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ENVIRONMENT MONOGRAPH NO. 68

STRUCTURE-ACTIVITY RELATIONSHIPS FOR BIODEGRADATION

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

Paris 1993

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Environment Directorate

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

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ENVIRONMENT MONOGRAPHS

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Foreword

OECD hazard assessment activities

The objective of OECD work on hazard assessment is to promote awareness and improvement of procedures for hazard assessment used in Member countries and, to the extent possible, to harmonize those procedures in order to assist Member countries in protecting human health and the environment from the potentially harmful effects of chemicals.

One of the focuses of hazard assessment activities in the period 1989-1991 was exposure assessment and, in particular, the application of Structure-Activity Relationships (SARs). Several OECD hazard assessment projects, such as "Application of SARs to the Estimation of Properties of Importance in Exposure Assessment" and "SARs for Biodegradation", have been carried out using a lead country approach. It is intended to integrate the results of these projects into an OECD scheme for hazard assessment of chemicals.

Orientation for work on hazard assessment is provided by the Hazard Assessment Advisory Body (HAAB), which also reviews the results obtained and reports the progress made to the Joint Meeting of the Chemicals Group and the Management Committee of the Special Programme on the Control of Chemicals. The current composition of the HAAB is given at the end of this document. Meetings of the HAAB are attended by an observer from the International Programme on Chemical Safety.

Structure-Activity Relationships (SARs) for biodegradation

The purpose of the project on SARs for Biodegradation was to review and evalutate existing models, and to derive new QSARs if necessary. The development of guidance for selecting reliable SARs for a given chemical structure was also an important expected outcome. The project was led by Germany, in co-operation with Japan.

In this document, 78 different SARs are presented which were either developed or validated by comparing estimated data with more than 700 experimental data. Only a few existing models were found to provide an adequate level of agreement between estimated and experimental data. It was also found that the qualitative prediction of biodegradability using SARs was mainly possible only for aliphatic and simple cyclic molecules. For chemicals with more complex structures, no SARs were available in most cases.

Five new substructure models for estimating biodegradability were developed for acyclic compounds and monocyclic aromatic substances by regression and discriminant analysis. Validation of these models was carried out, as shown in Annex 2, by using additional test results for about 120 chemicals. A decision tree (a hierarchic model) was developed as guidance for users in selecting appropriate SARs validated in this study.

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Summary

This document is the report resulting from an OECD Hazard Assessment Project on Structure-Activity Relationships (SARs) for Biodegradation. The project was led by the Germany [the Federal Environment Agency (UBA)] in co-operation with Japan, which provided test results of ready biodegradability for more than 700 chemicals.

The purposes of the study were:

- to review existing models found in the literature;
- to evaluate their reliability;
- to derive new SARs, if necessary; and
- to give guidance for selecting reliable SARs for a given chemical structure.

Predictive models from the literature were evaluated against experimental data on degradability according to OECD Test Guideline 301C, Modified MITI Test (I). These data were available for a wide variety of compounds. The study revealed that only a few SAR models can be recommended for predictive purposes. The limited applicability can be traced back, at least partly, to deficiencies in the starting points for the various models: lack of endpoint homogeneity, inconsistent test data, and use of restricted data sets. A considerable number of SARs (23 of 64) have been derived from experimental data for compounds classified on the basis of the MITI test as either easily degradable or non-easily degradable. Hence, these models cannot discriminate between levels of degradability. Most of the models derived for specific chemical classes (27 of 35) were not found to be predictive of MITI test results either.

To complement the few successfully validated SARs, further models were derived for the qualitative estimation of biodegradability. On the assumption that functional groups have an enhancing or retarding effect on degradation, weighted substructure indicators were used. In the models for acyclic compounds only terminal substructures and substituents were considered, as only these have been shown to affect degradability in a significant way. Negative factors for the substructures indicate a decrease in biodegradability as the level of branching increases. For monocyclic aromatics it was found that some substituents are determinative for biodegradability regardless of their position in the molecule. Using indicators for nine aryl-substituents (three enhancing, six retarding degradation), 84 per cent of polysubstituted aromatics were correctly classified. Application to monosubstituted aromatics resulted in a 93 per cent level of agreement.

In addition, five newly developed substructure models for the quantitative estimation of the biodegradabiilty of acyclic compounds and monocyclic aromatic compounds were evaluated by comparing estimations with experimental data for about 120 additional chemicals (see Annex 2). The validation study showed that:

- recommended SARs were available for 53 per cent of the chemicals; and that

- 89 per cent of compounds not included in the original data set from which the models were derived were correctly classified in respect of biodegradability.

In order to allow the rational selection of the appropriate SAR for a chemical, hierarchic decision trees were established, reflecting the various relevant degradation pathways for a wide variety of environmental chemicals.

Résume

La présente monographie constitue le rapport d'un projet OCDE sur l'Evaluation des dangers, "Relations structure-activité (RSA) relatives à la biodégradabilité". Ce projet, mené par l'Allemagne [Agence fédérale pour l'environnement (UBA)] en coopération avec le Japon, a procuré des résultats d'essais de biodégradabilité facile pour plus de 700 produits chimiques.

Les objectifs de l'étude étaient:

- de passer en revue les modèles existants rencontrés dans les publications scientifiques ;
- d'en évaluer la fiabilité ;
- le cas échéant, de dériver de nouvelles RSA ; et
- de donner des orientations en ce qui concerne le choix de RSA fiables pour un produit chimique donné.

Des modèles de prédiction pris dans les publications scientifiques ont été évalués par rapport à des données expérimentales de dégradabilité d'après la Ligne directrice de l'OCDE 301c, Essai MITI modifié (I) ; ces données étaient disponibles pour un grand nombre de composés. L'étude a révélé que seul l'usage d'un petit nombre de modèles RSA peut être recommandé à des fins de prédiction. L'applicabilité limitée peut être attribuée, du moins en partie, à des déficiences dans les bases à partir desquelles les différents modèles ont été construits: effets mesurés non comparables, incohérence des données et ensembles de données trop restreints. Un nombre considérable de RSA (23 sur 64) ont été dérivées à partir de données expérimentales pour des composés classifiés sur les bases de l'essai MITI comme étant soit facilement dégradables, soit difficilement dégradables. Ces modèles ne peuvent donc pas servir à déterminer le degré de dégradabilité. En outre, il s'est avéré que la plupart des modèles dérivés pour des classes spécifiques de produits chimiques (27 sur 35) ne permettent pas de prédire les résultats des essais MITI.

En complément aux quelques RSA validées avec succès, d'autre modèles ont été dérivés en vue de l'estimation qualitative de la biodégradabilité. Partant de l'hypothèse que des groupements fonctionnels jouaient un rôle promoteur ou inhibiteur sur la dégradation, des indicateurs pondérés ont été utilisés. Dans les modèles pour les composés acycliques, seuls les groupements et substituents terminaux ont été utilisés, qui sont les seuls pour lesquels on a pu démontrer un effet significatif sur la dégradabilité. Des facteurs négatifs pour les groupements indiquent une biodégradabilité inversément proportionelle au degré de ramification. Dans le cas des aromatiques monocycliques il s'est avéré que certains substituents sont déterminants pour la biodégradabilité quelle que soit leur position dans la molécule. En utilisant les indicateurs pour neuf substituents (trois promoteurs, six inhibiteurs de la dégradation), 84 pour cent des aromatiques polysubstitués ont été classifiés correctement. L'application à des aromatiques monosubstitués a donné un degré de concordance de 93 pour cent.

En outre, cinq modèles nouveaux de groupements pour l'estimation quantitative de la biodégradabilité des composés acycliques et aromatiques monocycliques ont été évalués en comparant les évaluations basées sur des données expérimentales pour environ 120 produits chimiques supplémentaires (voir Annexe 2). L'étude de validation a révélé que:

- pour 53 pour cent des produits chimiques, des RSA recommandées étaient disponibles ; et que

- 89 pour cent des composés, qui n'étaient pas inclus dans l'ensemble de données d'origine à partir duquel le modèle a été dérivé, ont été classés correctement en ce qui concerne la biodégradabilité.

Afin de permettre un choix rationnel de la RSA appropriée pour un produit chimique donné, des réseaux hiérarchiques de décision, reflétant les divers cheminements de dégradation d'importance pour un grand nombre de produits chimiques environnementaux, ont été établis.

Structure-Activity Relationships for Biodegradation

Estimating the Biodegradability of Chemicals by Computer Assisted Reactivity Simulation[1]

1. Introduction

Test procedures for assessing the biotic degradability of chemicals have been harmonized within the framework of the OECD (OECD 1989). The objective of the guidelines which have been elaborated is to classify the chemicals into easily degradable, inherently degradable, and persistent substances on the basis of 28-day degradation tests.

In recent years, Structure-Activity Relationships (SARs) have been developed for various areas of application for estimating the characteristics of substances as well as toxicity levels. In contrast, the development and application of structure-biodegradation relationships have proven problematic. The applicability and validity of published SARs have been examined and proposals for estimating biodegradability by means of SARs have been made, with due regard to their restrictions (Degner 1991).

2. Fundamental aspects, endpoint inhomogeneity

Microbial degradation is defined as the transformation of substances caused by microorganisms. Primary biodegradation of a molecule refers to any microbial process which leads to the formation of metabolites and thereby contributes to the degradation of the original substance. Ultimate biodegradation refers to the complete mineralization of a substance into carbon dioxide, water and mineral salts.

Biodegradability is not a standard parameter with a well defined endpoint. Primary degradation, ultimate degradation, and the assessment of biological degradation in the environment from the path-level[2] of test procedures are used to characterize microbial degradability. In the

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[1] *This report was written by Dr. P. Degner, Dr. M. Müller, Dr. M. Nendza and Dr. W. Klein (Fraunhofer-Institut für Umweltchemie und Ökotoxikologie, Germany) on behalf of the Federal Environmental Agency (Umweltbundesamt) of Germany, under the Hazard Assessment activity of the OECD Chemicals Programme.*

[2] *Path-levels: the percentage of degradation over which a chemical is considered as easily biodegradable.*

environment, the concentration and structure of a compound, the duration of exposure, soil type, water content, oxygen concentration, nutrients, temperature, pH value, and the diversity of the microbial community and their adaptability to xenobiotics affect the microbial degradation or persistence of a compound.

Bacteria possess a variety of enzyme systems for degradation of chemicals. The high adaptive and mutational capacity of bacteria may, under suitable environmental conditions, result in the degradation of any substrate (Alexander 1965). The probability and extent of degradation are dependent on the similarity of the xenobiotics to the natural substrate of an enzyme (Knackmus 1981). Numerous degradation mechanisms observed in pure cultures have been described, but their relation to enzymatic transformation processes under environmental conditions is subject to uncertainty (Fewson 1981, Leisinger 1983). Grady (1985) described a large number of degradation pathways which occur parallel in mixed populations under natural conditions, and which require the combined action of various types of bacteria in order to mineralize a substance.

2.1 Test procedures

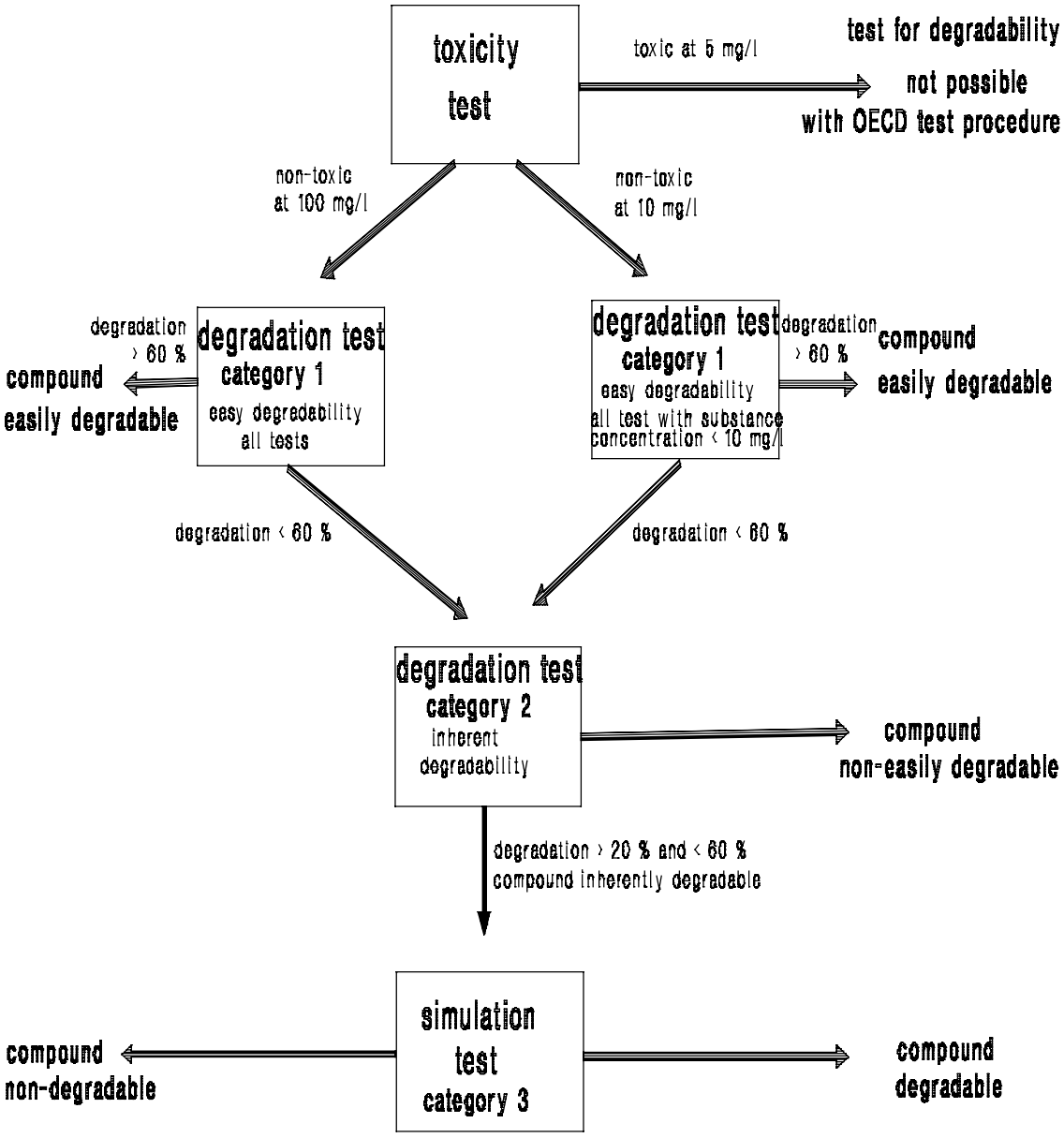
Only limited consideration of the diverse environmental factors affecting microbial degradation is possible in degradation tests, as they are carried out under optimum conditions for the microorganisms. Test procedures under laboratory conditions nevertheless represent a possibility of estimating the hazard of a substance to the environment. Influencing factors in the degradation test are: toxicity, solubility and concentration of a substance, quantity and diversity of the microorganisms, and technical factors connected with the procedure employed, such as temperature, pH value and the duration of the experiments. Test procedures employing different methods and the corresponding differences in the measured degradability of a substance caused by the different test methods result from the fact that the endpoint of biodegradability is difficult to define.

The importance of evaluating biodegradation is increasing due to the growing number of xenobiotics released into the environment. Degradation studies are therefore necessary not only to recognize the metabolites but also in order to obtain assessment criteria which are relevant to the environment. Degradation tests specifying path-levels are required, in order to estimate the potential risk represented by chemicals. The test procedures have been harmonized in the course of OECD (1984) and EEC (1979) activities. Based on a test duration of 28 days, a test scheme was established involving three categories of degradation testing (**Figure 1**). In addition to the duration of testing, the harmonization applies in particular to the concentrations of inocula and of test substances. Tests carried out within one category are supposed to produce equivalent degradation results. The test procedure to be employed is selected in accordance with the physical-chemical characteristics of a compound (solubility, vapour pressure and toxicity).

The test procedures according to the three categories specified in the OECD Test Guidelines have been put into an environmental context by Howard and Banerjee (1984). The degradability in category 1 test procedures (OECD 1989, Guidelines 301) corresponds to the degradation potential of surface waters; the degradability of substances in category 2 tests (OECD 1989, Guidelines 302) corresponds to the degradation potential of municipal sewage treatment plants; and the degradability of substances in category 3 tests (OECD 1989, Guidelines 303) corresponds to the degradation potential of industrial sewage treatment plants.

Figure 1: Test scheme in accordance with the OECD Test Guidelines

(modified from Painter and King 1980)



2.1.1 Endpoints in biodegradability testing

The biodegradation of a substance can be measured via the primary degradation or the mineralization of the substance. Metabolic processes in the bacteria, such as oxygen consumption and carbon dioxide production, are employed for the indirect assessment of degradation in the test procedures specified in the OECD Test Guidelines (OECD 1984, 1989). Primary degradation is assessed via direct measurement of the test substance concentration (**Table 1**).

Table 1: Analytical methods for assessing biodegradation

Indirect methods:

- BOD measurement: electrolytic measurement of the oxygen demand from microorganisms during the test; example: MITI degradation test (OECD 301C, 1989).
- COD measurement: assessment of the chemical oxygen demand during the test; example: Pitter (1976).
- CO_2 production measurement: assessment of the carbon dioxide produced during the test; example: STURM degradation test (OECD 301 B, 1984).
- DOC measurement: measurement of the dissolved organic carbon content in the nutrient broth during the test; example: ZW (Zahn-Wellens) degradation test (OECD 302 A, 1989).

Reference points for indirect degradation measurement:

- DOC measurement: measurement of the dissolved organic carbon at time t_0
- COD measurement: measurement of the chemical oxygen demand at time t_0
- ThOD: calculation of the theoretical oxygen demand for complete mineralization of the substances with nitrification, based on the number of C, H, Cl, N, Na, O and P atoms in the molecules (OECD 1989):

$$ThOD: \frac{16[2C+ 1/2(H-hal) + 5/2N + 3S + 5/2P + 1/2\ Na - O]}{MW}$$

Direct (specific) methods:

Measurement of the test substance concentration:

Chromatographic methods
- Thin-layer chromatography (non-quantitative)
- High-pressure liquid chromatography
- Gas chromatography

^{14}C method

Colorimetric methods

Spectrometric methods

2.1.2 Experimental assessment of degradation

In addition to the test procedures as specified in the OECD Test Guidelines (OECD 1984, 1989), degradation tests are carried out under various test conditions. The measured degradability varies according to the test procedure employed. **Table 2** shows the measured variables for several test procedures.

Table 2: Measured variables in degradation tests

CFU: resultant number of colony-forming units; TG: dry weight; BOD: biological O_2 demand; DOC: dissolved organic carbon; COD: chemical O_2 demand; CO_2: CO_2 production; spec.: specific analysis.

test procedure	inoculum [CFU/ml]	test conc. [mg/l]	measured variable	duration [d]	path-level
OECD*[1]	10^7-10^8	5-40*[2]	DOC	28	70%
STURM*[1]	10^7-10^8	10+20	CO_2	28	60%
AFNOR*[1]	10^7	40*[2]	DOC	28	70%
CB*[1]	10^4-10^6	2-10	BOD	28	60%
MITI1*[1]	10^7-10^8	100	BOD	28	60%
ZW*[1]	10^5-10^6	50-400*[2]	DOC	28	70%/20%
Tabak 1981	-	5-10	DOC	7-28	60%
Pitter 1976	100 mg TG/l		200	COD	5+20*[3] 90%, 15mg/g*h
Babeu 1987	10^5-10^6	0.4-3.2	BOD	5-20	16%
Bridie 1979	100 mgTG/l	30	BOD	5	-
Urano 1986a	30 mgTG/l	100	BOD	14	40%/25%
			DOC		0.02mg/g*h
Kondo 1988a	< 3mgTG/l	0.1-1000	spec.	3	50%/15%

*[1] Test procedure in accordance with the OECD Test Guidelines (OECD 1984, 1989)
*[2] Test concentration in mg DOC/mg*1
*[3] Test duration with adaptation time

2.2 Available degradation data

The basis for this study is degradation data from the MITI test procedure (OECD 301C), supplied by the Chemicals Inspection and Testing Institute (1-1, Higashi-Mukojima 4-chome, Simida-ku, Tokyo 131). The data cover approximately 800 compounds, which are referred to below as MITI data. The compounds were divided into chemical classes (**Table 3**).

Table 3: Assignment of compounds to chemical classes, and differentiation between easily degradable and non-easily degradable substances in accordance with the MITI test

chemical class	number of compounds	examples
1. aliphatic		
1.1 acyclic	287 (207/80)*	butanol, hexanoic acid
1.2 cyclic		
1.2.1 monocyclic	21 (10/11)	cyclohexane, cyclohexanol
1.2.2 polycyclic	11 (2/9)	bicyclooctane
2. aromatic		
2.1 monocyclic	244 (87/157)	benzenes
2.2 polycyclic	122 (21/101)	biphenyl, naphthalene
3. heterocyclic		
3.1 monocyclic	55 (32/23)	epoxides, furan, thiophene
3.2 polycyclic	34 (9/25)	bipiperidine, quinoline

* (number of easily degradable substances/number of non-easily degradable substances)

The respective proportions of easily degradable and non-easily degradable compounds (BOD/THOD > 60 per cent: easily degradable; BOD/THOD < 60 per cent: non-easily degradable) for the chemical classes are not uniform (**Table 3**). Acyclic compounds are more easily degradable than cyclic compounds, while more heterocyclic compounds are more easily degradable than carbocyclic compounds. In view of the differing proportions of easily degradable and non-easily degradable substances, the chemical classes are considered separately below.

Further degradation data were taken from the literature for the purpose of comparison (Pitter 1976, Bridie et al. 1979, Zahn and Wellens 1980, Tabak et al. 1981, Kitano 1983, Urano and Kato 1986b, Babeu and Vaishnav 1987, Niemi et al. 1987, Kondo et al. 1988b, Wellens 1990; test conditions: Table 2; degradation data: **Table 4**).

Table 4: Degradation data

Reference 1: Zahn and Wellens (1980), Wellens (1990); 2: Pitter (1976); 3: Babeu and Vaishnav (1987) and Niemi et al. (1987); 4: Kondo et al. (1988b); 5: Urano and Kato (1986b); 6: Tabak et al. (1981); 7: Kitano (1983).

reference	number of degradation data						
	aliphatic			aromatic		heterocyclic	
	acycl.	mono-cycl.	poly-cycl.	mono-cycl.	poly-cycl.	mono-cycl.	poly-cycl.
1	10	-	-	62	-	2	-
2	10	3	1	46	3	3	-
3	22	2	-	13	1	3	1
4	30	2	-	49	11	10	3
5	16	-	-	30	1	-	-
6	9	3	2	18	6	-	1
7	7	1	-	7	4	2	2
MITI data	79	6	3	117	20	17	3

2.3 Comparison of degradation data from various test procedures

Varying test conditions contribute to discrepancies with regard to the determination of the degradability of a substance. **Figure 2** shows the percentage of compounds whose degradation results correspond to the MITI classification, covering twelve test procedures. Due account is taken of the path-levels, which differ in some test procedures from those of the MITI procedure. Agreement of the degradation results with the MITI degradation results was assessed separately for easily degradable and non-easily degradable substances. Higher or lower degradation rates respectively indicate a higher or lower degradative capacity for the test procedure.

The degradation processes are listed in order of degradative capacity. Disparity between the degradation results for the easily degradable (or non-easily degradable) substances and the MITI data indicates a different level of degradability in comparison with the MITI test procedure. A low level of correspondence in the case of both easily degradable and non-easily degradable substances reveals that the tests are not comparable.

Ring tests have revealed that unusually large deviations in the degradation results can occur when degradation measurements are carried out at different laboratories (Kitano and Takatsuki 1988). Taking into account the fact that a deviation of 20 per cent is considered permissible when carrying out a test procedure at the same laboratory (OECD 1984), the

discrepancies in the experimental data obtained from the different test procedures as a result of the differing test conditions appear almost in accordance with expectations. In general, fewer substances are degraded in the degradation procedures involving low inoculum and substrate concentrations (e.g. CB test) than in test procedures with higher inoculum concentrations (e.g. MITI test).

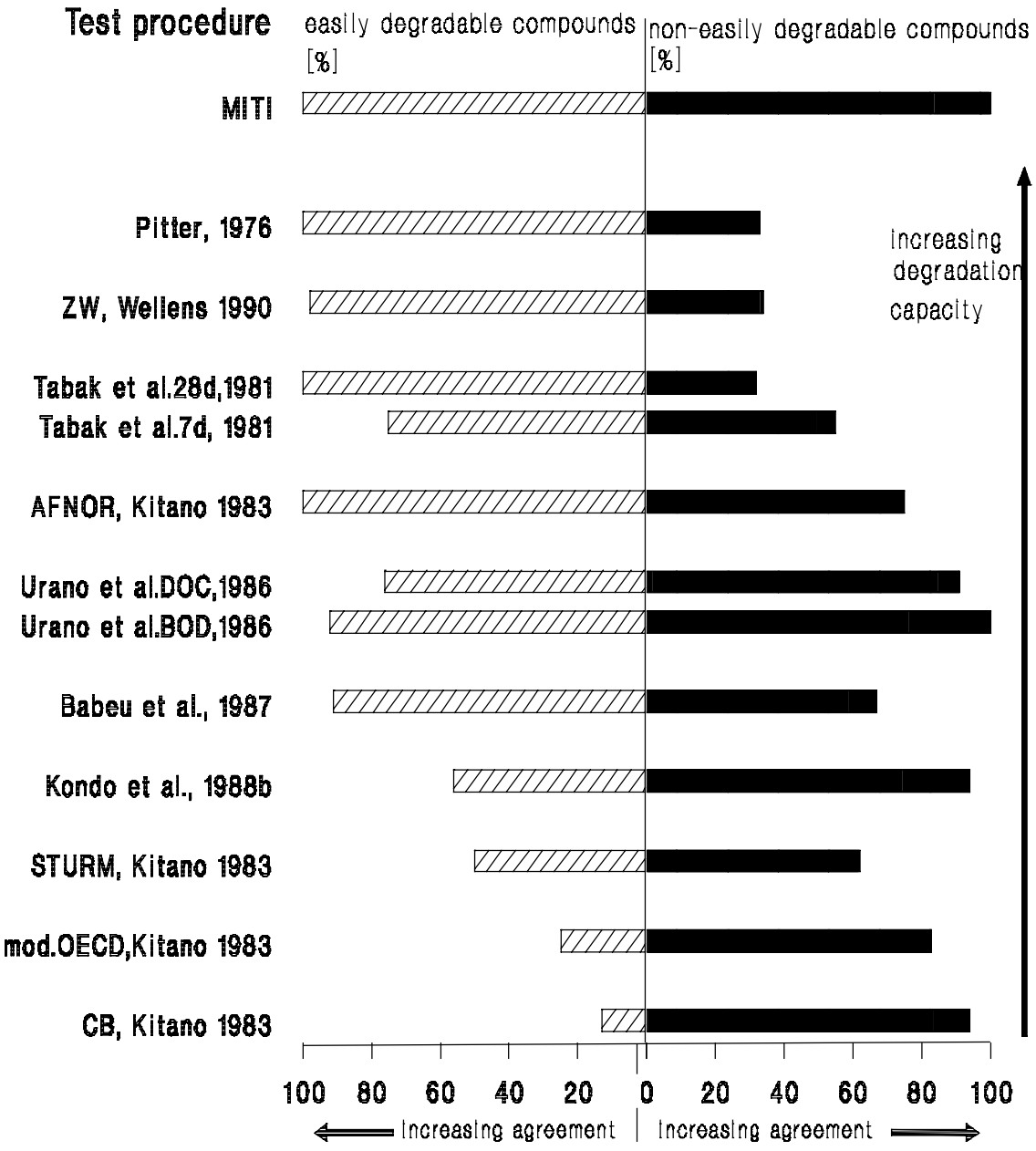
Additional discrepancies result from the fact that the suitability of the various test procedures varies for different substances. For example, due to the low test concentration, the degradation of low-solubility substances is detected more effectively in the CB test than in a test procedure applying high substrate concentrations. The tests according to Pitter (1976) and Tabak et al. (1981), which are carried out after adaptation of the microorganisms to the substrate, display a trend towards a higher level of degradability. The degradation tests carried out over short periods of time, according to Babeu and Vaishnav (1987) and Kondo et al. (1988b), result in low degradation rates, which may be accounted for by the fact that the duration of the experiments is too short for adaptation.

