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APPLICATION OF STRUCTURE-ACTIVITY RELATIONSHIPS TO THE ESTIMATION OF PROPERTIES IMPORTANT IN EXP0SURE ASSESSMENT

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

Paris 1993

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APPLICATION OF STRUCTURE-ACTIVITY RELATIONSHIPS TO THE ESTIMATION OF PROPERTIES IMPORTANT IN EXPOSURE ASSESSMENT

Environment Directorate

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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.

Application of SARs to the estimation of physical-chemical properties of importance in exposure assessment

The project on "Application of SARs to the Estimation of Physical-Chemical Properties of Importance in Exposure Assessment" was led by Germany. Its objectives were to identify and compare practical approaches used in Member countries in the estimation of key physical-chemical properties of importance in exposure assessment.

This document presents the results of a survey on the state of validation of various Quantitative Structure Activity Relationship (QSAR) models for exposure-related parameters. It also contains recommended QSARs which can be used at the stage of initial screening of substances in order to substitute missing information.

This document is based on a discussion document presented to the special session on SARs at the OECD Workshop on Application of Simple Models for Exposure Assessment (11-13 December 1991, Berlin), which was sponsored by the German Federal Ministry of the Environment and organised by the Federal Environment Agency of Germany (Umweltbundesamt). It was reviewed taking into account the results of the workshop discussions. The document has also been reviewed by several experts on SARs.

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Summary

This document results from an OECD Hazard Assessment project on "Application of Structure-Activity Relationships (SARs) to the Estimation of Physical-Chemical Properties of Importance in Exposure Assessment", which was led by Germany. The projects's objectives were to identify and compare practical approaches in use in Member countries to estimate key physical-chemical properties of importance in exposure assessment. In this document are presented the results of a survey of the validation status of the various Quantitative Structure-Activity Relationship (QSAR) models for exposure-related parameters, as well as the QSARs recommended for application at the stage of initial screening of substances to obtain substitutes for missing information.

SAR models have been developed for the estimation of a variety of parameters relevant to the exposure assessment of existing chemicals. They are based on descriptors numerically encoding structural features or physical measurements related to the chemical structure. Descriptors for a chemical can be grouped according to physical-chemical, geometrical, topological, and electronic properties. The physical-chemical descriptors have been applied in the modelling of processes such as partitioning between two phases, e.g. adsorption, diffusion, solubility. The geometric and topological descriptors are mainly used in correlations estimating properties such as partition coefficients and adsorption coefficients. The geometric and electronic properties can be calculated using empirical and semi-empirical quantum mechanical methods.

Procedures of varying accuracy exist to obtain quantifications for most of the parameters which are relevant for hazard and risk assessment. The estimates for the partition coefficient (P_{OW}), the water solubility (S_W), the acid dissociation constant (pKa), the Henry's law constant (H), the vapour pressure (P_V), the atmospheric degradation (K_{OH}), and the bioconcentration factor (BCF) are in good or sufficient agreement with the experimental data. In particular the P_{OW} values, which are extensively used in SAR studies, are accessible for many types of chemicals by an automated technique based on the fragment constant method developed by Hansch and Leo. The conservative approach of correspondence of P_{OW} and BCF allows determination of the bioconcentration potential of a compound. However, sufficiently reliable estimation procedures for estimating the melting point (T_m), the boiling point (T_b), the adsorption coefficient (K_{OC}), or for more complex parameters such as degradation rate constants, are not yet available.

Gaps still exist for several parameters which are crucial in exposure assessment. Due to the lack of systematic definition, some phenomena, such as biodegradation or soil sorption, are not accessible to comprehensive modelling. Satisfactory SARs are only available for strictly limited chemical classes. It is necessary to investigate further the experimental as well as the theoretical aspects of these parameters.

Many of the descriptors discussed are required as input parameters for computer programs that model exposure, for example: MACKAY LEVEL I (P_V, S_W, P_{OW}), SESOIL (S_W, D_g, D_l, K_{OC}, H, hydrolysis (K_{hyd}, photolysis, biodegradability), PRZM (D_g, D_l, K_{OC}, H, K_{hyd}, photolysis, biodegradability), TA-LUFT (δ, particle diameter, input based on environmental and meteorological conditions), EXAMS (S_W, P_{OW}, K_{OC}, H, K_{hyd}, degradability, etc.). Because of the complexity of distribution processes, all multimedia models are based on several assumptions (e.g. constancy of environmental parameters, exclusion of transformation processes, homogeneous mixture) limiting their validity. Nevertheless, the models are valuable tools to estimate distribution, propagation and persistence of chemicals in environmental compartments.

Résumé

Ce document résulte d'un projet de l'OCDE relatif à l'évaluation des dangers, "Application des RSA dans l'évaluation des propriétés physico-chimiques ayant une importance dans l'évaluation de l'exposition" dirigé par l'Allemagne. Les objectifs du projet étaient d'identifier et de comparer les approches pratiques en usage dans les pays Membres dans l'évaluation des propriétés physico-chimiques clés présentant une importance dans le cadre de l'évaluation de l'exposition. Le document présente, outre les résultats d'une étude sur l'état de validation de divers modèles de RQSA relatifs à des paramètres liés à l'exposition, des RQSA dont l'application est recommandée dans la phase initiale de sélection de substances afin de fournir des données de remplacement pour les données manquantes.

Des modèles de RSA ont été élaborés pour l'estimation d'un nombre de paramètres ayant une importance dans le cadre de l'évaluation de l'exposition aux produits chimiques existants. Les modèles sont basés sur des descripteurs codifiant numériquement des caractéristiques structurales ou des mesures physiques ayant trait à la structure chimique. Les descripteurs d'une substance peuvent être groupés selon qu'il s'agisse de propriétés physico-chimiques, géométriques, topologiques ou électroniques. Les descripteurs physico-chimiques ont été utilisés dans l'élaboration de modèles de processus tels que le partage entre deux phases, par exemple l'adsorption, la diffusion, la solubilité. Les descripteurs géométriques et topologiques sont principalement utilisés dans l'estimation de propriétés telles que log P_{oe} et coefficients d'adsorption. Les propriétés géométriques et électroniqüse peuvent être calculées en utilisant des méthodes empiriques et semi-empiriques de la mécanique quantique.

Des procédés de précision variable existent pour obtenir des quantifications de la plupart des paramètres ayant une importance dans le domaine de l'évaluation des dangers et des risques. Les valeurs estimées du coefficient de partage (P_{oe}), de la solubilité dans l'eau (S_W), de la constante de dissociation acide (pKa), de la constante de la loi d'Henry (H), de la pression de vapeur (P_V), de la dégradation atmosphérique (K_{OH}), et du facteur de bioconcentration (BCF), sont en bon accord ou en accord suffisant avec les données de l'expérimentation. En particulier, les valeurs de P_{oe}, largement utilisées dans les études de RSA, sont accessibles pour de nombreux types de substances grâce à une technique automatisée basée sur la méthode de fragmentation développée par Hansch et Leo. La corrélation traditionelle entre le P_{oe} et le BCF permet de déterminer la bioconcentration potentielle d'un composé. Cependant, des méthodes suffisamment fiables pour l'estimation du point de fusion (T_m), du point d'ébullition (T_b), du coefficient d'adsorption (K_{OC}), ou de paramètres plus complexes tels que les constantes de vitesse de dégradation ne sont pas encore disponibles.

Il existe encore des lacunes quant à certains paramètres d'une importance cruciale dans l'évaluation de l'exposition. En raison de l'absence d'une définition systématique, des phénomènes tels que la biodégradation ou la sorption dans le sol ne peuvent pas être cernés par des modèles précis. Des RSA satisfaisantes ne sont disponibles que pour des classes de substances très limitées. Il est nécessaire d'approfondir les recherches en ce qui concerne les aspects expérimentaux et théoriques de ces paramètres.

Bon nombre des descripteurs nommés plus haut sont nécessaires en tant que données paramétriques dans la création de programmes informatiques modelant l'exposition, tels que MACKAY LEVEL I (P_V, S_W, P_{oe}), SESOIL (S_W, D_g, D_l, K_{OC}, H, K_{hyd}, photolyse, biodégradabilité), PRZM (D_g, D_l, K_{OC}, H, K_{hyd}, photolyse, biodégradabilité, etc.), TA-LUFT (δ, diamètre des particules, données fondées sur les conditions environnementales et météorologiques), EXAMS (S_W, P_{OW}, K_{OC}, H, K_{hyd}, dégradabilité, etc.). En raison de la complexité des processus de distribution, tous les modèles multimédia sont

basés sur plusieurs suppositions (par exemple la constance des paramètres de l’environnement, l’exclusion de processus de transformation, l’homogénéité du mélange) limitant leur validité. Ces modèles représentent néanmoins des outils de valeur dans l’estimation de la distribution, de la propagation et de la persistance de produits chimiques dans des compartiments environnementaux.

Application of Structure-Activity Relationships to the Estimation of Properties Important in Exposure Assessment[1]

1. Introduction

Relationships between the structure of a chemical and its chemical, physical, and biological properties are becoming of increasing interest for application in environmental hazard assessment (see, for example, Sheehan et al. 1985, Karcher and Devillers 1990, Hermens and Opperhuizen 1991). Depending on the type of variable calculated, these methods use one or several structurally derived descriptors of a chemical to predict activity, partitioning or other interactions with the environment.

The estimation of biological activity using **Q**uantitative **S**tructure-**A**ctivity **R**elationships (QSARs) has been widely applied in the design of pharmaceutical and agrochemical substances (Martin 1978, Seydel and Schaper 1979, Franke 1980). The application of QSARs in the field of environmental hazard assessment is still hindered by the complexity of toxic effects, distribution and accumulation processes, and biodegradation. Knowledge is limited concerning the relevant interactions between contaminants and the impact compartments of the ecosphere, which are relevant for assessing the exposure of chemicals. Eventually the interactions have to be traced back to well defined processes and described by separate models, as is the case for the different mechanisms of aerobic and anaerobic degradation of xenobiotics.

Although QSARs for the estimation of biodegradation potential of chemicals exist, they have not been included in this report because this subject will be dealt with in detail within further OECD activities. For other important properties like thermolysis or photolysis, satisfactory SAR models are not available for a wide variety of compounds.

The QSARs assembled in the flowcharts in this document are recommended for application at the stage of initial screening of substances to obtain substitutes for missing information, i.e. if experimental data are not available. The criteria to select appropriate QSAR models for predictive purposes depend on features related to general aspects of the method with respect to development, derivation, statistical quality, status of validation, and the intended application, as well as on features related to the specific endpoint (parameter). Because the QSARs assembled in this document should be usable in any Member country, special attention has been given to the methods' availability and applicability.

A survey of the validation status of the various QSAR models for exposure-related parameters revealed that further evaluation will be required as many SAR methods, including the generation of the parameters describing a chemical's properties, need further development and improvement in order to provide reliable evaluation of potentially hazardous chemicals.

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[1] *This report was written by Dr. P. Degner, Dr. H. Jäckel, Dr. M. Müller, Dr. M. Nendza and Dr. B. von Oepen (Fraunhofer-Institut für Umveltchemie und Ökotoxikologie, Germany) on behalf of the Federal Environment Agency (Umweltbundesamt) of Germany under the Hazard Assessment activity of the OECD Chemicals Programme.*

2. Principles of SARs

SAR models are tools to interpret the results achieved from experiments by mathematically relating molecular structures to the respective endpoint (Martin 1983). Statistical methods are applied to extract the information contained in test data. One objective of the extensive data evaluation is to optimize and eventually reduce the testing.

Structure-activity models are derived using selected training sets of compounds, small series of chemicals characterized by maximized variance, and minimized intercorrelation in the descriptors of properties related to the effect or process under study. If the descriptors are intercorrelated, the significant parameters (properties) cannot be recognized. The probability of interference between a chemical and the environmental compartment due to partitioning, hydrogen bonding, polar-, covalent-, steric-, reactive interactions determines the activity or availability of this compound. The physical-chemical and/or structural features of chemicals can be characterized either for the entire structure or for varied substructures with respect to the unsubstituted parent compound. The data sets for derivation of SAR models should comprise enough compounds to allow statistically significant analyses with several variables (parameters). The variation in activity within the series should exceed the experimental variance of the test results. The wide parameter space is needed to obtain estimates for untested compounds by intrapolation; extrapolations have to be avoided. The activity data should be generated using well defined endpoints relevant for the effects and processes under study. The criterion of well defined endpoints is rarely fulfilled when regarding endpoints like soil sorption behaviour or biodegradation processes.

