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Contents

1. Introduction

Microbial degradation of chemicals is the major process, which determines the fate of organic compounds in aquatic and terrestrial environment. This fact determines biodegradation as a key property in the environmental risk assessment of substances. Its use in many legislative and regulatory frameworks makes the development of adequate biodegradation models an important problem for environmental science. The generation of reliable quantitative structure-biodegradability relationships (QSBRs) requires appropriate utilization of existent knowledge on the mechanism of biodegradation and collecting of reliable experimental data. Depending on the aim of the study, biodegradation can be quantified by the rate of biodegradation, rate constants, half-lives, dissolved organic carbon, biological oxygen demand, CO2 productions, etc. The biodegradability measurement can be carried out in aerobic or anaerobic conditions by making use of mixed culture (natural samples, inoculated natural samples or inoculated media) or in vitro test with crude extracts or purified enzymes. The high complexity of the microbial degradation process usually forces the modelers to avoid quantification of biodegradability and simplify the model outcomes to boolean interpretation of the compound's biodegradability. The aim of the deliverable is to provide an overview of the currently available models of practical value for predicting biodegradation.

2. Biodegradation models

Starting with the work of Dorn and Knakmuss [1], a number of attempts have been made to mathematically describe the relationships between the structure of organic compounds and their biodegradability [2,3]. Different approaches may be distinguished in this avenue. The first

one is based on identification of the rate-limiting step within the whole biodegradation process. The derived structure activity relationships are usually valid for small groups of congeneric chemicals and therefore not suited for risk assessment of large and heterogeneous databases. In another approach, referred as a black-box approach, large training sets are submitted to different statistical techniques such as simple or multiple linear/nonlinear regression, principal component analysis, partial least squares, neural networks, genetic algorithms, etc, resulting in empirical QSBRs. Various structural descriptors are regressed with biodegradability, such as octanol-water partition coefficient [4], Hammett's substituent constant [5], quantum-chemical descriptors (such as lowest unoccupied molecular orbit) [6], molecular weight [7], van der Waals radii [8], connectivity indices [7], accessible surface area [9], submolecular fragments [11], etc. A common characteristic of traditionally used modeling methodologies is that biodegradability of chemicals is related to the properties of parent chemicals only. Such models were developed by the EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation [11-14].

Microbial degradation of chemicals is a complex process during which a portion of the chemical is oxidized to carbon dioxide, water and metabolic products. The later are subject of further metabolism until full mineralization or stable metabolites are not produced. The sequence of produced metabolites, called catabolic pathway, is a compact expression of the biodegradation process and contains valuable information about the fate of the chemical in biota. Different systems have been developed to predict metabolic pathways for biodegradation. The research project, initiated by CompuDrug resulted in MetabolExpert family of expert systems [15]. The META metabolic-pathway prediction program is an expert system originally designed to predict pathways for mammalian detoxification of drugs and was lately transformed into a microbial-degradation prediction tool [16-18]. Presently, it contains a dictionary of 665

enzymatic and 286 spontaneous reactions. The BESS, or Biodegradability Evaluation and Simulation System, also simulates the transformation of chemical compounds operating with approximately 300 general rules and 2700 specific rules [19]. Logic of argumentation was used by Lhasa Ltd. to develop the system METEOR considering the potential metabolism of xenobiotics [20, 21]. To make prediction about the metabolism METEOR uses two stages by consecutive application of absolute and relative reasoning rules. Probabilistic approach was also used to model biodegradation. The developed expert system CATABOL [22, 23] predicts quantitatively biodegradation of chemicals by analyzing biotransformation pathways generated during the system implementation.

3.1.BIOWIN

The Biodegradation Probability Program (BIOWIN) includes six models [24]:

1. Linear Model Prediction
2. Non-Linear Model Prediction
3. Ultimate Biodegradation Timeframe
4. Primary Biodegradation Timeframe
5. MITI Linear Model Prediction
6. MITI Non-Linear Model Prediction

The models estimate the rate of aerobic biodegradation of an organic chemical in the presence of mixed populations of environmental microorganisms. Estimates are based upon 36 fragment constants that were developed using multiple linear and non-linear regression analyses.

