Institute for Health and Consumer Protection

European Chemicals Bureau

Technical Guidance Document on Risk Assessment

in support of

Commission Directive 93/67/EEC
on Risk Assessment for new notified substances

Commission Regulation (EC) No 1488/94
on Risk Assessment for existing substances

Directive 98/8/EC
of the European Parliament and of the Council
concerning the placing of biocidal products on the market

Part III

TGD

Part III

EUROPEAN COMMISSION
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European Commission

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FOREWORD

I am pleased to present this Technical Guidance Document which is the result of in-depth co-operative work carried out by experts of the Member States, the Commission Services, Industry and public interest groups. This Technical Guidance Document (TGD) supports legislation on assessment of risks of chemical substances to human health and the environment. It is based on the Technical Guidance Document in support of the Commission Directive 93/67/EEC on risk assessment for new notified substances and the Commission Regulation (EC) No. 1488/94 on risk assessment for existing substances, published in 1996. This guidance was refined taking into account the experience gained when using it for risk assessments of about 100 existing substances and hundreds of new substances. Furthermore, it has been extended to address some of the needs of the Biocidal Products Directive (Directive 98/8/EC of the European Parliament and of the Council).

Concerning Chapter 2 on Risk assessment for human health, the Exposure assessment (Assessment of workplace exposure and Consumer exposure assessment) as well as the Effects assessment were improved and refined. However, for the following sections the revision process is not yet finalised and thus, the current TGD version uses the previous text: section 2.4 on Assessment of indirect exposure via the environment and section 4 on Risk characterisation. These sections are expected to be available by the end of 2003.

With respect to Chapter 3 on Environmental risk assessment, the Environmental exposure assessment and the Effects assessment underwent major improvements. A new chapter on Marine risk assessment was added.

Concerning Chapter 7, five out of eight available Emission scenario documents (ESDs) were revised (IC-3 Chemical industry: Chemicals used in synthesis, IC-7 Leather processing industry; IC-8 Metal extraction industry, refining and processing industry; IC-10 Photographic industry; IC-13 Textiles processing industry). Furthermore, a document on Rubber industry (IC-15) and a number of ESDs for the Biocidal Product Types or parts thereof were added. Some of the Emission scenario documents are still subject to on-going consultation in the OECD and thus, may need to be revised at a later stage. In addition, ESDs to cover all 23 Biocidal Product Types are under development. Consequently, it is anticipated that the set of Emission scenario documents will be continuously expanding in the future.

The White Paper outlining a future chemicals policy was adopted in February 2001 by the Commission. This TGD is therefore to be used in support of the current legislative instruments as described above until they are revoked and replaced by the future legislation implementing the White Paper.

I hope you will agree that this TGD makes a valuable contribution to the development and harmonisation of risk assessment methodologies not only within the Community but also worldwide in the context of the activities of the Organisation of Economic Co-operation and Development and the WHO/ILO International Programme on Chemical Safety.

Ispra, April 2003

Kees van Leeuwen
Director
Institute for Health and Consumer Protection

OVERVIEW

This Technical Guidance Document is presented in four separate, easily manageable parts.

PART I

PART II

PART III

PART IV

Chapter 4

USE OF (QUANTITATIVE) STRUCTURE ACTIVITY RELATIONSHIPS ((Q)SARS) IN RISK ASSESSMENT

CONTENTS

1 INTRODUCTION

1.1 BACKGROUND

(**Q**uantitative) **S**tructure-**A**ctivity **R**elationships ((**Q**)**SAR**s) are estimation methods developed and used in order to predict certain effects or properties of chemical substances which are primarily based on the structure of the substance. They have been developed on the basis of experimental data on model substances. (Q)SAR models are available in the open literature for a wide range of endpoints which are required for a risk assessment, including several toxicological and ecotoxicological endpoints and physico-chemical/fate parameters. The predictive methods for toxicological endpoints are generally non-quantitative methods of an expert judgement type while for ecotoxicological effects and physico-chemical/fate characteristics normally quantitative methods are available.

When carrying out the risk assessment for man and the environment (see Chapter 2: Risk Assessment for Human Health and Chapter 3: Environmental Risk Assessment) the exposure of the substance to humans and the environmental compartments needs to be estimated. The exposure assessments will be carried out based on available monitoring data and/or modelling. For establishing an exposure level or exposure concentration based on modelling, several physico-chemical/fate parameters are used. In the absence of experimental data, e.g. because it is not possible to obtain reliable measured data, these parameters may be derived by applying QSARs.