The Hansch-type QSAR analysis is based on the assumption that the biological effect (BE) or interaction is a function of the properties of a chemical (Hansch 1977, Rekker 1980, Hansch 1984, Ariens 1984, Lipnick 1985).

$$\log BE = a(L) + b(EL) + c(ST) + \ldots\ldots. + \text{const.}$$

The lipophilic (L), electronic (EL), and steric (ST) properties of a compound determine the mode and the intensity of its interaction with the environmental compartments. SARs can serve to study the mechanism of interaction between chemicals and biological/environmental systems (Hansch 1963, Martin 1978, Seydel and Schaper 1979, Franke 1980, Rekker 1980). QSAR modelling has been successfully applied in ecotoxicology to rank non-reactive, non-specific compounds (e.g. Yalkowsky et al. 1973, Biagi et al. 1975, Könemann 1981, Liu et al. 1982, Saarikoski et al. 1982, Mackay 1982, Nendza and Seydel 1988, OECD 1991). The identification of "outliers", i.e. chemicals exerting "excess" activity, is of special relevance in hazard assessment. The successful application of QSARs for predictive purposes depends heavily on two criteria: the selection of the appropriate model and its validation status.

The development of QSAR models is based on the assumption that for all those compounds that interact by the same mechanism with target sites, these effects shall depend on the same principal properties of the chemicals. They are not different with respect to the qualitative mode of the effect but only with respect to the quantitative appearance (strength) of the effect. Accordingly, they can be modelled with one QSAR based on the same parameter(s). On the other hand, for all those compounds that interact differently, their effects will depend on different principal properties and hence will follow different QSAR models. As a consequence, a QSAR cannot be applied successfully for all compounds, but only for those that interact according to the presumed underlying mode of interaction. In order to obtain reliable predictions, the chemicals have to be classified by mode of interaction with the target, which has to be done mostly from structural analogies. If the class has been determined, the corresponding QSAR(s) can be identified. For the selection of the appropriate model further limitations have to be considered, such as statistical quality, parameter range, detected outliers, and validation status.

The validation status of a QSAR model with respect to predictive power can be tested only in an external manner. For that purpose, experimental data for a variety of chemicals are compared to QSAR predictions. Only in case of adequate agreement between measured and calculated values can validity be assumed. The result of this analysis is the determination of the range of reliable applicability as well as the limitations for each individual QSAR. The use of a QSAR within the validated domain allows sufficient estimates for most exposure related parameters for a wide variety of substances.

SAR methods do not provide means to calculate "absolute" data; complete substitution of testing by computational methods is illusory. It is not yet feasible to deal with complex, undefined mixtures, e.g. effluents, or to account for all probable effects of a chemical in the environment. The applicability of SARs in environmental assessment is severely restricted by the lack of consistent data sets to develop reliable models for general application, and by insufficient knowledge about the interactions between contaminants and biosystems or environmental compartments on the molecular level.

3. Molecular descriptors

The derivation and application of SARs requires molecular descriptors of geometrical, topological and electronic properties. A selection of descriptors which have been applied in SAR studies is given below:

Geometrical descriptors

Molecular volume	(V_M)
Molecular surface area	(SA)
Solvent accessible volume	(SAV)
Solvent accessible surface area	(SASA)
Taft steric constant	(E_S)
Verloop constants	($L, B_1, B_2, B_3, B_4, B_5$)

Topological descriptors

Connectivity indices

Electronic descriptors

Hammett σ constants	(σ)
Molar refraction	(MR)
Polarizability	(α)
Dipole moment	(μ)

Quantum-chemical descriptors

Ionization potential	(IP)
Atomic charges	

Further physical-chemical properties which may be used in exposure assessment, such as partition coefficients, are discussed in the next chapter.

Geometrical descriptors:

Molecular volume (V_M), molecular surface area (SA): The molecular volume (van der Waals volume), as well as the molecular surface area, may be estimated by fragment additive procedures or by using atomic van der Waals radii and optimized structures. An example of the first approach is the method described by Bondi (1964), where the molecular volume is expressed as the sum of empirically determined atom or fragment van der Waals volumes.

$$V_M = \Sigma\, (V_M)_{\text{atoms, fragments}}$$

Van der Waals volumes for a wide variety of atoms and functional groups are tabulated (e.g. Seydel and Schaper 1979). One of the most important disadvantages of this method is the neglect of volume and surface dependence on the conformation of the molecule. Calculating molecular volume and surface area from optimized three-dimensional structures is to account for different conformations, but application of different, time-consuming geometry optimization procedures results in at least slightly different three-dimensional structures.

The ***solvent accessible volume (SAV)*** and ***solvent accessible surface area (SASA)*** consider the size of the solvent molecule (generally water). The accessible surface is defined as the locus of the centre of a "solvent sphere" which is rolled over the van der Waals surface of the solute.

Taft steric constants: The steric constant E_S for a substituent R is defined by:

$$E_S = \log\, (k_R / k_{CH3})\, [H^+]$$

where k_R and k_{CH3} are the rate constants for the acidic hydrolysis of $R - COOC_2H_5$ and $CH_3 - COOC_2H_5$ respectively (Taft 1956). The E_S constants reflect the shielding of a reactive centre by the substituent R.

Verloop constants ($L, B_1, B_2, B_3, B_4, B_5$): The Verloop constants (Verloop et al. 1976) are calculated using van der Waals radii, standard bond length and angles, and "reasonable" conformations. The constants are a function of the following substituent properties:

L : length of the substituent along the axis of bond between the substituent and the parent molecule

B_1 - B_4 : substituents' widths in the four directions perpendicular to the L-axis and rectangular to each other.

Topological descriptors:

Topological indices describe both the size and shape of a molecule. The connectivity indices defined by Kier and Hall (1976) are an extension of the branching index defined by Randic (1975). An example of other topological indices is the Wiener Path number W (Wiener 1947).

Connectivity indices: The calculation of connectivity indices is based on atomic parameters (δ) for each atom in the molecule, with δ_i being the number of non-hydrogen atoms adjacent to atom i, and $\delta^v{}_i$, the valence corrected δ-value, defined as the difference between the number of valence electrons (Z^v) and the number of adjacent hydrogen atoms (H):

$$\delta^v{}_i = Z^v - H$$

For several atoms (e.g. halogen atoms), empirically determined δ^v-values are used instead of calculated values. The connectivity index of order 1 is a summation over all pairs of atoms i and j ($i < j$):

$${}^1X = \Sigma\, (\delta_i * \delta_j)^{-1/2} \quad \text{resp.} \quad {}^1X^v = \Sigma\, (\delta^v{}_i * \delta^v{}_j)^{-1/2}$$

Higher indices are based on paths, clusters or chains of atoms.

Electronic descriptors:

Hammett σ constants (σ): The Hammett σ constants for molecular fragments have been extensively used in QSARs. In the original work (Hammett 1940), the Hammett σ constants are defined by:

$$\log\,(k/k_0) = \delta * \sigma \quad \text{resp.} \quad \log\,(K/K_0) = \delta * \sigma$$

k (k_0) and K (K_0) are rate constants and equilibrium constants of the substituted (unsubstituted) compounds, δ is the reaction constant measuring the sensitivity of the reaction to substituent effects with respect to the ionization of benzoic acid ($\delta = 1$). σ is the substituent constant expressing the polar effect of the substituent relative to hydrogen. Further σ constants have been defined such as σ^+ and σ^- for +M and -M substituents (Taft 1956) and σ_I and σ_R separating the inductive and resonance effects in polarity. An overview is given by Franke (1984).

Molar refraction (MR): For liquids, the molar refraction may be calculated by the Lorentz-Lorenz equation:

$$MR = MV * (n^2 - 1) / (n^2 + 2)$$

where MV is molar volume and n is the refractive index (Castellan 1971). Furthermore, molar refraction is proportional to ***polarizability (α)***:

$$MR = (4\pi / 3) * N_A * \alpha$$

with N_A as the Avogadro number.

From both these equations it becomes evident that molar refraction is a steric parameter, reflected by the MV term, as well as an electronic parameter indicating the flexibility of the electron system, reflected by the proportionality to polarizability. For QSAR purposes the molar refraction is often calculated using tabulated atomic and group contributions. The methods given by Vogel (1977) and by Hansch et al. (1973) are recommended. Commercial software is available for calculation of molar refraction [e.g. MedChem (1989), ADAPT (1989)].

Quantum-chemical descriptors:

The application of quantum-chemical methods such as the Hückel Molecular Orbital method (HMO, Hückel 1934), the Extended Hückel Theory (EHT, Hoffmann 1963), or semi-empirical methods like MNDO (Dewar and Thiel 1977), AM1 (Dewar et al. 1985), or PM3 (Stewart 1989), yields a number of "classical" electronic descriptors such as ionization potential polarizability, or the ***dipole moment (μ)***. Furthermore, a number of "theoretical" descriptors such as charge densities, HOMO and LUMO energies or atomic charges can be derived from quantum-chemical calculations.

Ionization potential: According to Koopmans (1934), the ionization potential IP is approximately defined by

$$IP = - HOMO$$

where HOMO is the orbital energy of the highest occupied molecular orbital. The electron affinity E_A is related to the energy of the lowest unoccupied molecular orbital (LUMO):

$$E_A = - LUMO$$

Atomic charges: The hypothetical charge q of an atom (r) in a neutral molecule (often referred to as partial charge) is calculated by semi-empirical MO methods.

4. Property estimation

A. Physical-chemical data

Exposure assessment requires physical-chemical data, which are known for only a limited number of compounds. For most environmentally relevant substances, experimental data are not available. Methods have therefore been developed to estimate these properties directly from chemical structure or from other properties. In the following, methods for estimating some of these properties are discussed with respect to their possibilities and limitations, also indicated by + or - in the flowcharts.

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

The 1-octanol/water partition coefficient P_{OW} (also referred to as K_{OW}) is a key parameter in studies of environmental fate, representing the distribution tendency of organic chemicals between organic and aqueous phases. Log P_{OW} has been related to water solubility, soil/sediment adsorption and bioconcentration.

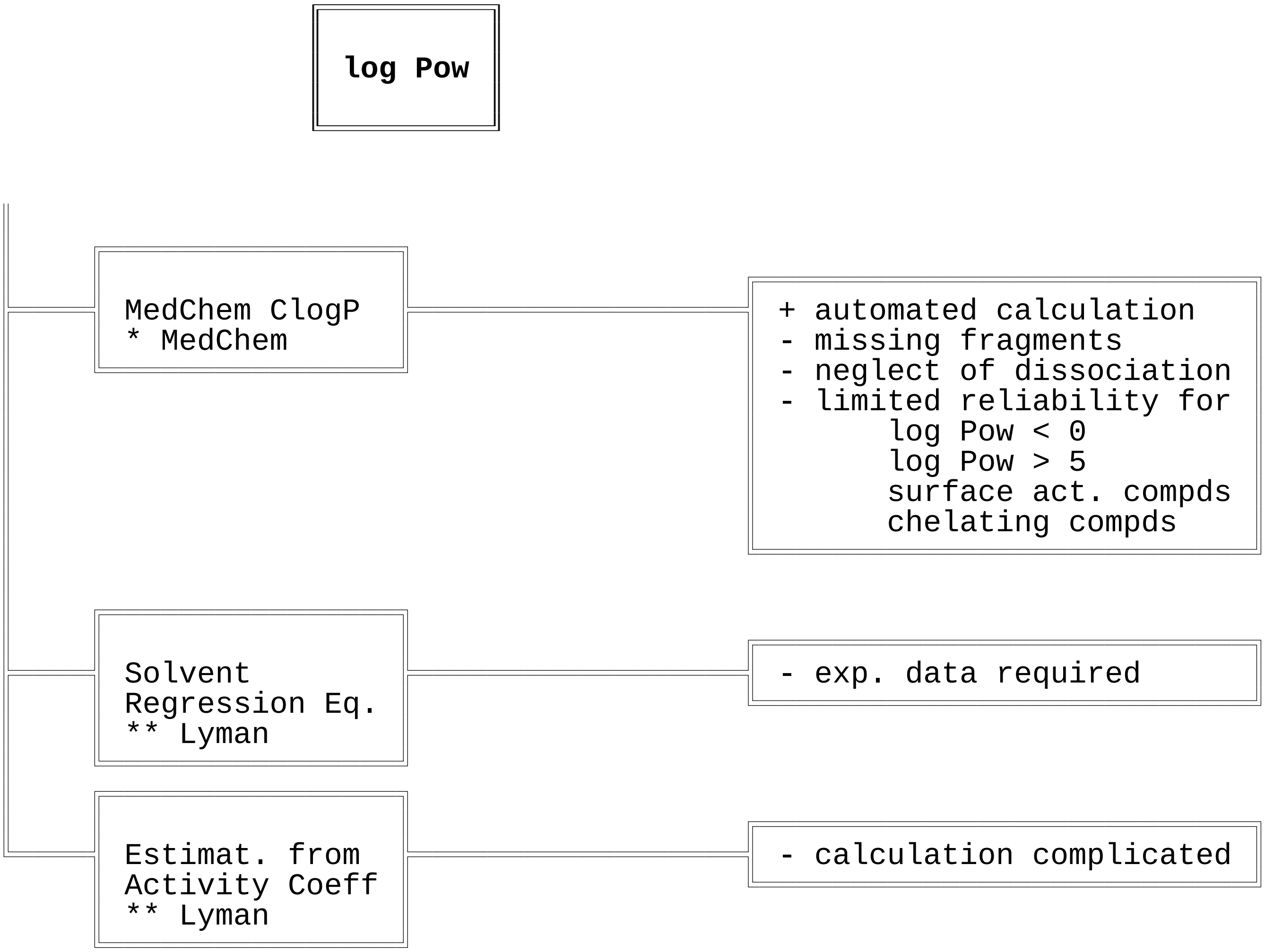
Several methods are available for the estimation of P_{OW}, such as fragment constant methods (Hansch and Leo 1979, Nys and Rekker 1973), solvent regression equations (Leo and Hansch 1971, Rekker 1977), and estimations from activity coefficients. The most frequently applied procedure is the fragment constant method by Leo and Hansch. The log P_{OW} is calculated from group fragment constants (f) and structural factors (F):

$$\log P_{OW} = \sum_{1}^{n} f_n + \sum_{1}^{n} F_n$$

or, for more complex structures:

$$\log P_{OW}\ (\text{molecule}) = \log P_{OW}\ (\text{similar molecule}) \pm \sum_{1}^{n} f_n \pm \sum_{1}^{n} F_{n.}$$

The group fragment constants (f) are tabulated for almost 100 fragments such as CH_3, COOH, etc. The structural factors (F) include factors for different bond types such as double bonds or conjugated double bonds, and factors for geometrical properties, for example rings or chains. This method gives fairly accurate results. Automated calculation is available (MedChem 1989).