The high degradative capacity of the ZW test, which is a standard test stipulated in the OECD Test Guideline for the category of "inherent degradability" (OECD 1984, Guidelines 302), is according to expectations. With regard to the test procedures for measuring high degradability (OECD 1989, Guidelines 301), the degradation tests involving low inoculum concentrations (CB Test and Modified OECD Screening Test) result in a smaller quantity of compounds being classified easily degradable than do the test procedures involving high inoculum concentrations (MITI, AFNOR). With regard to the degradation results of the STURM test, large discrepancies are observed for both those compounds being classified as easily degradable and those classified as non-easily degradable.

The different degradative capacities among the OECD Test Guidelines compared here correspond to the information provided in the literature. A slightly lower degradative capacity is specified for the CB and Modified OECD Screening Test in comparison with AFNOR and STURM. Kitano (1983) observed an increasing level of degradative capacity in the order CB < mod. OECD < STURM < MITI < AFNOR. Gerike and Fischer (1979) reported increasing degradative capacity in the order MITI < CB < mod. OECD < AFNOR < STURM. Block et al. (1985) state an increasing degradative capacity in the order CB < MITI < mod. OECD < STURM. The MITI degradation test occupies an intermediate position in terms of degradative capacity, and can be regarded as representative of degradation tests for category 1, easy degradability.

Figure 2: Comparison of degradability in the MITI test with that in other procedures, for different chemicals by each procedure

(The tests are listed in order of degradative capacity. Results of the MITI test are shown as 100 per cent for comparison.)



3. Descriptors

The derivation and application of SARs requires descriptors for molecules and molecule fragments: physical-chemical, geometric, electronic and topological parameters.

Physical-chemical descriptors

molecular weight	(MW)
partition coefficients	(P_{OW}, R_m)

Geometric descriptors

van der Waals radius	(Y_{vdw})
accessible molecular surface area	(ASA)
sterimol parameters	

Electronic descriptors

Hammett substituent constant	(σ)
molar refraction	(MR)
quantum chemical descriptors	
atomic charges	(δ)
electrophilic superdelocalizability	(SE)

Topological descriptors

connectivity indices	(X)
Kappa index	(K)
substructural indicators	
atom types	
bond types	

3.1 Physical-chemical descriptors

Partition coefficient 1-octanol/water (P_{OW}):

Several methods are available for calculating P_{OW}. The most commonly employed procedure is the fragment method according to Hansch and Leo (1979). The P_{OW} is obtained from group fragment constants and structural factors. The group fragment constants are available for approximately 100 fragments, for example CH_3, COOH. The structural factors specify various bond types, for example double bonds or conjugated double bonds, and geometric factors, for example rings and chains. The P_{OW} can be calculated with the Medchem program CLOGP (Leo 1986).

R_m values (R_m):

R_m values are obtained by means of thin-layer chromatography. The retention of a substance is dependent on its interaction with the lipophilic stationary phase and the aqueous mobile phase (Seydel and Schaper 1979).

3.2 Geometric descriptors

Van der Waals radius (Y_{vdw}):

Van der Waals radii are tabulated by Bondi (1964) and Charton (1969) as substituent constants for many substructures.

Accessible molecular surface area (ASA):

The molecular surface area can be calculated with van der Waals radii, taking atom overlaps into account, using the SAREA (QCPE 1986) and SAVOL (ADAPT 1989) programs. A correction factor for the surface area accessible to a solvent is included in the calculation procedure.

Sterimol parameters:

Sterimol parameters (Verloop et al. 1979) specify the shape of a molecule or of a substituent with directional radii, on the basis of Verloop constants. The constants are established via van der Waals radii, standardized bond lengths and bond angles, assuming conformation with minimum energy. Constants are tabulated according to Verloop for 280 substituents.

3.3 Electronic descriptors

Hammett substituent constant (σ):

Hammett substituent constants specify the electron-attracting or electron-repelling effect of substituents. The Hammett substituent constant can be regarded as an approximate measure of the relative electron density at the centre of reaction. Substituent constants are tabulated (Hammett 1949). For polysubstituted compounds, it may be assumed that the individual effects are additive when strong interactions do not prevail.

Molar refraction (MR):

Molar refraction specifies the three-dimensional shape and polarity in a molecule. The available methods of calculating molar refraction include the fragment addition method according to Vogel (1977), using the ADAPT program MRFRAC (ADAPT 1989).

Quantum chemical descriptors:

Quantum chemical methods, such as the Hückel molecular orbital method (HMO, Hückel 1932), the extended Hückel theory (EHT, Hoffmann 1963) or semi-empirical methods (MNDO, Dewar and Thiel 1977; AM1, Dewar et al. 1985; CNDO/2, Pople et al. 1965) are available for calculating ionisation potentials, dipole moments, charge densities, HOMO and LUMO energies (highest occupied molecular orbital, lowest unoccupied molecular orbital) and atomic charges. These parameters are dependent on the conformation of the molecules. All calculation processes are based on the assumption that the most probable conformation is that involving the minimum amount of energy. Depending on the method employed, however, varying results are obtained.

Electrophilic superdelocalizability (SE):

Electrophilic superdelocalizability is a measure of the energy stabilisation which is attained when an electrophile attacks a reactive centre. Here, the electrophilic superdelocalizability has been calculated according to Schürmann (1990).

Atomic charges (δ):

Differences in the atomic charges of neighbouring atoms are used as descriptors for the reactivity of functional groups. Major differences are obtained, however, depending on the quantum chemical method applied.

3.4 Topological descriptors

Connectivity indices (X):

Connectivity indices specify the topology of a molecule. Each atom of a molecule is assigned a number (δ) corresponding to the number of adjacent non-hydrogen atoms. The first order connectivity index (^1X) is obtained via summation of the products $(\delta_i\ \delta_j)^{-1/2}$ for all pairs of adjacent atoms i and j. The second order connectivity index (^2X) is obtained from all δ products of three neighbouring atoms (Kier and Hall 1979). Calculating the connectivity indices is feasible by, for example, the program DMCON (ADAPT 1989).

Kappa index (K):

The Kappa index (Kier 1987) is a topological parameter derived from the molecular skeleton without hydrogen atoms. The Kappa index is based on two-bond fragments, which are compared with its maximum possible number in the isomeric highly branched form and the minimum number in the isomeric linear form. The index is standardized to the number of atoms in the molecule.

4. Structure-biodegradation relationships

Numerous SAR models for estimating biodegradation have been developed in recent years. Compilations are to be found in, for example, Kuenemann and Vasseur (1989), Parsons and Govers (1990) and Lyman et al. (1982).

Structural characteristics of the substances provide an indication for the expected degradability (Kawasaki 1980, Alexander and Aleem 1961) and can be employed to classify degradable and persistent substances (Alexander 1973, Vaishnav et al. 1987). In general, biodegradation of non-cyclic substances tends to be dependent on the degree of branching, the chain length, the saturation state, and the oxidation state. The type and quantity of substituents, their positions, and the charges on the ring determine the degradability of aromatic compounds (**Table 5**).

Physical-chemical properties of the chemicals affect their degradability. Permeation through the bacterial cell wall and adsorption phenomena can represent barriers to the degradation of a chemical. In some chemical classes the degradation rate is determined by the lipophilic properties of the chemicals (Vaishnav et al. 1987). Prolonged test duration reduces the effects of the lipophilic properties on the rate of biodegradation. Transport through membranes and enzyme-substrate bond can be affected by the molecular weight and steric characteristics, such as the surface area size and volumes of the molecules (Paris et al. 1982, 1983, 1987, Dearden and Nicholson 1987a, Boethling 1986).

Electronic parameters are employed in order to account for the different mechanisms of degradation of the substances, which may vary according to their polarity. The electron density on the aromatic ring, which is dependent on the functional groups, is regarded as a determinative for the ring cleavage during biodegradation of aromatic compounds (Pitter 1985, Dearden and Nicholson 1986). Correlations between topological indices and biodegradation have been developed, but the interpretability of these parameters is not clear.

The SAR models developed for the purpose of estimating biodegradation can be categorized according to data base and statistical processes:

(1) For homologous substances, SARs have been developed by univariate methods (regression analysis).

(2) Multivariate processes (multiple regression, discriminant analysis) are employed in order to derive substructure based models, which are intended for application to various chemical classes.

(3) Diverse substructures associated with degradable and non-degradable compounds are used to approximate potential degradability of substances qualitatively (cluster and ranking analysis).

MITI degradation data are used throughout this study to assess SAR models, as (a) the MITI degradation test is standardized in the OECD guidelines, (b) the MITI degradation test occupies an intermediate position with regard to degradative capacity among the OECD degradation tests of category 1 "easy degradability"; and (c) a large quantity of consistent degradation data is available.

Table 5: Structural characteristics related to degradability

1. Functional groups (Dias and Alexander 1971, Hammond and Alexander 1972, Paris et al. 1982, Pitter 1985, Kawasaki 1980, Kobayashi 1981): Alcohols, acids, esters, amides and aldehydes are easily degradable; nitro groups, halogens, sulphonic acids, methyl groups are less degradable.

2. Number of substituents (Alexander and Lustigman 1966): Monosubstituted aromatics are more easily degradable than polysubstituted aromatics.

3. Positions of the substituents (Chambers and Kabler 1964, Tabak et al. 1964, Kobayashi 1981): In general, parasubstituted aromatics are more easily degradable than meta- or orthosubstituted aromatics. But metasubstituted phenols are more easily degradable than ortho- or parasubstituted phenols, while metasubstituted nitrobenzoic acids are more resistant than ortho- or parasubstituted nitrobenzoic acids.

4. Degree of branching (Webley et al. 1959, Swisher 1963, Niemi et al. 1985, Kawasaki 1980): Unbranched alkylphenols are more easily degradable than phenols with branched C-chains; unbranched alkylbenzene sulphonates are more easily degradable than branched ones; substances with tertiary carbon atoms are always more resistent to degradation.

5. Chain length (Ladd 1956, Sugatt et al. 1984): In general, the degradation of linear aliphatic chains is with some exeptions reduced with increasing chain length.

6. Number of rings (Niemi et al. 1985): The degradability decreases as the number of rings increases.

4.1 Models related to specific chemical classes

SAR models for estimating the microbial degradability of homologous substances are based on physical-chemical, geometric, electronic or topological parameters, according to the transformation processes which are assumed to be relevant (**Table 6**).

The degradation data to derive the models originate from various degradation tests with short test durations, whereby mostly the primary degradation is measured. For the purpose of validation, the degradation calculated on the basis of Models 1-64 was compared with the experimental data (MITI). This comparison revealed that only a few models can be validated: **(A)** models which enable classification in accordance with the MITI test data (correspondence > 75 per cent); and **(B)** models which result in no agreement between the calculated degradation data and the measured MITI data.

In contrast to these two groups, the overwhelming majority of the models could not be validated despite the comprehensive data material: **(C_1)** models for chemical classes which are all easily degradable in the MITI degradation test; **(C_2)** models for chemical classes which are all non-easily degradable in the MITI degradation test; and **(D)** models for which no MITI degradation data are available.

The **(B)** models reveal no dependence of degradability (MITI) on the respective parameters (**Figure 3**). For obvious reasons, the percentage level of coincidence between the calculated and experimental degradability is not specified for models **(B)**-**(D)**.

Table 6: SAR models for specific chemical classes

Application of Models 1-64 to MITI degradation data results in: **(A)** coincident classification, **(B)** non-coincident classification, **(C_1)** all substances easily degradable in MITI test, **(C_2)** all substances non-easily degradable in MITI test, **(D)** no degradation data available.

Descriptors: phyc: physical-chemical; topo: topological; geo: geometric; elec: electronic.

Degradation tests: k_{rate}: kinetic degradation measurement; % K: per cent disappearance of substrate; BOD_5: O_2 consumption measurement after 5d; COD_r: chemical O_2 consumption rate.

Reference 1: Dearden and Nicholson 1986, 1987a, 1987b; 2: Boethling 1986; 3: Vaishnav et al. 1987, 4: Paris et al. 1982, 1983, 1986, 1987; 5: Pitter 1985; 6: Urushigawa and Yonezawa 1979.

class	model no.	assessment test	degra-dation	desc.	ref.
aliphatic compounds					
alcohols					
alcohols	28,29,34,35	B	BOD_5	elec	1
alcohols	44,45,46,47	B	BOD_5	topo	2
linear alcohols	2	C_1	BOD_5	elec	3
glycols	19,32,34	B	BOD_5	elec	1
aldehydes	20,30,32,33,34	B	BOD_5	elec	1
amines	18,33,34	B	BOD_5	elec	1
esters	23,32,34	B	BOD_5	elec	1
ethers					
ethers	27,34,35	B	BOD_5	elec	1
dialkyl ethers	48,49	B	BOD_5	topo	1
ketones					
ketones	3,4	C_1	BOD_5	phyc	3
ketones	34,35,39	C_1	BOD_5	elec	1
hydrocarbons					
alkanes	13	B	BOD_5	geo	1
hal. hydrocarbons	12	C_2	BOD_5	geo	1
hal. hydrocarbons	33,34,38	C_2	BOD_5	elec	1
acids					
carbonic acids	21,22,32,33,34,35	B	BOD_5	elec	1
monocarbonic acids	56,57,58,59	C_1	BOD_5	topo	2

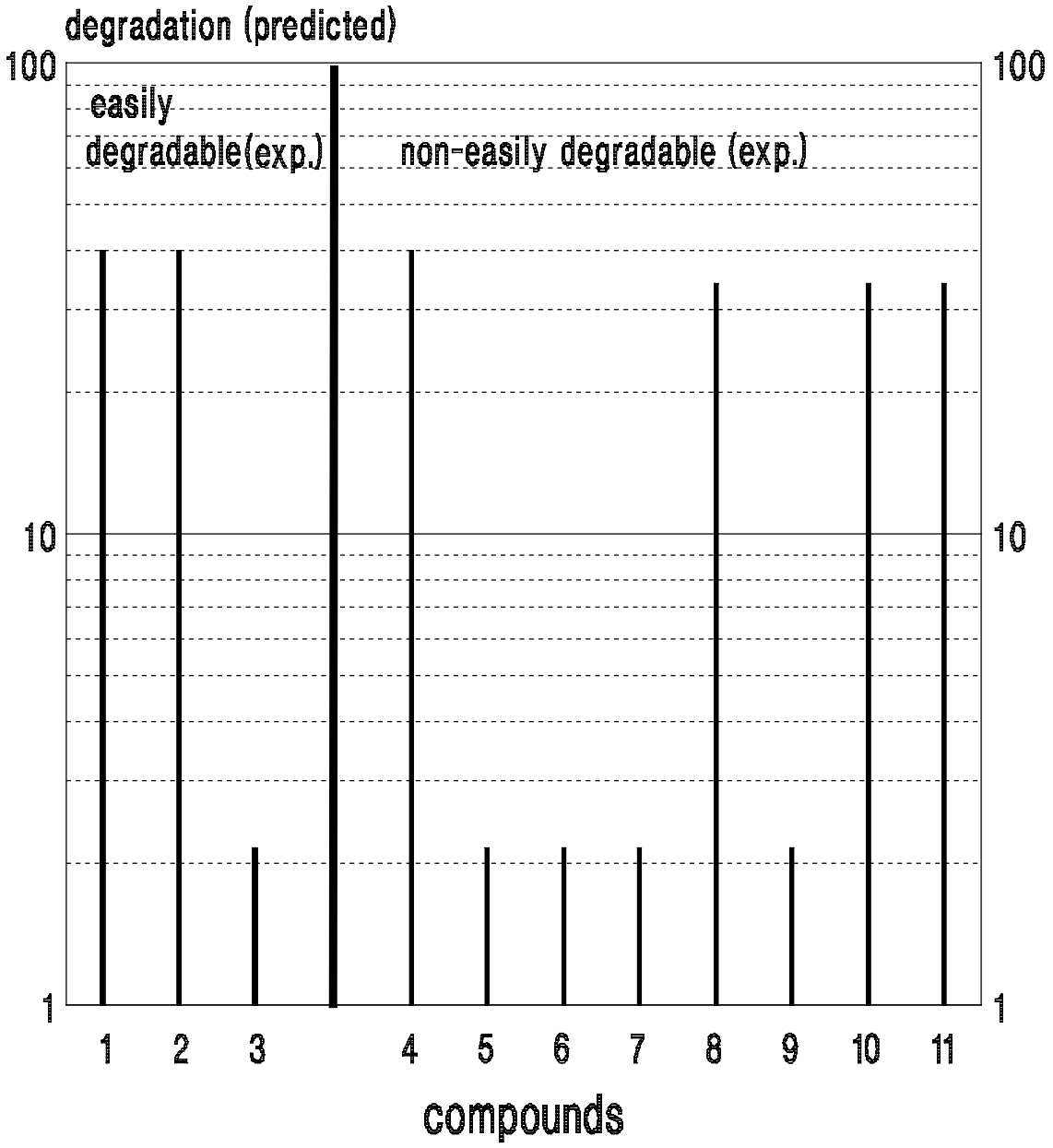
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Table 6, continued:

lin. monoc. acids	46,47	C_1	BOD_5	topo	2
bran. monoc. acids	54,55	C_1	BOD_5	topo	2
sulphonic acids	34,35,40	C_1	BOD_5	elec	2
amino acids	33,34,42	D	BOD_5	elec	1
sugars	34	D	BOD_5	elec	1
aliphatic cyclic compounds					
alcohols (P_{OW} > 1.27)	1	A	COD_r	phyc	3
ketones (P_{OW} > 1.27)	1	A	COD_r	phyc	3
alicyclics (> 1 subst.)	43	A	COD_r	topo	3
alicyclics (monosub.)	60	B	COD_r	topo	3
aromatic compounds					
aldehydes	30	B	BOD_5	elec	1
anilines					
anilines	18	B	BOD_5	elec	1
anilines (disubst.)	11	B	k_{rate}	geo	4
o-anilines (disubst.)	36	B	k_{rate}	elec	5
m-anilines (disubst.)	41	C_2	k_{rate}	elec	5
p-anilines (disubst.)	17	A	k_{rate}	elec	5
2,4-dichlorophenoxy-acetic acids					
2,4-dichlorophenoxy-acetic acids	8	D	k_{rate}	phyc	4
2,4-dichlorophenoxy-acetic acids	61,62	D	k_{rate}	topo	2
chlorophenyl carbamates	63,64	D	% K	topo	2
hydrocarbons	31	B	BOD_5	elec	1
phenols					
phenols	24,25,26,33,34,35	B	BOD_5	elec	1
phenols (disubst.)	9,10	A	k_{rate}	geo	4
phenols (disubst.)	14	A	k_{rate}	elec	5
o-phenols (disubst.)	15	A	k_{rate}	elec	5
m-phenols (disubst.)	16	A	k_{rate}	elec	5
p-phenols (disubst.)	37	B	k_{rate}	elec	5
phthalates					
phthalates	6	C_1	k_{rate}	phyc	6
phthalates	5,7	C_1	k_{rate}	phyc	2
phthalates	50,51,52,53	C_1	k_{rate}	topo	2

Figure 3: Example of a (B) model

(No coincidence with MITI degradation data. Model 11 was tested with eleven disubstituted anilines. The calculated degradation rate of the easily degradable substances did not differ from the calculated degradation rate of the non-easily degradable substances.)



4.1.1 Models with physical-chemical parameters

SAR models with physical-chemical parameters were developed with the descriptors molecular weight (MW) and lipophilicity. In Models 1-5 calculated, and in Models 6 and 8 measured partition coefficients are utilized. For validation purposes, only calculated log P_{OW} values (Leo 1986) were used.

(A): The following model results in the classification of substances into easily degradable and non-easily degradable compounds.

Model 1: Alicyclic alcohols and ketones (P_{ow} >1.27)

Vaishnav et al. (1987); COD (5d+20d adaptation) [$mg*g^{-1}*h^{-1}$]
$\log (COD_{rate}) = - 0.510 (\log P_{OW}) + 2.532$
n = 4, r = 0.98, F = 87, s = 0.0672

The classification of five alicyclic compounds (three easily degradable/two non-easily degradable) was achieved (degradation rate > 15 mg $COD*g^{-1}*h^{-1}$: easily degradable alicyclics; degradation rate < 15 mg $COD*g^{-1}*h^{-1}$: non-easily degradable alicyclics This corresponds to the path-level specified by Pitter (1976).

(C): The following models cannot be validated with MITI data, as all the corresponding compounds are easily degradable in the MITI test: linear alcohols (63), ketones (10), phthalates (6).

Model 2: Linear alcohols

Vaishnav et al. (1987): BOD_5
$\log (\%\ BOD/ThOD) = - 0.192 (\log P_{OW}) + 2.338$
n = 5, r = 0.99, F = 579, s = 0.0129

Models 3/4: Ketones

Vaishnav et al. (1987): BOD_5
$\log (\%\ BOD/ThOD) = 0.698 (\log P_{OW}) - 0.867 \log (P_{OW} + 1) + 1.87$
n = 10, r = 0.99, F = 18.585, s = 0.02
$\log (\%\ BOD/ThOD) = 0.241 (\log P_{OW}) - 0.106 (\log P_{OW})^2 + 1.682$
n = 10, r = 0.99, F = 11.068, s = 0.03

Model 5: Phthalate

Boethling (1986): k_{rate} [$CO_2*d^{-1}*1000$]
$k_{rate} = - 24.308 (\log P_{OW}) + 394.84$
n = 12, r = 0.93, F = 65.1, s = 37.477

Model 6: Phthalates

Urushigawa and Yonezawa (1979):
k_{rate} (1-2d) [l*Bkt^{-1}*h^{-1}]
log (k_{rate}) = - 2.09 (log R_m)^2 + 1.19 (log R_m) - 1.15
n = 5, r^2 = 0.98

Model 7: Phthalates

Boethling (1986): k_{rate} [CO_2*d^{-1}*1000]
k_{rate} = - 0.977 MW + 532.98
n = 12, r = 0.95, F = 100.5, s = 30.895

(D): The following model cannot be validated, as no MITI degradation data are available for these compounds.

Model 8: 2,4 dichlorophenoxyacetic acids (2,4 D)

Paris et al. (1984): k_{rate} (1-2d) [l*Bkt^{-1}*h^{-1}]
log (k_{rate}) = 0.799 (log P_{OW}) - 11.643
n = 6, r^2 = 0.94

4.1.2 Models with geometric parameters

SAR models with geometric descriptors were derived with van der Waals radii (Y_{vdw}), the accessible surface area (ASA), and the Sterimol length parameter (L). The van der Waals radius (Y_{vdw}) employed by Paris et al. (1982, 1983, 1987) for substituents on anilines and phenols was calculated according to Bondi (1964) and Charton (1969); for nitrile, methoxy and acetyle groups, however, minimum radii of the Stereo model according to Dreiding (Paris et al. 1982) were employed. Due to the calculation of the descriptor values within one SAR model by different methods, the validation is possible to a limited extent only.

(A): The following models result in the classification of substances into easily degradable and non-easily degradable compounds.

Models 9/10: Phenols (disubstituted)

Paris et al. (1982, 1983): k_{rate} (1-2d) [l*Bkt^{-1}*h^{-1}]
log (k_{rate}) = - 1.36 Y_{vdw} - 9.3
n = 8, r^2 = 0.96
log (k_{rate}) = 0.9071 Y_{vdw} - 8.313
n = 6, r^2 = 0.91

The classification of 14 phenols (nine easily degradable/five non-easily degradable) was achieved (Model 9: degradation rate > 2.2*10-10 $l*Bkt^{-1}*h^{-1}$ easily degradable compounds, degradation < 2.2*10-10 $l*Bkt^{-1}*h^{-1}$ non-easily degradable compounds No path-level is specified by Paris. Restriction to hydroxy, methoxy, methyl, bromine and chlorine substituents is necessary.

(B): The following model leads to classifications which do not correspond to the MITI degradation results.

Model 11: Anilines (disubstituted)

Paris and Wolfe (1987): k_{rate} (1-2d) [$l*Bkt^{-1}*h^{-1}$]
$\log (k_{rate}) = - 14.1\ Y_{vdw} - 11.0$
$n = 7$, $r^2 = 0.92$

Tested with 11 anilines (three easily degradable/eight non-easily degradable).

(C): The following models cannot be validated with MITI data, as all the corresponding compounds are either easily degradable or non-easily degradable in the MITI test: non-substituted alkanes (40, easily degradable), acyclic halogenated hydrocarbons (45, non-easily degradable).

Model 12: Halogenated hydrocarbons

Dearden and Nicholson (1986): BOD_5
% (BOD/ThOD) = 8.29 L - 1.187
n = 9, r = 0.98, s = 4.118

Model 13: Alkanes

Dearden and Nicholson (1986): BOD_5
% (BOD/ThOD) = 0.996 ASA + 0.055
n = 12, r = 1.00, s = 0.27

4.1.3 Models with electronic parameters

SAR models with electronic parameters have been derived using σ Hammett substituent constants (Hansch et al. 1973, Hansch and Leo 1979) and quantum chemical parameters. The parameters, atomic charge (δ), superdelocalizability (SE) and electronic energy (E) were calculated by Dearden and Nicholson (1986, 1987a, 1987b) with the CNDO/2 method. The models of Dearden and Nicholson were tested with quantum chemical parameters calculated by MNDO methods for the compounds of the respective chemical classes.

None of these models provides coincident degradation results for easily degradable and non-easily degradable compounds. The use of different calculation procedures and different geometric optimization may be partially responsible for the discrepancy between the calculated and experimental degradation data. No classification was possible with new regression equations based on the parameters calculated here. The models employing Hammett substituent constants were examined with the values specified by Pitter (1985).

(A): The following models result in classification of substances into easily degradable and non-easily degradable compounds.