A total dataset of 295 chemicals was used to derive the fragment probability values that are applied in the first two models. The dataset consists of 186 chemicals that were critically evaluated as "biodegrades fast" and 109 chemicals that were critically evaluated as "does not biodegrade fast". The evaluation was either 1 (the chemical biodegrades fast; probability of 1.0) or 0 (the chemical does not biodegrade fast; probability of 0.0). The Linear Biodegradation Probability of a chemical is calculated by summing the values f_i (fragment coefficients) of each fragment and then adding the summation to a constant coefficient a determined for the entire data set:

$$\mathrm{Pr} = a + \sum_i f_i \qquad (1)$$

The Non-Linear Biodegradation Probability is calculated from the following formula (where the constant coefficient b is determined for the entire data set):

$$\mathrm{Pr} = \frac{\exp\left(b + \sum_i f_i\right)}{1 + \exp\left(b + \sum_i f_i\right)} \qquad (2)$$

The interpretation of the predicted biodegradation probability is as follows:

- A probability greater than or equal to 0.5 indicates ‘Biodegrades Fast’
- A probability less than 0.5 indicates ‘Does NOT Biodegrade Fast’

The models for primary biodegradation (the transformation of a parent compound to an initial metabolite) and the ultimate biodegradation (the transformation of a parent compound to an initial metabolite) are based upon a survey of 17 biodegradation experts conducted by EPA in which the experts were asked to evaluate 200 chemicals in terms of the time required to achieve ultimate and primary biodegradation. In the current survey, each expert rated the ultimate and primary biodegradation of each chemical on a scale of 1 to 5. For the purposes of the Biodegradation Probability Program, the ratings correspond to the following time units: 5 - hours; 4 - days; 3 - weeks; 2 - months; 1 - longer. The ratings were then averaged for each chemical. The same 36 fragments and molecular weight parameter were used in the linear regression. The interpretation of model predictions is summarized in Table 1.

MITI Linear (1) and Non-Linear Models (2) were derived on the basis of 884 compounds tested in the Ministry of International Trade and Industry (MITI)-1 test [25]. The data were divided into a training dataset (589 compounds) and a validation dataset (295 compounds). The critical biodegradation evaluations (results of the MITI tests) were either "readily degradable" or "not readily degradable"; "readily degradable" was assigned a numeric value of 1 and "not readily degradable" was assigned a numeric value of 0 (0 to 1 is the full probability range). The MITI models contain 42 fragments and molecular weight as independent variables. Prediction accuracy of the training set by both models varied from 79% to 85%. Correctness of predictions of the validation set was from 79% to 82%.

An independent external validation of BIOWIN models by making use of 482 chemicals [26] resulted in 50% (Linear Model) to 71% (Ultimate Biodegradation) correctness of predictions. Prediction accuracy of the MITI models was 66%.

3.2. METEOR

METEOR is a knowledge-based expert system: its knowledge base of information about metabolic reactions is compiled and maintained by scientists and is based on a mechanistic intepretation of observed metabolism. For example, it is known that P-450 enzymes hydroxylate aromatic rings and so the METEOR knowledge base contains a description of that reaction. Scientists working on the knowledge base use a graphical editor to depict generalised versions of reactions, as a chemist would. The program interprets the information and at run time if it detects in a query molecule the sub-structural features needed to key a reaction the program proposes it as a potential metabolic step. For example, if the query molecule contains an aromatic ring with unsubstituted positions, METEOR will propose hydroxylation. Reaction descriptions include constraints to take account of factors such as electron-directing and steric effects. METEOR matches reaction keys in its knowledge base to the query, to the products generated from the query, and so on, to create a metabolic tree.