* MedChem (1989) MedChem Software Version 3.54. Daylight Chemical Information Systems Inc., Claremont, California.

** Lyman, W.J., et al. (1982) *Handbook of Chemical Property Estimation Methods*. McGraw Hill, New York.

Water solubility (S_W)

The water solubility of chemicals determines their distribution by the hydrologic cycle. Most of the highly water soluble substances show low log P_{OW} values, low adsorption to soil and sediment, and low bioconcentration. They tend to be readily biodegradable. For liquid compounds, water solubility is highly correlated with the octanol/water partition coefficient. Several equations are given for "mixed" compound classes.

Examples of Linear log S_w/log P_{OW} Correlations:

$\log S_w = a * \log P_{OW} + b$ [mol/l]

	a	b	r	n	log P_{OW} range
[1]	-1.49	1.46	0.98	34	1-7
[2]	-1.34	0.98	0.93	156	0-5
[3]	-1.38	1.17	0.97	300	0-8
[4]	-1.02	0.52	0.92	111	-1-5
[5]	-1.16	0.79	0.97	156	0-5

a: regression coefficient, b: intercept, r: correlation coefficient, n: number of compounds analysed.
[1] Chiou et al. (1977), [2] Hansch et al. (1968), [3] Isnard and Lambert (1989),
[4] Valvani et al. (1981), [5] Müller and Klein (1992) (based on solubilities given in [2]).

These QSARs are based on experimental as well as calculated partition coefficients, except the last equation which is based exclusively on calculated partition coefficients. Equation 3 is recommended, since it is based on a large variety of substances with a wide log P_{OW} range. Equation 5 is recommended, when using calculated log P_{OW}-values and log P_{OW} is in the range 0-5, since the standard deviation is lower than for equation 3.

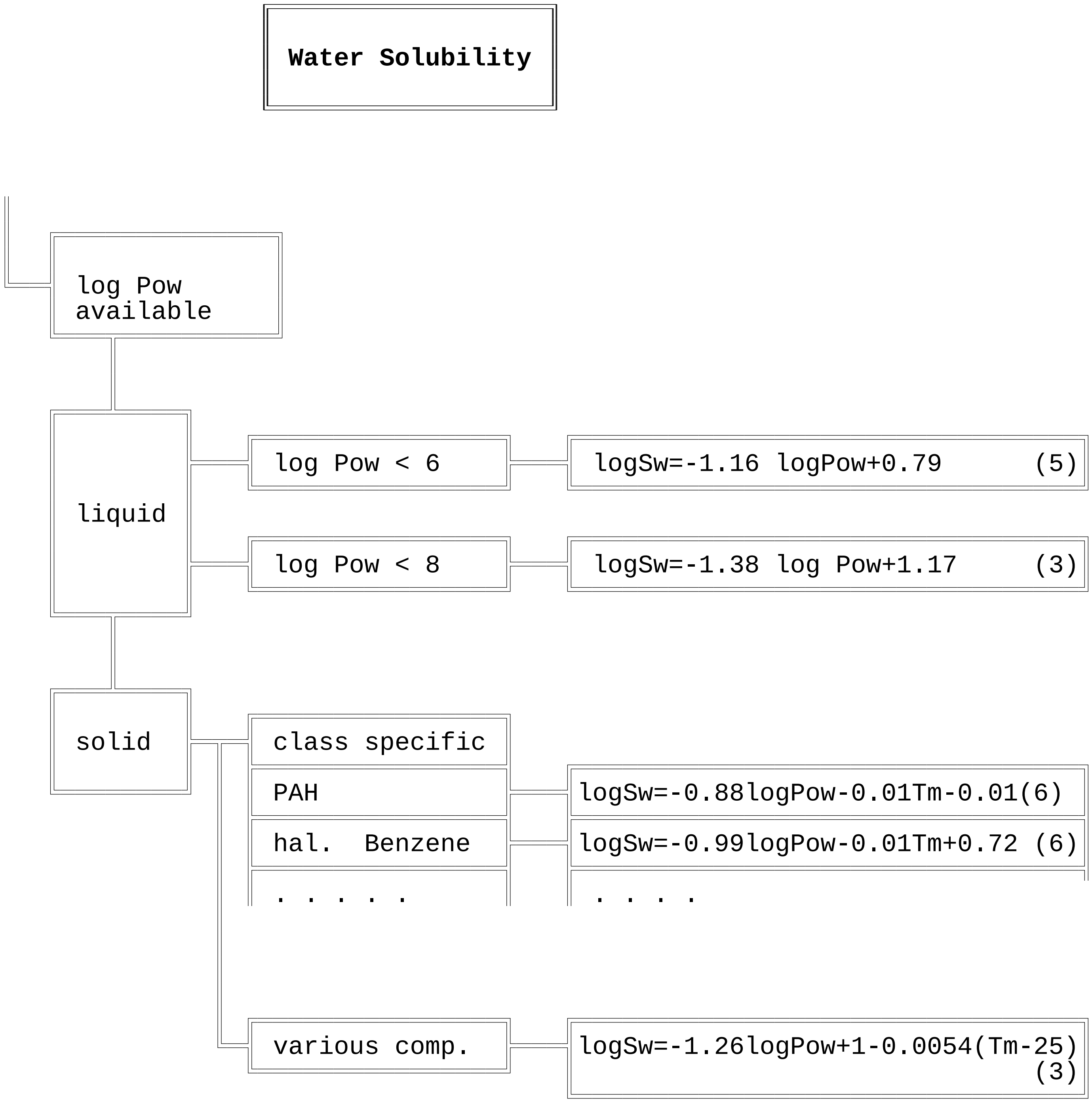
For estimating the solubility of solids, regression equations involving log P_{OW} have to be extended by the melting point (T_m) of the compound. The thermodynamic basis for this correction is discussed by e.g. Valvani and Yalkowsky (1980), where equations are also given for several compound classes. No recommendation is given for substance class specific equations, since validation status and applicability are not yet proved. For a "mixed" compound class, an equation is given by Isnard and Lambert (1989):

$$\log S_W = - 1.26 \log P_{OW} + 1.0 - 0.0054 (T_m - 25)$$

$$n = 300, \quad r: \text{ n. a.}, \quad s = 0.582$$

T_m is the melting point (° C), which is set for liquid compounds to 25° C. Due to the large database involved, the use of this equation is recommended for estimating the solubility of solid compounds when no reliable compound class specific QSAR is available.

Estimates based on connectivity indices, molecular surface area, or solvatochromic parameters are not generally applicable.



(3) Isnard, P. and Lambert, S. (1989) Aqueous solubility and n-octanol/water partition coefficient correlations. *Chemosphere* 18, 1837-1853.

(5) Müller, M. and Klein, W. (1992) *Comparative evaluation of methods predicting water solubility for organic compounds* (submitted).

(6) Valvani, S.C. and Yalkowski, S.H. (1980) Solubility and partitioning in drug design. In: Yalkowski, S.H., Sinkula, A.A. and Valvani, S.C. (eds.), *Physical-chemical properties of drugs*. Marcel Dekker, New York and Basel.

Vapour pressure (P_V)

The persistence of a chemical in soil and water is determined partly by its rate of evaporation. Several methods exist for calculating the vapour pressure P_V. Two methods described by Grain (1982) can be used for different chemical classes. The first one (P_V1) is derived from the Antoine equation, which describes the temperature dependence of vapour pressure. Transformation and assuming some approximations leads to the following equation (for details, see Grain 1982):

$$\ln P_V = K_F\,(8.75 + R \ln T_b)\,(T_b - C)^2/(0.97\,RT)\,[1/(T_b - C) - 1/(T - C)] \qquad (P_V1)$$

with:
P_V = vapour pressure [atm]
K_F = compound class specific constant
R = gas constant [cal/mol * K]
T_b = boiling point [K]
T = environmental temperature [K]
C = $-18 + 0.19\,T_b$

The second method (P_V2) is based on the Watson correlation, which describes the temperature dependence of the heat of vaporization. Transformations and approximations result in (for details, see Grain 1982):

$$\ln P_V = K_F\,(8.75 + R \ln T_b)/(0.97\,R) * [1 - (3 - 2T^*)^m/T^* - 2m(3 - 2T^*)^{m-1} \ln T^*] \qquad (P_V2)$$

with:
P_V = vapour pressure [atm]
K_F = compound class specific constant
R = gas constant [cal/mol * K]
T_b = boiling point [K]
T = environmental temperature [K]
$T^* = T/T_b$

The constant m depends on T^* and the physical state of the compound at the temperature of interest:

Liquids: $m = 0.19$
Solids: $T^* > 0.6 : m = 0.36$
$0.6 > T^* > 0.5 : m = 0.8$
$T^* < 0.5 : m = 1.19$

The compound specific constant K_F is assumed to describe the polarity of the compound. K_F values are tabulated for simple compound classes by Grain (1982) and range between 0.97 and 1.23. For compound classes not included in the tables, a K_F value of 1.06 is recommended. The factor K_F is derived for monofunctional compounds, but it is also applicable for polyfunctional compounds if assuming the respective highest K_F value.

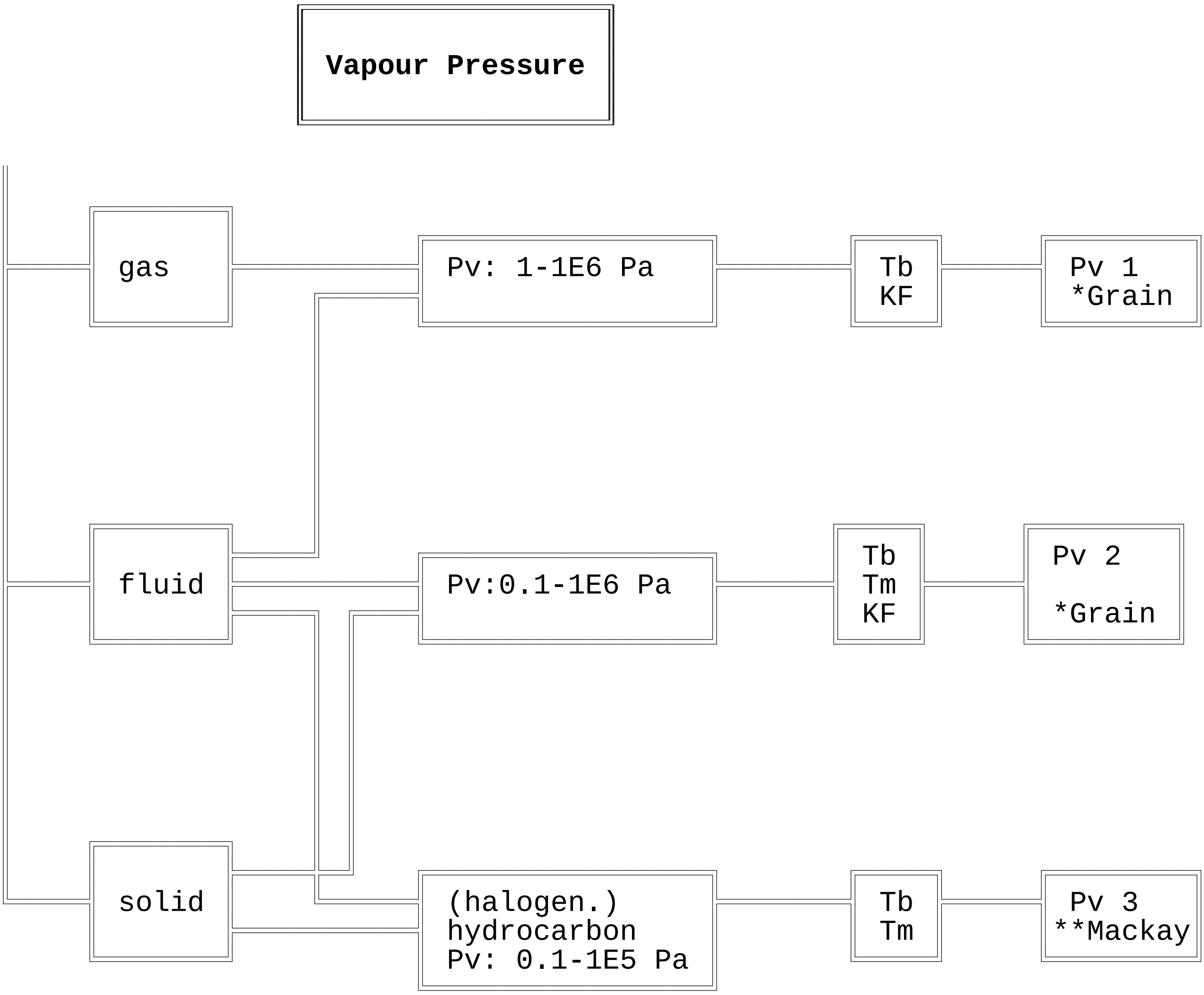
Equation P_V1 applies only for compounds which are liquid or gaseous at the temperature of interest; equation P_V2 can be used for solid and liquid compounds.