Model 14: Phenols (disubstituted)

Pitter (1985): COD (5d+20d adaptation) [mg*g^{-1}*h-1]
log (COD_{rate}) = - 0.32 σ + 1.43
n = 7, r = 0.95

Classification of 80 per cent of the phenols (ten easily degradable/five non-easily degradable) was achieved (degradation rate > 21 mg*g^{-1}*h^{-1}: easily degradable compounds, degradation rate < 21 mg*g^{-1}*h^{-1}: non-easily degradable compounds). This does not correspond to the specified path-level of 15 mg*g^{-1}*h^{-1}. Restriction to phenols with COOH, Cl, CH_3 and SO_3 substituents is necessary.

Model 15: Phenols (ortho-substituted)

Pitter (1985): COD (5d+20d adaptation) [mg*g^{-1}*h^{-1}]
log (COD_{rate}) = - 0.43 σ_o + 1.70
n = 5, r = 0.98

Classification of 83 per cent of the ortho-phenols (three easily degradable/three non-easily degradable) was achieved (degradation rate > 30 mg*g^{-1}*h^{-1}: easily degradable phenols, degradation rate < 30 mg*g^{-1}*h^{-1}: non-easily degradable phenols). This does not correspond to the specified path-level of 15 mg*g^{-1}*h^{-1}. Restriction to phenols with COOH, OH, CH_3, NO_2 and Cl substituents is necessary.

Model 16: Phenols (metasubstituted)

Pitter (1985): COD (5d+20d adaptation) [mg*g^{-1}*h^{-1}]
log (COD_{rate}) = - 0.616 σ_o + 1.72
n = 4, r = 0.94

Classification of 80 per cent of the metasubstituted phenols (four easily degradable/one non-easily degradable) was achieved (degradation rate > 32 mg*g^{-1}*h^{-1}: easily degradable phenols, degradation rate < 32 mg*g^{-1}*h^{-1}: non-easily degradable phenols This does not correspond to the specified path-level of 15 mg*g^{-1}*h^{-1}. Restriction to phenols with COOH, CH_3, OH and Cl substituents is necessary.

Model 17: Anilines (parasubstituted)

Pitter (1985): COD (5d+20d adaptation) [$mg*g^{-1}*h^{-1}$]
$\log (COD_{rate}) = - 0.78\ \sigma_p + 1.04$
n = 5, r = 0.94

Classification of 80 per cent of the parasubstituted anilines (one easily degradable/four non-easily degradable) was achieved (degradation rate > 14.5 $mg*g^{-1}*h^{-1}$: easily degradable anilines, degradation rate < 14.5 $mg*g^{-1}*h^{-1}$: non-easily degradable anilines). This does not correspond to the specified path-level of 15 $mg*g^{-1}*h^{-1}$. Restriction to anilines with CH_3, NH_2, NO_2 and Cl substituents is necessary.

(B): The following models lead to classifications which do not correspond to the MITI degradation results ($\mid \delta(X)-\delta(Y) \mid$: differences in the atomic charge between atoms X-Y, with the following X-Y atoms: C-N for amines, C-hal for halogens, C-O for alcohols, carbonic acids, esters, glycols, phenols, ethers and amino acids, CO for aldehydes, S-O for sulphonic acids).

Model 18: Aromatic and aliphatic amines

Dearden and Nicholson (1986): BOD_5
$\%\ (BOD/ThOD) = 1.004*10^3 \mid \delta(C)-\delta(N) \mid - 0.106$
n = 15, r = 0.99, s = 1.043

Tested with 32 amines (19 easily degradable/13 non-easily degradable).

Model 19: Glycols

Dearden and Nicholson (1987a): BOD_5
$\%\ (BOD/ThOD) = 0.993*10^3 \mid \delta(C)-\delta(O) \mid - 1.309$
n = 8, r = 0.99, s = 2.736

Tested with five glycols (four easily degradable/one non-easily degradable).

Model 20: Aldehydes

Dearden and Nicholson (1987a): BOD_5
$\%\ (BOD/ThOD) = 1.067*10^3 \mid \delta(C)-\delta(O) \mid - 4.231$
n = 9, r = 0.99, s = 2.175

Tested with six aldehydes (five easily degradable/one non-easily degradable).

Model 21/22: Carbonic acids

Dearden and Nicholson (1986, 1987a): BOD_5
% (BOD/ThOD) = $1.000*10^3$ | δ(C)-δ(O) | - 2.794
n = 36, r = 0.99, s = 2.446
% (BOD/ThOD) = $0.996*10^3$ | δ(C)-δ(O) | - 3.234
n = 40, r = 0.99, s = 4.412

Tested with 20 carbonic acids (18 easily degradable/two non-easily degradable).

Model 23: Esters

Dearden and Nicholson (1987a): BOD_5
% (BOD/ThOD) = $1.001*10^3$ | δ(C)-δ(O) | - 2.340
n = 19, r = 0.98, s = 3.086

Tested with six esters (five easily degradable/one non-easily degradable).

Models 24/25/26: Phenols

Dearden and Nicholson (1986, 1987a, 1987b):
COD (5d+20d adaptation) [$mg*g^{-1}*h^{-1}$], BOD_5
log (COD_{rate}) = 72.6 | δ(C)-δ(O) | - 0.284
n = 16, r = 0.94, s = 0.104
% (BOD/ThOD) = $1.012*10^3$ | δ(C)-δ(O) | + 0.076
n = 5, r = 0.99, s = 1.435
% (BOD/ThOD) = $0.998*10^3$ | δ(C)-δ(O) | + 2.108
n = 11, r^2 = 0.98, s = 4.044

Tested with eleven phenols (eight easily degradable/three non-easily degradable).

Model 27: Ethers

Dearden and Nicholson (1987b): BOD_5
% (BOD/ThOD) = $1.020*10^3$ | δ(C)-δ(O) | + 1.486
n = 14, r^2 = 0.98, s = 2.721

Tested with 16 ethers (eleven easily degradable/five non-easily degradable).

Models 28/29: Alcohols

Dearden and Nicholson (1987b): BOD_5
% (BOD/ThOD) = $1.023*10^3$ | δ(C)-δ(O) | + 1.504
n = 20, r = 0.99, s = 2.538
% (BOD/ThOD) = 9.3 * SE -3.163
n = 19, r = 0.96, s = 4.304

Tested with 22 alcohols (14 easily degradable/eight non-easily degradable).

Model 30: Aromatic and aliphatic aldehydes

Dearden and Nicholson (1986): BOD_5
% (BOD/ThOD) = $1.008*10^3$ | δ(C)-δ(O) | + 0.497
n = 6, r = 0.99, s = 1.953

Tested with seven aldehydes (six easily degradable/one non-easily degradable).

Model 31: Aromatic hydrocarbons

Dearden and Nicholson (1987a): BOD_5
% (BOD/ThOD) = 0.0762 E - 757.08
n = 12, r = 0.94, s = 9.177

Tested with eight aromatic hydrocarbons (seven easily degradable/one non-easily degradable).

Model 32: Aldehydes, carbonic acids, esters, glycols

Dearden and Nicholson (1987a): BOD_5
% (BOD/ThOD) = $0.998*10^3$ | δ(C)-δ(O) | + 2.398
n = 76, r = 0.99, s = 3.807

Tested -- see Models 20-23, 30.

Model 33: Amines, amino acids, aldehydes, carbonic acids, halogenated hydrocarbons, phenols

Dearden and Nicholson (1986): BOD_5
% (BOD/ThOD) = $1.015*10^3$ | δ(X)-δ(Y) | + 1.193
n = 79, r = 0.98, s = 3.459

Tested -- see Models 18, 20-22, 24-26, 30, 38, 42.

Model 34: Aldehydes, alcohols, amines, amino acids, carbonic acids, esters, ethers, glycols, halogenated hydrocarbons, ketones, phenols, sulphonic acids, sugars

Dearden and Nicholson (1987a): BOD_5
% (BOD/ThOD) = $1.015*10^3$ | δ(X)-δ(Y) | + 1.523
n = 197, r = 0.99, s = 3.822

Tested -- see Models 18-30, 38-40, 42.

Model 35: Alcohols, carbonic acids, ethers, ketones, phenols, sulphonic acids

Dearden and Nicholson (1987b): BOD_5
% (BOD/ThOD) = $1.015*10^3$ | δ(X)-δ(Y) | + 1.906
n = 112, r^2 = 0.98, s = 4.308

Tested -- see Models 21-22, 24-26, 27-29, 38-40, 42.

Model 36: Anilines (orthosubstituted)

Pitter (1985): COD (5d+20d adaptation) [$mg*g^{-1}*h^{-1}$]
log (COD_{rate}) = - 0.30 σ_o + 1.24
n = 4, r = 0.98

Tested with four orthosubstituted anilines (one easily degradable/three non-easily degradable).

Model 37: Phenols (parasubstituted)

Pitter (1985): COD (5d+20d adaptation) [$mg*g^{-1}*h^{-1}$]
log (COD_{rate}) = - 0.323 σ_p + 1.65
n = 4, r = 0.99

Tested with five parasubstituted phenols (four easily degradable/one non-easily degradable).

(C): The following models cannot be validated with MITI data, as all the corresponding compounds are easily degradable or non-easily degradable in the MITI test: halogenated hydrocarbons (45, non-easily degradable), ketones (ten, easily degradable), aliphatic sulphonic acids (two, easily degradable), metasubstituted anilines (five, non-easily degradable) (| δ(X)-δ(Y) |: differences in the atomic charges between atoms X-Y, with the following X-Y atoms: C-N for anilines, C-hal for halogens, CO for ketones, S-O for sulphonic acids).

Model 38: Halogenated hydrocarbons

Dearden and Nicholson (1986): BOD_5
% (BOD/ThOD) = $1.009*10^3$ | δ(C)-δ(hal) | + 0.204
n = 9, r = 0.99, s = 0.933

Model 39: Ketones

Dearden and Nicholson (1987b): BOD_5
% (BOD/ThOD) = $1.021*10^3$ | δ(C)-δ(O) | + 0.605
n =^_, r = 0.99, s = 4.34

Model 40: Sulphonic acids

Dearden and Nicholson (1987b): BOD_5
% (BOD/ThOD) = $1.037*10^3$ | δ(S)-δ(O) | + 1.453
n = 20, r^2 = 0.94, s = 6.735

Model 41: Anilines, metasubstituted

Pitter (1985): COD (5d+20d adaptation) [$mg*g^{-1}*h^{-1}$]
log (COD_{rate}) = - 1.53 σ_m + 1.31
n = 3, r = 0.97

(D): The following model cannot be validated, as no MITI data are available for these compounds (| δ(X)-δ(Y) |: differences in the atomic charge between atoms C-O).

Model 42: Amino acids

Dearden and Nicholson (1986): BOD_5
% (BOD/ThOD) = $1.087*10^3$ | δ(C)-δ(O) | - 2.986
n = 8, r = 0.99, s = 1.637

4.1.4 Models with topological descriptors

SAR models with topological descriptors employ zero to fourth order connectivity indices (^nX, with n = 0 to 4) as path or cluster indices, in some cases valence-corrected ($^nX^v_{pc}$) (Kier and Hall 1979).

(A): The following model results in the classification of substances into easily degradable and non-easily degradable compounds.

Model 43: Aliphatic cyclic compounds with > 1 substituents

Vaishnav et al. (1987); COD_{rate} (5d+20d adaptation) [$mg*g^{-1}*h^{-1}$]
log (COD_{rate}) = - 0.293 $^oX^v$ + 3.216
n = 6, r = 0.970, s = 0.0915, F = 64

The classification of four alicyclic compounds (three easily degradable/one non-easily degradable) was achieved (degradation rate > 8.5 mgCOD*g^{-1}*h^{-1}: easily degradable alicyclics; degradation rate < 8.5 mgCOD*g^{-1}*h^{-1}: non-easily degradable alicyclics). This does not correspond to the specified path-level of 15 mg*g^{-1}*h^{-1}.

(B): The following models lead to classifications which do not correspond to the MITI degradation results.

Models 44/45: Aliphatic alcohols

Boethling (1986): BOD (10d)
% (BOD/ThOD) = - 34.451 ^{2}X + 122.765
n = 14, r = 0.87, s = 15.586, F = 37.6
% (BOD/ThOD) = - 141.493 $^{4}X_{c}$ - 32.147 $^{3}X^{v}_{p}$ + 83.613
n = 14, r = 0.95, s = 10.256, F = 51.7

Tested with 80 alcohols (69 easily degradable/eleven non-easily degradable).

Models 46/47: Aliphatic monocarbonic acids and alcohols

Boethling (1986): BOD (10d)
% (BOD/ThOD) = - 148.734 $^{4}X_{c}$ + 56.678
n = 24, r = 0.85, s = 16.148, F = 57.2
% (BOD/ThOD) = - 161.432 $^{4}X_{c}$ - 27.083 $^{3}X^{v}_{p}$ + 85.192
n = 24, r = 0.93, s = 11.626, F = 65.9

Tested with 80 alcohols (69 easily degradable/eleven non-easily degradable).

Models 48/49: Dialkyl ethers

Boethling (1986): BOD (25d)
log % (BOD/ThOD) = - 0.517 $^{2}X^{v}$ + 2.597
n = 6, r = 0.99, s = 0.076, F = 149.3
log (% BOD/ThOD) = - 0.899 $^{4}X_{pc}$ + 1.816
n = 6, r = 0.98, s = 0.100, F = 84.8

Model tested with four dialkyl ethers (three easily degradable/one non-easily degradable).

(C): The following models cannot be validated with MITI data, as all the corresponding compounds are easily degradable in the MITI test: phthalates (six), linear monocarbonic acids (18), branched monocarbonic acids (three), monosubstituted aliphatic cyclic compounds (two).

Models 50/51/52/53: Phthalates

Boethling (1986): k_{rate} [CO_2*d-1*1000]
k_{rate} = - 37.312 $^{2}X_{v}$ + 436.429
n = 12, r = 0.97, s = 25.857, F = 147.8
k_{rate} = - 37.156 ^{2}X + 547.519
n = 12, r = 0.97, s = 25.523, F = 151.9
k_{rate} = - 73.343 $^{4}X_{p}$ - 59.181 $^{3}X^{v}_{c}$ + 613.022
n = 12, r = 0.98, s = 24.169, F = 85.8
k_{rate} = - 73.343 $^{4}X_{p}$ - 59.207 $^{3}X_{c}$ - 643.506
n = 12, r = 0.98, s = 24.173, F = 85.8

Models 54/55: Branched aliphatic monocarbonic acids

Boethling (1986): BOD (10d)
% (BOD/ThOD) = - 194.107 $^{4}X_{c}$ - 64.651
n = 10, r = 0.95, s = 10.03, F = 67.9
% (BOD/ThOD) = - 56.763 $^{3}X_{c}$ - 15.424 $^{3}X_{p}$ + 131.160
n = 10, r = 0.98, s = 7.151, F = 71.2

Models 56/57/58/59: Linear and branched aliphatic monocarbonic acids

Boethling (1986): BOD (10d)
% (BOD/ThOD) = - 286.999 $^{4}X_{c}$ + 86.069
n = 10, r = 0.94, s = 16.461, F = 55.1
% (BOD/ThOD) = - 252.507 $^{4}X_{c}$ - 22.048 $^{3}X_{p}$ + 122.303
n = 10, r = 0.98, s = 9.799, F = 85.6
% (BOD/ThOD) = - 67.158 $^{3}X^{v}_{c}$ + 96.557
n = 20, r = 0.91, s = 15.433, F = 88.7
% (BOD/ThOD) = - 62.954 $^{3}X^{v}_{c}$ - 18.765 $^{3}X_{p}$ + 126.828
n = 20, r = 0.96, s = 11.419, F = 89.0

Model 60: Monosubstituted aliphatic cyclic compounds

Vaishnav et al. (1987); COD_{rate} (5d+20d adaptation) [mgCOD*g^{-1}*h^{-1}]
log (COD_{rate}) = - 0.399 $^{o}X^{v}$ + 3.26
n = 4, r = 0.996, s = 0.0177, F = 260

(D): The following models cannot be validated, as no MITI data are available for these compounds.

Models 61/62: 2,4-dichlorophenoxyacetic acids (2,4-D)

Boethling (1986): k_{rate} (1-2d) [l*Bkt-1*h-1]
log (k_{rate}) = 0.816 $^{2}X^{v}$ - 11.928
n = 6, r = 0.98, s = 0.185, F = 82.2
log (k_{rate}) = 1.198 $^{3}X_{p}$ - 14.378
n = 6, r = 0.98, s = 0.195, F = 73.0

Models 63/64: N-3-chlorophenylcarbamate

Boethling (1986): K: disappearance of substrate (2d)
log (%K) = - 1.565 $^{4}X_{pc}$ + 3.768
n = 7, r = 0.99, s = 0.112, F = 167.2
log (%K) = - 2.145 $^{4}X^{v}_{pc}$ + 2.765
n = 7, r = 0.98, s = 0.129, F = 125.3

4.2 Models not related to specific chemical classes

Multiple regression analysis, discriminant analysis and cluster analysis are employed to classify large data sets. In multivariate analysis, indicator variables for functional groups and physical-chemical characteristics are applied as parameters for estimating degradability.

Model 65: Substructure model (Desai and Govind 1990)

The model, developed with substructures for 18 aliphatic and aromatic substances, is based on degradation data from a 14-day mineralization test (**Table 7**). The path-level for easily degradable substances has been specified by Urano and Kato (1986b) at a transformation rate of 0.02 mg*g^{-1}*h^{-1}. The substances were selected so as to provide a balanced substructural distribution. Desai and Govind (1990) carried out validation of the model with eleven previously untested compounds. The discrepancy between the calculated and the experimental data is given with < 20 per cent.

The calculation of degradation data on the basis of Model 65 is limited to compounds which contain the substructures specified in Table 7. A lack of factors for halogen and nitro groups, secondary and tertiary amines and branching allows application to only 179 MITI substances (23 per cent), resulting in coincident classification for 92 (51 per cent) of the compounds (**Table 8**). Application of the model to MITI degradation data leads to incorrect classification of the non-easily degradable compounds in particular: 88 (64 per cent) of the easily degradable compounds are classified correctly, while only four (10 per cent) of the non-easily degradable compounds are identified as such. Virtually all compounds containing the substituents halogen and nitro group are incorrectly classified as easily degradable, while acyclic compounds (< 29 C atoms), carbonic acids and, in particular, benzoic acids are incorrectly classified as non-easily degradable.

For acyclic compounds, permissible application of Model 65 can be interpreted as a criterion for easily degradable substances. As a result of the negative sign of all factors (positive degradation criteria) apart from the aromatic carbon compound, only easily degradable compounds can be classified with adequate reliability by means of Model 65. Factors which lead to delayed degradation are not taken into consideration. Consequently, Model 65 cannot be recommended for estimating ecological risk potential, as the persistence of substances may be significantly underestimated.

Table 7: Factors assigned to substructures (Model 65)

The degradation rate (k) of a compound is calculated according to:

$$l(k) = \Sigma\ Nj\ \alpha j, \text{ whereby j (substructure): 1-8}$$

N: number of substructures (j) in the compound
αj: factor assignment (α) for substructures (j) 1 to 8

substructure (j)	factor (α)
(1) methyl (CH_3)	-1.3667
(2) methylene (CH_2)	-0.0438
(3) hydroxy (OH)	-1.7088
(4) carbonic acid (COOH)	-1.3133
(5) ketone (CO)	-0.5073
(6) amine (NH_2)	-1.4654
(7) aromat. carbon ($_{aromat.}$C-H)	-0.5016
(8) aromat. carbon ($_{aromat.}$C)	1.0659

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Table 8: Agreement of the classification of 179 compounds tested in the MITI degradation procedure with the degradation data calculated from Model 65

The figures in parentheses indicate the respective proportions of easily degradable and non-easily degradable substances (easily degradable/non-easily degradable).

substance	MITI	correct classification	
class	n	n	%
acyclic	92 (92/0)	59 (59/0)	64 (64/0)
arom. monocycl.	50 (34/16)	25 (24/1)	50 (71/6)
arom. polycycl.	37 (11/26)	8 (5/3)	22 (45/12)
total MITI	179 (137/42)	92 (88/4)	51 (64/10)

Model 66: Substructural model (Geating 1981)

Geating (1981) developed a degradation model based on 39 substructures and 357 degradation data obtained from literature using discriminant analysis. To derive the model, substances were classified as non-degradable when 0-10 per cent degradation took place after 10d. The coincidence of calculated and experimental degradation data is specified as 84 per cent for non-degradable substances and 98 per cent for degradable substances. The calculated degradation data are categorized into degradable, non-degradable and not definitely determinable (indifferent) (**Table 9**).

On the basis of the substructural indicators, Model 66 can be applied to 752 of the 774 MITI substances, providing classification corresponding to the MITI degradation results for 461 (61 per cent) of the compounds. The calculated degradation data differ from the experimental degradation results with regard to the non-easily degradable compounds in particular: 276 (78 per cent) of the easily degradable compounds are correctly classified, while only 186 (47 per cent) of the non-easily degradable compounds are identified as such. Degradability cannot be definitely assessed for 63 compounds (**Table 10**).

Table 9: Probability of degradation (P) of a substance is calculated from Model 66 with factors assigned to the substructures

Substances are classified as persistent at a probability level of P < 0.39, degradable at a probability level of P > 0.69; P values between 0.39 and 0.69 denote inherent compounds.
sub.: substituents on rings; ch.: substructures on chains.

$P = e^{(Px1)} / (e^{(Px1)} + e^{(Px2)})$
$Px^1 = \Sigma$ substructure * x^1 + intercept
$Px^2 = \Sigma$ substructure * x^2 + intercept

substructure		factor x^1	factor x^2
1.	not C, H, N, O, S or halogen atom	2.74	-2.27
2.	branched term. NO_2 group, not on ring	0.11	3.31
3.	1 tert. C atom, not on ring	-0.03	4.27
4.	triple bond, not on ring	-0.81	7.45
5.	ethyl/ethylene group (ch.)	3.93	1.37
6.	alkyl chain with $(CH_2$ or $CH_3)_n$, n= 3-9	3.77	1.48
7.	alkyl chain, unbranched, n > 10	5.49	0.46
8.	1 O- group (ch.)	-1.64	1.33
9.	> 2 O- groups (ch.)	-1.92	3.53
10.	> 2 OH groups (ch.)	4.25	1.47
11.	1 CO group (ch.)	2.70	-0.35
12.	> 2 COOH groups (ch.)	7.46	3.62
13.	> 2 methyl/methylene groups (ch.)	0.79	3.24
14.	tert. amide (ch.)	-1.79	4.41
15.	phosphonyl (ch.)	-6.98	-0.38
16.	> 2 NH groups (sub.)	-1.98	-6.80
17.	> 2 N= or HN= groups (sub.)	-3.58	8.53
18.	1 OH group (sub.)	3.17	0.14
19.	> 2 OH groups (sub.)	1.52	-0.07
20.	1 CO group (sub.)	1.96	-2.75
21.	1 COOH group (sub.)	1.58	-0.52
22.	prim. amide (sub.)	-0.24	11.19
23.	hydroxylamine (sub.)	-8.60	7.77
24.	barbiturate	7.65	-4.99
25.	ring with 1 S	-4.82	9.06
26.	ring with 1 CO (carbonyl group)	4.17	-1.98
27.	> 1 aromat. 6-atom ring(s)	4.26	6.61
28.	> 1 5-C atom. ring(s)	4.65	9.74
29.	> 3 heteroatoms in ring	-1.43	5.92
30.	1 C/C ring link	0.62	4.01
31.	bridge indicator	0.39	-12.46
32.	2 bonded rings	-0.99	1.11
33.	benzene derivative	1.77	-2.17
34.	> 2 carbonrings	-0.23	10.25
35.	1 heterocycl. ring	6.34	3.99
36.	> 2 triple-branched C atoms	0.18	3.55
37.	halogenated aromatic	-0.71	7.75
38.	pyrimidine derivative	-7.01	4.04
39.	MW	0.02	0.03
intercept		-6.34	-9.76

Table 10: Agreement of the classification of 752 compounds tested in the MITI degradation procedure with the degradation data calculated from Model 66 for the different chemical classes

The figures in parentheses indicate the respective proportions of easily degradable and non-easily degradable substances (easily degradable/non-easily degradable).

substance class	MITI n	indifferent n	correct classification n	%
aliphatic				
acyclic	269 (196/73)	16 (9/7)	191 (162/29)	71 (83/40)
monocyclic	21 (10/11)	2 (1/1)	9 (7/2)	43 (70/18)
polycyclic	11 (2/9)	1 (1/0)	1 (1/0)	9 (50/0)
aromatic				
monocyclic	244 (87/157)	25 (4/21)	137 (73/64)	56 (84/41)
polycyclic	122 (21/101)	12 (4/8)	67 (7/61)	55 (32/60)
heterocyclic				
monocyclic	51 (30/21)	6 (4/2)	32 (22/10)	62 (73/48)
polycyclic	34 (9/25)	1 (0/1)	24 (4/20)	75 (44/80)
total MITI	752 (355/397)	63 (23/40)	461 (276/186)	61 (78/47)

Despite the 39 substructures employed, classification in agreement with the MITI degradation data is not achieved. Deviating classifications occur with branched polyalcohols, halogenated hydrocarbons and secondary and tertiary amines, which are incorrectly calculated to be easily degradable. Non-easily degradable aromatic compounds are often incorrectly classified as easily degradable, on account of a lack of parameters for secondary and tertiary amines and overestimation of the degradability of functional groups, such as nitro and sulphate groups. Virtually all polyaromatics are classified non-easily degradable.

One reason for the poor level of agreement between the calculated and the experimental degradation data may be the unequal distribution of degradable and non-degradable compounds (296 degradable/61 non-degradable) in the discriminant analysis which was carried out. On the other hand, the degradation data obtained from various publications may lead to misinterpretation of the influence of functional groups on biodegradation.

Model 67: Substructure model (Mudder 1981)

Mudder (1981) developed a substructure model for calculating the degradability of aromatics by means of multiple regression analysis, based on the transformation rates of 54 parent compounds as measured by Pitter (1976) in a five-day degradation test (20d adaptation) (**Table 11**). The path-level for degradable substances was specified by Pitter (1976) at 15 mg DOC*g^{-1}*h^{*-1}.

Application of Model 67 to 170 mono- and disubstituted aromatic compounds from the MITI data base (82 easily degradable, 88 non-easily degradable) resulted in agreement between calculated and experimental degradation data for 103 (61 per cent) compounds: 41 (50 per cent) easily degradable and 62 (70 per cent) non-easily degradable compounds were correctly classified.

Compounds containing alkyl chains (n > 8), compounds with substituents which are not considered as substructures, such as esters and amides, and compounds with hydroxy groups, which are assigned a negative factor, are all incorrectly classified as non-easily degradable.

Substructures which commonly occur in non-easily degradable compounds, such as nitriles and ether groups, are not taken into consideration in regression analysis, resulting in several incorrect classifications for non-easily degradable compounds.

Table 11: Degradability calculated from Model 67 with factors assigned to substructures

Compounds are designated as degradable at a degradation rate (B) of >15 mg DOC*g^{-1}*h^{*-1};
Position: position of the substituents 1: meta, 2: para, 3: ortho, 4: mono;
F = 13.92, r = 0.91.