How likely it is that a particular reaction will be observed depends on factors such as the fat-water partition coefficient of the query molecule, because this influences both distribution of the compound in a mammalian system and interaction with the binding sites of enzymes. In addition, there are typically several possible metabolic reactions that a given molecule could undergo and in practice only the products of those that dominate are usually significant. METEOR uses the Logic of Argumentation [20, 21] to reason about these influences in order to constrain its predictions to the more likely metabolic pathways. The user can elect to see

pathways at any level of likelihood, from seeing only the most likely to seeing even the most unlikely. The user can also apply other constraints, such as limiting pathways to those where an isotopic label in the query molecule is retained, or those leading to metabolites with particular exact masses, for comparison with results from mass spectrometry studies.

Validation of METEOR has been by commercial users of the system who compare predictions for proprietary compounds with experimental results but work is in progress that it will be possible to publish.

The current knowledge base for METEOR is dominated by information about mammalian metabolism. However, the program infrastructure and interface allow nesting of knowledge base for microbial catabolism which could be used for predictive purposes. Lhasa Limited is in a process of transferring biodegradation rules derived at UM-BBD (http://umbbd.ahc.umn.edu/) to the Meteor framework, to create Meteor PPS (MEPPS).

3.3. CATABOL

The CATABOL system is a probabilistic scheme for simulating aerobic microbial degradation based on a hierarchically ordered set of principal metabolic transformations [22, 23]. Currently the set of transformations includes 143 abiotic and biologically mediated reactions, which occur very rapidly, compared to the duration of the biodegradation tests. These rapid transformations were predicted to occur with the following highly reactive groups and intermediates: oxiranes, ketenes, acyl halides, thiocarboxylic acids, hydroperoxides, nitrenes and geminal diols. Various chemical equilibrium processes like carboxylic acids hydrolysis, keto-

enol tautomerism, thiol-thion tautomerism, and cyanuric acid isomerization were also included in this class of transformations. Many of the other 488 metabolic transformations such as oxidation, hydrolysis, decarboxylation and dehalogenation were grouped into subsets of reactions depending on the similarity of their target fragment and transformation products. The probabilities of 324 rate-determining reactions grouped in 50 subsets were estimated on the basis of experimental biodegradation data. Due the lack of sufficient data the probabilities of the remaining 164 reactions were determined on the basis of expert knowledge.

CATABOL was created to predict the most probable biodegradation pathway, distribution of stable metabolites and extent of biological oxygen demand or CO_2 production compared to theoretical limits. CATABOL matches the parent molecule with the source fragment associated with each transformation starting with the transformation having highest probability of occurrence. When a match is identified, the molecule is metabolised and transformation products are treated as parent molecule. The sequence of transformations that is obtained represents the most plausible catabolic pathway for the biodegradation of the parent chemical. Biological oxygen demand or CO_2 production is calculated on the basis of the generated most plausible catabolic pathway for the parent chemical. The generated metabolic trees can be used also to evaluate the quantitative distribution of the produced metabolites. The latter can be submitted for predicting their endpoints of interest, such as octanol-water partition coefficient (log KOW), bioconcentration factor (log BCF), fish acute toxicity (log 1/LC50), estrogen receptor binding affinity, mutagenicity, and other endpoints.

Documented microbial catabolic pathways were used to train CATABOL to reproduce the biodegradation pathways. Observed catabolic pathways for more than 300 organic

compounds were collected from monographs [27-29] and the University of Minnesota Biocatalysis/Biodegradation Database (UM-BBD, http://umbbd.ahc.umn.edu/) [30-32]. Articles devoted to microbial degradation of specific classes of chemicals such as halogenacetic acids, terpenes, linear alkylbenzene sulfonate surfactants, bisphenols, etc. were also used [33-37]. The collection includes catabolism of C_1-compounds, aliphatic hydrocarbons, alicyclic rings, furans, halogenated hydrocarbons, aromatic hydrocarbons, haloaromatics. The rest of the collected microbial degradation pathways describe catabolism of amines, sulfonates, nitrates, nitro-derivates, nitriles, etc., and complex compounds containing more than one functional group. Similarity between observed biodegradation pathways and predicted by CATABOL maps can be evalusted by the following statistics:

Predictability (probability that the metabolite is observed, given that the metabolite is predicted):

$$\Pr = \frac{Card\left(S_{\text{Obs}} \cap S_{\text{Pred}}\right)}{Card\left(S_{\text{Pred}}\right)} \qquad 3$$

False positive (probability that the metabolite is predicted given that the metabolite is truly not observed):

$$Fp = \frac{Card\left(S_{\text{Pr}ed} \backslash S_{Obs}\right)}{Card\left(S_{\text{Pr}ed}\right)} \qquad 4$$

Sensitivity (probability that the metabolite is observed, given that the metabolite is truly observed):

$$Se = \frac{Card(S_{Obs} \cap S_{Pred})}{Card(S_{Obs})} \quad 5$$

False negatives (probability that the metabolite is not predicted given that the metabolite is truly observed):

$$Fn = \frac{Card(S_{Obs} \setminus S_{Pred})}{Card(S_{Obs})} \quad 6$$

In Eqs. 3 – 6 S_{Obs} and S_{Pred} are observed and predicted metabolites. The overall statistics for similarity between observed and predicted catabolism for chemicals in the model domain is as follows:

Pr = 84 %; Fp = 16 %; Sn = 71 %; Fn = 29 %

The CATABOL system is trained to predict biodegradation within 28 days on the basis of 743 chemicals from MITI database [25] obtained by OECD 301 C test. In order to verify the model applicability for legislative purposes, the original quantitative data of MITI database and model predictions were transformed into binary data: ready (if %BOD >= 60%) and not ready (if %BOD < 60%) biodegradability. The obtained sensitivity, i.e. probability that the prediction is ready biodegradable, given that the chemical is truly readily biodegradable was 86%. The

predictions were slightly better for not-readily biodegradable substances. The specificity or in other words the probability that the prediction is not readily biodegradable, given that the chemical is truly not readily biodegradable was 91%.

The predictive power of the derived model was examined by internal cross-validation. Randomly selected 25% of the training data was kept out of the model training. Predictions for the eliminated chemicals were obtained on the basis of the transformation probabilities assessed from the rest of training sets. The procedure was performed four times until each observation was left out once. The sensitivity and specificity evaluated on the bases of predicted values were 82% and 91%, respectively. An external validation with 347 completely independent of the training set chemicals resulted in 75% sensitivity and 79% specificity. In another independent external validation of CATABOL by making use of 482 proprietary chemicals [26] the obtained overall correctness of predictions was 72%. In order to improve the creditability in CATABOL predictions a stepwise approach to determine the applicability domain was implemented in the system [38]. The correctness of classification for ready and not-ready chemicals in the model domain was 82%, while the correct classification of 74% was obtained for chemicals that were recognized to be out of the model domain.

3. Summary

The complexity and variety of characteristics of biodegradation are premise for the development of different approaches and as a result different models. Among models of practical value for screening large inventory of chemicals can be mentioned BIOWIN models, METEOR and CATABOL. These models usually describe different characteristics of the

biodegradation process. For example, BIOWIN models are unable to provide information for potential formation of persistent or toxic metabolites and MEPPS could not quantify the rate of biodegradation in term of half-lives, biological oxygen demand or CO_2 production. On the other hand, the mathematical formalism of CATABOL could be used to provide quantitative and qualitative description of microbial degradation of xenobiotics. The confidence in model prediction could be significantly improved by combining different approaches and design of the so called composite models.

Another drawback of these models is that they were developed predominantly on the bases of information for biodegradation in water and aerobic conditions. Taking into account that biodegradation is context dependent some modifications should be included in already available models in order to increase their specificity with respect to predicting biodegradation in soil compartments.

4. References

1. Dorn E, Knakmuss HJ, Chemical structure and biodegradability of halogenated aromatic compounds. Substituent effects on 1,2-dioxygenation of catechol. Biochem J, 1978, 174:85-94.
2. Damborsky J, Lynam M, Kuty M, Structure-Biodegradability Relationships for Chlorinated Dibenzo-p-Dioxins ans Dibenzofurans, In Wittich R.-M., ed., Biodegradation of Dioxins and Furans, Springer-Verlag and R.G. Landes Company, 1998, 165-228.