The method described by Mackay et al. (1982) is only applicable for hydrocarbons and halogenated hydrocarbons:

$$1n\ P_V = -\,(4.4 + \ln T_b)\,(1.803\,(T_b/T-1) - 0.803 \ln (T_b/T) - 6.8\,(T_m/T-1) \qquad (P_V3)$$

with:
T_b = boiling point [K]
T_m = melting point [K]
T = environmental temperature [K]

Estimated P_V values may be subject to considerable uncertainty, especially when P_V [see section below on boiling point (T_b)] is calculated to be < 1 Pa and no experimental boiling point is used, but a "Meissner estimation". The uncertainty is of major importance when the calculated P_V value is used together with S_W, calculated from P_{OW}, to estimate the Henry's Law constant.



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* Grain, C.F. (1982) Vapour Pressure. In: Lyman, W.J., et al. (eds.) *Handbook of Chemical Property Estimation Methods*. McGraw Hill, New York.

** Mackay, D., Bobra, A., Chan, D.W. and Shiu, W.Y. (1982) Vapour-Pressure Correlations for Low Volatility Environmental Chemicals. *Environ. Sci. Technol.* 16, 645-649.

Henry’s Law constant (H, H’)

The Henry’s Law constant describes the partitioning of a chemical between air and water. It is expressed either as the ratio of the partial pressure in the vapour phase and the concentration in water [H (Pa * m^3/mol)], or as the ratio of the concentrations in air and water (H’, dimensionless).

$$H = P / C_w \qquad \text{resp.} \qquad H' = C_a / C_w$$

with:
P = partial pressure
C_w = concentration in water
C_a = concentration in air

Since the concentration in air and the partial pressure are related by the ideal gas law, both types of Henry’s Law constants are related:

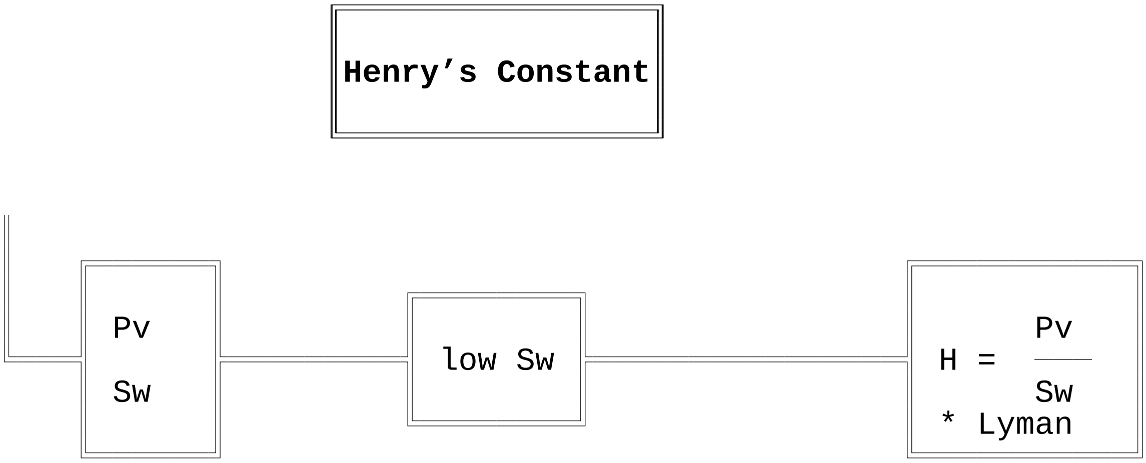
$$H' = H/RT$$

with:
R = gas constant
T = environmental temperature [K]

A widely used method calculates the Henry’s Law constant from water solubility and vapour pressure, assuming constant activity coefficients of the liquid phase over the entire range of solubility:

$$H = P_V / S_W$$

This method is limited to substances with low water solubility (< 1. 0 mol/l), and is fairly accurate under the above conditions. For solid compounds, P_V and S_W have to be determined for the same state of the chemical, either solid or subcooled. If calculated P_V and S_W values are used to estimate H, the respective uncertainties have to be considered.



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* Lyman, W. J., et al. (1982) *Handbook of Chemical Property Estimation Methods*. McGraw Hill, New York.

Hine and Mookerjee (1975) described two methods for estimating the Henry's Law constant directly from molecular structure. The first one uses group contributions for about 70 groups, and the second uses bond contributions for 34 different bond types. As discussed by the authors, the group contribution method gives more reliable results than the bond contribution method. The bond contribution method has been updated recently by Meylan and Howard (1991), who also provide a computer program performing the respective calculations. The validation status of these methods is unknown, so no recommendation is given. However, since both methods use compound class specific correction terms in addition to the bond/group contribution, care should be taken when using the methods for compounds with unconsidered structure fragments.

Melting point (T_m)

No reliable T_m estimation methods are available. Hence the use of measured values is recommended. The use of CHEMEST procedures for melting point predictions is not recommended.

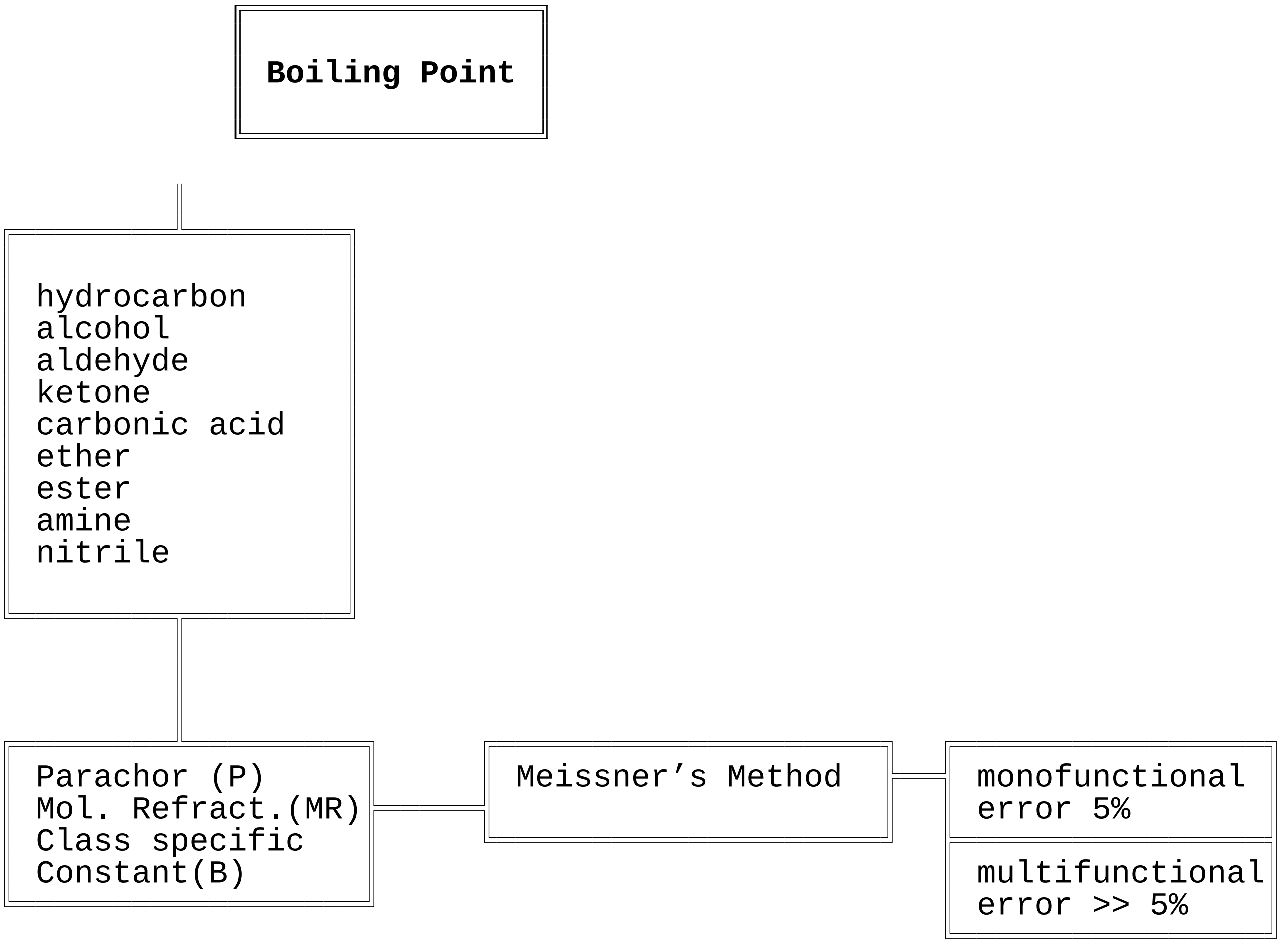
Boiling point (T_b)

Boiling point is required for the estimation of vapour pressure. The recommended estimation method for boiling point (K) is based on parachor (Pr), molar refraction (MR) and a chemical class dependent variable B [Meissner's method, Rechsteiner (1982)].

$$T_b = (637 * (MR)^{1.47} + B) / Pr$$

The equation is derived only for monofunctional compounds. The accuracy of this method depends on the quality of the MR and the Pr values, the average error in absolute temperature being 5 per cent. Multifunctional compounds can only be estimated with larger errors.

Constant B for Various Chemical Classes (Lyman et al. 1982)	
Compound class	B
Acid (monocarboxylic)	28000
Alcohol (monohydroxy), incl. phenols, cresols, etc.	16500
Primary amine	6500
Secondary amine	2000
Tertiary amine	-3000
Ester (monocarboxylic acid/monohydroxy alcohol)	15000
Ester (dibasic acid/monohydroxy alcohol)	30000
Ether, mercaptan	4000
Acetylenic hydrocarbon	-500
Aromatic hydrocarbon	-2500
Paraffinic, naphtalenic hydrocarbon	-2500
Olefinic hydrocarbon	-4500
Ketone, aldehyde	15000
Monochlorinated normal paraffin	4000
Nitrile	20000



* Meissner, H.P. (1949) Critical Constants from Parachor and Molar Refraction. *Chem. Eng. Prog.* 45, 149-153.