$B = \Sigma_{1-13}$ (substructure * factor) + intercept

substructure	factor
(1) O	-56.09
(2) N	-27.73
(3) CH	-71.17
(4) CC1	-131.79
(5) CO	7.93
(6) CHO	16.43
(7) COOH	24.34
(8) NH_2	-89.18
(9) NO_2	-10.41
(10) CH_3	129.16
(11) OH	-29.12
(12) position	2.87
(13) MW	1.13
intercept	381.11

Models 68/69: Substructure models with topological indices (Boethling and Sabljic 1989)

Boethling and Sabljic (1989) derived models for predicting degradability from connectivity indices based on expert assessments of the expected degradative behaviour for 46 substances; no experimental data were employed. The proportion of substances classified correctly by Model 68 is given as 80.4 per cent (**Table 12**). This model was extended by the addition of correction factors for functional groups (Model 69). The level of substances classified correctly is stated as 89.1 per cent for this model (**Table 13**).

The application of Model 68 to 774 MITI degradation data resulted in correct classification of 423 (55 per cent) of the compounds: 74 per cent (273) of the easily degradable compounds, but only 36 per cent (146) of the non-easily degradable compounds were identified as such.

Acyclic compounds with amide groups, ester groups and long alkyl chains (C > 18) are incorrectly classified as non-easily degradable, while polyalcohols and secondary amines are often incorrectly classified as easily degradable. The degradability of the aromatic compounds is generally assessed as too positive, with 70 per cent of the non-easily degradable substances being incorrectly classified as easily degradable (Table 13).

Application of Model 69 to 774 MITI degradation data resulted in correct classification of 422 (55 per cent) of the compounds: 77 per cent (284) of the easily degradable compounds are correctly classified, while only 34 per cent (138) of the non-easily degradable compounds are identified as such (Table 13). The extension of Model 68 by the addition of substructural indicators did not result in an improvement in classification of the MITI degradation data. Application of Model 68 with the smaller number of parameters and equally good agreement between experimental and calculated degradation data is therefore to be preferred to Model 69.

Table 12: Coefficients of the topological and structural parameters of Models 68/69 for estimating the degradability of chemicals

Degradability (estimated as AERUD: ultimate aerobic degradation) is specified as 1: degradation within days, 2: within weeks, 3: within months, 4: > months. Calculated degradation levels of < 2.50 denote easily degradable substances, values > 2.50 denote non-easily degradable substances. $^{2}X^{v}$: 2nd order valence corrected connectivity index, $^{4}X_{pc}$: 4th order path-cluster connectivity index, n Cl: number of chlorine atoms, MW: molecular weight, Sub.: substructure indicators; Model 68: r = 0.868, s = 0.328; Model 69: r = 0.942, s = 0.219.

Model 68 AERUD 1 = 0.60 ln $^{2}X^{v}$ + 57.25 n Cl/MW + 17.56 $^{4}X_{pc}$/MW + 1.45

Model 69 AERUD 2 = 0.946 * (AERUD 1 + $Sub_{(a,b,c,d,e,f)}$ + 0.137

Sub_a: N-heterocycl. and ester or amide or anhydride	+0.128
Sub_b: Ester or amide or anhydride (not Sub_a)	-0.235
Sub_c: N-heterocycl. with O-C bond (not $Sub_{a,b}$)	+0.385
Sub_d: O-C bond (not $Sub_{a,b,c}$)	-0.147
Sub_e: lin. alkyl chain with C > 4 (not $Sub_{a,b,c,d}$)	-0.156
Sub_f: Substructure different to $Sub_{a,b,c,d,e}$	+0.241

Table 13: Agreement of the classification of 774 compounds tested in the MITI degradation procedure with degradation results calculated on the basis of a) Model 68 and b) Model 69

The figures in parenthesis specify the respective proportions of easily degradable and non-easily degradable substances (easily degradable/non-easily degradable).

	MITI	correct classification	
a) Model 68	n	n	%
aliphatic			
acyclic	287 (207/80)	190 (149/41)	66 (72/51)
monocyclic	21 (10/11)	14 (7/7)	67 (70/64)
polycyclic	11 (2/9)	8 (1/7)	73 (50/78)
aromatic			
monocyclic	244 (87/157)	118 (75/42)	48 (86/27)
polycyclic	122 (21/101)	45 (11/34)	37 (52/34)
heterocyclic			
monocyclic	57 (32/23)	31 (25/6)	54 (78/26)
polycyclic	34 (9/25)	17 (5/9)	50 (55/36)
total MITI	774 (368/406)	423 (273/146)	55 (74/36)
b) Model 69			
aliphatic			
acyclic	287 (207/80)	216 (174/42)	75 (84/53)
monocyclic	21 (10/11)	13 (6/7)	62 (60/64)
polycyclic	11 (2/9)	8 (0/8)	73 (0/89)
aromatic			
monocyclic	244 (87/157)	115 (74/41)	47 (85/26)
polycyclic	122 (21/101)	28 (11/17)	23 (52/17)
heterocyclic			
monocyclic	57 (32/23)	27 (16/11)	49 (50/48)
polycyclic	34 (9/25)	15 (3/12)	44 (33/48)
total MITI	774 (368/406)	422 (284/138)	55 (77/34)

Models 70/71: Substructure models (Babeu and Vaishnav 1987)

Models 70/71 were developed by means of regression analysis with the calculated theoretical oxygen demand (ThOD) as a parameter, based on 45 BOD_5 degradation data (**Table 14**). The ThOD is calculated from the maximum oxidation of the atoms of a molecule, and can be regarded as a total parameter for C, H, Cl, N, O, P and S atoms. Babeu and Vaishnav (1987) carried out validation with 43 substances: Model 70 provided results which agreed to a level of 86 per cent, while the level for Model 71 was 88 per cent.

The application of Model 70 to 774 MITI degradation data resulted in correct classification of 508 (66 per cent) of the compounds: 83 per cent (304) of the easily degradable compounds were correctly classified easily degradable; 50 per cent (204) of the non-easily degradable compounds were identified as such (**Table 15**).

Application of Model 71 to 774 MITI degradation data resulted in correct classification of 506 (65 per cent) of the compounds: 75 per cent (275) of the easily degradable compounds were correctly classified easily degradable, 60 per cent (242) of the non-easily degradable compounds were identified as such (Table 15). Deviating classifications occur with easily degradable acyclic compounds, in particular short-chained alcohols (C_1-C_3), amines and carbonic acids. Polyalcohols and amines are incorrectly classified as easily degradable. From the non-easily degradable aromatic compounds, only the polyhalogenated compounds are identified as such.

Table 14: Models 70/71 for calculating the degradability of chemicals

ThOD: theoretical oxygen demand; Model 70: r = 0.84; Model 71: r = 0.86.

Model 70 $\log (BOD) = 0.813 (\log ThOD) - 0.183$

Model 71 $\log (BOD) = 1.560 (\log ThOD) - 0.532 (\log ThOD)^2 - 0.391$

4.3 Models involving substructure evaluation

These models do not result in quantitative estimates. Qualitative estimation is carried out, on the basis of which only an order of degradability is established.

Model 72: Substructure model (HDI 1990)

The biodegradation model is based on a discriminant analysis carried out with 31 substructure indicators and topological indices. The original 283 degradation data, which were reduced to 248 compounds (117 easily degradable, 166 non-easily degradable) for the purposes of the discriminant analysis, were established at various laboratories and in various test procedures (Howard et al. 1987). The parameters employed for the purpose of discrimination are listed in order of declining importance in **Table 16**. As the discriminating factors are not specified, no quantitative validation is possible.

The model was assessed by examining the substructure distribution with regard to easily degradable and non-easily degradable MITI data. Agreement with the MITI degradation data applies to the substructures associated with degradable compounds: (1) saturated aliphatic alcohols, (2) esters, (3) aliphatic carbonic acids, (6) aliphatic ketones, (8) non-cyclic aliphatic hydrocarbons, (9) aliphatic aldehydes and (20) primary aliphatic amines. These chemical classes are all easily degradable in the MITI degradation test. Substructures (4) amides without C-C double bonds, (10) benzene derivatives with OH and NH_2 groups, (11) SO_2, SO_3, SO_4 and (13) heteroaromatic carbonic acids with more than one nitrogen atom, also assigned to degradable compounds, are equally found in easily degradable and non-easily degradable MITI compounds.

Table 15: Agreement between the classification of 774 MITI data and the degradation data calculated on the basis of a) Model 70 and b) Model 71

The figures in parentheses specify the respective proportions of easily degradable and non-easily degradable substances (easily degradable/non-easily degradable).

a) Model 68

	MITI	correct classification	
	n	n	%
aliphatic			
acyclic	287 (207/80)	227 (177/50)	79 (86/63)
monocyclic	21 (10/11)	15 (10/5)	71 (100/45)
polycyclic	11 (2/9)	7 (2/5)	73 (100/65)
aromatic			
monocyclic	244 (87/157)	168 (67/101)	69 (77/64)
polycyclic	122 (21/101)	49 (21/28)	40 (100/28)
heterocyclic			
monocyclic	57 (32/23)	31 (22/9)	56 (69/39)
polycyclic	34 (9/25)	11 (5/6)	32 (56/24)
total MITI	774 (368/406)	508 (304/204)	66 (83/50)

b) Model 69

	MITI	correct classification	
	n	n	%
aliphatic			
acyclic	287 (207/80)	217 (166/51)	76 (80/64)
monocyclic	21 (10/11)	15 (10/5)	71 (100/45)
polycyclic	11 (2/9)	7 (2/5)	73 (100/65)
aromatic			
monocyclic	244 (87/157)	173 (55/118)	71 (63/75)
polycyclic	122 (21/101)	47 (21/36)	39 (100/36)
heterocyclic			
monocyclic	57 (32/23)	32 (16/16)	58 (50/70)
polycyclic	34 (9/25)	16 (5/11)	47 (55/44)
total MITI	774 (368/406)	506 (275/242)	65 (75/60)

Table 16: Substructures and parameters of Model 72	
A:	**Criteria for degradable substances**
1.	saturated aliphatic alcohol, no tertiary C atoms; in the case of an ether, 3 CH_2 fragments must follow
2.	C(O)-O-R, with R = C_1-C_4
3.	aliphatic carbonic acid, not 9 CH_2 groups
4.	amide, no unsaturated C=C bonds
5.	mono- or poly-OH substituted benzene derivative
6.	aliphatic ketone
7.	benzoic acid with NH_2 or OH substituents
8.	non-cyclic aliphatic hydrocarbon
9.	aliphatic aldehyde
10.	benzene derivative with no other substituents than NH_2 or OH
11.	SO_2, SO_3, SO_4
12.	charge on aromatic C with carbocyclic ring, not PAH or benzene
13.	heteroaromatic carbonic acid with > 1 N, with 6-atom aromatic ring
14.	connectivity index, ^5X
15.	2 electron releasing groups (position: 1, 4), no electron withdrawing groups
16.	specific Kappa index, 14th order
17.	aryl methyl
18.	2-ethylhexyl substituents, bonded to heteroatom or acyl
19.	simple Kappa index, 7th order
20.	primary aliphatic amine
21.	charge on nitroaromatic fragment
22.	organic acid
B:	**Criteria for non-degradable substances**
23.	charge on secondary aliphatic amine
24.	isobutyl group
25.	tertiary amine with substituents > methyl
26.	simple Kappa index, 5th order
27.	3 electron releasing groups (1,2,4-substituted), no electron withdrawing groups
28.	CH_3, CH_2 on benzene ring
29.	Cl on 6-ring, in case of heteroatom N only
30.	connectivity index, ^6X
31.	charge on aromatic amine

Only six substructure parameters are employed to indicate non-degradable compounds. Agreement with the MITI degradation data applies to two substructures: (25) tertiary amines and (29) halogens on the aromatic ring. Substructures (22) organic acids, (24) isobutyl group, (15) electron withdrawing and (27) electron releasing substituents prove indifferent. The substructure parameters for non-easily degradable substances are not adequate for classifying the majority of non-easily degradable MITI data.

The connectivity indices and Kappa indices, which are also indicated negatively, were not considered, however. With these high-order parameters only highly branched substances are covered. The method of calculation for the charge parameters in the model is not specified. The application of the model is not possible due to the lack of factors for the substructure variables.

Model 73: Qualitative substructure model (Niemi et al. 1987)

Using degradation data for 261 chemicals, Niemi et al. (1987) developed a model for estimating biodegradation by weighting various functional groups and substructures (**Table 17**). The model is based on BOD_5 degradation data. The probability of correctly classifying the substances employed in development of the model is stated as 92 per cent.

Table 17: Criteria employed in Model 73 for calculating degradative behaviour. Criteria for degradable substances are taken into consideration only when no criterion for non-degradable substances applies previously.

	A: Criteria for non-degradable substances	
1.	> 1 tertiary terminal butyl group	>15 d
2.	nitrile group on a chain with > 8 atoms	>100 d
3.	2 terminal C atoms with double bonding to unbranched substance	>100 d
4.	highly branched substance	>100 d
5.	> 1 halogen atom on branched substance	>5 d
6.	2 terminal diamino groups on acyclic substance	>35 d
7.	2 terminal isopropyl groups on acyclic substance	>35 d
8.	> 2 halogen atoms on unbranched acyclic substance	>15 d
9.	> 1 isopropyl or dimethylamine substituent on cyclic substance without further degradable substituents	>25 d
10.	> 2 rings (exception - no. 28 degradable)	>20 d
11.	aliphatic ring without branching	>40 d
12.	aliphatic condensed ring without branching	>35 d
13.	hydroxy groups on aromatic ring	>15 d
14.	benzene derivative with > 2 substituents (not OH) and P_{OW} > 2.18	>100 d
15.	> 1 amino branch on a ring containing nitrogen	>100 d
16.	epoxide	>20 d
	B: Criteria for degradable substances	
17.	aldehyde	2-11 d
18.	hydrocarbon	3-17 d
19.	alcohol, ester, amine	2-16 d
20.	acid	3-12 d
21.	amino acid	2-5 d
22.	sulphonic acid	2-17 d
23.	1 halogen atom on unbranched substance	>12 d
24.	1 nitrile group on unbranched substance	>10 d
25.	cyclic substance with only C, H, N, O atoms	2-15 d
26.	benzene derivative with various substituents and P_{OW} < 2.18	2-16 d
27.	biphenyl or polyaromatic with < hydroxy groups	<15 d
28.	2 aromatic rings (e.g. naphthalene or aminonaphthalene)	<15 d

The model provides 16 criteria for classifying non-degradable substances **(A)** and 12 criteria for classifying degradable substances **(B)** Application of Model 72 to 774 chemicals revealed that no classification was possible for 18 (2 per cent) chemicals, due to the lack of indicator variables for the respective substructures. The model provided classifications in agreement with the MITI data for 576 (76 per cent) compounds: 83 per cent of the compounds which were easily degradable in the MITI test were classified degradable and 70 per cent of the non-easily degradable compounds were classified non-degradable (**Table 18**).

When this model is applied, virtually all polycyclic compounds are classified non-degradable. Incorrect classifications of the compounds which were non-easily degradable in the MITI test were caused by the lack of factors for secondary amines, tertiary amines and ethers. The substructures employed for the classification of heterocyclic compounds and monocyclic aromatics are not adequate.

Table 18: Agreement between the calculated degradation data and the MITI degradation data

The figures in parentheses specify the respective proportions of easily degradable and non-easily degradable substances (easily degradable/non-easily degradable).

	MITI	correct classification	
	n	n	%
aliphatic			
acyclic	269 (195/74)	231 (189/42)	86 (97/57)
monocyclic	21 (10/11)	14 (7/7)	67 (70/64)
polycyclic	11 (2/9)	9 (0/9)	82 (0/100)
aromatic			
monocyclic	244 (87/157)	162 (71/91)	66 (82/58)
polycyclic	122 (21/101)	99 (4/95)	81 (19/94)
heterocyclic			
monocyclic	57 (32/23)	36 (26/10)	65 (81/43)
polycyclic	34 (9/25)	25 (0/25)	74 (0/100)
Total MITI	756 (368/406)	576 (297/279)	76 (83/70)

5. Substructure models for specific chemical classes

The few SAR models succesfully validated resulted in the development of new SAR models. Substructure models for estimating biodegradation were developed by regression and discriminant analysis for acyclic compounds and monocyclic aromatic substances (**Table 19**).

For the purpose of developing the models, training sets and validation sets were selected first, so models derived from the training sets can subsequently be validated using the validation sets.

The training sets were selected so as to ensure that broad ranges of the parameters considered relevant, distribution coefficient (P_{OW}) and molar refraction, were represented by the compounds. For statistical reasons, only substructures contained in at least five compounds of the training set were taken into consideration. For the acyclic compounds, an initial training set of 47 compounds and an extended training set of 60 compounds accounting for further substructures were selected. For the aromatic compounds, a training set of 65 substances was selected. Correlation coefficients are not stated, as the proportion of compounds classified correctly in the validation set provides most comprehensive information on the reliability of the predictions (1/0 degradation criterion). Table 19 summarizes the applicability of the developed Models 74-78, together with the respective proportions of correctly classified compounds and the MITI data employed.

Model 74: Substructure model for acyclic compounds

Model 74 was derived by means of regression analysis, using five indicators for terminal substructures with a training set of 47 compounds (24 easily degradable, 23 non-easily degradable) (**Table 20**).

The negative factors for the substructures indicate a decrease in biodegradability as the level of branching increases. Model 74 classifies 85 per cent of the compounds correctly: 92 per cent of the easily degradable and 79 per cent of the non-easily degradable compounds are identified as such. Classification of non-easily degradable substances as easily degradable occurs with phosphoric acids and tertiary amines in particular.

Validation of the model with 240 compounds (183 easily degradable, 57 non-easily degradable) results in the correct classification of 89 per cent of the compounds. The proportion of compounds correctly classified as easily degradable is 97 per cent, while only 61 per cent of the non-easily degradable compounds are identified as such. The exclusion of phosphoric acids identified during the model development as "outliers", together with hydrazines and dithioethers, results in a level of agreement of 81 per cent between experimental and calculated values for the non-easily degradable compounds, and a subsequent overall agreement level of 96 per cent.

Further incorrect classifications as easily degradable occur for functional groups with non-terminal heteroatoms, such as ethers and esters, and for triple bonds. When compounds containing phosphoric acids, tertiary amines and hydrazines are excluded, the model can be employed to estimate the degradability of acyclic compounds. Application to compounds containing only the substructures employed in the regression analysis results in a high level of reliability (97 per cent) in estimating biodegradability.

Table 19: Summary of Models 74-78

Proportion of correctly classified compounds: (+): easily degradable, (-): non-easily degradable; Ts: training set; Vs: validation set; Ts1: 47 acyclic compounds (+:24,-:23); Ts2: 65 acyclic compounds (+:34,-:31); Ts3: 151 acyclic compounds (+:61,-:90); Ts4: 60 monocyclic disubst. aromatic compounds (+:30,-:30); Vs1: 240 acyclic compounds (+:183,-:57); Vs2: 225 acyclic compounds (+:182,-:43); Vs3: 120 acyclic compounds (+:103,-:17); Vs4: 222 acyclic compounds (+:173, -:49); Vs 5: 217 acyclic compounds (+:173,-:44); Vs6: 142 acyclic compounds (+:115,-:27); Vs7: 57 disubst. monocyclic aromatic compounds (+:21,-:36); Vs8: 46 disubst. monocyclic aromatic compounds (+:19,-:27); Vs9: 24 monosubst. monocyclic aromatic compounds (+:13,-:11); Vs10: 69 polysubst. monocyclic aromatic compounds (+:3,-:66); Vs11: 59 disubst. monocyclic aromatic compounds (+:22,-:37); Vs12: 30 monosubst. monocyclic aromatic compounds (+:16,-:14); R_1: H or unbranched alkyl chain; R_2: O or N or S; R_3: chain with terminal heteroatoms, or branched alkyl chain.

Model	**development**		**validation**		
	Ts	**%**	**Vs**	**%**	**compounds of Vs**
acyclic compounds:					
74	Ts1	85	Vs1	89 (97/61)	all acycl. MITI data
			Vs2	96 (97/81)	not: phosphoric acids, tert. amine, N-N, S-S
			Vs3	97 (96/100)	only: OH,CO,hal,CH_3,C-NH_2
75	Ts2	92	Vs4	91 (95/78)	all acycl. MITI data
			Vs5	93 (95/86)	not: S-S or N-N
			Vs6	96 (96/100)	only: OH,CO,hal,CH_3,-CNH_2 phosphoric acids, tert. amine
76	Ts3	98			see Table 22
monocyclic aromatic compounds:					
77	Ts4	88	Vs7	75 (90/66)	all disubst. MITI data
			Vs8	87 (89/84)	only: OH,NO_2,NH_2,COO(R_1), SO_2(R_2),amide,CO,hal,CH_2(R_1)
			Vs9	74 (75/71)	monosubst.
			Vs10	72 (30/74)	polysubst.
78	Ts4	85	Vs7	84 (87/83)	all disubst. MITI data
			Vs11	92 (91/92)	only: OH,NO_2,NH_3,COO(R_1), R_3,SO_2(R_2),amide,CO,hal, CH_2(R_1)
			Vs12	93 (87/100)	monosubst.
			Vs10	83 (33/85)	polysubst.

Table 20: Model 74 for estimating the degradative behaviour of acyclic compounds based on five terminal substructures

B: biodegradation factor; B > 0: easily degradable substances; B < 0: non-easily degradable substances.

$B = \Sigma_{1-5}$ substructure * factor + intercept

substructure	factor
(1) CO	+0.07
(2) CH_2-NH_2	+0.14
(3) CH_3	-0.11
(4) OH	-0.13
(5) hal	-0.20
intercept	+0.39

Model 75: Substructure model for acyclic compounds

Model 75 represents a modification of Model 74. Using an extended training set of 65 compounds (34 easily degradable, 31 non-easily degradable), Model 75 was developed by means of a discriminant analysis with five indicators for terminal substructures and two factors to account for phosphoric acids and tertiary amines (**Table 21**). The proportion of correctly classified compounds is 92 per cent for the training set. Model 75 can be applied as a supplement to Model 74 when primary amines, phosphoric acids and tertiary amines are involved.

Table 21: Model 75 for estimating the degradability of acyclic compounds based on seven substructures

B: biodegradation factor; B > 0: easily degradable substances; B < 0: non-easily degradable substances; MV: mean value; SD: standard deviation.

$B = \Sigma_{1-7}$ standardized substructure * factor + intercept
standardardized substructure: (substr. - MV of substr.)/SD

substructure	factor	MV	SD
(1) CH_2-NH_2	+0.960	0.092	0.341
(2) CH_3	+0.004	1.431	1.571
(3) CO	+0.001	0.431	0.684
(4) OH	-0.002	0.583	0.967
(5) hal	-0.008	0.831	1.842
(6) phosphoric acid	-0.089	0.062	0.242
(7) tert. amine	-0.212	0.108	0.312
intercept	+0.164		

Validation of Model 75 with 222 compounds (173 easily degradable, 49 non-easily degradable) results in correct classification of 91 per cent of the acyclic substances: 95 per cent of the easily degradable and 78 per cent of the non-easily degradable compounds are identified as such. Incorrect classification of non-easily degradable substances as easily degradable substances occurs for non-terminal heteroatoms, for example ethers, dithioethers and hydrazines, and with triple bonds. Application of Model 75 is possible when compounds containing these functional groups are excluded. Application to compounds which contain only the substructures taken into consideration in the discriminant analysis results in a high level of reliability (96 per cent) in estimating biodegradability.

Model 76: Substructure model for acyclic compounds

Model 76 was developed as a supplement to Models 74 and 75 to recognize substructures affecting degradability in acyclic compounds. The substructures of acyclic compounds were analysed by the substructure program SSD (ADAPT 1989). Fragments which occur more frequently in easily degradable than in non-easily degradable substances were identified. Fragments represented at an equally high level in class 1 (easily degradable substances) and class 2 (non-easily degradable substances) were not taken into consideration, as it may be assumed that these do not have any significant effect on the degradability. On the basis of this analysis, substructures were divided into degradation-relevant factors (**Table 22**). The substructure indicators specified in Niemi et al. (1987) and Desai and Govind (1990) were taken into consideration during development of the model. Out of 287 MITI data for acyclic compounds, 151 can be classified with ten negative degradation factors and two positive degradation factors. One hundred per cent of the compounds containing only the specified substructures are correctly classified easily degradable, while 96 per cent of the defined compounds are correctly classified non-easily degradable.

Model 77: Substructure model for monocyclic aromatic compounds

Model 77 was developed with a training set of 60 monocyclic disubstituted aromatic compounds (30 easily degradable, 30 non-easily degradable) and eight substructures (**Table 23**). The level of correctly classified compounds of the training set is 88 per cent.

Validation with 57 compounds (21 easily degradable, 36 non-easily degradable) resulted in correct classification of 84 per cent of the compounds: 90 per cent of the easily degradable compounds and 66 per cent of the non-easily degradable compounds were identified as such. Incorrect classification of non-easily degradable substances as easily degradable occurred for two benzene sulphonic acids and two nitrobenzene derivatives. The majority of incorrect classifications concerns substances for which only one of the two substituents is accounted for by the model.

With regard to compounds containing the substituents methoxy, hydroxy, carboxy, halogen, nitro group, sulphonic acid derivative and amide group, 89 per cent of the easily degradable and 84 per cent of the non-easily degradable compounds are correctly classified. Model 77 can be applied for estimating the biodegradability of disubstituted monocyclic aromatic compounds containing these substituents. The application of Model 77 for monosubstituted and polysubstituted compounds is not recommended: only 74 per cent of the monosubstituted and 72 per cent of the polysubstituted substances are classified correctly.

Table 22: Criteria for easily degradable and non-easily degradable acyclic compounds of Model 76

The figures in parentheses refer to incorrect classifications.

A: Criteria for non-easily degradable compounds	
substructures	number
(1) > 1 halogen atom	37 (2)
(2) tert. butyl group, tert. C-atom	17
(3) tert. amine with > 2 CH_2 fragments (non-amide)	9
(4) atoms other than C, H, N, O, P, S, halogen	3
(5) 2 terminal isopropyl groups (Niemi et al. 1987)	2
(6) phosphoric acid, phosphite and thiophosphoric acid	14 (1)
(7) azo group	2
(8) dithioether	1
(9) hydrazine	4
(10) C-C triple bond	1
B: Criteria for easily degradable compounds	
(11) substance with only CH_3, CH_2, OH, CO, COOH, NH_2 groups, not tert. or quart. C atom (Desai and Govind 1990)	59
(12) linear aliphatic sulphonic acid	2

Table 23: Substructure indicators of Model 77 for estimating degradability of monocyclic aromatic compounds

B: biodegradability factor; B > 0: easily degradable substances; B < 0: non-easily degradable substances; R_1: H or alkyl; R_2: O, N or S.

