. The evolution of quantities of the target chemical and its biodegradation products for the 28-day period of the test are also provided.



Generated microbial metabolic map



Model results for one training set chemical

- ○ – experimental data series;
- ● – experimental data average;
- —— – predicted biodegradation of parent chemical;
- – – – predicted quantity of parent chemical;
- ····· – predicted quantity of a metabolite;
- $t_{1/2\ pr}^{calc}$ – predicted primary half-life;
- $t_{1/2\ ult}^{obs}$ – observed ultimate half-life;
- $t_{1/2\ ult}^{calc}$ – predicted ultimate half-life;

SUMMARY AND CONCLUSIONS

1. 230 kinetic curves (2565 biodegradation points) have been modeled with accuracy R^2=0.74 for all available biodegradation points and R^2=0.77 for biodegradation at the 28th day
2. The model reproduced correctly the classification of 94% of the readily biodegradable and 80% of the not readily biodegradable training set chemicals
3. The model performance is extremely good for biodegradation thresholds <0.2 and ≥0.4

The poster can be downloaded at: **http://oasis-lmc.org/posters/QSAR2012**