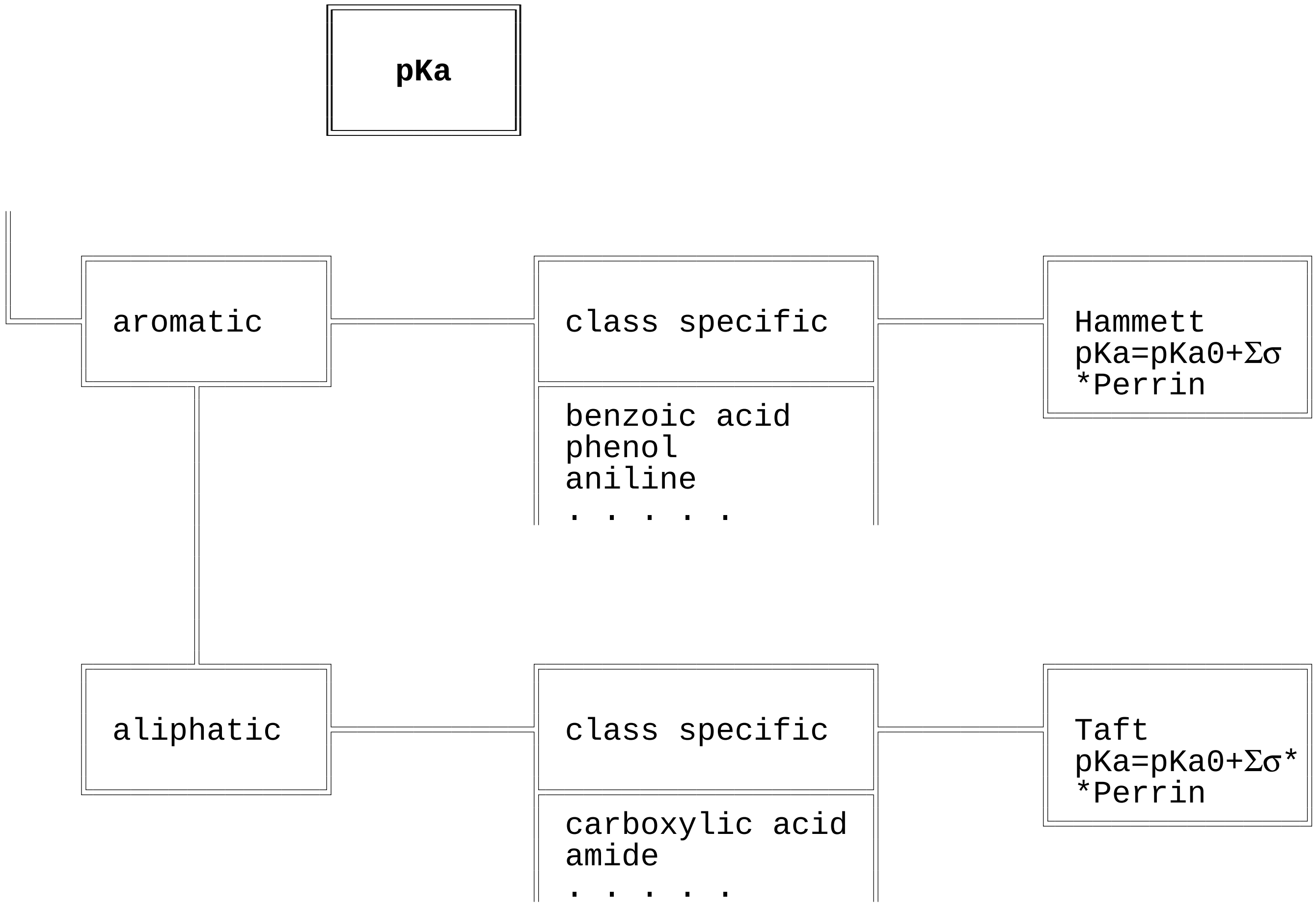
Acid dissociation constant (pK_a)

The estimation with linear free energy relationships (LFERs) uses the Hammett correlation for aromatic acids, phenols, anilines, etc. and the Taft correlation for aliphatic acids:

$$pK_a = pK_a' - \delta (\Sigma \sigma).$$

pK_a' is the pK_a of the unsubstituted parent compound, δ is a constant depending on the parent compound, and σ is the substituent constant according to Hammett (σ) or Taft (σ^*). The average error is about 0. 2 pK_a units. Problems arise from the need for σ values, especially for substituents in orthoposition. A compilation by Perrin et al. (1981) includes about 100 basic structures and 660 substituents, where $\sigma_{m,p}$ and σ^* values are given. σ_o values (also covering steric effects on the reaction centre) are given for many fewer substituents.

Quantum-chemical approaches have been used for the estimation of pK_a, but the method requires further development.



* Perrin, D.D., Dempsey, B. and Serjeant, E. P. (1981) *pKa Prediction for Organic Acids and Bases*. Chapman and Hall, London.

B. Degradation rate constants

Rate constants for abiotic degradation reactions are important for the exposure assessment of organic chemicals. The most important degradation pathways are reactions with reactive species (especially hydroxyl radicals and ozone) in the atmosphere and, for several compound classes, hydrolysis in the aquatic environment.

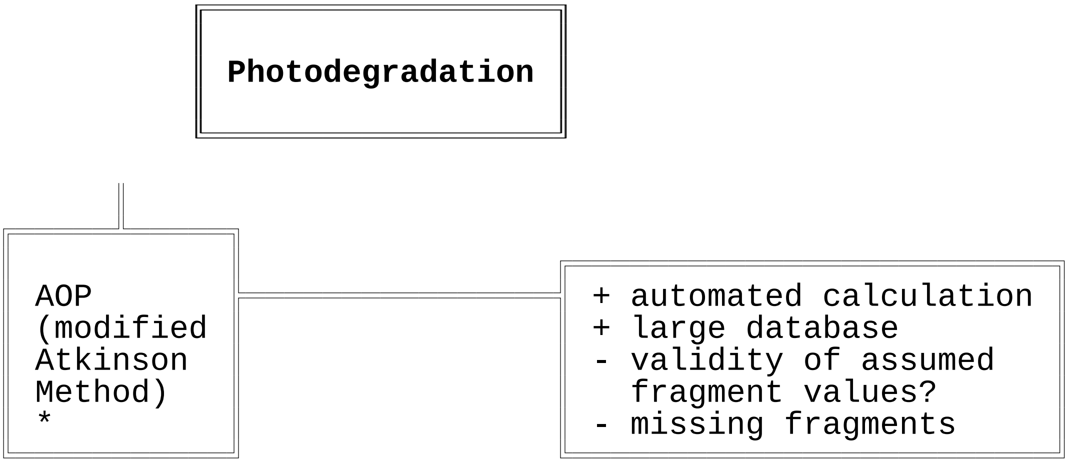
Reactions with hydroxyl radicals

The atmospheric residence time of a chemical is determined by the evaporation from terrestrial and aqueous compartments, the removal by wet and dry deposition, and transformation. The reaction with reactive species in the atmosphere, often referred to as photodegradation, has been recognized as the major transformation pathway in the troposphere: up to 90 per cent of organic compounds are transformed more rapidly by hydroxyl radicals than by any other process.

The recommended method for estimating reaction rate constants for the reaction of an organic compound with hydroxyl radicals is given by Atkinson (1987, 1988). The method is based on molecular fragment constants. The total hydroxyl reaction rate constant is constructed from rate constants of four important types of reactions: H-atom abstraction from C-H and O-H bonds (1), addition of hydroxyl radicals to C-C double and triple bonds (2), addition to aromatic rings (3), and reactions with N, S, or P (4).

$$k_{total} = k_{H\text{-}abst} + k_{add\ (C=C)} + k_{add\ (aromat.)} + k_{N,S,P}$$

Estimation methods for all four types of reactions were derived by Atkinson (1987, 1988). A computer program is available (AOP 1990) for the calculation of hydroxyl radical and ozone rate constants. This program was used for calculating rate constant of about 370 compounds with known experimental rate constants (Müller and Klein 1991). For only 34 compounds (9.2 per cent) did the experimental and calculated rate constants differ by more than a factor of two. Due to the fact that the computer program uses assumed fragment values when no data are given by Atkinson, this program is an extension of the Atkinson method. Although some assumptions are not validated, the overall good agreement of experimental and calculated data justifies the application of this program for the estimation of rate constants. Estimates based on ionization potential are not significantly different from AOP results.



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* Atkinson, R. (1988) Estimation of Gas-Phase Hydroxyl Radical Rate Constants for Organic Chemicals. *Environ. Toxicol. Chem.* 7, 453-462; AOP (1990) Atmospheric Oxidation Program Version 1.31. Syracuse Research Corporation, Chemical Hazard Assessment Division, Environmental Chemistry Centre, Syracuse, New York.

Hydrolysis

The persistence of a contaminant in aqueous compartments is among other factors dependent on the chemical reactions between the contaminant and water.

Only some compound classes are potentially hydrolyzable: e.g. alkyl halides, amines, carbamates, ester, epoxides and nitriles (Harris 1982). Estimation methods are reported for the hydrolysis of several types of carboxylic acid ester, carbamates, and phosphoric acid ester. All methods are based on Hammett or Taft correlations. A compilation is given by Harris (1982). The accuracy of these equations is sufficient. However, further development is needed since only a few compound classes are considered. The available equations are based on only a few compounds, and therefore the predictive power is limited.

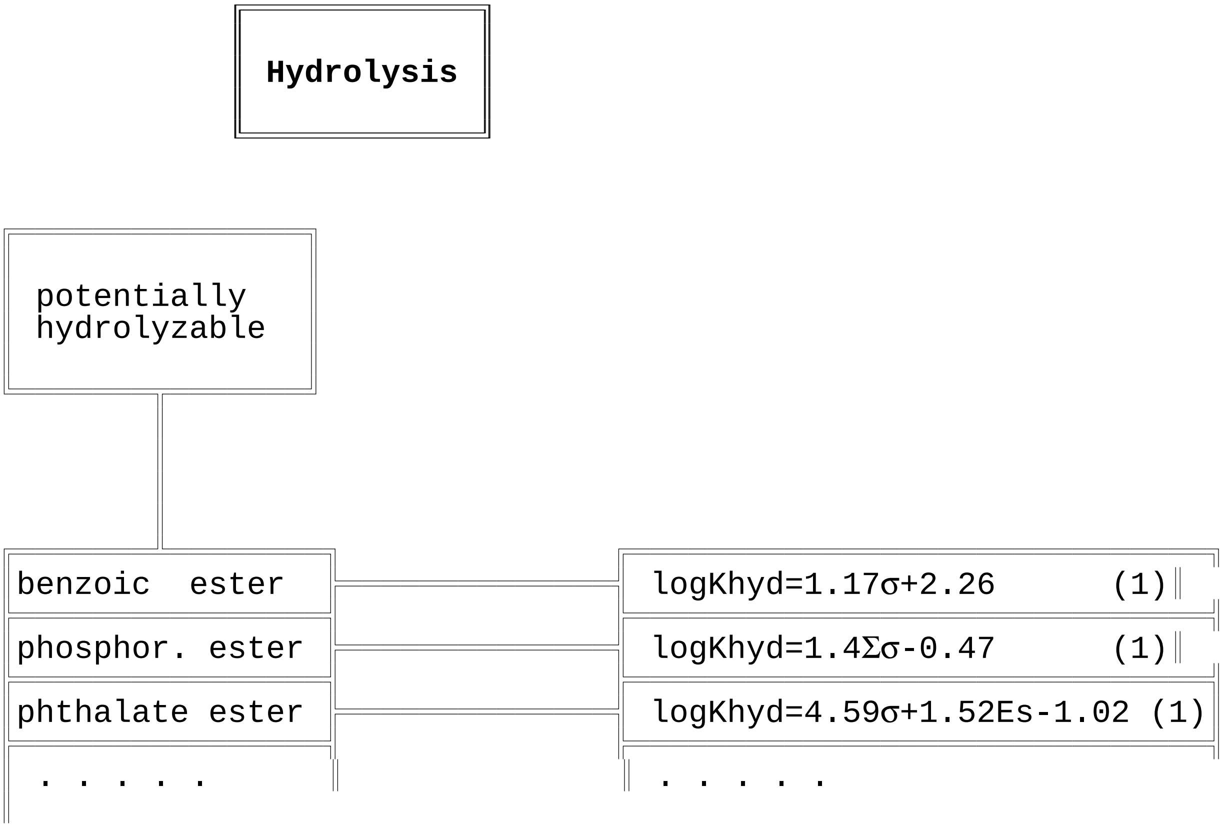
Examples of Linear log K_{hyd}/σ (E_S) Correlations:

$$\log K_{hyd} = a * \sigma + b * E_S + c \quad [M^{-1}s^{-1}]$$

compounds	a	b	c	r	n
[1]benzoic ester	1.17	--	2.26	0.996	18
[1]phosphor. ester	1.4	--	-0.47	0.995	4
[1]phthalate ester	4.59 (σ*)	1.52	-1.02	0.986	5

a, b: regression coefficients, c: intercept, r: correlation coefficient, n: number of compounds analysed.

[1] Lyman et al. (1982).



(1) Lyman, W. J. et al. (1982) *Handbook of Chemical Property Estimation Methods*. McGraw Hill, New York.

C. Sorption

Soil sorption coefficients reflect processes of distribution of a compound to the four major soil components: mineral and organic matter, water, air and (micro)organisms. The transport rate of chemicals between these phases is determined by the physical and chemical properties of both the chemical and the soil, and it is influenced by the initial concentration and environmental conditions such as temperature, pH value, etc. Normalizing the distribution coefficients to an organic carbon basis reduces the variance of sorption coefficients measured in different soils for hydrophobic chemicals to one order of magnitude, but for more polar chemicals the normalized K_{OC} values may still vary by a factor of 100-1000 (Lambert et al. 1965, 1968, Hamaker and Thompson 1972).

As a consequence of the multifunctional nature of the sorption parameter K_{OC}, recent developments are directed to testing schemes using HPLC with various stationary phases. The basic principle is to determine separately the different interactions involved in sorption on standardized material, and then to recombine the data from the individual measurements for comprehensive sorption parameterization. For predicting soil sorption coefficients, various descriptors have been used: log P_{OW}, water solubility (S_W), molar refraction (MR), Parachor and Randic Indices [connectivity indices (X)], and bioconcentration factor (BCF). The respective relationships are valid only for defined series of compounds, mostly persistent hydrophobic compounds, and cannot be used for other classes.

Soil Sorption and Partition Coefficient

Examples of Linear log K_{oc}/log P_{ow} Correlations:

$$\log K_{OC} = a * \log P_{OW} + b$$

compounds	a	b	r	n	log P_{OW} range
[1] pesticides	0.52	1.12	0.95	105	-0.6-7.4
[2] pesticides	0.54	1.38	0.86	45	2-6
[3] aromatic, PAHs	0.83	0.29	0.95	20	1-6
[4] arom. herbic.	0.94	-0.01	0.97	19	n.a.
[5] aromatic	0.99	-0.35	1.00	5	2-5.2

a: regression coefficient, b: intercept, r: correlation coefficient, n: number of compounds analysed.