$B = \Sigma_{1\text{-}8}$ substructure * factor + intercept

substructure	factor
(1) aryl $COO(R_1)$	+0.22
(2) aryl OH	+0.15
(3) aryl $CH_3(R_1)$	+0.14
(4) aryl amide	+0.03
(5) aryl NH_2	-0.19
(6) aryl NO_2	-0.38
(7) aryl hal	-0.32
(8) aryl $SO_2(R_2)$	-0.16
intercept	+0.08

Model 78: Substructure model for monocyclic aromatic compounds

Model 78 represents a modification of Model 77 based on the same training set. The introduction of an additional parameter allows the model to be applied to monocylic aromatics which, in addition to the substituents specified in Model 77, may also contain functional groups such as secondary and tertiary amines, branched alkyl chains and ethers (**Table 24**). Correct classification of 85 per cent of the compounds was attained during development of the model.

Validation with 57 compounds (21 easily degradable, 36 non-easily degradable) resulted in correct classification of 87 per cent of the easily degradable and 83 per cent of the non-easily degradable compounds. Application for compounds which contain only the substructures employed in the regression analysis results in 92 per cent correct classification.

Application of the model to monosubstituted monocyclic aromatic compounds is possible. Validation did not enable the degradative behaviour to be estimated for 14 compounds. Correct classification was attained for 14 (87 per cent) easily degradable and 14 (100 per cent) non-easily degradable compounds.

Application of the model to polysubstituted monocyclic aromatic compounds (substituents > 2) is possible. Validation with only five easily degradable and 63 non-easily degradable aromatics resulted in the correct classification of 59 compounds (87 per cent): 60 per cent of the easily degradable and 89 per cent of the non-easily degradable compounds were classified as such. Classification of easily degradable substances as non-easily degradable occurred with two polyhalogenated aromatics. The more problematic classification of non-easily degradable substances as easily degradable concerns methylated compounds. To apply the model to polysubstituted aromatics, a correction factor for methyl groups can be introduced.

Table 24: Substructure indicators of Model 78 for estimating degradability of monocyclic aromatic compounds

B: Biodegradation factor; B > 0: easily degradable substances, B < 0: non-easily degradable substances; R_1: H or unbranched alkyl chain; R_2: O or N or S; aryl (R_3): chain with non-terminal heteroatoms, or branched alkyl chain.

$B = \Sigma_{1\text{-}9}$ substructure * factor + intercept

substructure	factor
(1) aryl COO(R_1)	+0.090
(2) aryl OH	+0.003
(3) aryl CH_2(R_1)	+0.003
(4) aryl amide	-0.052
(5) aryl NH_2	-0.338
(6) aryl NO_2	-0.551
(7) aryl hal	-0.480
(8) aryl SO_2(R_2)	-0.320
(9) aryl (R_2)	-0.500
intercept	+0.380

6. Applicability of the models

The application of SAR models published to date has revealed only a limited suitability for predicting the MITI degradation data. The reasons for misclassification by many models are the inconsistent test data and the selection of homologous compounds, impeding the application to variant structures.

MITI data were employed in all cases for assessing the applicability of the models for estimating biodegradability, even when the degradation data used in developing the models were not directly comparable. In validating the models, the specified path-levels were therefore regarded only as reference. Classifications were considered adequate when the MITI data could be discriminated into easily degradable and non-easily degradable substances for any arbitrary path-level. Correct classification of less than 75 per cent for the MITI data was judged inadequate for use of these models to estimate the degradability of chemicals. Only those SAR models for which a level of agreement between calculated and experimental data of > 75 per cent was found are regarded sufficiently valid for predictions. Many of the models could not be validated with the MITI data, as they were developed for chemical classes the compounds of which are all easily degradable or all non-easily degradable in the MITI degradation test, or they have been developed for chemical classes for which no MITI data were available.

6.1 Applicability of models for specific chemical classes

The applicability of 64 SAR models for estimating the degradability of specific chemical classes was examined with MITI degradation data. Only eight of the 35 models (23 per cent) which allowed for testing with the MITI data could be validated and resulted in coincident classification of the MITI data (**Figure 4**). **Table 25** provides a summary of the agreement between calculated and experimental degradation data. The models were developed with four to eight homologous compounds and were suitable for application to corresponding substances only, due to their specificity.

Classifications of the MITI degradation data are attained only at path-levels which deviate, in some cases substantially, from the specified levels and which vary with respect to the model employed (**Table 26**). Of 35 models examined with MITI data, 27 (77 per cent) could not be validated as they do not lead to coincident classification of the MITI data. Of 24 models developed with electronic parameters, only four models based on substituent constants resulted in coincident classification of the MITI data. The majority of models for which the calculated and experimental data do not agree are SARs which employ quantum chemical parameters. The validation status of the models based on these parameters is uncertain, due to the different descriptor values resulting from different quantum chemical methods.

The poor level of agreement between calculated and experimental results may be due in part to inadequate documentation of the restrictions regarding application of the models and a lack of information on the compounds employed in development of the models. It is possible that the models categorised under (B) may be applicable, if appropriate restrictions are considered for homologous series.

Figure 4: Comparison of the classification of MITI degradation data by Models 1-64 for specific chemical classes, with respect to the parameters employed

(A) the model was subjected to validation and classifies MITI data (agreement > 75 per cent); (B) the model was subjected to validation and does not classify MITI data coincidently (agreement < 75 per cent); (C) the model was not subjected to validation, as all compounds are easily degradable or non-easily degradable in the MITI test; (D) the model could not be validated, as no MITI data are available.

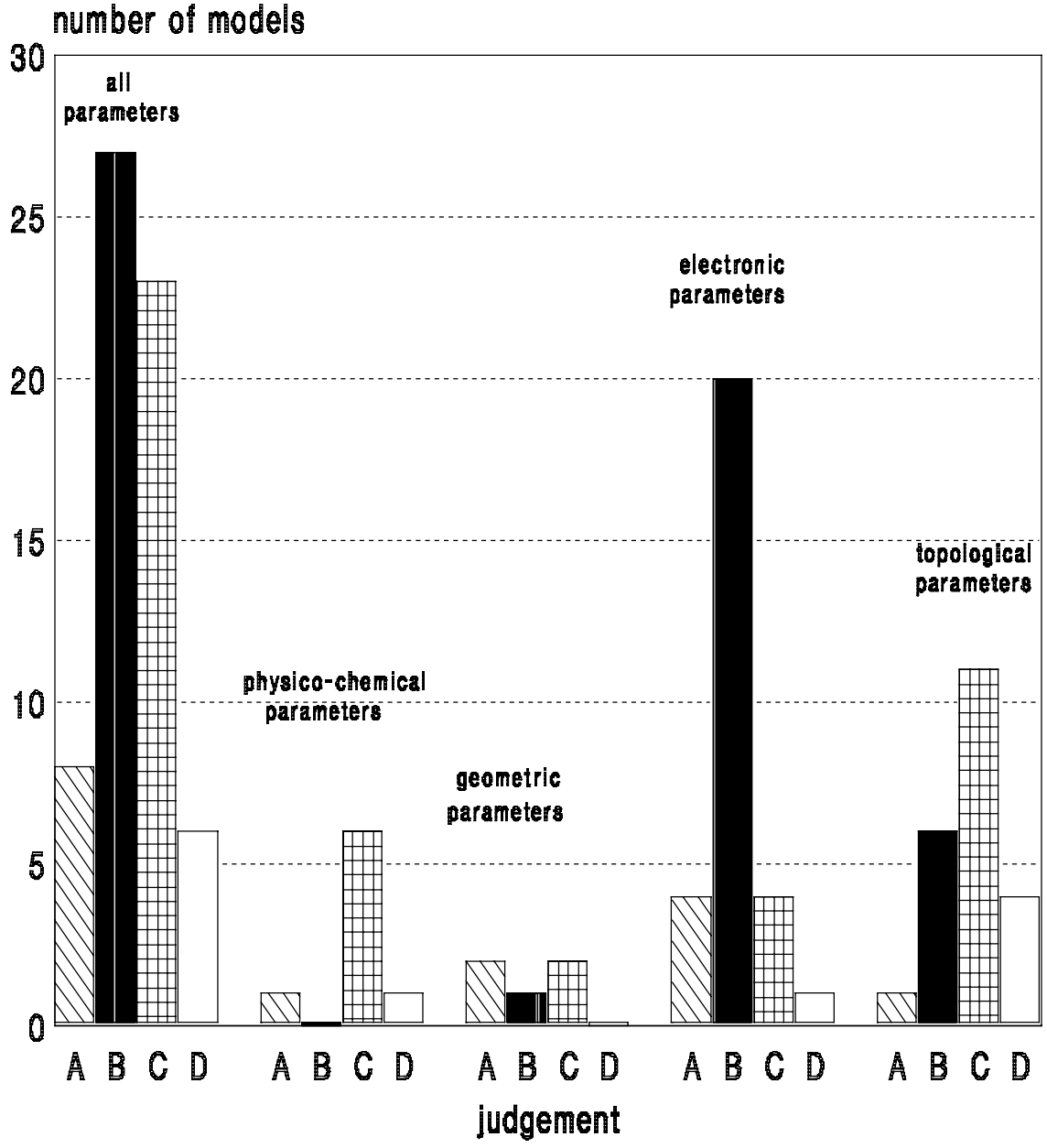


Table 25: Criteria for the development of models for specific chemical classes and their application to MITI data

Degradation data: COD [mg*g^{-1}*h^{-1}]: chemical O_2 demand; spec. [l*10-12*Bkt^{-1}*h^{-1}]: transformation rate of substrate; References: 1) Vaishnav et al. 1987; 2) Paris et al. 1983; 3) Pitter 1985.

chemical class	development			validation with MITI data		
	n	desc.	degra-dation	n	classif. correct	ref.
1 alicycl. alcohols	4	P_{ow}	COD	5	100%	1
9 phenols (disubst.)	8	Y_{vdw}	spec.	14	100%	2
14 phenols (disubst.)	7	σ	COD	14	80%	3
15 phenols (orthosubst.)	5	σ_o	COD	6	83%	3
16 phenols (metasubst.)	4	σ_m	COD	5	80%	3
17 anilines (parasubst.)	5	σ_p	COD	4	80%	3
43 alicycl. (monosubst.)	6	$^oX^v$	COD	4	100%	1

Table 26: Application of the validated SAR models (Models 1, 9/10, 14, 15, 16, 17 and 43) to MITI data

The path-level for COD models is specified in Pitter (1976) at 15 mgCOD/g*h.
B: biodegradation factor; P_{ow}: partition coefficient; Y_{vdw}: van der Waals radius;
σ: Hammett substituent constant; ^oX: connectivity index.

model	path-level for classification of MITI data
1 log (B) = -0.51 log P_{ow} +2.53	easily degradable at B > 15 [mgCOD*g^{-1}*h^{-1}]
9 log (B) = -1.36 Y_{vdw} -9.3	easily degradable at B > 2.2 [l*10^{-12}*Bkt^{-1}*h^{-1}]
14 log (B) = -0.32 σ - 1.43	easily degradable at B > 21 [mgCOD*g^{-1}*h^{-1}]
15 log (B) = -0.43 σ_o + 1.70	easily degradable at B > 30 [mgCOD*g^{-1}*h^{-1}]
16 log (B) = -0.62 σ_m - 1.72	easily degradable at B > 32 [mgCOD*g^{-1}*h^{-1}]
17 log (B) = -0.78 σ_p - 1.04	easily degradable at B > 14.5 [mgCOD*g^{-1}*h^{-1}]
43 log (B) = +0.29 $^oX^v$ + 3.22	easily degradable at B > 8.5 [mgCOD*g^{-1}*h^{-1}]

Restrictions for the models:

Model 9: disubst. phenols with the substituents: OH, CH_3, OCH_3, Br, Cl
Model 14: disubst. phenols with the substituents: OH, COOH, CH_3, Cl, SO_3
Model 15: orthosubst. phenols with the substituents: OH, CH_3, NO_2, Cl
Model 16: metasubst. phenols with the substituents: OH, COOH, CH_3, Cl
Model 17: parasubst. anilines with the substituents: CH_3, CH_2, NO_2, Cl

Twenty-three models were developed for chemical classes of which the compounds are all easily degradable or all non-easily degradable in the MITI degradation test. These models were taken into consideration for the purpose of classifying chemicals into easily degradable and non-easily degradable compounds. The following compounds were established as easily degradable: linear alcohols, linear ketones, monocarbonic acids, aliphatic sulphonic acids and phthalates. The compounds established as non-easily degradable were halogenated aliphatic hydrocarbons and metasubstituted anilines. In spite of the comprehensive data base, it was not possible to carry out validation of all models due to a lack of degradation data. The respective models cannot be recommended for predictive purposes.

Monoparametric SAR models can be applied successfully only to estimate the degradability of homologous substances. However, the number of validated SAR models for specific chemical classes is too low to carry out predictions solely on this basis. SARs for specific chemical classes are applicable to estimate the degradability of only 3 per cent of the MITI data. None of these models is suitable for estimating the degradability of acyclic MITI compounds, as many of the models have been developed with compounds which are all easily degradable in the MITI test. Prediction of degradability by these models is feasible only for some cyclic compounds. Within a hierarchic model, it is possible to employ Models 1, 9/10, 14, 15, 16, 17 and 43 to estimate the degradability of cyclic compounds.

6.2 Applicability of models not related to specific chemical classes

The level of agreement between the degradation data calculated on the basis of the models not related to specific classes 65-72 and the MITI data is mostly < 70 per cent, with only Model 73 leading to correct classification of 76 per cent of the compounds (**Table 27**).

Compounds incorrectly classified as easily degradable can represent a high potential risk to the environment. In virtually all models the proportion of compounds correctly classified as non-easily degradable is very low in comparison with the proportion of compounds correctly classified as easily degradable, i.e. the models lead to a large number of compounds which are incorrectly classified as easily degradable. For this reason, application of Models 65, 66, 68 and 69 is not recommended (**Figure 5**).

Application of the models resulted in varying classifications, according to the chemical classes concerned. None of the models yielded satisfactory classification of heterocyclic and monocyclic aromatics; only for acyclic and polycyclic compounds is > 75 per cent of agreement between calculated and experimental data attained with some models (**Table 28**).

Classification in complete agreement with the MITI degradation data is not achieved with any of the models. Models 70/71 and 73 appear to have only limited suitability for approximation of the degradability of acyclic compounds regarding the frequent misclassification of compounds as easily degradable. The other models (65-69, 72) do not correctly predict the MITI degradation. In contrast to the application by Desai and Govind (1990), the substructures identified for Model 65 can be employed to identify easily degradable acyclic compounds when only these substructures occur.

Table 27: Validation of Models 66-73

Proportion of compounds classified in accordance with the MITI degradation data (easily degradable/non-easily degradable): *[1] : for mono- and disubstituted monocyclic aromatics only; *[2]: > 2.5 means degradation between weeks and months.

Model			development		validation	reference
	degrad. data	path-level	desc. n	MITI data n	correct classif. %	
65	BOD_{14}	>60%	8	179	51 (64/10)	Desai 1990
66	heterogen.	>10%	39	752	61 (78/47)	Geating 1981
67*[1]	DOC_5	>15mg	13	170	61 (50/70)	Mudder 1981
68	estimated	>2.5 *[2]	4	774	55 (74/36)	Boethling 1989
69	estimated	>2.5 *[2]	9	774	55 (77/34)	Boethling 1989
70	BOD_5	>16%	1	774	66 (83/50)	Babeu 1987
71	BOD_5	>16%	2	774	66 (75/60)	Babeu 1987
72	heterogen.	-	31	no validation possible		HDI 1990
73	BOD_5	>16%	756	28	76 (83/70)	Niemi 1987

Table 28: Summary of SAR models which lead to > 75 per cent correct classification within chemical classes (easily degradable/non-easily degradable)

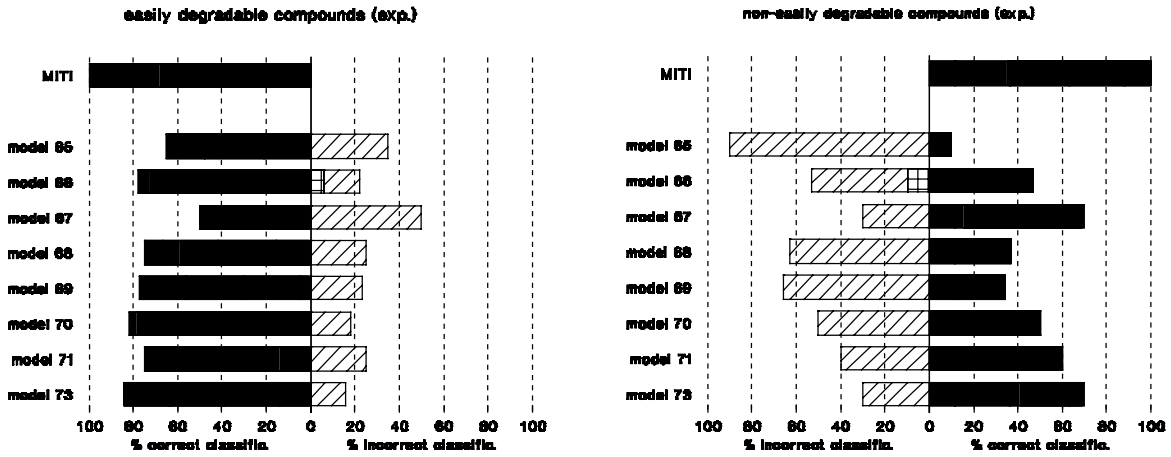
Evaluation of the models. B1: limited suitability (agreement < 80 per cent and non-symmetric distribution of easily degradable/non-easily degradable); B2: not suitable (highly non-symmetric distribution of easily degradable/non-easily degradable); B3: not suitable (insufficient number of compounds).

substance class	Model	evaluation	correct classification %		reference
aliphatic					
acyclic	73	B1	86 (97/57)	231 (189/42)	Niemi et al. 1987
acyclic	70	B1	79 (86/63)	227 (177/50)	Babeu and Vaishnav 1987
polycyclic	73	B2, B3	82 (0/100)	9 (0/9)	Niemi et al. 1987
aromatic					
polycyclic	73	B2	80 (19/94)	99 (4/95)	Niemi et al. 1987

Figure 5: Classification of the MITI degradation data according to Models 65-73

The proportions of correct and incorrect classifications are compared for (a) easily degradable and (b) non-easily degradable MITI substances. For the purpose of comparison, the MITI degradation data are shown in each case as 100 per cent correctly classified compounds; correct classification; incorrect classification; indifferent degradation result.

Problems arise from the non-symmetrical distribution of easily degradable and non-easily degradable substances within chemical classes. For polyaromatic compounds this results in SARs which underestimate the degradability since, due to the factors derived, these compounds are consistently classified as non-easily degradable. From the different proportions of compounds correctly classified as easily degradable and compounds correctly classified as non-easily degradable, the application of Model 73 to polycyclic aliphatics and aromatics cannot be recommended. Accordingly, the incorrect classification of 55 per cent of the non-easily degradable acyclic compounds by Model 73 appears very critical despite the fact that the overall level of correct predictions is 85 per cent. Additional problems regarding interpretation of the level of agreement apply in the case of aliphatic polycyclic compounds, as a result of the small number of compounds available for validation.



7. Hierarchic models for application of SARs

For estimating biodegradability using SARs, it has been assumed that there cannot be only one universal model for simulating the diverse degradation processes. It is therefore necessary to discriminate between categories of chemicals, and then to apply specific SARs. The respective hierarchic model for estimating degradability requires the user first of all to allocate a compound to a class on the basis of its structural characteristics. The categorisation of substances according to their skeletons and substructures is intended to identify substances with similar degradative behaviour. Within the classes obtained in this manner, the biodegradability can be related to parameters depending on the structures. Incorrect categorisation, i.e. application of an unsuitable SAR model, may result in substantial errors in predicting biodegradability. The models developed in the course of this project represent SARs which are suitable for estimating biodegradability. Validation revealed levels of agreement between calculated and experimental values ranging from 61 per cent to 100 per cent (Tables 19 and 29). The application of models with < 75 per cent correct classifications is not recommended. The restrictions specified for the individual models must be respected.

All SARs which could be validated with the MITI data are included in the hierarchic models, whereby detailed documentation is essential to allow reliable predictions. The user should be provided with information regarding (a) compounds on which the model is based, (b) compounds which are misclassified, and (c) the degree of probability with which a calculated degradability level coincides with experimental results.

Figures 6-8 provide decision nets for estimating the degradability of acyclic, monocyclic, aromatic and heterocyclic substances, stating the correct classifications to be expected in each case. At present, it is not possible to establish the respective schemes for further compound classes due to a lack of data. However, estimation should be possible for most environmental chemicals when applying these models. Reference is made to the restrictions of the models to specific chemical classes.

The user must first determine whether the compound for which calculation is to be carried out is an acyclic, aromatic monocyclic or aliphatic cyclic substance. If an acyclic compound is concerned, the decision net for acyclic compounds (**Figure 6**) can be applied. If monocyclic aromatic compounds or aliphatic cyclic compounds are concerned, appropriate decision nets are also available (**Figures 7 and 8**). For these models, the calculated biodegradability corresponds to the OECD testing for category 1, test procedures for the assessment of easily degradable compounds, such as the MITI test.

No model for estimating biodegradability can be recommended at present for polycyclic aromatic compounds and heterocyclic compounds.

Table 29: Summary of Models 74-78

R_1: H or unbranched alkyl chain; R_2: O or N or S; aryl (R_3): chain with non-terminal heteroatoms, or branched alkyl chain; V_2: validation set.

	applicability of the models	classification correct %	incorrectly classified substances
Acyclic compounds:			
74	all acyclic MITI data of Vs	89	PO_4, tert.N, S-S, N-N, -O-
	not: PO_4, tert. N, N-N, S-S	96	-O-, -O-C(CO)-, x=x
	only: OH, COOH, hal, CH_3, C-NH_2	97	
75	all acyclic MITI data of Vs	91	S-S, N-N, -O-
	not: -S-S, -N-N	93	-O-, -O-C(O)-, x=x
	only: OH, COOH, hal, CH_3, C-NH_2, PO_4, amine	96	
76	> 1 halogen atom; tert. butyl group; tert. amine (subst. >2 CH_2 groups); atoms other than C, H, O, N, P, S and halogen; 2 term. isopropyl groups; phosphoric acid, phosphite and sulphuric phosphoric acid; azo group; dithioether; hydrazine; C=C; substance with only: CH_3, CH_2-, OH, CO, COOH, NH_2 groups; lin. aliph. sulphonic acid		
Aromatic compounds:			
77	all disubst. MITI data of VS	75	non-defined compounds
	only: OH, NO_2, NH_2, COO(R_1), CH_2(R_1), SO_2(R_2), amide, CO, hal	87	sulphonic acids
78	all disubst. MITI data of Vs	84	non-defined compounds
	only: OH, NO_2, NH_2, COO(R_1), CH_2(R_1), SO_2(R_2), amide, CO, hal, aryl (R_3)	92	sulphonic acids
	all monosubst. MITI data of Vs	93	
	all polysubst. MITI data of Vs	83	methylated compounds

7.1 Hierarchic models for estimating the degradability of acyclic compounds

Three models are available for estimating the degradability of acyclic substances. Models 74 and 75 are based on regression and discriminant analyses; Model 76 is based on frequency distribution for functional groups. Application of Model 76 yields a high level of probability for the correct estimation of degradability. The model is resticted to substances containing the substructures previously defined, however. Models 74 and 75 can be additionally used to estimate degradability, provided that the compounds are not hydrazines or dithioethers.

The decision net for acyclic compounds (**Figure 6**) is to be read as follows:

(1) If an acyclic compound is concerned, application of the models can be examined.

(2) For substances with the functional groups of Model 76, initial estimation of degradability can be carried out.

(3) If the compound is a hydrazine, a dithioether or a compound with atoms other than C, H, N, O, P, S or halogen, no further prediction is possible.

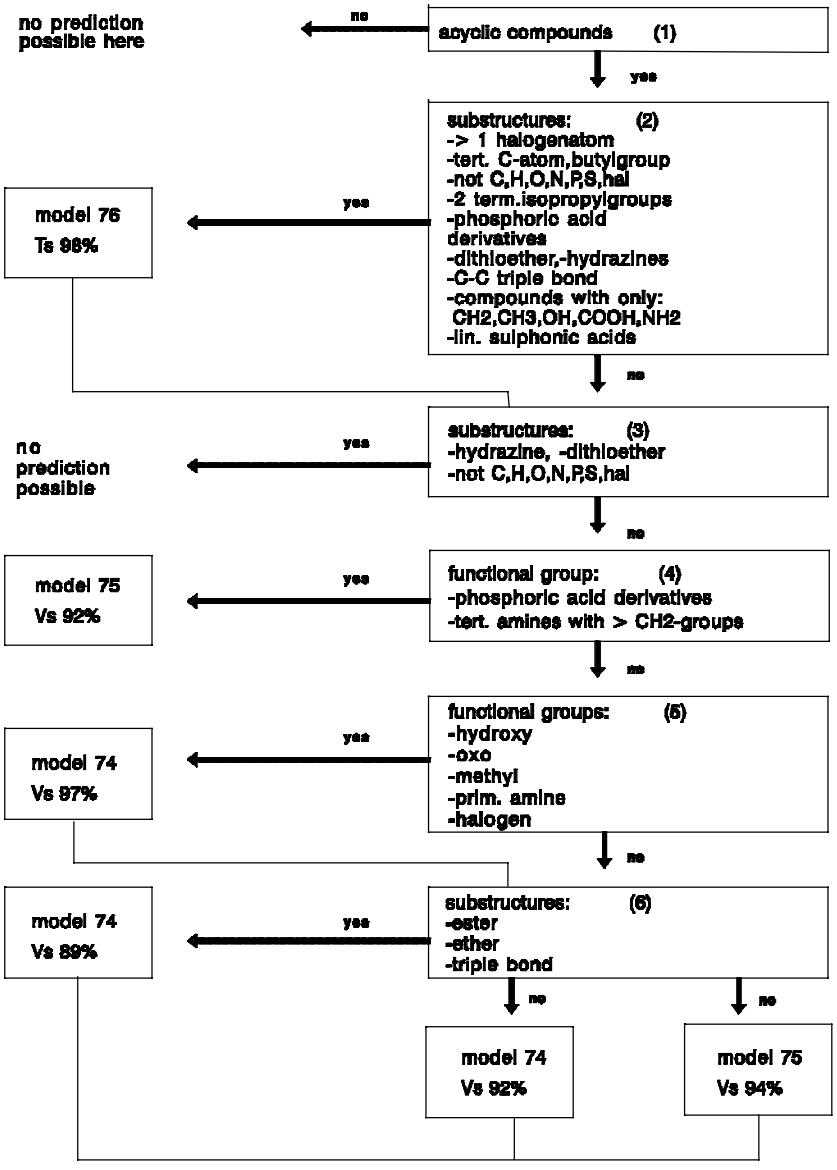
(4) If the compound concerned is a phosphoric acid or a tertiary amine, Model 75 has to be applied.

(5) For substances with the functional groups hydroxy, ketone, methyl, primary amine or halogen, Model 74 can be applied with a high level of probability of correct estimation. If the acyclic compound to be tested is neither a phosphoric acid, tertiary amine, hydrazine nor disulphide ether and does not contain any atoms other than C, H, N, O, P, S and halogen, Model 74 can also be applied to compounds with other substructures, though estimation is then less reliable.