3. Handbook of property estimation methods for chemicals: environmental and health science, eds. Boethling RS, Mackay D.,Lewis Publishers, 2000, 281-310.

4. Paris DF, Wolfe NL, Steen WC, Microbial transformation of esters of halogenated carboxylic acids, Appl Environ Microbial, 1984, 47:7-11.

5. Pitter P, Correlation of microbial degradation rates with the chemical structures. Acta Hydrochimica, 1985, 13:453-460.

6. Eriksson L, Jonsson J, Tysklind M, Multivariate QSBR modeling of biodehalogenation half-lives of halogenated aliphatic hydrocarbons, Environ Toxicol Chem, 1995, 14: 209-217.

7. Boethling RS, Application of molecular topology to quantitative structure-biodegradability relationships, Environ. Toxicol Chem, 1986, 5:797-806.

8. Paris DF, Wolfe NL, Steen WC, et al., Effect phenol molecular structure on bacterial rate transformation constant in pond and river samples, Appl Environ Microbial, 1983, 45:1153-1155.

9. Dearden JC, Nicholson RM, The prediction of biodegradability by the use of quantitative -structure-activity relationships: correlation of biological oxygen demand with atomic charge differences, Pestic Sci, 1986, 17: 305-310.

10. Desai SM, Govind R. Tabak HH, Development of quantitative structure-activity relationships for predicting biodegradation kinetics, Environ Toxicol Chem, 1990, 9: 473-477.

11. Howard PH, Meylan WM, Biodegradation Probability Program Syracuse Research Corporation, Syracuse, NY 13210 United States, 1992.

12. Howard PH, Boethling RS, Stiteler WM, Meylan WM, Hueber AE, Beauman JA, Larosche ME, Predictive model for aerobic biodegradability developed from a file of evaluated biodegradation data, Environ Toxicol Chem, 1992, 11: 593-603.

13. Boethling RS, Howard PH, Meylan WM, Stiteler WM, Beauman JA, Tirado N, Group Contribution method for predicting probability and rate of aerobic biodegradation, Environ Sci Technol, 1994, 28:459-465.

14. Tunkel J, Howard PH, Boethling RS, Stiteler WM, Loonen H, (2000) Predicting ready biodegradability in the Ministry of International Trade and Industry test, Environ Toxicol Chem 19:2478-2485.

15. Darvas F, Marokhazi S, Kormos P, Kulkarni G, Kalasz H, Papp A, MetabolExpert: Its Use in Metabolism Research and in Combinatorial Chemistry, In Erhard PW (ed.) “Drag Metabolism. Databases and High Throughput Testing during drug design and development” IUPAC, Blackwell Science, University Press, Gamburg, GB, 1999, pp. 237 – 270.

16. Klopman G, Zhang Z, Balthasar DM, Rosenkanz HS, Computer-automated predictions of aerobic biodegradation of chemicals, Environ Toxicol Chem, 1995 (or 6?), 14: 395-403.

17. Klopman G, Tu M, Structure-Biodegradability study and computer-automated prediction of aerobic biodegradation of chemicals, Environ Toxicol Chem, 1997, 16: 1829-1835.

18. Rorije E, Peijnenburg WJGM, Klopman G, Structural requirements for the anaerobic biodegradation of organic chemicals: A fragment model analysis, Environ Toxicol Chem, 1998, 17: 1942-1950.

19. 2000 Progress Report: BESS, A System for Predicting the Biodegradability of New Compounds, http://es.epa.gov/ncer/progress/grants/97/sust/punch00.html

20. Judson PN, Vessey JD, A Comprehensive Approach to Argumentation, J. Chem. Inf. Comp. Sci, 43: 1356-1363.

21. Button WG, Judson PN, Long A, Vessey JD, Using Absolute and Relative Reasoning in the Prediction of the Potential Metabolism of Xenobiotics, J. Chem. Inf. Comp. Sci, 43: 1371-1377.