[1] Briggs (1981), [2] Kenaga et al. (1980), [3] Hodson et al. (1988), [4] Brown et al. (1981), [5] Karickhoff (1981).

Soil Sorption and Water Solubility

Examples of Linear log K_{oc}/log S_w Correlations:

$$\log K_{OC} = a * \log S_W + b$$

compounds	a	b	r	n
[2] pesticides	0.55	3.64	0.84	106
[5] aromatic	0.54	0.44	0.97	10
[6] chlor. hydrocarb.	0.56	4.28	0.99	10

a: regression coefficient, b: intercept, r: correlation coefficient, n: number of compounds analysed.
[2] [mg/l] Kenaga et al. (1980), [5] [mole fraction] Karickhoff et al. (1979),
[6] [μmoles/l] Chiou et al. (1979).

Soil Sorption and Molar Refraction

Examples of Linear log K_{oc}/MR Correlations:

$$\log K_{OC} = a * MR + b$$

compounds	a	b	r	n
[7] PCBs, chlor. benzenes	0.08	-0.27	0.99	15
[8] ester	0.06	-0.27	0.95	10
[8] amines	0.09	-0.68	0.96	8

a: regression coefficient, b: intercept, r: correlation coefficient, n: number of compounds analysed.
[7] Koch et al. (1988), [8] von Oepen (1990).

Soil Sorption and Connectivity Indexes

Examples of Linear log $K_{oc}/^{n}X$ Correlations:

$$\log K_{OC} = a * {}^{n}X + b$$

compounds	parameter	a	b	r	n
[9] PAHs	$^{2}X^{V}$	1.03	0.76	0.99	8
[10] PAHs, benzenes, phenols	^{1}X	0.53	0.78	0.98	72
[11] anilines, benz., heterocycl.	$^{1}X, ^{1}X^{V}$	0.53, 2.09	0.64	0.97	56
[12] phenols, polycycl.	$^{1}X^{v}$	0.67	0.37	0.97	32

a: regression coefficient, b: intercept, r: correlation coefficient, n: number of compounds analysed.

[9], [10] Sabljic (1982, 1987), [11] Bahnick (1988), [12] Koch et al. (1988).

Due to the considerable variability in experimental sorption data, only a few correlations can be assumed to be generally valid. Even normalized adsorption coefficients restricted to an organic carbon content between 1 per cent and 10 per cent can hardly be regarded as a soil-independent sorption parameter. Accordingly, the same problems arise when selecting the "correct" K_{OC} value from a variety of experimental data or when choosing the appropriate QSAR for predictions.

Whenever available, a chemical class specific model should be applied, taking advantage of the presumably similar mode of sorption within the class. If no definite QSAR for the respective compound class exists, a log P_{OW} dependent model may be used for non-polar compounds, provided that sorption does depend predominantly on van der Waals or hydrophobic interactions. Only for a very rough first approximation, the simplistic approach of log K_{OC} being approximately equal to log P_{OW} (OECD 1992) can be recommended. Major problems arise for polar compounds, where other modes of sorption, e.g. ionic or ligand exchange interactions, can be assumed. Appropriate QSARs are not yet available.

Soil Sorption

class-specific	
anilines, anilides, nitrobenzenes, phenylureas, phenylcarbamates	logKoc=0.52logPow+1.12 (1)
chlor. hydrocarb.	logKoc=0.56Sw+4.28 (6)
PCBs	logKoc=0.08MR-0.27 (7)
aromat./aliph. ester	logKoc=0.06MR-0.27 (8)
aromat./aliph. amines	logKoc=0.09MR-0.68 (8)
PAHs	logKoc=0.53X+0.78 (10)
. . . . .	. . . . .

(1) Briggs, G.G. (1981) Theoretical and experimental relationships between soil adsorption, octanol-water partition coefficients, water solubilities, bioconcentration factors, and the parachor. *J. Agric. Food Chem.* 29, 1050-1059.

(6) Chiou, C.T., Peters, L.J. and Freed, V. H. (1979) A physical concept of soil-water equilibria for nonionic organic compounds. *Science* 206, 831-832.

(7) Koch, R. and Nagel, M. (1988) Quantitative structure-activity relationships in soil ecotoxicology. *The Science of the Total Environment* 77, 269-276.

(8) von Oepen, B. (1990) *Sorption organischer Chemikalien an Böden.* Dissertation, Wissenschafts-verlag Maraun, Frankfurt.

(10) Sabljic, A. (1987). On the prediction of soil sorption coefficients of organic pollutants from molecular structure: Application of molecular topological model. *Environ. Sci. Techn.* 21, 358-366.

D. Accumulation

The accumulation of chemicals in living organisms and/or in abiotic compartments of the ecosphere such as water bodies, sediment and soil is of major concern for environmental hazard assessment. The uptake of contaminants into the biophase occurs mostly by direct adsorption, but also along the trophic web. The internal concentration, e.g. in fish, may increase by accumulation to a level causing toxic effects, even if the external concentration remains below the critical limit.

Investigations in the 1970s produced some understanding of the fundamentals of bioaccumulation (Hansch 1969, Hamelink et al. 1971 and 1977, Hunn and Allen 1974, Isensee et al. 1975, Kanazawa et al. 1975, Bahner et al. 1977, Clayton et al. 1977, Macek et al. 1979, Mackay 1979, Zitko 1980). Procedures for the estimation of the bioconcentration potential have been reviewed by Bysshe (1982), Calamari and Vighi (1987), Connell (1988) and Nendza (1991).

Chemical legislation, except in Japan, does not require any experimental determination of bioconcentration potential in the basic tier, but relies on extrapolations from the compounds' physical-chemical properties (log P_{OW}). The simplistic evaluation procedure assumes no substantial bioconcentration for compounds having log $P_{OW} < 2.7$ to 3 (BCF < 100). Chemicals ranging in log P_{OW} between 2.7 to 3 and 6 are classified highly accumulating, eventually resulting in the demand for testing. Superlipophilic compounds characterized by log $P_{OW} > 6$ and molecular weight > 500 are regarded as modestly accumulating. Basically, this assessment scheme represents the application of QSARs for legislative purposes.

Comparison of non-ionic organic chemicals exhibiting substantial bioconcentration reveals several common characteristics. The bioconcentration potential of a contaminant is directly related to its lipophilicity and inversely related to its water solubility, molecular charge and degree of ionization (Bysshe 1982, Connell 1988). Increase in the size of molecules, as expressed by the molecular weight, reduces the permeation through biological membranes to reach the site of potential accumulation, the upper limit being a molecular weight of about 500 (Umweltbundesamt 1990); Opperhuizen et al. (1985) reported a loss in membrane permeability with molecules having widths > 9. 5 Å. Bioconcentration processes require a considerable period of time. Only upon continuous exposure, due to either persistence or continuous release, can chemicals reach the steady state. The chemicals' properties associated with bioconcentration are highly intercorrelated for accumulating chemicals; i.e. they are descriptors of the same principal properties.

Interphase distribution for application in QSAR studies is mostly characterized by log P_{OW}. Since the lipid tissue of the fish is the principal site for bioaccumulation and 1-octanol is often a satisfactory surrogate for lipids, linear correlations are usually observed between log BCF and log P_{OW}. This corresponds to the underlying assumption that exchange between the water phase and the organic phases (e.g. fish) is governed by diffusion processes. The partitioning in different systems has been assumed to be directly related (Collander 1951). Numerous QSARs estimating bioconcentration based on lipophilicity have been published. In general, an increase in BCF is associated with an increase in log P_{OW}. Analogous relationships between BCF and aqueous solubility have been described by Metcalf et al. (1973, 1975), Chiou et al. (1977), and Kenaga and Goring (1980).

Examples of Linear log P_{OW}/log BCF_{FISH} Correlations:

$$\log BCF_{FISH} = a * \log P_{OW} + b$$

compounds	a	b	r	n	log P_{OW} range
[1] halog. aromat.	0.54	0.12	0.95	8	2.6-7.6
[2] ?	0.94	-1.50	0.87	26	?
[3] misc.	0.79	-0.40	0.93	122	1.0-6.9
[4] misc.	1.00	-1.32	0.97	44 (?)	1.3-6.0
[5] chlorobenz.	1.02	-0.63	0.99	11	3.4-5.5
[6] chlorobenz.	0.89	0.61	0.95	18	3.4-5.0

a: regression coefficient, b: intercept, r: correlation coefficient, n: number of compounds analysed.

[1] Neely et al. (1974), [2] Kenaga and Goring (1980), [3] Veith and Kosian (1983), [4] Mackay (1982), [5] Oliver and Niimi (1983), [6] Chiou (1985).

The linear log P_{OW} /log BCF correlations, which are assumed to describe the same processes, reveal a wide variation in slopes and intercepts, attributed to the physiological differences of the tested organisms, e.g. varying lipid content, and to the various classes of chemicals under study.

The bioconcentration factors for daphnia, molluscs, mussels, algae and microorganisms have also been related to log P_{OW} or water solubility.

Examples of Linear log P_{OW}/log BCF Correlations:

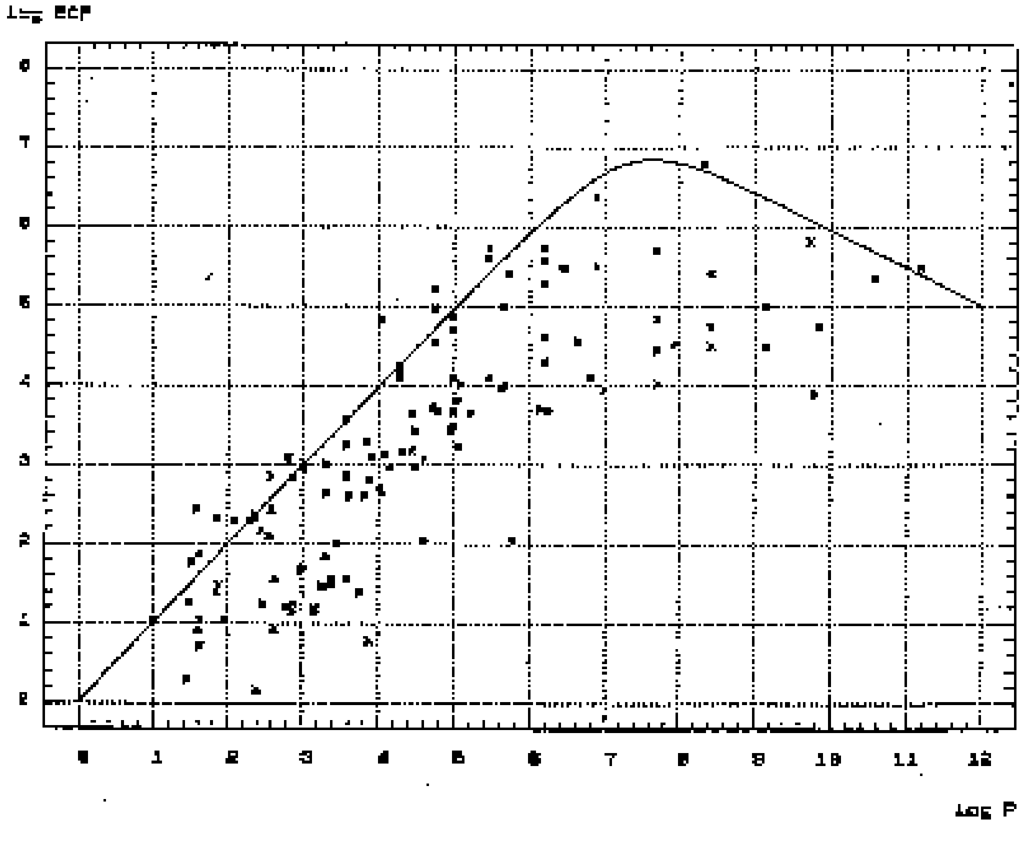
$$\log BCF = a * \log P_{OW} + b$$

organism/compounds compartment	a	b	r	n	log P_{OW} range
[7] daphnia/misc.	0.90	-1.32	0.96	22	1.8-6.2
[7] molluscs/misc.	0.84	-1.23	0.83	33 (?)	3. 4-7. 8
[8] mussel/misc.	0.86	-0.81	0.96	16	1. 7-6. 2
[9] oyster/dibenzothioph.	0.49	1.03	0.62	14	4. 4-5. 9
[10] algae/misc.	0.68	0.16	0.90	41	0. 6-6. 2
[11] microorganism/pesticides	0.91	-0.36	0.98	14	3. 1-6. 9
[12] sediment/aromatic	1.00	-0.21	1.00	10	2. 1-6. 3

a: regression coefficient, b: intercept, r: correlation coefficient, n: number of compounds analysed.