(6) If ethers, esters or compounds with triple bonds are concerned, the proportion of correctly classified compounds is 89 per cent when Model 74 is applied.

For all other substances, the substructures of which also occur in the compounds employed for validation, Models 74 and 75 can be used to estimate biodegradability. At 93 per cent and 92 per cent respectively, the reliability of estimation is, however, slightly lower than for compounds which contain only those substructures which were applied in development of the model.

Figure 6: Decision net for estimating the biodegradability of acyclic compounds



7.2 Hierarchic models for estimating the degradability of monocyclic aromatic compounds

Seven models are available for estimating the degradability of monocyclic aromatic compounds. Model 77 applies for disubstituted aromatic compounds; Model 78 can also be employed for monosubstituted compounds. Models 9, 14, 15, 16 and 17 were validated for phenols and anilines.

The decision net for monocyclic aromatic compounds (**Figure 7**) is to be read as follows:

(1) If a monocyclic aromatic compound is concerned, application of the models to estimate biodegradability is possible.

(2) The number of substituents must be determined. If monosubstituted compounds are involved, Model 78 should be applied.

(3) If polysubstituted (> 2 substituents) compounds are involved, Model 78 should be employed, but estimation is less reliable than for monosubstituted compounds. For methyl substituents, a correction factor must be included.

(4) For disubstituted compounds, proceed further along the decision net. If the compounds are phthalates, it can be assumed that these will generally be easily degradable substances. The decision net should nevertheless be proceeded with.

(5) If disubstituted phenols with the substituents OH, OCH_3, CH_3, Br, Cl are concerned, Model 9 can be applied.

(6) If disubstituted phenols with the substituents OH, COOH, CH_3, Cl, SO_3 are concerned, Model 14 can be applied.

(7) If orthosubstituted phenols with the substituents OH, COOH, CH_3, Cl, NO_2 are concerned, Model 15 can be applied.

(8) If metasubstituted phenols with the substituents OH, COOH, CH_3, Cl are concerned, Model 16 can be applied.

(9) If parasubstituted anilines with the substituents CH_3, NH_2, NO_2, Cl are concerned, Model 17 can be applied.

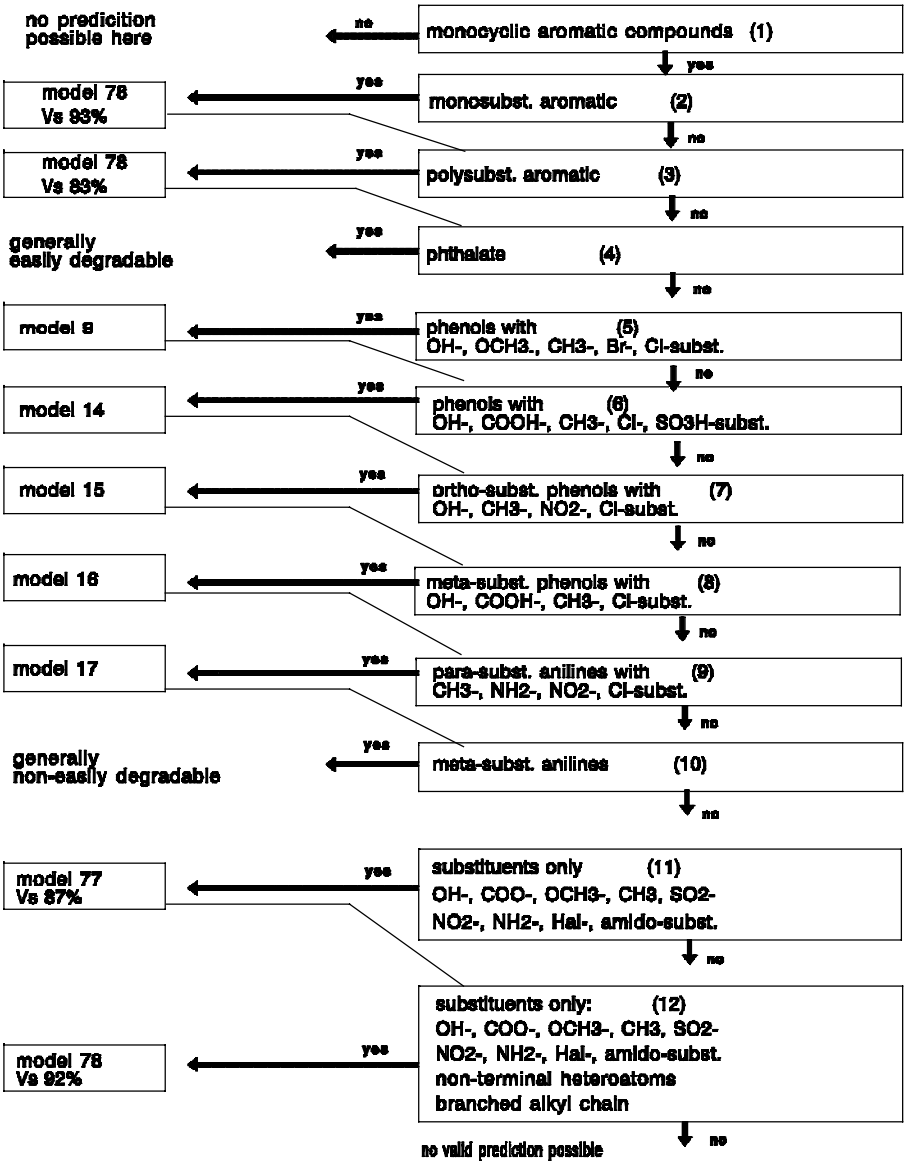
(10) If the compounds are metasubstituted anilines, it can be assumed that these will generally be non-easily degradable substances. Nevertheless, proceed with the decision net.

(11) Further regard to the functional groups is necessary. If compounds with the substituents OH, NH_2, hal, COOH, CH_3, NO_2 or sulphonic acids and amides are concerned, Model 77 can be applied.

(12) If these substituents are concerned (see 11 above), it must be established whether they contain non-terminal heteroatoms such as ethers, secondary amines, or branched hydrocarbon chains. In this case, Model 78 can be applied.

If further functional groups are present, it is possible to apply Models 77 and 78, but due to limited validation, application is not recommended.

Figure 7: Decision net for estimating the degradability of monocyclic aromatic compounds



7.3 Hierarchic models for estimating the degradability of aliphatic cyclic compounds

Two models are available for estimating the degradability of aliphatic cyclic compounds (see **Figure 8**).

7.4 Validation status

Numerous SAR models for estimating biodegradability have been published, but only a few models were found to provide an adequate level of agreement between calculated and experimental data. The models which can be validated with MITI data are comprised in decision nets for acyclic, monocyclic aromatic and aliphatic cyclic compounds. The degradability of compounds belonging to other chemical classes can be predicted only at a low level of reliability at present. Accordingly, application of these models to estimate biodegradability cannot be recommended due to the high degree of uncertainty involved in the results obtained. The validated SAR Models, 1, 9, 14-17, 43, 74-78, will be incorporated into the SAR program (UBA F&E 106 04 019/02).

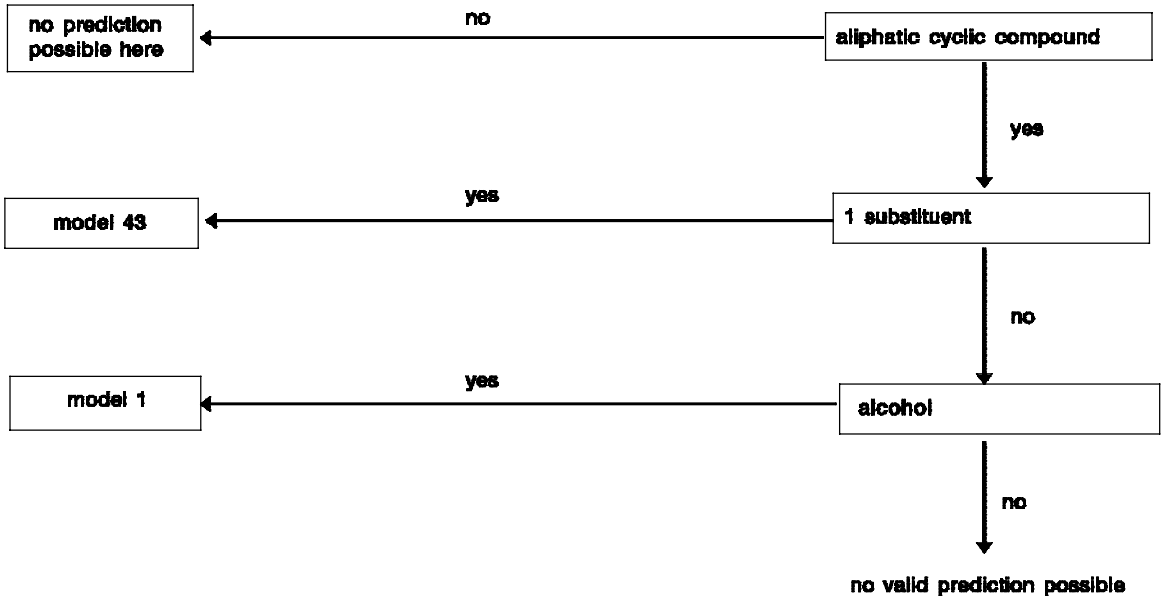
Figure 8: Decision net for estimating the degradability of aliphatic cyclic compounds

The decision net for aliphatic cyclic compounds is to be read as follows:

(1) If aliphatic cyclic compounds are concerned, application of the decision net is possible.

(2) If monosubstituted compounds are concerned, Model 43 can be applied.

(3) If alcohols are concerned, Model 1 can be applied.



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Annex 1

List of Chemicals Used for this Study

1. ALIPHATIC COMPOUNDS

1.1 ACYCLIC COMPOUNDS

1.1.1 EASILY DEGRADABLE ACYCLIC COMPOUNDS

No.	Compound	CAS number
1	1,4-BUTANEDIOL	110-63-4
2	2-[(2-HYDROXYETHOXY)-ETHOXY]-1-ETHANOL	112-27-6
3	2-PROPENE-1-OL	107-18-6
4	3-METHOXY-1-BUTANOL	2517-43-3
5	3-HEXINE-1-OL	1002-28-4
6	2-METHOXY-1-ETHANOL	109-86-4
7	2-BUTOXY-1-ETHANOL	111-76-2
8	2-ETHYL-1-HEXANOL	104-76-7
9	2-PROPANOL	67-63-0
10	1,2-ETHANEDIOL	107-21-1
11	1,5-PENTANEDIOL	111-29-5
12	2-METHYL-1,3-PROPANEDIOL	2163-42-0
13	3-CHLORO-1,2-PROPANEDIOL	96-24-2
14	2,2'-THIODIETHANOL	111-48-8
15	2,4-PENTANEDIOL	625-69-4
16	1,2,3-PROPANETRIOL	56-81-5
17	ETHOXYMETHANOL	
18	2-BUTANONE	78-93-3
19	6-UNDECANONE	927-49-1
20	4-METHYL-2-PENTANONE	108-10-1
21	ETHOXYPROPANONE	
22	3,5-HEPTANEDIONE	7424-54-6
23	ETHANEDIALDEHYDE	107-22-2
24	ETHANAL	75-07-0
25	PROPANAL	123-38-6
26	BUTANAL	123-72-8
27	2-METHYLPROPANAL	78-84-2
28	2-CHLOROACETIC ACID	79-11-8
29	2,2-DICHLOROACETIC ACID	79-43-6
30	2-PROPENOIC ACID	79-10-7
31	2-MERCAPTOACETIC ACID	68-11-1
32	HEXADECANEDIACID	505-54-4
33	8-HEXADECENEDIACID	
34	ACETIC ACID ETHYLESTER	141-78-6

35	ACETIC ACID (2-ETHOXYETHYL) ESTER	111-15-9
36	ACETIC ACID (3-METHOBUTYL) ESTER	4435-53-4
37	2-CHLOROACETIC ACID ETHENYLESTER	2549-51-1
38	2-METHYL-2-PROPENOIC ACID METHYLESTER	80-62-6
39	3-MERCAPTOPROPIONIC ACID METHYLESTER	2935-90-2
40	2-PENTENOIC ACID ETHYLESTER	2445-93-4
41	9-OCTADECENOIC ACID BUTYLESTER	142-77-8
42	2,3-DICHLORO-TRANS-2-BUTENEDIACID DIETHYL-ESTER	
43	DECANEDIACID DIOCTYLESTER	2432-87-3
44	FORMAMIDE	75-12-7
45	N-METHYLACETAMIDE	79-16-3
46	N-ETHYLACETAMIDE	625-50-3
47	2-PROPENOIC ACID AMIDE	79-06-1
48	2-AMINO-1-ETHANOL	141-43-5
49	1-BUTYLAMINE	109-73-9
50	2-METHYL-1-PROPYLAMINE	78-81-9
51	1-METHYL-1-PROPYLAMINE	13952-84-6
52	12-AMINODODECANOIC ACID	693-57-2
53	2,2’-IMINO-DI-(1-ETHANOL)	111-42-2
54	DIMETHYLAMINE	124-40-3
55	2-(HYDROXYMETHYLAMINO)-1-ETHANOL	65184-12-5
56	N-BUTYL-N-ETHYLAMINE	13360-63-9
57	DIPROPYLAMINE	142-84-7
58	N-(3-METHYLBUTYL)-N-PENTYLAMINE	
59	DIPENTYLAMINE	2050-92-2
60	TRIMETHYLAMINE	75-50-3
61	2-DIMETHYLAMINO-1-ETHANOL	108-01-0
62	DODECYL-DIMETHYLAMINE	112-18-5
63	ETHANENITRILE	75-05-8
64	2-METHYLPROPANENITRILE	78-82-0
65	PROPANE	74-98-6
66	BUTANE	106-97-8
67	PENTANE	109-66-0
68	HEXANE	110-54-3
69	HEPTANE	142-82-5
70	OCTANE	111-65-9
71	NONANE	111-84-2
72	DECANE	124-18-5
73	UNDECANE	1120-21-4
74	DODECANE	112-40-3
75	TRIDECANE	629-50-5
76	TETRADECANE	629-59-4
77	HEPTADECANE	629-78-7
78	OCTADECANE	593-45-3
79	NONADECANE	629-92-5
80	ICOSANE	112-95-8
81	HENICOSANE	629-94-7
82	DOCOSANE	629-97-0
83	TRICOSANE	638-67-5
84	TETRACOSANE	646-31-1
85	PENTACOSANE	629-99-2
86	HEXACOSANE	630-01-3

87	HEPTACOSANE	593-49-7
88	OCTACOSANE	630-02-4
89	NONACOSANE	630-03-5
90	TRIACONTANE	638-68-6
91	UNTRIACONTANE	630-04-6
92	DOTRIACONTANE	544-85-4
93	TRITRIACONTANE	630-05-7
94	TETRATRIACONTANE	14167-59-0
95	PENTATRIACONTANE	630-07-9
96	HEXATRIACONTANE	630-06-8
97	HEPTATRIACONTANE	7194-84-5
98	OCTATRIACONTANE	7194-85-6
99	NONATRIACONTANE	
100	TETRACONTANE	4181-95-7
101	UNTETRACONTANE	
102	DOTETRACONTANE	
103	TRITETRACONTANE	
104	TETRATETRACONTANE	7098-22-8
105	PENTATETRACONTANE	
106	HEXATETRACONTANE	
107	1-ETHANOL	64-17-5
108	1-PROPANOL	71-23-8
109	1-BUTANOL	71-36-3
110	1-PENTANOL	71-41-0
111	1-HEXANOL	111-27-3
112	1-HEPTANOL	111-70-6
113	1-OCTANOL	111-87-5
114	1-NONANOL	143-08-8
115	1-DECANOL	112-30-1
116	1-UNDECANOL	112-42-5
117	1-DODECANOL	112-53-8
118	1-TRIDECANOL	112-70-9
119	1-TETRADECANOL	112-72-1
120	1-PENTADECANOL	629-76-5
121	1-HEXADECANOL	36653-82-4
122	1-HEPTADECANOL	1454-85-9
123	1-OCTADECANOL	112-92-5
124	1-NONADECANOL	1454-84-8
125	PROPANE-1-OL-2-ONE	116-09-6
126	2-METHYL-1-PROPANOL	78-83-1
127	4-HYDROXY-2-BUTANONE	590-90-9
128	1-BUTENE-3-OL	598-32-3
129	DIOCTYL ETHER	629-82-3
130	DIDECYL ETHER	2456-28-2
131	DIDODECYL ETHER	4542-57-8
132	ACETIC ACID	64-19-7
133	PROPANOIC ACID	79-09-4
134	BUTANOIC ACID	107-92-6
135	HEXANOIC ACID	142-62-1
136	HEPTANOIC ACID	111-14-8
137	OCTANOIC ACID	124-07-2
138	NONANOIC ACID	112-05-0
139	DECANOIC ACID	334-48-5

140	UNDECANOIC ACID	112-37-8
141	2-PROPENOIC ACID METHYLESTER	96-33-3
142	2-PROPENOIC ACID BUTYLESTER	141-32-2
143	2-PROPENOIC ACID HEXYLESTER	2499-95-8
144	2-CHLOROPROPANOIC ACID METHYLESTER	17639-93-9
145	O-ACETYL-2-HYDROXY-1,2,3-PROPANE TRICARBONOIC ACID TRIBUTYLESTER	77-90-7
146	METHYLAMIDEACETOACETATE	20306-75-6
147	ETHYLAMIDEACETOACETATE	
148	HEPTANOIC ACID BIS-(2-HYDROXYETHYL) AMIDE	
149	OCTANOIC ACID BIS-(2-HYDROXYETHYL) AMIDE	3077-30-3
150	NONANOIC ACID BIS-(2-HYDROXYETHYL) AMIDE	3077-37-0
151	DECANOIC ACID BIS-(2-HYDROXYETHYL) AMIDE	136-26-5
152	UNDECANOIC ACID BIS-(2-HYDROXYETHYL) AMIDE	
153	DODECANOIC ACID BIS-(2-HYDROXYETHYL) AMIDE	120-40-1
154	TRIDECANOIC ACID BIS-(2-HYDROXYETHYL) AMIDE	
155	TETRADECANOIC ACID BIS-(2-HYDROXYETHYL) AMIDE	7545-23-5
156	PENTADECANOIC ACID BIS-(2-HYDROXYETHYL) AMIDE	
157	HEXADECANOIC ACID BIS-(2-HYDROXYETHYL) AMIDE	7545-24-6
158	HEPTADECANOIC ACID BIS-(2-HYDROXYETHYL) AMIDE	
159	OCTADECANOIC ACID BIS-(2-HYDROXYETHYL) AMIDE	93-82-3
160	NONADECANOIC ACID BIS-(2-HYDROXYETHYL) AMIDE	
161	1,6-HEXYLDIAMINE	124-09-4
162	1,8-OCTYLDIAMINE	373-44-4
163	1,4-DICYANOBUTANE	111-69-3
164	1,4-BIS-(BROMOACETOXY)-2-BUTENE	20679-58-7
165	2-BUTANOL	78-92-2
166	1-BUTOXY-2-PROPANOL	5131-66-8
167	BUTYLACETOACETATE	591-60-6
168	(1-METHYLPROPYL) ACETOACETATE	13562-76-0
169	(CHLOROMETHYL) METHYLETHER	107-30-2
170	1,3-DICHLORO-2-PROPANOL	96-23-1
171	DIETHYLSULFATE	64-67-5
172	3,3'-THIO BIS-(PROPIONOIC ACID DODECYLETHER)	123-28-4
173	3,7-DIMETHYL-1-HYDROXY-2,6-OCTADIENE	624-15-7
174	PHOSPHORIC ACID MONODODECYLESTER	2627-35-2
175	2-ETHOXYETHANOL	110-80-5
176	1-HEXACOSANOL	506-52-5
177	2,4-HEXADIENOIC ACID	72138-88-6
178	2-HYDROXY-2-METHYLPROPANENITRILE	75-86-5
179	2-METHYL-2,4-PENTANEDIOL	107-41-5
180	2-METHYL-2-PENTENE-4-ONE	141-79-7
181	HEXANEDIACID MONOETHYLESTER	626-86-8
182	NONADECANENITRILE	28623-46-3
183	1-NONADECYLAMINE	14130-05-3
184	NONANENITRILE	2243-27-8
185	2-METHYL-2-PROPENOIC ACID OCTADECALESTER	32360-05-7

186	2-PROPENOIC ACID OCTYLESTER	2499-59-4
187	PENTANOIC ACID	109-52-4
188	1-PENTYLAMINE	110-58-7
189	DIETHYLENEGLYCOLMONO-N-BUTYLETHER	112-34-5
190	1,12-DODECANEDICARBONIC ACID	821-38-5
191	CIS-13-DOCOSENEAMIDE	112-84-5
192	HEXANEDIACID	124-04-9
193	1-HEXADECENE	629-73-2
194	3-CHLOROPROPENE	107-05-1
195	12-OXADECANOIC ACID	106-14-9
196	2-METHYLPROPENOIC ACID MONO-2-HYDROXY-ETHYLESTER	868-77-9
197	CHLOROFORMIATE ETHYLESTER	541-41-3
198	1-METHOXY-2-PROPANOL	107-98-2
199	4-HYDROXY-4-METHYL-2-PENTANONE	123-42-2
200	DI(2-ETHYLHEXYL)FUMARIC ACID ESTER	142-16-5
201	ACETIC ACID ETHENYLESTER	108-05-4
202	ALLYLIDENDIACETIC ACID ESTER	869-29-4
203	7-METHYL-3-METHYLENE-1,6-OCTADIENE	2436-90-0
204	DIMETHYL-CIS-BUTENEDIACID ESTER	624-49-7
205	DI(2-ETHYLHEXYL)HEXANEDIACID ESTER	103-23-1
206	1-HEXENE	592-41-6
207	HEXANEDIACID-BIS-[2-(2-BUTOXYETHOXY) ETHYLESTER]	141-17-3

1.1.2 NON-EASILY DEGRADABLE ACYCLIC COMPOUNDS

208	2-BUTINE	503-17-3
209	2,2,4,4,6,8,8-HEPTAMETYLNONANE	4390-04-9
210	TRICHLOROMETHANE	67-66-3
211	TETRACHLOROMETHANE	56-23-5
212	1,2-DICHLOROETHANE	107-06-2
213	1,2-DICHLOROETHENE	540-59-0
214	1,2-DIBROMOETHANE	106-93-4
215	1,1,1-TRICHLOROETHANE	71-55-6
216	1,1,2-TRICHLOROETHANE	79-00-5
217	1,1,2-TRICHLOROETHENE	79-01-6
218	1,1,2,2-TETRACHLOROETHANE	79-34-5
219	1,1,2,2-TETRABROMOETHANE	79-27-6
220	1,1,2,2-TETRACHLOROETHENE	127-18-4
221	HEXACHLOROETHANE	67-72-1
222	1,2-DICHLOROPROPANE	78-87-5
223	1,2-DIBROMO-3-CHLOROPROPANE	96-12-8
224	3,4-DICHLORO-1-BUTENE	760-23-6
225	2-METHYL-2-PROPANOL	75-65-0
226	2,2-DIMETHYL-1,3-PRONDIOL	126-30-7
227	2-HYDROXYMETHYL-3-METHYL-1,3-BUTANEDIOL	
228	3-METHYL-1,3,5-PENTANETRIOL	7564-64-9
229	2,2-BIS-(HYDROXYMETHYL)-1-BUTANOL	77-99-6
230	2,2-BIS-(HYDROXYMETHYL)-1,3-PROPANEDIOL	115-77-5
231	TERT-BUTYLMETHYLETHER	1634-04-4
232	BIS-(3-METHYLBUTYL) ETHER	544-01-4

233	BIS-(2-CHLOROETHYL) ETHER	111-44-4
234	BIS-(2,3,3,3-TETRACHLOROPROPYL) ETHER	127-90-2
235	TRIFLUOROETHENYL-HEPTAFLUOROPROPYL) ETHER	1623-05-8
236	2,3-DIBROMOBUTANEDIACID	526-78-3
237	2,3-DICHLOROBUTANEDIACID	
238	2-METHYL-2-PROPENOIC ACID TERT-BUTYLESTER	585-07-9
239	N,N-DIMETHYLFORMAMIDE	68-12-2
240	2,2',2''-NITRILO-TRI-(1-ETHANOL)	102-71-6
241	1,1',1''-NITRILO-TRI-(2-PROPANOL)	122-20-3
242	TRIOCTYLAMINE	1116-76-3
243	TRIS-(N,N-DIMETHYL-3-AMINOPROPYL) AMINE	33329-35-0
244	PHOSPHORIC ACID TRIBUTYLESTER	126-73-8
245	PHOSPHORIC ACID TRIS-(2,3-DIBROMOPROPYLESTER)	126-72-7
246	PHOSPHORIC ACID TRIS-[2-CHLORO-1-(CHLOROMETHYL) ETHYLESTER]	13674-87-8
247	2-PROPENOIC ACID ETHYLESTER	140-88-5
248	PHOSPHORIC ACID BIS-(2-ETHYLHEXYLESTER)	298-07-7
249	BIS-(1-METHYL-2-CHLOROETHYL) ETHER	108-60-1
250	BROMOCHLOROMETHANE	74-97-5
251	1,3-DIBROMO-2,2-BIS-(BROMOMETHYL) PROPANE	3229-00-3
252	1,10-DIBROMODECANE	4101-68-2
253	DIBUTYLETHER	142-96-1
254	DIBUTYLTINDIDODECANOAT	77-58-7
255	DICHLOROMETHANE	75-09-2
256	DITHIOPHOSPHORIC ACID ESTER DERIVATIVE	60-51-5
257	3,3'-IMINODIPROPANENITRILE	111-94-4
258	TRI-(NONAFLUOROBUTYL) AMINE	311-89-7
259	1,2,2,3-TETRACHLOROPROPANE	13116-53-5
260	TRI-2-PROPENYLAMINE	102-70-5
261	1,1,1-TRICHLORO-2-METHYL-2-PROPANOL	6001-64-5
262	1,2,3-TRICHLOROPROPANE	96-18-4
263	PHOSPHORIC ACID TRIETHYLESTER	78-40-0
264	PHOSPHORIC ACID TRIMETHYLESTER	512-56-1
265	PHOSPHORIC ACID TRIS-(2-CHLOROETHYLESTER)	115-96-8
266	PHOSPHORIC ACID TRIS-(2-ETHYLHEXYLESTER)	78-42-2
267	HYDRAZINE	302-01-2
268	DIPROPANOLETHER	2396-61-4
269	METHYLHYDRAZINE	60-34-4
270	DIDECYLDISULFIDE	10496-18-1
271	OCTADECANETHIOL	2885-00-9
272	2,2-BIS-(BROMOMETHYL)-1,3-PROPANEDIOL	3296-90-0
273	TRIETHYLAMINE	121-44-8
274	2-ETHYLHEXYLVINYLETHER	103-44-6
275	2,2'-AZOBIS(2,4-DIMETHYL) VALERONITRILE	4419-11-8
276	NITRILOTRIACETIC ACID	139-13-9
277	2,2'-BIS-(METHYL) PROPIONNITRILE	78-67-1
278	TRI-N-OCTYLAMINE	1116-76-3
279	N,N-DIMETHYLHYDRAZINE	57-14-7
280	O,O'-DIETHYLDITHIOPHOSPHATE	298-06-6
281	TRI-DIMETHYLAMINEPHOSPHATE	680-31-9
282	TRICHLORONITROMETHANE	76-06-2