22. J. Jaworska, S. Dimitrov, N. Nikolova, O. Mekenyan, (2002) Probabilistic Assessment of Biodegradability Based on Metabolic Pathways: CATABOL System, SAR and QSAR in Environmental Research, 13(2): 307-323.

23. Dimitrov S., Kamenska V., Walker J.D., Windle W., Purdy R., Lewis M., Mekenyan O. 2004. Predicting the biodegradation products of perfluorinated chemicals using CATABOL, SAR and QSAR in Environmental Research, 15, No. 1, 69-82.

24. http://www.epa.gov/opptintr/exposure/docs/episuitedl.htm

25. Chemicals Investigation and Testing Institute. (1992). Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan, ISBN 4-98074-101-1. Japan Chemical Industry Ecology-Toxicology & Information Center.

26. SETAC world congress, November14 – 18, 2004, XXXX, USA

27. Wackett L.P., and Hershberger, C.D. (2001). *Biocatalysis and biodegradation: microbial transformation of organic compounds*, ASM Press, Washington, DC 20036-2904.

28. Gibson, D.T., (ed.) (1984). *Microbial degradation of organic compounds*, Marcel Dekker, Inc., New York.

29. Schwarzenbach, R.P., Qschwend, P.M., and Imboden, D.M. (1993). *Environmental organic chemistry*, Jhon Wiley & Sons, Inc., New York.

30. Ellis, L.B.M., Hershberger, C.D., and Wackett, L.P. (1999). The University of Minnesota Biocatalysis/Biodegradation Database: specialized metabolism for functional genomics, *Nucleic Acids Research*, **27**, 373-376.

31. Ellis, L.B.M., Hershberger, C.D., and Wackett, L.P. (2000). The University of Minnesota Biocatalysis/Biodegradation Database: microorganisms, genomics, and prediction, *Nucleic Acids Research*, **28**, 377-379.

32. Ellis, L.B.M., Hershberger, C.D., Bryan, E.M., and Wackett, L.P. (2001). The University of Minnesota Biocatalysis/Biodegradation Database: emphasizing enzymes, *Nucleic Acids Research*, **29**, 340-343.

33. Lobos, J.H., Leib, T.K., and Su, T.-M. (1992). Biodegradation of bisphenol A and other bisphenols by gram-negative aerobic bacterium, *Appl. Environ. Microbiol.* **58**, 1823-1831.

34. Casellas, M., Grifoll, M., Bayona, J.M., and Solanas, A.M. (1997). New metabolites in the degradation of fluorine by *Arthrobacter sp.* Strain F101, *Appl. Environ. Microbiol.* **63**, 819-826.

35. van der Werf, M.J., Swarts, H.J., and de Bont, J.A. (1999). *Rhodococcus erythropolis* DCL14 contains a novel degradation pathway for limonene, *Appl. Environ. Microbiol.* **65**, 2092-2102.

36. Cook, A.M., and Hrsak, D. (2000). The complete degradation of LAS is becoming better understood with pure cultures of bacteria, *The CLER Review*, **6**, 46-53.

37. Ellis, D.A., Hanson, M.L., Sibley, P.K., Shahid, T., Fineberg, N.A., Solomon, K.R., Muir, D.C.G., and Mabury, S.A. (2001). The fate and persistence of trifluoroacetic and chloroacetic acids in pond waters, *Chemosphere* **42**, 309-318.

38. Dimitrov S., Dimitrova G., Pavlov T., Dimitrova N., Patlevitz., Niemela J., Mekenyan O., (2005) A stepwise approach for defining applicability domain of SAR and QSAR models, *Journal of Chemical Information and Modeling*, 45, 839-849.

Table 1. Interpretation of predictions provided by models for primary ultimate biodegradation

#	**Model prediction**	**Time Required for Biodegradation**
1	5.0	hours
2	4.5	hours - weeks
3	4.0	days
4	3.5	days - weeks
5	3.0	weeks
6	2.5	weeks - months
7	2.0	months
8	1.0	longer