[7] Hawker et al. (1986), [8] Geyer et al. (1982), [9] Ogata et al. (1984), [10] Geyer et al. (1984), [11] Baughman et al. (1981), [12] Karickhoff et al. (1979).

The correlation between log BCF and log P_{OW} will be linear as long as the ratio of the respective activity coefficients remains constant. Several factors may cause deviations and apparent loss of the linear log P_{OW}/log BCF correlation, predominantly due to variable experimental conditions. The evident variability in parametrization of lipophilicity by log P_{OW} should be recognized (Schüürmann and Klein 1988), but it is only a minor factor introducing uncertainty as compared to the substantial problems arising from the quantification of the biological endpoint. A loss of linear correlation has been observed for the range of high lipophilicity. To account for the reduced bioconcentration of superlipophilic compounds, non-linear QSAR models have been derived. A parabolic relationship has been developed by Könemann and van Leeuwen (1980) for chlorobenzenes. Connell and Hawker (1988) derived a polynominal log P_{OW} dependent function to describe BCFs of chlorinated hydrocarbons with a maximum bioconcentration for compounds with log P_{OW} 6.7. Spacie and Hamelink (1982) proposed a sigmoid model, without stating the corresponding function, to account for the fact that the linear correlations also break down for very hydrophilic compounds. Nendza (1991) suggested a non-linear function based on log P_{OW} describing the highest BCF associated with a given lipophilicity, which corresponds to the bioconcentration potential of a chemical. If discrepancies between measured and calculated values then occur, the measured BCFs are lower than calculated. Thus, this function will result in "worst case" estimates of bioconcentration, corresponding to the empirically postulated coincidence of log P_{OW} and log BCF.



Comparison of experimental BCF data with a bilinear "worst-case" log P_{OW}/log BCF model (Nendza 1991)

Examples of Non-linear log P_{OW}/log BCF_{FISH} Correlations:

[13] chlorobenzenes

$$\log BCF = 3.41 \log P_{OW} - 0.26 (\log P_{OW})^2 - 5.51$$

r = n.a. n = 6 log P_{OW} range: 3.5-6.4

[14] chlorinated hydrocarbons

$$\log BCF = 0.0069 (\log P_{OW})^4 - 0.185 (\log P_{OW})^3 + 1.55 (\log P_{OW})^2 - 4.18 \log P_{OW} + 4.79$$

r = n.a. n = 45-46 (?) log P_{OW} range: 2.6-9.8

[15] diverse compounds

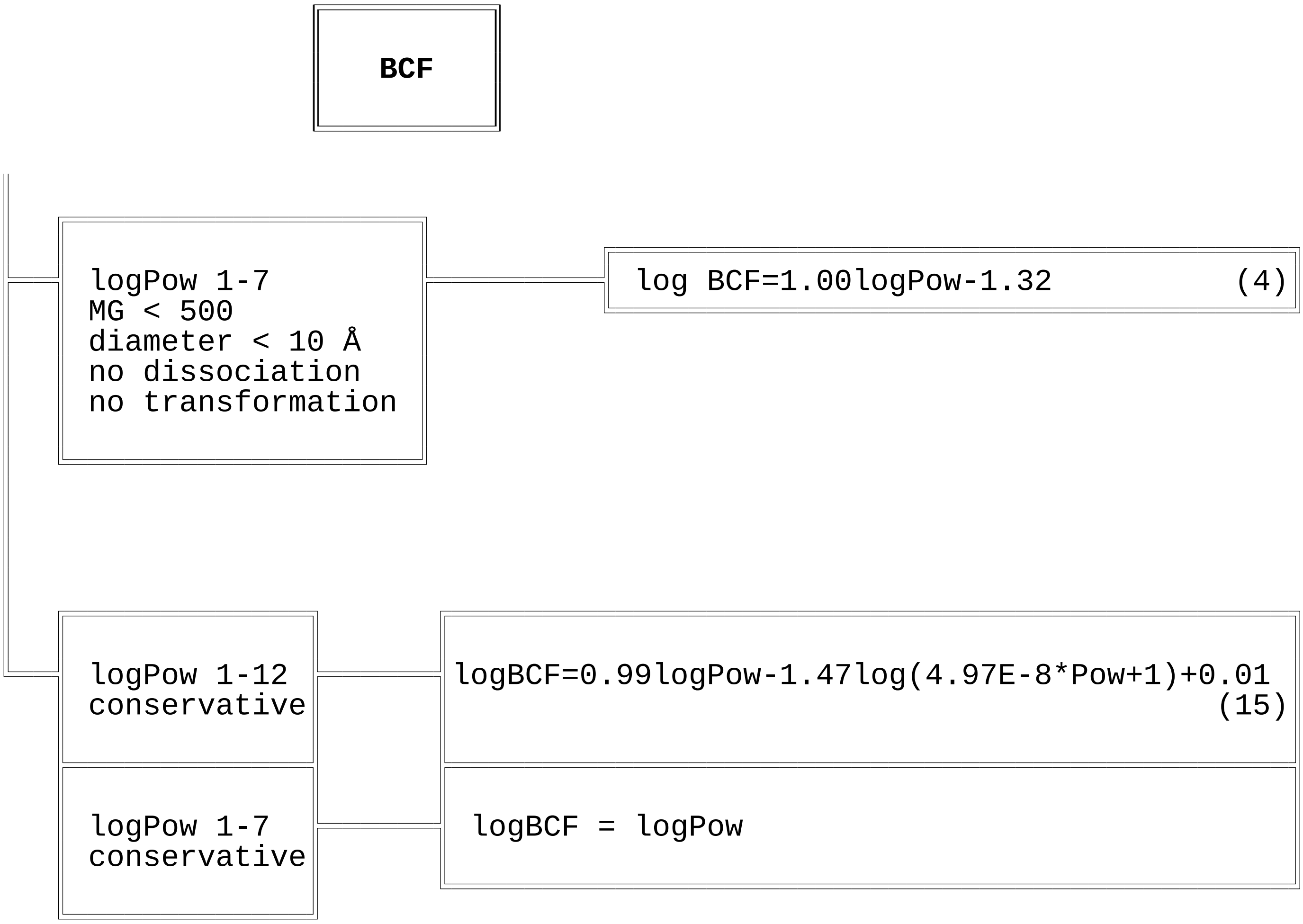
$$\log BCF = 0.99 \log P_{OW} - 1.47 \log (4.97 * 10^{-8} P_{OW} + 1) + 0.0135$$

r = n. a. n = 132 log P_{OW} range: 1.0-11.2

r: correlation coefficient, n: number of compounds analysed, n.a.: not available.
[13] Könemann et al. (1980), [14] Connell et al. (1988), [15] Nendza (1991).

Several factors may cause major discrepancies between QSAR-estimated BCFs and experimental values. Due to the non-linearity of the log P_{OW}/ log BCF correlations, extrapolations have to be restricted to the parameter range covered. The deviations due to extreme lipophilicity have been attributed to differences in transfer rates for lipid/water and 1-octanol/water partitioning processes, differences in solvent phase characteristics between natural lipids and 1-octanol, and size-limited diffusion (Opperhuizen et al. 1985, 1988, Gobas et al. 1987, Anliker et al. 1988, Hawker and Connell 1989). Further deviations may be due to substructure effects, e.g. 2,4-dinitro-substitution (Butte 1987, Deneer et al. 1987, Hauk et al. 1990), as well as degradation and metabolic transformation (Spacie et al. 1983, Gobas and Schrap 1990).

The major limitation for the derivation of reliable QSARs and, eventually, the prediction of BCF values is posed by the substantial variability in measured BCF values. The data may range over several orders of magnitude, depending on, for example, the compounds' purity and exposure concentration (bioavailability), exposure time (steady state), loss of chemical by evaporation, test species and protocol. Even though the estimation of BCF values from log P_{OW} is founded on a relatively profound theoretical basis, the predictive power of the respective QSARs should not be overestimated and their limitations should be realized. In principle, QSARs predict BCF values corresponding to the average accumulation observed with the class of compounds investigated. Hence the estimates do not necessarily reflect the potential "worst case". The respective function reflects the highest accumulation potential associated with the assumed lipophilicity, formalizing the empirical rules for estimating log BCF (based on the lipid content of the organism) from log P_{OW}: the bioconcentration potential corresponds to log P_{OW}. Compounds of higher lipophilicity (log $P_{OW} > 6$) reveal no further increase in BCF. Additional factors resulting in less bioconcentration are neglected, as the various contributions are not systematically accountable. This procedure is justified as a conservative approach (realistic "worst case") necessary for assessing environmental hazard.



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5. Propagation and distribution

The propagation and distribution of chemicals can be described at three levels: (1) the whole environment, (2) adjacent environmental compartments, (3) one single compartment. Obviously, the three aspects are interrelated and may strongly influence one another. Nevertheless, as to theoretical considerations and evaluation of environmental models, a separation seems useful. (1) and (2) require several assumptions to avoid an unmanageable complexity and as a consequence are of general relevance. The experimental evaluation of such global models is barely possible, as concentrations can be measured only in defined compartments. Processes (3) can best be described by equations using physical-chemical parameters, slightly modified for environmental scenarios. Therefore, they are often valid by definition.

Exposure of the whole environment:

When a chemical is released into the environment, it may reach any of the basic compartments: air, water, soil, biota. Depending on its physical-chemical properties, the chemical will prefer some of these compartments and avoid others in order to reach the level of lowest free energy. Decisive physical-chemical properties are: vapour pressure (P_V), Henry's Law constant (H), water solubility (S_W), soil sorption coefficient (K_{OC}), and n-octanol/water partition coefficient (P_{OW}), in this order with respect to the chemical's affinity to air, water, soil, biota.

Several models of varying complexity have been developed to calculate and predict the distribution of chemicals in the environment from these parameters. Most of them are derived from the Mackay model (Mackay 1979, Mackay and Paterson 1981, Mackay et al. 1982, Mackay and Paterson 1982, Paterson and Mackay 1985, EEP: Klein et al. 1988, ENPART: EPA 1987 and 1986; MNSEM 1.3: Yoshida et al. 1988; Zitko and McLeese 1980, Calamari et al. 1987).

The main physical-chemical parameter of the Mackay models is fugacity [f (Pa)], which is linearly proportional to the concentration of the chemical in the respective phase [c (mol/m^3)]

$$f = c * 1 / Z$$

and can be interpreted as the tendency to escape from a phase [fugacity capacity Z (mol/m^3*Pa)]. The compartment size and characteristics have to be defined either according to the unit world concept or corresponding to local conditions. If two phases A and B of different fugacity ($f_A > f_B$) are in contact, the chemical will move from A to B until $f_A = f_B$. Based on f, Mackay evaluated a model which is divided into four levels of increasing complexity.

Level I assumes equilibrium between all compartments, i.e. constant f

$$f_{total} = f_{air} = f_{water} = f_{soil} = f_{biota}$$

hence

$$c_{total} / Z_{total} = c_{air} / Z_{air} = c_{water} / Z_{water} = c_{soil} / Z_{soil} = c_{biota} / Z_{biota}$$

and the ratio $c_{compartment} / c_{total}$ can be calculated from $Z_{compartment}$.

For the vapour phase of volume V, f_{air} is equal to the partial pressure P.

$$Z_{air} = n / V * P = 1 / R * T$$

For the water phase, f_{water} corresponds to the concentration calculated from Henry's Law (P = H * c).

$$Z_{water} = 1 / H$$

For the soil, f_{soil} is estimated from soil sorption (K_{OC}) and Henry's Law constant (H), and the density of the soil is assumed to be 1.5 g/cm^3.

$$Z_{soil} = K_{OC} / H$$

For biota, f_{biota} corresponds to lipophilicity (P_{OW}) and the Henry's Law constant (H).

$$Z_{biota} = P_{OW} / H$$

According to Mackay Level I, the environmental distribution can be easily calculated from P_V, S_W and P_{OW}. However, the model's limitations have to be recognized. The assumed equilibrium distribution of chemicals in the environment without any transformation is very unlikely. Furthermore, homogeneous mixtures within each compartment are assessed, as well as fast transport between the phases.

Level II also assumes equilibrium, but includes transformation such as hydrolysis, photolysis, oxidation, biodegradation and advection as well as steady state input. All processes are assumed to be a first order function of concentration. If the kinetics of the various transformations are known, the persistence and percentage of the degradation of a chemical in each compartment can be calculated as a function of the input rate. The distribution between the compartments corresponds to Level I.

Level III is an extension of Level II, in that it allows slow transport between the compartments. A transfer rate is established, which is a function of fugacity difference, transfer area and diffusion rate. Mackay Level III elucidates interdependencies such as accumulation higher than expected under equilibrium conditions, caused by very slow transport.

Level IV, in addition, allows variations in fugacity, input rate and concentration with time. The change in concentration with time can be calculated for each compartment, as well as the persistence of the chemical after its input has ceased.

Overall, the Mackay models are very useful, especially the most applied Level I. It is a rough but sufficient estimate of the compartment in which a chemical is most likely to be found. The further levels involve complicated mathematics, and assume a homogeneous mixture, first order processes throughout, and clear discrimination between total sorbed and dissolved concentrations in each compartment. Global models that are not based on the Mackay concept combine several media-specific models (EXINT: Trenkle et al. 1987; TOX-SCREEN: Hetrick 1983).