283	THIOSEMICARBAZIDE	79-19-6
284	TRIS(1-CHLORO-2-PROPYL) PHOSPHATE	13674-84-5
285	TRIDODECANOYLTRITHIOPHOSPHITE	1656-63-9
286	BIS-N-TRIBUTYLTINOXIDE	56-35-9
287	TETRABUTYLTIN	1461-25-2

1.2 ALIPHATIC MONOCYCLIC COMPOUNDS

1.2.1 EASILY DEGRADABLE ALIPHATIC MONOCYCLIC COMPOUNDS

288	CYCLOHEXANOL	108-93-0
289	CYCLOHEXYLAMINE	108-91-8
290	CYCLOHEXANONE	108-94-1
291	4-(1-METHYLETHENYL)-1-METHYLCYCLOHEXENE	7705-14-8
292	4-(1-HYDROXY-1-METHYLETHYL)-1-METHYL-CYCLOHEXENE	10482-56-1
293	CYCLOPENTENE	142-29-0
294	1-METHYL-4-(1-METHYLETHENYL)-1-METHYL-CYCLOHEXANE	6252-33-1
295	1-ISOPROPYL-4-METHYLCYCLOHEXANE	99-82-1
296	2-(2-PENTYL-3-OXO-CYCLOPENTYL)-METHYLACETATE	24851-98-7
297	1-ISOPROPYL-4-METHYL-1,4-CYCLOHEXADIENE	99-85-4

1.2.2 NON-EASILY DEGRADABLE ALIPHATIC MONOCYCLIC COMPOUNDS

298	CYCLODODECANE	294-62-2
299	CHLOROCYCLOHEXANE	542-18-7
300	HEXACHLOROCYCLOHEXANE	319-86-8
301	4-CYCLOHEXENE-1,2-DICARBONIC ACID	2305-26-2
302	3,5,5-TRIMETHYLCYCLOHEX-2-ENE-1-ONE	78-59-1
303	5-METHYL-2-(1-METHYLETHYL) CYCLO-HEXANE-1-OL	2216-51-5
304	4-ETHENYL-1-CYCLOHEXENE	100-40-3
305	CHLORO-2,3,4,5,6-PENTABROMOCYCLOHEXANE	87-84-3
306	1,1-BIS-(TERT-BUTYLPEROXY)-3,3,5-TRI-METHYLCYCLOHEXANE	6731-36-8
307	HEXACHLOROCYCLOPENTADIENE	77-47-4
308	1,2,5,6,9,10-HEXABROMOCYCLODODECANE	3194-55-6

1.3 ALIPHATIC POLYCYCLIC COMPOUNDS

1.3.1 EASILY DEGRADABLE ALIPHATIC POLYCYCLIC COMPOUNDS

309	1,7,7-TRIMETHYL-BICYCLO-[2.2.1]-2-HEPTANOL	464-45-9
310	DICYCLOHEXYLAMINE	101-83-7

1.3.2 NON-EASILY DEGRADABLE ALIPHATIC POLYCYCLIC COMPOUNDS

311	1,3,7,8,9,10,10-HEPTACHLORO-TRICYCLO-[5.2.1.0(2,6)]-4,8-DECADIENE	76-44-8
312	1,8,9,10,11,11-HEXACHLORO-TETRACYCLO-[6.2.1(3,60(2,7)]-4,9-DODECADIENE	465-73-6
313	1,4,5,6,7,7-HEXACHLORO-BICYCLO-[2.2.1]-5-HEPTENE-2,3-DICARBONIC ACID	115-28-6
314	1,3,4,7,8,9,10,10-OCTACHLORO-TRICYCLO-[5.2.1.0(2,6)]-8-DECENE	57-74-9
315	1,6,7,8,9,14,15,16,17,17,18,18-DODECACHLORO-PENTACYCLO-7,15-OCTADECADIENE	13560-89-9
316	2-(1-CYCLOHEXENE-1-YL)-1-CYCLOHEXANONE	1502-22-3
317	N,N'-DICYCLOHEXYLTHIOUREA	1212-29-9
318	5-ETHYLIDENE-2-NORBORNENE	16219-75-3
319	CAMPHENE	5794-04-7

2. AROMATIC COMPOUNDS

2.1 MONOCYCLIC AROMATIC COMPOUNDS

2.1.1 EASILY DEGRADABLE MONOCYCLIC AROMATIC COMPOUNDS

320	PHENOL	108-95-2
321	BENZALDEHYDE	100-52-7
322	METHOXYBENZENE	100-66-3
323	ETHOXYBENZENE	103-73-1
324	BENZOIC ACID	65-85-0
325	BENZENESULFONIC ACID	98-11-3
326	BENZENESULFINIC ACID	618-41-7
327	BENZYLSULFOCHLORIDE	1939-99-7
328	BENZONITRILE	100-47-0
329	2-PHENYLETHANENITRILE	140-29-4
330	BENZYLALCOHOL	100-51-6
331	2-PHENYLETHANOL	60-12-8
332	METHYLBENZENE	108-88-3
333	(1-METHYLETHYL) BENZENE	98-82-8
334	ETHENYLBENZENE	100-42-5
335	N-PHENYLACETAMIDE	103-84-4
336	BENZYLAMINE	100-46-9
337	N-BENZYLACETAMIDE	588-46-5
338	2-PHENYLETHYLAMINE	64-04-0
339	PHENYLAMINE	62-53-3
340	2-METHYLPHENYLAMINE	95-53-4
341	4-METHYLPHENYLAMINE	106-49-0
342	4-METHOXYPHENYLAMINE	104-94-9
343	2,4-DICHLOROBENZYLALCOHOL	1777-82-8
344	2,4,6-TRICHLOROPHENOL	88-06-2
345	2,4,6-TRIBROMOPHENOL	118-79-6
346	METHYLPHENYLKETON	98-86-2
347	N-BENZOYL-2-AMINOACETIC ACID	495-69-2
348	1-PHENYL-1,3-BUTANEDIONE	93-91-4
349	BENZENE-1,2-DICARBONIC ACID	88-99-3

350	BENZENE-1,4-DIALDEHYDE	623-27-8
351	3-HYDROXYBENZOIC ACID	99-06-9
352	4-HYDROXYBENZOIC ACID	99-96-7
353	2-METHOXYBENZOIC ACID	579-75-9
354	3-METHOXYBENZOIC ACID	586-38-9
355	4-METHOXYBENZOIC ACID	100-09-4
356	2-METHOXYPHENOL	90-05-1
357	3-METHOXYPHENOL	150-19-6
358	4-METHOXYPHENOL	150-76-5
359	1,3-DIMETHOXYBENZENE	151-10-0
360	1,4-DIMETHOXYBENZENE	150-78-7
361	4-HYDROXYBENZENESULFONIC ACID	98-67-9
362	3-CHLOROBENZOIC ACID	535-80-8
363	4-CHLOROBENZENESULFONIC ACID	98-66-8
364	N-(4-AMINOPHENYL) ACETAMIDE	122-80-5
365	3-METHYLBENZOIC ACID	99-04-7
366	4-METHYLBENZOIC ACID	99-94-5
367	2-METHYLPHENOL	95-48-7
368	3-METHYLPHENOL	108-39-4
369	1,2-DIMETHYLBENZENE	95-47-6
370	1,3-DIMETHYLBENZENE	108-38-3
371	1,4-DIMETHYLBENZENE	106-42-3
372	N-ACETOACETYL-2-METHYLPHENYLAMINE	93-68-5
373	N-ACETOACETYL-4-METHYLPHENYLAMINE	2415-85-2
374	1,2-DIMETHOXY-4-(2-PROPENYL) BENZENE	93-15-2
375	BENZENE	71-43-2
376	BENZYLCHLORIDE	100-44-7
377	4-(CHLOROACETYLAMINO) BENZOIC ACID ETHYLESTER	
378	3-PHENYL-2-PROPENE-1-OL	104-54-1
379	BENZENE-1,2-DICARBONIC ACID DIBUTYLESTER	84-74-2
380	(DICHLOROMETHYL) BENZENE	24154-22-1
381	1,3-DICHLORO-4-(TRICHLOROMETHYL) BENZENE	13014-18-1
382	BENZENE-1,2-DICARBONIC ACID DIOCTYLESTER	117-84-0
383	4-DODECYLPHENYLAMINE	104-42-7
384	1,4-DIHYDROXYBENZENE	123-31-9
385	BENZENE-1,3-DICARBONIC ACID	121-91-5
386	2-(METHYLAMINO) BENZOIC ACID	119-68-6
387	2-NITROBENZOIC ACID	552-16-9
388	4-NITROBENZOIC ACID	62-23-7
389	3-NITROPHENOL	554-84-7
390	2-PENTYL-3-PHENYL-2-PROPENE ACID ALDEHYDE	122-40-7
391	1,2-DIHYDROXYBENZENE	120-80-9
392	1,3-DIHYDROXYBENZENE	108-46-3
393	2-HYDROXYBENZOIC ACID	69-72-7
394	BENZENE-1,4-DICARBONIC ACID	100-21-0
395	BENZENE-1,4-DICARBONIC ACID DIMETHYLESTER	120-61-6
396	AMINOMACETIC ACID (3-METHYLPHENYL) METHYLESTER	39076-18-1
397	2-METHYLBENZOIC ACID	118-90-1
398	4-METHYLBENZENESULFONIC ACID	16722-51-3
399	4-METHYLBENZENESULFONYLCHLORIDE	98-59-9
400	BENZENE-1,2,4-TRICARBONIC ACID TRIBUTYLESTER	1726-23-4

401	TRICHLOROMETHYLBENZENE	98-07-7
402	1,2-DIMETHOXYBENZENE	91-16-7
403	BENZYLACETATE	140-11-4
404	DIMETHYLPHTHALATE	131-11-3
405	4-ISOPROPYLBENZOIC ACID	536-66-3
406	4-ISOPROPYL-1-METHYLBENZENE	99-87-6

2.1.2 NON-EASILY DEGRADABLE MONOCYCLIC AROMATIC COMPOUNDS

407	2-AMINOPHENOL	95-55-6
408	2,3-DIMETHYLPHENYLAMINE	87-59-2
409	2,5-DIMETHYLPHENYLAMINE	95-78-3
410	3-METHYLPHENYLAMINE	108-44-1
411	4-AMINOPHENOL	123-30-8
412	2,4-DINITROPHENOL	51-28-5
413	MONOTHIOPHOSPHORIC ACID O,O-DIMETHYL-O-(3-METHYL-4-NITROPHENYL) ESTER	122-14-5
414	THIOPHENOL	108-98-5
415	BROMOBENZENE	108-86-1
416	CHLOROBENZENE	108-90-7
417	NITROBENZENE	98-95-3
418	(TRIFLUOROMETHYL) BENZENE	98-08-8
419	(2-BROMOETHENYL) BENZENE	103-64-0
420	METHYLPHENYLAMINE	100-61-8
421	ETHYLPHENYLAMINE	103-69-5
422	DIMETHYLPHENYLAMINE	121-69-7
423	DIETHYLPHENYLAMINE	91-66-7
424	N-METHYL-N-PHENYLACETAMIDE	579-10-2
425	1-PHENYLETHYLAMINE	618-36-0
426	BENZENESULFAMIDE	98-10-2
427	3,4-DIMETHYLPHENYLAMINE	95-64-7
428	2,4-DIMETHYLPHENYLAMINE	95-68-1
429	3-METHOXYPHENYLAMINE	536-90-3
430	2-METHOXY-5-METHYLPHENYLAMINE	120-71-8
431	1,2-DIAMINOBENZENE	95-54-5
432	1,3-DIAMINOBENZENE	108-45-2
433	1,4-DIAMINOBENZENE	106-50-3
434	1,3-DIAMINO-4-METHYLBENZENE	95-80-7
435	2-NITROPHENYLAMINE	88-74-4
436	3-NITROPHENYLAMINE	99-09-2
437	4-NITROPHENYLAMINE	100-01-6
438	2-CHLOROPHENYLAMINE	95-51-2
439	3-CHLOROPHENYLAMINE	108-42-9
440	4-CHLOROPHENYLAMINE	106-47-8
441	4-CHLORO-3-METHYLPHENYLAMINE	7149-75-9
442	4-CHLORO-2-NITROPHENYLAMINE	89-63-4
443	3,4-DICHLOROPHENYLAMINE	95-76-1
444	2,5-DICHLOROPHENYLAMINE	95-82-9
445	3-AMINOBENZENESULFONIC ACID	121-47-1
446	2-AMINO-5-METHYLBENZENESULFONIC ACID	88-44-8
447	3-METHYL-4-NITROPHENOL	2581-34-2
448	5-METHYL-2-NITROPHENOL	700-38-9

449	4-METHYL-2-NITROPHENOL	119-33-5
450	2-METHYL-6-NITROPHENOL	13073-29-5
451	4-METHYL-1,2-DINITROBENZENE	610-39-9
452	1-CHLORO-2,4-DINITROBENZENE	97-00-7
453	5-CHLORO-2-NITROBENZENESULFONIC ACID	
454	3-NITROBENZENE-1,2-DICARBONIC ACID	603-11-2
455	5-CHLORO-2-NITROBENZOTRIFLUORIDE	118-83-2
456	1,3,5-TRIMETHYLBENZENE	108-67-8
457	1,2,3-TRIMETHYLBENZENE	526-73-8
458	5-CHLORO-2-METHYLPHENOL	5306-98-9
459	3-CHLORO-4-METHYLPHENOL	615-62-3
460	4-CHLORO-2-METHYLPHENOL	1570-64-5
461	2-CHLORO-4,6-DIMETHYLPHENYLAMINE	63133-82-4
462	1,2-DICHLOROBENZENE	95-50-1
463	1,3-DICHLOROBENZENE	541-73-1
464	2,4,6-TRICHLOROPHENYLAMINE	634-93-5
465	2,4,6-TRICHLORO-1-NITROBENZENE	18708-70-8
466	1,2,3-TRICHLOROBENZENE	87-61-6
467	1,2,4-TRICHLOROBENZENE	120-82-1
468	1,3,5-TRICHLOROBENZENE	108-70-3
469	1,2,4,5-TETRACHLOROBENZENE	95-94-3
470	1,2,3,4-TETRACHLOROBENZENE	634-66-2
471	PENTACHLOROBENZENE	608-93-5
472	HEXACHLOROBENZENE	118-74-1
473	2-CHLOROPHENOL	95-57-8
474	3-CHLOROPHENOL	108-43-0
475	2,3-DICHLOROPHENOL	576-24-9
476	2,4-DICHLOROPHENOL	120-83-2
477	2,5-DICHLOROPHENOL	583-78-8
478	2,6-DICHLOROPHENOL	87-65-0
479	3,4-DICHLOROPHENOL	95-77-2
480	3,5-DICHLOROPHENOL	591-35-5
481	2,4,5-TRICHLOROPHENOL	95-95-4
482	4-BROMO-2,5-DICHLOROPHENOL	1940-42-7
483	2,3,4,6-TETRACHLOROPHENOL	58-90-2
484	PENTACHLOROPHENOL	87-86-5
485	PENTACHLORONITROBENZENE	82-68-8
486	PENTABROMOMETHYLBENZENE	87-83-2
487	HEXABROMOBENZENE	87-82-1
488	6-TERT-BUTYL-2,4-DIMETHYL-1,3,5-TRINITROBENZENE	81-15-2
489	4-PHENYL-3-BUTENE-2-ONE	122-57-6
490	2-PHENYL-1-PROPENE	98-83-9
491	3-NITROBENZOIC ACID	121-92-6
492	2-NITROPHENOL	88-75-5
493	1,2-DINITROBENZENE	528-29-0
494	1,3-DINITROBENZENE	99-65-0
495	1,4-DINITROBENZENE	100-25-4
496	1-METHOXY-3-NITROBENZENE	555-03-3
497	2-SULFOBENZOIC ACID	632-25-7
498	3-SULFOBENZOIC ACID	121-53-9
499	4-SULFOBENZOIC ACID	636-78-2
500	2-NITROBENZENESULFONIC ACID	

501	3-NITROBENZENESULFONIC ACID	98-47-5
502	4-NITROBENZENESULFONIC ACID	138-42-1
503	1,3-BENZENEDISULFONIC ACID	98-48-6
504	1-CHLORO-3-NITROBENZENE	121-73-3
505	2-CHLORO-1-METHYLBENZENE	95-49-8
506	4-CHLORO-1-METHYLBENZENE	106-43-4
507	2-IODOBENZOIC ACID	88-67-5
508	2-BROMOPHENOL	95-56-7
509	3-BROMOPHENOL	591-20-8
510	4-BROMOPHENOL	106-41-2
511	1,4-DIBROMOBENZENE	106-37-6
512	1,2-DICYANOBENZENE	91-15-6
513	1,3-DICYANOBENZENE	626-17-5
514	1,4-DICYANOBENZENE	623-26-7
515	N-(4-ETHOXYPHENYL) ACETAMIDE	62-44-2
516	4-(ACETYLAMINO) PHENYLSULFONIC ACID	121-62-0
517	4-(METHYLAMINO) BENZOIC ACID	10541-83-0
518	1-METHYL-3-(METHYLAMINO) BENZENE	696-44-6
519	2-CHLORO-1-ETHENYLBENZENE	2039-87-4
520	3-CHLORO-1-ETHENYLBENZENE	2039-85-2
521	4-CHLORO-1-ETHENYLBENZENE	1073-67-2
522	1-METHYL-3-NITROBENZENE	99-08-1
523	2-AMINO-5-CHLORO-4-METHYL-BENZENESULFONIC ACID	88-53-9
524	4-TERT-BUTYLPHENOL	98-54-4
525	2-CHLOROBENZOIC ACID	118-91-2
526	1-CHLORO-2-NITROBENZENE	88-73-3
527	1-CHLORO-4-NITROBENZENE	100-00-5
528	4-ETHOXYPHENYLAMINE	156-43-4
529	2-METHOXY-1-NITROBENZENE	91-23-6
530	4-METHOXY-1-NITROBENZENE	100-17-4
531	2-METHYL-1-NITROBENZENE	88-72-2
532	4-METHYL-1-NITROBENZENE	99-99-0
533	2-METHYLPHENYLSULFONAMIDE	88-19-7
534	1,2,4-TRIMETHYLBENZENE	95-63-6
535	1,3-BIS-(AMINOMETHYL) BENZENE	1477-55-0
536	4-CHLORO-3-METHYLPHENOL	59-50-7
537	2-CHLORO-5-METHYLPHENOL	615-74-7
538	4-CHLOROPHENYL-(3-IODO-2-PROPINYLOXYMETHYL) ETHER	29772-02-9
539	PHOSPHORIC ACID ESTER DERIVATIVE	22248-79-9
540	1,2-DICHLORO-4-NITROBENZENE	99-54-7
541	2,4-DICHLORO-6-NITROPHENOL	609-89-2
542	N'-(3,4-DICHLOROPHENYL)-N-METHOXY-N-METHYLUREA	330-55-2
543	DITHIOPHOSPHORIC ACID ESTER DERIVATIVE	2597-03-7
544	N-ETHYL-4-METHYLPHENYLAMINE	622-57-1
545	N-METHYL-2-METHYLPHENYLAMINE	611-21-2
546	N,N-DIMETHYLBENZYLAMINE	103-83-3
547	O,O-DIETHYL-O-(CYANOBENZYLIDENAMINO) THIOPHOSPHATE	14816-18-3
548	3-ISOPROPYL-1-METHYLBENZENE	535-77-3
549	4-TERT-BUTYL-1-BENZOIC ACID	98-73-7

550	2-SEC-BUTYLPHENYL-1-N-METHYLCARBAMATE	3766-81-2
551	N,N-DIETHYL-3-TOLUAMIDE	134-62-3
552	2-ISOPROPYLPHENYL-1-N-METHYLCARBAMATE	2631-40-5
553	4-ISOPROPENYL-1-CHLOROBENZENE	1712-70-5
554	1,2-DIBUTOXYBENZENE	
555	2-ISOPROPYL-1-METHYLBENZENE	527-84-4
556	2-NITRO-4-METHOXY-1-ANILINE	96-96-8
557	3,5-DIMETHYLANILINE	108-69-0
558	2,3,6-TRICHLOROBENZOIC ACID	50-31-7
559	2-METHOXY-4-NITRO-1-ANILINE	97-52-9
560	2,6-DI-TERT-BUTYL-4-ETHYL-1-PHENOL	4130-42-1
561	1,3,5-TRI-TERT-BUTYLBENZENE	1460-02-2
562	2,4-DI-TERT-BUTYLPHENOL	96-76-4
563	3-(3,4-DICHLOROPHENYL)-1,1-DIMETHYL-UREA	330-54-1

2.2 POLYCYCLIC AROMATIC COMPOUNDS

2.2.1 EASILY DEGRADABLE POLYCYCLIC AROMATIC COMPOUNDS

564	PHOSPHORIC ACID TRIS-[2-METHYLPHENYL) ESTER	78-30-8
565	BIPHENYL	92-52-4
566	2-HYDROXYBIPHENYL	90-43-7
567	2,2'-BIPHENYLDICARBONIC ACID	482-05-3
568	2-HYDROXY-1,2-DIPHENYLETHANE-1-ONE	119-53-9
569	1,3-DIPHENYL-1,3-PROPANEDIONE	120-46-7
570	1-NAPHTHALENECARBONIC ACID	86-55-5
571	2-NAPHTHALENECARBONIC ACID	93-09-4
572	1-HYDROXYNAPHTHALENE	90-15-3
573	2-HYDROXYNAPHTHALENE	135-19-3
574	PHENANTHRENE	85-01-8
575	BENZENE-1,2-DICARBONIC ACID MONOBUTYL-MONOBENZYLESTER	85-68-7
576	CHLORODIPHENYLMETHANE	24161-14-6
577	DIBENZOYLPEROXIDE	94-36-0
578	BENZENE-1,2-DICARBONIC ACID DICYCLOHEXYLESTER	84-61-7
579	2,3-DIMETHYLNAPHTHALENE	581-40-8
580	DIPHENYLMETHANOL	91-01-0
581	2-HYDROXYNAPHTHALENE-1-ALDEHYDE	708-06-5
582	AMINOMACETIC ACID (1-NAPHTHYLMETHYLESTER)	63-25-2
583	TRIBENZYLPHOSPHITE	
584	PHOSPHORIC ACID TRIPHENYLESTER	115-86-6

2.2.2 NON-EASILY DEGRADABLE POLYCYCLIC AROMATIC COMPOUNDS

585	BIS-(2,4-DICHLOROBENZOYL) PEROXIDE	133-14-2
586	4-CYANO-4'-HEXYLBIPHENYL	41122-70-7
587	3,5-DI-TERT-BUTYL-4-HYDROXYBIPHENYL	2668-47-5
588	DECABROMOBIPHENYL	13654-09-6
589	3,3'-DICHLORO-4,4'-BIPHENYLDIAMINE	91-94-1

590	3,3'-DIMETHYL-4,4'-BIPHENYLDIAMINE	119-93-7
591	3,3'-DIMETHOXY-4,4'-BIPHENYLDIAMINE	119-90-4
592	1,4-DIPHENYLBENZENE	92-94-4
593	DIPHENYLETHER	101-84-8
594	DECABROMODIPHENYLETHER	1163-19-5
595	2,4,6-TRICHLORO-4'-NITRODIPHENYLETHER	1836-77-7
596	DIPHENYLETHER-4,4'-DISULFONOHYDRAZID	80-51-3
597	4,4'-THIOBIS-(2-TERT-BUTYL-5-METHYLPHENOL)	96-69-5
598	DIBENZYLETHER	103-50-4
599	DIPHENYLAMINE	122-39-4
600	4-NITROSODIPHENYLAMINE	156-10-5
601	N-NITROSODIPHENYLAMINE	86-30-6
602	4-METHOXYDIPHENYLAMINE	1208-86-2
603	N,N'-DIPHENYL-1,4-DIAMINOBENZENE	74-31-7
604	4-(1-METHYLETHYL-AMINO) DIPHENYLAMINE	101-72-4
605	2-HYDROXY-2,2-DIPHENYLACETIC ACID	76-93-7
606	TRIPHENYLMETHYLCHLORIDE	76-83-5
607	4-BENZYLPHENOL	101-53-1
608	BIS-(4-AMINOPHENYL) METHANE	101-77-9
609	1,1,1-TRICHLORO-2,2-BIS-(4-CHLOROPHENYL) ETHANE	50-29-3
610	2,2,2-TRICHLORO-1,1-BIS-(4-CHLOROPHENYL) ETHANOL	115-32-2
611	2,2-BIS-(3,5-DIBROMO-4-HYDROXYPHENYL) PROPANE	79-94-7
612	2,2-BIS-[3,5-DIBROMO-4-(2-HYDROXYETHOXY) PHENYL] PROPANE	4162-45-2
613	2,2-BIS-(4-HYDROXYPHENYL) PROPANE	80-05-7
614	BENZOPHENONE	119-61-9
615	2-HYDROXY-4-OCTYLOXY BENZOPHENONE	1843-05-6
616	BIS-(4-DIMETHYLAMINO) BENZOPHENONE	90-94-8
617	1-NAPHTHYLAMINE	134-32-7
618	N-PHENYL-1-NAPHTHYLAMINE	90-30-2
619	4-(N-1-NAPHTHYLIMINO)-2-BUTANOL	
620	8-AMINO-1-NAPHTHALENESULFONIC ACID	82-75-7
621	2-AMINO-1-NAPHTHALENESULFONIC ACID	81-16-3
622	N-PHENYL-2-NAPHTHYLAMINE	135-88-6
623	2-(1-NAPHTHYL)-ACETIC ACID	86-87-3
624	3-HYDROXYNAPHTHALENE-2-CARBONIC ACID	92-70-6
625	2,4-DICHLORO-1-HYDROXYNAPHTHALENE	2050-76-2
626	6-AMINO-4-HYDROXYNAPHTHALENE-2-SULFONIC ACID	90-51-7
627	7-AMINO-4-HYDROXYNAPHTHALENE-2-SULFONIC ACID	87-02-5
628	2-MERCAPTONAPHTHALENE	91-60-1
629	3-HYDROXYNAPHTHALENE-2-CARBOXY-(N-PHENYL) AMIDE	92-77-3
630	ANTHRACENE	120-12-7
631	2,3-DICHLORO-1,4-NAPHTHOQUINONE	117-80-6
632	1-CHLORO-9,10-ANTHRAQUINONE	82-44-0
633	2-ETHYL-9,10-ANTHRAQUINONE	84-51-5
634	BENZO[D]ANTHRACENE-9-ONE	82-05-3
635	2-CHLORO-9,10-ANTHRAQUINONE	131-09-9

636	2-PENTYL-9,10-ANTHRAQUINONE	13936-21-5
637	BENZO[A]-9,10-ANTHRAQUINONE	2498-66-0
638	1,2,3,4-TETRAHYDRONAPHTHALENE	119-64-2
639	DIPHENYLMETHANE	101-81-5
640	BIS-(4-HYDROXY-3,5-DI-TERT-BUTYLPHENYL) METHANE	118-82-1
641	3-PHENOXYBENZALDEHYDE	39515-51-0
642	4,4’-DIMETHOXYDIPHENYLAMINE	101-70-2
643	2,2’,3,3’-TETRACHLORO-4,4’-DIAMINODIPHENYL METHANE	
644	2-BIPHENYLAMINE	90-41-5
645	BIS-(ALPHA,ALPHA-DIMETHYLBENZYL) PEROXIDE	80-43-3
646	5-CHLORO-2-(2,4-DICHLPHENOXY) PHENOL	3380-34-5
647	4,4’-DIAMINO-5,5’-DICHLORO-3,3’-BIPHENYL-DISULFONIC ACID	
648	(DIPHENYLMETHYL)-2-CHLOROETHYLETHER	32669-06-0
649	N-ETHYL-1-NAPHTHYLAMINE	118-44-5
650	(2-METHYLPROPYL)-2-NAPHTHYLETHER	2173-57-1
651	NAPHTHALENE-2,6-DICARBONIC ACID	2666-06-0
652	4-PHENYLPHENOL	92-69-3
653	PHOSPHORIC ACID TRIS-[4-(1-METHYLETHYL) PHENYLESTER]	26967-76-0
654	TRIPHENYLTINFLUORIDE	379-52-2
655	TRIPHENYLTINHYDROXIDE	
656	FLUORENE	86-73-7
657	ACENAPHTHYLENE	208-96-8
658	ACENAPHTHENE	83-32-9
659	1,8-DIAMINONAPHTHALENE	479-27-6
660	1,5-DIAMINONAPHTHALENE	2243-62-1
661	4,4’-DIBROMOBIPHENYL	92-86-4
662	DISPERSE BLUE 54	20241-76-3
663	2,2’-BIS(4-CHLOROPHENYL)-2-HYDROXY-ETHYLACETATE	510-15-6
664	3,3’-DICHLORO-4,4’-DIAMINODIPHENYLMETHANE	101-14-4
665	2,2’-DIHYDROXY-5,5’-DICHLORODIPHENYLMETHANE	97-23-4
666	DISPERSE YELLOW 42	5124-25-4
667	BIS(2,3,5-TRICHLORO-6-HYDROXYPHENYL) METHANE	70-30-4
668	N-(3,4-DICHLOROPHENYL)-N’-[2’-(4’’-CHLORO 2’’-SULFOPHENOXY)-5’-CHLOROPHENYL] UREA	3567-25-7
669	2,2’-METHYLENE-BIS(6-TERT-BUTYL-4-METHYLPHENOL	119-47-1
670	DISPERSE YELLOW 163	67923-43-7
671	DISPERSE RED 167	
672	2,2’-DICHLOROHYDRAZOBENZENE	782-74-1
673	2-HYDROXY-4-METHOXYBENZOPHENONE	131-57-7
674	2-AMINOANTHRAQUINONE	117-79-3
675	1-AMINOANTHRAQUINONE	82-45-1
676	DISPERSE RED 207	59722-76-8
677	1-HYDROXYANTHRAQUINONE	129-43-1
678	PHENYL-2,5-XYLYLMETHANE	13540-50-6
679	O-ETHYL-O-2,4-DICHLOROPHENYL PHENYLTHIOPHOSPHONAT	

680	DIPHENYLMONOTRIDECYLPHOSPHITE	60628-17-3
681	DISPERSE ORANGE 73	
682	O-ETHYL-O-4-NITROPHENYLPHOSPHONOTHIOATE	2104-64-5
683	2-NAPHTHALENETHIOL	529-36-2
684	TETRAPHENYLTIN	595-90-4
685	TRIPHENYLTINDIMETHYLDITHIOCARBAMATE	1803-12-9

3. HETEROCYCLIC COMPOUNDS

3.1 MONOCYCLIC HETEROCYCLIC COMPOUNDS

3.1.1 EASILY DEGRADABLE MONOCYCLIC HETEROCYCLIC COMPOUNDS

686	CIS-2-BUTENEDIACID ANHYDRIDE	108-31-6
687	TETRAHYDROFURANE	109-99-9
688	DODECANOIC ACID (2-OXA-4,5,6-TRIHYDROXY-CYCLOHEXYL) METHYLESTER	
689	HEXADECANOIC ACID (2-OXA-4,5,6-TRIHYDROXY-CYCLOHEXYL) METHYLESTER	
690	PIPERIDINE	110-89-4
691	1,3,5-TRIETHYLHEXAHYDRO-1.3.5-TRIAZINE	7779-27-3
692	N-DODECYL-CIS-BUT-2-ENE-DIACID IMIDE	
693	BUTYL-(2,3-EPOXYPROPYL) ETHER	2426-08-6
694	HEXANOIC ACID LACTAM	105-60-2
695	3-ACETYL-6-METHYL-1-OXA-CYCLOHEX-5-ENE-2,4-DIONE	520-45-6
696	ACETIC ACID (2,6-DIMETHYL-1,3-DIOXANE-4-YL) ESTER	828-00-2
697	1,3-DIOXOLANE-2-ONE	96-49-1
698	1-CHLORO-2,3-EPOXYPROPANE	106-89-8
699	1,3,5-TRIS-(2-HYDROXETHYL) HEXAHYDRO-1,3,5-TRIAZINE	4719-04-4
700	3-HYDROXYPROPIONOIC ACID LACTONE	57-57-8
701	DIKETENE	674-82-8
702	2,3-EPOXYPROPANE	75-56-9
703	N-METHYL-2-PYRROLIDINONE	872-50-4
704	y-BUTYROLACTONE	96-48-0
705	2-HYDROXYMETHYL-1-OXACYCLOPENTA-2,4-DIENE	98-00-0
706	FURFURAL	98-01-1
707	PYRIDINE	110-86-1
708	2-HYDROXYPYRIDINE	142-08-5
709	3-HYDROXYPYRIDINE	109-00-2
710	4-HYDROXYPYRIDINE	108-96-3
711	2-METHYLPYRIDINE	109-06-8
712	PYRROL	109-97-7
713	N-METHYLPYRROL	96-54-8
714	2,4,6-TRIHYDROXYPYRIMIDINE	
715	3-HYDROXY-5-HYDROXYMETHYL-2-METHYLPYRIDYL-4-ALDEHYDE	66-72-8
716	PYRIDINE-2,6-DICARBONIC ACID	499-83-2
717	4-FORMYL-3-HYDROXY-5-HYDROXYMETHYL-2-METHYLPYRIDINE	66-72-8

3.1.2 NON-EASILY DEGRADABLE MONOCYCLIC HETEROCYCLIC COMPOUNDS

718	SULFOLANE	126-33-0
719	1,4-DIOXANE	123-91-1
720	PARALDEHYDE	123-63-7
721	2,6-DIMETHYLPIPERIDINE	504-03-0
722	N-METHYLPIPERIDINE	626-67-5
723	2,4,6-TRIOXOHEXAHYDRO-1,3,5-TRIAZINE	
724	1,3,5-TRIS-(2-HYDROXYETHYL)-2,4,6-TRIOXOHEXAHYDRO-1,3-TRIAZINE	839-90-7
725	LAURYLLACTAM	947-04-6
726	N-ISOBUTYLMORPHOLINE	10315-98-7
727	MONOTHIOPHOSPHORIC ACID O,O-DIETHYL-O-(2-AZA-3,4,6-TRICHLOROPHENYLESTER	2921-88-2
728	MONOTHIOPHOSPHORIC ACID O,O-DIETHYL-O-(2,4-DIAZAPHENYL) ESTER DERIVATIVE	333-41-5
729	FURANE	110-00-9
730	THIOPHENE	110-02-1
731	2-AMINOPYRIDINE	504-29-0
732	3-AMINOPYRIDINE	462-08-8
733	4-AMINOPYRIDINE	504-24-5
734	4-ETHENYLPYRIDINE	100-43-6
735	2-CHLOROPYRIDINE	109-09-1
736	2-BROMO-3,5-DICHLOROPYRIDINE	14482-51-0
737	2,3,5-TRICHLOROPYRIDINE	16063-70-0
738	2,4,6-TRIAMINO-1,3,5-TRIAZINE	108-78-1
739	6-CHLORO-2,4-BIS-(ETHYLAMINO)-1,3,5-TRIAZINE	122-34-9
740	3-AMINO-1,2,4-TRIAZOL	61-82-5

3.2 POLYCYCLIC HETEROCYCLIC COMPOUNDS

3.2.1 EASILY DEGRADABLE POLYCYCLIC HETEROCYCLIC COMPOUNDS

741	HEXAMETHYLENETETRAMINE	100-97-0
742	QUINOLINE-2-CARBONIC ACID	93-10-7
743	BENZENE-1,2-DICARBONIC ACID ANHYDRIDE	85-44-9
744	CHROMENE-2-ONE	91-64-5
745	N-(2-CHLORO-1-ETHOXYETHYL) BENZENE-1,2-DICARBONIC ACID	
746	N-(4-METHYLPHENYL)-CIS-BUT-2-ENE DIACID IMIDE	
747	2,3-EPOXYPROPYLPHENYLETHER	122-60-1
748	STYROLOXIDE	96-09-3
749	3,4-DICARBONIC ACID ANHYDRIDE-1-BENZOIC ACID	552-30-7

3.2.2 NON-EASILY DEGRADABLE POLYCYCLIC HETEROCYCLIC COMPOUNDS

750	1,8,9,10,11,11-HEXACHLORO-4,5-EPOXY-TETRA-CYCLO-[6.2.1.1.(3,60(2,7)]-9-DODECANE	72-20-8
751	PENTANEDIACID IMIDE DERIVATIVE	
752	BICYCLO-[2.2.2]-OCTA-5-ENE-2,3-DICARBOXIMIDE DERIVATIVE	
753	1,2,5,6-TETRAHYDRONAPHTHALIMIDE	85-40-5
754	2-MERCAPTOBENZO[D]-1.3-THIAZOL	45769-89-9
755	2-(4-MORPHOLINOTHIO) BENZO[D]-1,3-THIAZOL	102-77-2
756	2-(CYCLOHEXYLAMINOTHIO) BENZO[D]-1,3-THIAZOL	95-33-0
757	BIS-[2-(BENZO[D]-1,3-THIAZOLO)] DISULFIDE	120-78-5
758	2-MERCAPTOBENZO[D]IMIDAZOL	583-39-1
759	PHENOTHIAZINE	92-84-2
760	5-NITROBENZO[D]IMIDAZOL	94-52-0
761	4-(2-BROMOPROPIONAMIDO) PHENAZONE	
762	QUINOLINE	91-22-5
763	CARBAZOL	86-74-8
764	DIBENZO[B,D] FURANE	132-64-9
765	N-(2-METHOXYPHENYL)-CIS-BUT-2-ENE-DIACID IMIDE	
766	N-(2,4,6-TRICHLOROPHENYL)-CIS-BUT-2-ENE-DIACID IMIDE	13167-25-4
767	N,N-BIS-(2,3-EPOXYPROPYL)-2-PHENYLAMINE	2095-06-9
768	N,N-BIS-(2,3-EPOXYPROPYL)-2-METHYL-PHENYLAMINE	40027-50-7
769	4,5-DICHLORONAPHTHALENE-1,8-DICARBONIC ACID ANHYDRIDE	
770	BENZIMIDAZOL-2-YL-CARBAMINIC ACID METHYLESTER	10605-21-7
771	BENZOTHIAZOL	95-16-9
772	2-(THIOCYANOMETHYLTHIO) BENZOTHIAZOL	21564-17-0
773	DISPERSE RED 206	
774	DIBENZOTHIOPHENE	132-65-0

Annex 2

Application of the SARs Developed

Introduction

Validation provides necessary information on the applicability of SARs. It reveals the models' predictive power, depending on the range of chemicals used for deriving the model. External validation with diverse chemicals allows identification of the substructures covered by the model. Further analysis to identify additional substructure indicators can be used either to extend existing models or to refine restrictions of their applicability.

Results

Within the UBA project on "estimating environmental fate of chemicals by computer assisted reactivity simulations", the validity of published SARs for estimating biodegradation was examined and new SARs were derived for several classes of compounds. The development of SARs was based on 600 MITI biodegradation data (OECD Test Guideline 301C) providing training sets and validation sets. Three models estimating biodegradation for acyclic compounds and two models for monocyclic aromatic compounds were obtained from training sets using substructure indicators. Misclassification of compounds from the validation sets results in restrictions on application of the models.

One hundred fourteen further MITI biodegradation data, provided by Dr. Takatsuki, made a second validation possible (**Table A1**). For validation of three models estimating biodegradation of acyclic compounds, 39 substances were available. For validation of two models for estimating biodegradation of aromatic compounds, 21 substances (ten disubstituted, three monosubstituted, eight polysubstituted) were available. Calculation of biodegradability for heterocyclics and polycyclic aliphatic and aromatic compounds has not been possible until now. The models derived are applicable to 53 per cent of the compounds.

Aliphatic acyclic compounds:

Model 74: Five substructure indicators are used for estimating biodegradation of acyclic compounds. The application of Model 74 to 39 acyclic compounds resulted in misclassification of 32 per cent of the compounds. The exclusion of phosphoric acids, tert. amines, hydrazines and disulphides yielded 90 per cent correct classification. The restriction of Model 74 to compounds with defined substituents (OH, CO, hal, CH_3, C-NH_2) resulted in 100 per cent correct classification. Respecting this limitation, the calculation is restricted to only 21 per cent of the compounds (**Table A2, Figures A1 and A2**).

Table A1: MITI biodegradation data for validation and extension of existing models

substance class	number of MITI biodegradation data		
	total	easily degradable	not easily degradable
aliphatic			
acyclic	39	18	21
monocyclic	7	3	4
polycyclic	2	0	2
aromatic			
monocyclic	21	3	18
polycyclic	30	0	30
heterocyclic			
monocyclic	8	5	3
polycyclic	7	2	5
total	114	31	83

Model 75: Model 75 is an extension of Model 74. It includes two additional substructure indicators. The application of Model 75 to 39 acyclic compounds resulted in about 20 per cent misclassified compounds. Exclusion of hydrazines and disulphides achieved 88 per cent correct classification. Using Model 75 for chemicals with defined substituents (OH, CO, hal, CH_3, C-NH_2, phosphoric acid and tert. amine), about 95 per cent of the compounds are correctly classified (Table A2, Figures A1 and A2).

Model 76: The qualitative Model 76 considers substructure indicators identified as being associated with readily degradable or non-readily degradable compounds. When new biodegradation data become available, additional substructure indicators can be added. The application of the extended Model 76 to acyclic compounds resulted in 100 per cent correct classification (Table A2, Figures A1 and A2).

Monocyclic aromatic compounds:

Model 77: Seven substructure indicators are used for estimating biodegradation of monocyclic compounds. The application of Model 77 to ten monocyclic disubstituted aromatic compounds resulted in misclassification of 57 per cent of the chemicals. The restriction for application of the model to chemicals with defined functional groups [ON, NO_2, NH_2, COO(R) SO_3H, amide, CO, hal, CH_2(R)] resulted in a 100 per cent correct classification (only one compound). Respecting the limitations, no results for the other disubstituted compounds can be achieved. Using Model 77 for estimating biodegradation of monosubstituted compounds, no reliable results can be obtained and only 57 per cent of the polysubstituted compounds are correctly classified (**Table A3, Figures A3 and A4**).

Model 78: Model 78 is an extension of Model 77. It includes one additional substructure indicator. The application of Model 78 results in a 90 per cent correct classification of compounds. Restrictions for application gave no better classification. Using Model 78 for monosubstituted compounds, 100 per cent correct classification is obtained (only one compound). The application to eight polysubstituted compounds results in 88 per cent correct classification (Table A3, Figures A3 and A4).

Table A2: Number of acyclic compounds for which prediction of biodegradability is possible using Models 74-76 and percentages of correct prediction of biodegradability

subst. class	total n	application possible n	%	correct classification n	%
Model 74:					
1	39	38	97	26	68
2	39	29	74	26	90
3	38	8	21	8	100
Model 75:					
4	39	38	97	30	79
5	39	34	87	30	88
6	39	16	41	15	94
Model 76:					
7	39	19	49	19	100

substance class:

1: all acyclic compounds
2: not phosphoric acids, disulphides, tert. amines, hydrazines
3: acyclic compounds with the substituents: OH, CO, CH_3, CH_2NH_2, hal
4: all acyclic compounds
5: not disulphides, hydrazines
6: acyclic compounds with the substituents: OH, CO, CH_3, CH_2NH_2, hal, phosphoric acids, tert. amines
7: specific compounds

Table A3: Number of monocyclic aromatic compounds for which prediction of biodegradability is possible using Models 77-78 and percentages of correct prediction of biodegradability

subst. class	total n	application possible n	%	correct classification n	%
Model 77:					
1	10	7	70	3	43
2	10	1	10	1	100
4	3	0	0	0	0
5	8	7	88	4	57
Model 78:					
1	10	10	100	9	90
3	10	9	90	8	88
4	3	1	33	1	100
5	8	8	100	7	88

substance class:

1: disubstituted monocyclic aromatic compounds
2: disubstituted aromatic compounds with the substituents: OH, NO_2, NH_2, COOR, SO_3H, amide, OC, hal, CH_2R
3: disubstituted aromatic compounds with the substituents: OH, NO_2, NH_2, COOR, SO_3H, amide, OC, hal, CH_2R, R
4: monosubstituted monocyclic aromatic compounds
5: polysubstituted monocyclic aromatic compounds

Conclusion

Most of the compounds that were not included in the original dataset to derive the SARs were correctly classified using Models 75, 77 and 78 (89 per cent; 49 from 55 compounds). Respecting the limitations for the application of the models, the calculations yielded reliable results. The application of the models to further biodegradation data gave additional information on the validity of the models: (1) the exclusion of some compounds is necessary to avoid serious misclassification; (2) the restrictions made for Model 77 result in low applicability of the model; (3) the supplemented functional groups in Model 75 and Model 78 make a contribution to the validity and applicability of the models, so that the biodegradability can be calculated for a broader range of compounds with sufficient agreement.

Figure A1: Number of acyclic compounds for which prediction of biodegradability is possible using Models 74-76[1]

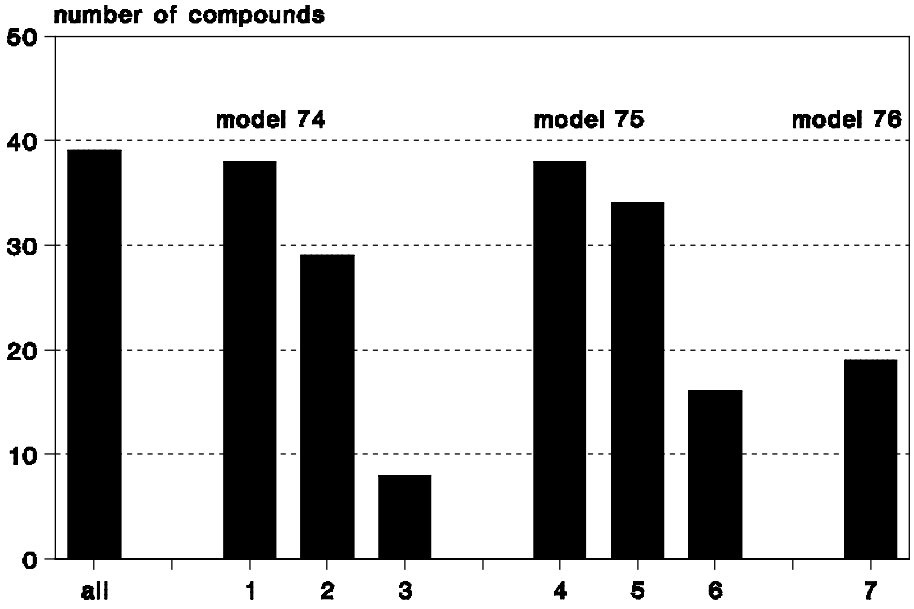
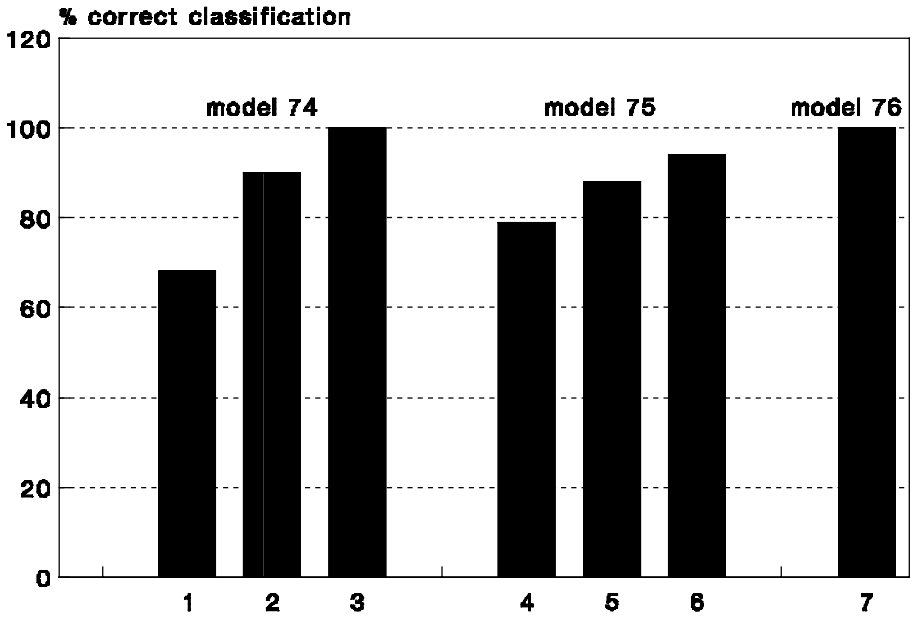


Figure A2: Percentage of correct prediction of biodegradability for acyclic compounds using Models 74-76[1]



[1] Substance classes: (1) all acyclic compounds; (2) not phosphoric acids, disulphides, tert. amines, hydrazines; (3) acyclic compounds with the substituents OH, CO, CH_3, CH_2NH_2, hal; (4) all acyclic compounds; (5) not disulphides, hydrazines; (6) acyclic compounds with the substituents OH, CO, CH_3, CH_2NH_2, hal, phosphoric acids and tert. amines; (7) specific compounds.

Figure A3: Number of monocyclic aromatic compounds for which prediction of biodegradability is possible using Models 77 and 78[1]

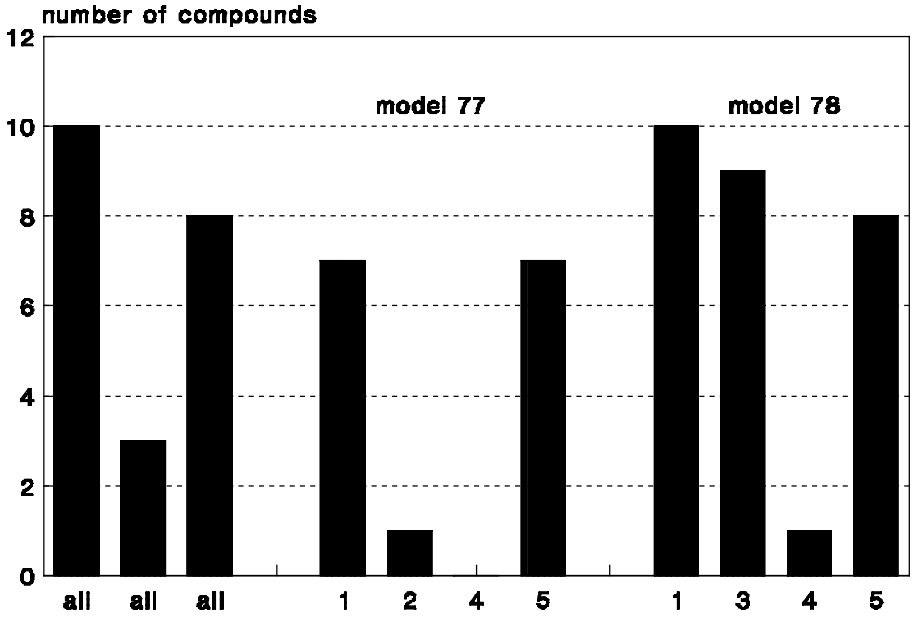
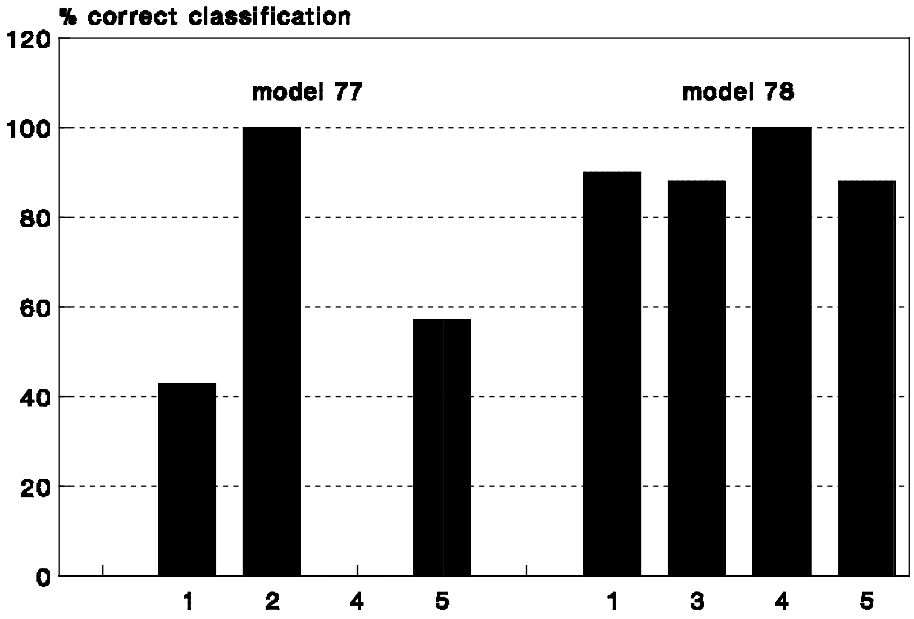


Figure A4: Percentage of correct prediction of biodegradability for monocyclic aromatic compounds using Models 77 and 78[1]



[1] Substance classes: disubstituted monocyclic aromatics [(1) all disubstituted monocyclic aromatics; (2) disubstituted aromatics with the substituents OH, NO_2, NH_2, COOR, SO_3H, amide, OC, hal, CH_2R; (3) disubstituted aromatics with the substituents OH, NO_2, NH_2, COOR, SO_3H, amide, OC, hal, CH_2R, R]; (4) monosubstituted monocyclic aromatics; (5) polysubstituted monocyclic aromatics.

Members of the Hazard Assessment Body (HAAB)

C. Auer, EPA (United States)

P. Cocoran, DOE (United Kingdom)

A. Gies-Reuschel, UBA (Germany)

N. Juul Jensen, Environmental Protection Agency (Denmark)

Y. Kurokawa, NIHS (Japan)

P. Murphy, DGXI (Commission of the European Communities)

C. Van Leeuwen (Chairman), Directorate General for Environmental Protection (Netherlands)