Transport between two environmental compartments:

Concerning **air/water exchange**, two layer zones on either side of the contact interface are assumed to be the main resistance to the transport of chemicals (Doskey and Arden 1981). The transfer rate N [mol * s/m^2] is given by

$$N = K_W * (c_W - c_{Wi}) = K_A * (c_{Ai} - c_A) \quad \text{with} \quad c_{Ai} / c_{Wi} = H / RT$$

with:
K_W = mass transfer coefficient in water [m/s]
K_A = mass transfer coefficient in air [m/s]
c_W = concentration in water
c_A = concentration in air
c_{Wi} = concentration in water at the interface
cAi = concentration in air at the interface

If $H > 250$ Pa * m^3/mol, the air phase resistance is very low compared with the water phase resistance and the above equation can be transformed to

$$N = K_W * (c_W - c_A / (H / RT))$$

for low c_A and/or high H: $N = K_W * c_W$

resulting in a predominance of the diffusion rate in water. If $H < 2.5$ Pa * m^3/mol, water phase resistance can be ignored, resulting in a predominance of the air diffusion:

$$N = K_A * (c_W * (H / RT) - c_A)$$

for low c_A: $N = K_A * c_W * (H / RT)$

With this model, air/water distribution and flux is easily calculated from H, K_w and K_A.

Assuming equilibrium between precipitation and air, transfer by the dissolution of chemicals in rain (G_R = rain rate [$m^3/(m^2/s)$]) can be described by

$$N = G_R * c_A * (RT / H) = G_R * P / H$$

RT/H can be regarded as washout ratio, i.e. a measure for wet deposition (Scott 1981).

Transfer by dry deposition (Chamberlain 1967) is described by

$$N = v_D * c_P$$

with:
v_D = deposition velocity (almost K_A)
c_P = concentration of the chemical in the particles

The concentration of the chemical in the particles is controlled by the air concentration and the partition coefficient of the chemical between air and particle.

The flux rate for **air/soil exchange**, perpendicular to underlying soil according to Bird et al. (1960), is described by

$$J_A = K_A * (c_{as} - c_a)$$

with:
K_A = mass transfer coefficient
c_{as} = concentration in an air layer in contact with the interface
c_a = concentration in the air far away from the interface

K_A is a complex function of physical-chemical properties of the chemical, air velocity, and the nature of the soil. Because of the influence of soil parameters, extensive experiments are necessary to obtain K_A values.

Many efforts have been made to evaluate models for **water/soil exchange** because of its importance for ground water contamination. Water/soil exchange is dominated by soil sorption processes that are discussed above. The models used most are PRZM (Carsel et al. 1984) and SESOIL (Bonazountas et al. 1984).

Distribution within an environmental compartment:

The complex motions in the **atmosphere** control the long-range transport and dilution of chemicals (TA-Luft: TA-Luft 1986). The mechanism varies with space and time, depending on the underlying surface and on meteorological conditions. The relationships can be described by a global mass balance model. The concentration c of a gas at time t is given by a function of source S, sink L (equal to reciprocal lifetime t_L), and a partial differential function of the three-dimensional velocity field of air. For simplification of this function, the atmosphere can be divided into any number of parts (Box model: Neely and Blau 1985). With a k-box model, the function is converted to a system of k simple differential equations, for the i-th box given by

$$dc_i / dt = S_i - (1 / t_{Li}) * c_i - F \quad \text{with} \quad dc/dt = S - (1 / t_L) * c$$

if only one single box is assumed. F is the flux density across the boundary of the box caused by wind and turbulent processes. In the one-box model, F is equal to zero because no boundaries are present. Although requiring complicated mathematical calculations, models using more boxes are often utilised, for example the two-box model (usually dividing atmosphere into the two hemispheres or into stratosphere and troposphere) up to the nine-box model dividing atmosphere into heights (EXATM: Trenkle et al. 1987).

If counteracting sorption processes are neglected, movement J [mol * s/m^2] of chemicals in **soil** is a summation of diffusion (J_D) described by Fick's law:

$$J_D = -D_M * dc/dz$$

with:
D_M = molecular diffusion coefficient
z = coordinate of flux

The mass flow (J_M) is caused by an external carrier as air or water with a carrier velocity v.

$$J_M = v * c$$

Transport within **water** can be separated into advection and diffusion or dispersion. Concerning advection, dissolved chemicals are entirely entrained in the water movement (PDM3: EPA 1987). Molecular diffusion is the result of molecular movement by vibration, rotation and translation, described by Fick's law. Turbulent diffusion, which is of a much larger magnitude, is caused by micro-scale turbulences. The interaction of turbulent diffusion with velocity profiles in the water is called dispersion. Velocity gradients are caused by shear forces such as wind and contact with the boundary or sediment. Dispersion also follows Fick's law with a dispersion coefficient D_D instead of D_M. D_D can be calculated as a function of D_M and geometric as well as flux properties of the aqueous medium. The transport of chemicals in rivers is mainly controlled by advection, while transport in lakes and estuaries is controlled by dispersion. The relative importance of both effects can be calculated as Peclet number Pe, with a Pe value > 1 indicating predominance of advection (Neely and Blau 1985).

$$Pe = v * l / D_D$$

with:
v = mean velocity
l = length of segment
D_D = dispersion coefficient

Distribution models are valuable tools for estimating the fate of chemicals in the environment. To take the complexity of environmental conditions into account, global models need several assumptions which limit validity. Precise quantitative calculations are difficult, and can also rarely be validated by comparison with environmental data. Yet the models give sufficiently reliable predictions for distribution, propagation and persistence of chemicals in the environment.

6. Complex computer programs

Many systems for SAR and exposure estimations have been developed. Some of the most applied will be briefly discussed. For further details and for descriptions of other available computer models, see *Compendium of Environmental Exposure Assessment Methods for Chemicals* (OECD Environment Monograph No. 27, 1989).

MedChem software provides estimates of physical-chemical properties and access to the Thor database (partition coefficients, pKa).

PC Properties: log P_{OW}, MR.

AOP is a computer program which calculates transformation rate constants for the gas phase reactions between hydroxyl radicals and organic chemicals in the atmosphere using the fragment method of Atkinson. Rate constants for the reaction between ozone and olefins/acetylenes are calculated.

PC Properties: atmospheric degradation.

The **UBA(FHG)-SAR System** provides tools for physical-chemical, toxicological and degradation properties estimation. The procedures are based on the molecular structure and correlations with measured properties of chemicals with similar structure, as well as on property-property relationships.

Descriptors: molar volume, surface area, Hammett σ constants, molar refraction, quantum-chemical descriptors (HOMO, LUMO, hardness, electronegativity, heat of formation, ionization potential, dipole moment), connectivity indices.

PC Properties: log P_{OW}, P_V, H, T_b, pk_a, K_{OC}, S_W.

Degradation: atmospheric and biodegradation.

Ecotox.: BCF, aquatic toxicity, mammalian toxicity and mutagenicity.

Exposure: Mackay I.

The **EPA-ASTER SYSTEM** provides estimates of chemical properties, environmental fate, and toxicity and access to the US EPA AQUIRE database.

Descriptors: heat of vaporization, molar volume, surface area, molar refraction, parachor, connectivity indices, functional group indices.

PC Properties: log P_{OW}, P_V, H, T_m, T_b, pk_a, K_{OC}, S_W.

Degradation: hydrolysis half life, atmospheric and biodegradation.

Ecotox.: BCF, aquatic toxicity, mammalian toxicity phytotoxicity, genetic/mutagenic assessment.

CHEMEST is an interactive computer system for environmentally important properties estimation of organic chemicals. The calculations are based upon (1) empirically derived regressions between two or more properties, (2) theoretical equations with empirically derived parameters, and (3) summation of fragment and structural constants.

PC Properties: P_V, H, T_m, T_b, pk_a, K_{OC}, S_W.

Ecotox.: BCF_{FISH}.

MACKAY LEVEL I represents a *distribution model* for chemicals in the compartments soil, water, and air.

Input: P_V, S_W, P_{OW}.

EXAMS (Exposure Analysis Modeling System) provides estimates of the *fate and persistence in the aquatic environment*. It treats non-steady state systems such as rivers and transport in soil or ground water.

Input: log P_{OW}, K_{OC}, S_W, H, volume and composition of water and sediment; optionally: transformation (photolysis, hydrolysis, biodegradation).

PRZM (Pesticide Root Zone Model) is a model for *vertical transport in soil*. The concentration of chemicals can be calculated as functions of time (magnitude of days) and soil depth.

Input: K_{OC}, H, BCF, D_g, D_l, hydrolysis constants, kinetics of advection, dispersion, and degradation, runoff, evapotranspiration, infiltration of water.

SESOIL (Seasonal Soil Transport Model) describes *transport in soil*. The processes considered concern the water cycle, the sediment cycle, and the chemical cycle.

Input: S_W, D_g, D_l, K_{OC}, H, hydrolysis constants, photolysis, biodegradability.

LEACHM (Leaching Estimation and Chemistry Model) is a process-based *leaching model* of water and solute movement, transformations, plant uptake and chemical reactions in the unsaturated zone.

TA-Luft is a *climatological model*. Annual concentrations of chemicals downwind from a point source or multiple source are calculated at distances and directions (up to 50 km). The model assumes that the chemical is not transformed by any process.

Input: δ, particle diameter, environmental and meteorological conditions. Dry deposition is included.

7. Status

Summary of methods for estimation of compound specific properties:

Parameter	**Method**	**Status**
P_{OW}	MedChem ClogP	**++**
S_W	liquids: log P_{OW} solids: log P_{OW}, T_m	**+** **-**
T_b	Meissner's method	**-**
T_m	T_b	**--**
P_V	liquids, gaseous: T_b, K_F solids, liquids: T_m, T_b, K_F (hal.) hydrocarbons: T_m, T_b	**+** **+** **+**
H	P_V/S_W for substances of low water solubility simple compounds: fragment/bond	**+** **+**
pK_a	aromatics: Hammett aliphatics: Taft	**++** **+**
K (hydrol.)	Hammett, Taft for a few chemical classes	**++**
K (photod.)	AOP	**+**
K_{OC}	apolar: log P_{OW} polar: diverse methods	**+** **--**
BCF	log P_{OW}	**+**
Biodegradation	diverse methods	**-**

++	valid procedure
+	procedure valid, but with limitations
-	procedure of limited applicability
--	procedure not recommended

List of symbols used in this report

BCF	Bioconcentration factor
BE	Biological effect
B_1 - B_5	Verloop constants
c	Concentration [mol/m^3]
$C_{W,}$ C_w	Concentration in water
C_A, C_a	Concentration in air
c_p	Concentration in particles
D_D	Dispersion coefficient
D_g	Diffusion coefficient in the gas phase
D_l	Diffusion coefficient in the liquid phase
D_M	Molecular diffusion coefficient
EL	Electronic properties
E_S	Taft steric constant
f	Fugacity [Pa]
f_n	Structural constants for P_{OW} calculation
F	Flux density
F_n	Structural constants for P_{OW} calculation
G_R	Rain rate [m^3(m^2/s)]
H, H’	Henry’s Law constant ([Pa(m^3/mol)] resp. dimensionless)
IP	Ionization potential
k	Rate constants of reactions
K	Equilibrium constants
K_A	Mass transfer coefficient in air [m/s]
K_F	Compound class specific constant for Pv calculation
K_{hyd}	Hydrolysis rate constant
K_{OC}	Soil sorption coefficient related to organic carbon content
K_{OH}	Atmospheric degradation rate constant (for the reaction with hydroxyl radicals)
K_W	Mass transfer coefficient in water [m/s]
J	Flux rate [mol * s/m^2]
J_M	Mass flow
L	Verloop constants or lipophilic properties
LFER$_s$	Linear Free Energy Relationships
l	length of segment
MR	Molar refraction
MV	Molar volume
N	Transfer rate between two phases [mol * s/m^2]
N_A	Avogadro number
P	Partial pressure

Pe	Peclet number
pK_a	Acid dissociation constant
P_{OW}	Partition coefficient l-octanol/water
Pr	Parachor
P_v	Vapour pressure
R	Gas constant: 8.314 [J/(mol * K)] (other units also in use, e.g. [cal/(mol * K)]
SA	Molecular surface area
SASA	Solvent accessible molecular surface area
SAV	Solvent accessible molecular volume
ST	Steric properties
S_W	Water solubility
T	Environmental temperature [K]
T_b	Boiling point [K]
T_m	Melting point [K]
v_D	Deposition velocity or carrier velocity
Vm	Molecular volume
${}^iX$, ${}^iX^v$	Connectivity indices of order
Z	Fugacity capacity [mol/m^3 * Pa]
Z^v	Number of valence electrons
z	Coordinate of flux
α	Polarizability
σ	Hammett constant
σ^*	Taft constant
μ	Dipole moment
δ	Atomic parameter for connectivity indicos
δ^v	Valence-corrected δ value

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