The exposure estimates are then in the risk characterisation step compared to the concentrations at which no effects are expected to occur, i.e. with the N(L)OAEL in the risk assessment for human health or with the PNEC in the environmental risk assessment or with a qualitative dose-response assessment where a N(L)OAEL or a PNEC cannot be established. Depending on the exposure/effect ratio the decision whether the substance presents a risk to man and/or the environment is taken or whether further data are necessary to clarify a concern. When the assessor considers the potential need for further (test) data, (Q)SARs may serve as a supporting tool in taking this decision. If further testing is needed, (Q)SARs may also be used to optimise the testing strategies.

According to the legal requirements for the minimum data set that has to be submitted for priority substances as laid down in Article 9(2) of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances, test data for all elements listed in Annex VII A to Council Directive 67/548/EEC, i.e. the base-set, are normally available for the risk assessment. In addition, for a number of substances information beyond the base-set will be available.

The amount and quality of data is expected to vary widely for existing substances: e.g. there may be several tests available giving information on a single endpoint/parameter which may not always show complementary results. Furthermore, there will be studies, in particular older studies, provided which have not been conducted according to current test guidelines and quality standards. In order to decide on the test results which are valid for use in the risk assessment, i.e. either for the exposure or the effects assessment, the assessor may use (Q)SARs as a tool to assist in taking this decision.

The base-set does not include data on all potential adverse effects that may occur in man and the environment. Further tests may be asked for, if a potential concern with regard to other effects is identified. (Q)SARs could also be used to identify the need to obtain those tests.

The use of (Q)SARs within the risk assessment process may, when evaluated methods, which are considered adequate, are used and they are used appropriately, save time and financial resources for both the rapporteur and industry. Furthermore, their use may result in fewer experimental tests involving animals which is in accordance with Council Directive 86/609/EEC. However, as a general principle, the use of (Q)SARs should not result in a reduction of the scientific basis on which the risk assessment is made.

When applying (Q)SARs it should be taken into account that a (Q)SAR is an estimation method and that therefore there is a certain probability that the estimate is poor, even for well evaluated models. Hence, estimates resulting from (Q)SAR models cannot be the only basis for preparing a risk assessment of a substance. (Q)SAR estimates should be seen as a complementary tool, which evaluated together with test results can provide a more complete understanding of the physico-chemical and (eco) toxicological characteristics of the substance. The result of a (Q)SAR should thus be evaluated for consistency in the light of available experimental data and validated estimates from other endpoints. Furthermore, it should be noted that (Q)SAR models generally only exist for discrete organic substances and not for, for example UVCBs (Unknown and Variable composition, Complex reaction mixtures and Biological materials).

(Q)SAR models should only be used in the risk assessment if they have been thoroughly evaluated. Within several national and international programs, in depth investigations and evaluations of various (Q)SAR models are currently being carried out. As far as possible, the outcome of these projects and other ongoing research projects in the field has been considered when preparing this document. Further results are expected in the near future and will be considered in any future revision of this document.

The objective of the current document is to present the general framework in which (Q)SARs can be used within the risk assessment process, to present general principles for the selection of (Q)SARs for that purpose, to present recommended QSARs for ecotoxicological effects and physico-chemical/fate parameters and to give guidance on their specific use within the risk assessment. This guidance is to be understood as a complement to the guidance given in Chapter 2: Risk Assessment for Human Health and in Chapter 3: Environmental Risk Assessment.

1.2 OUTLINE OF THIS GUIDANCE DOCUMENT

Sections 1 to 3 deal with the general aspects concerning the use of (Q)SARs in risk assessment such as definitions and general principles for the selection, evaluation and use of (Q)SARs. In Section 4, guidance is given for specific endpoints, which are relevant in the environmental risk assessment process. For the effects assessment, QSARs have been included to predict acute and long-term toxicity of non-polar narcotics and polar narcotics in several species. Furthermore, a discussion is presented on (Q)SARs for bioconcentration in fish and worms for the assessment of secondary poisoning. For exposure assessment, (Q)SARs are included for the following endpoints: *n*-octanol-water partition coefficient, soil and sediment sorption, biodegradation, photolysis in atmosphere, hydrolysis and Henry's Law Constant. Section 4 also sets out the scope of application of the described prediction methods.

Validated QSARs are not currently available for human health-related toxicity endpoints. Instead, expert judgement is used in the light of data on close structural analogous and/or the presence of "structural alerts" (i.e. fragments associated with affects) in the substance. This document therefore presents detailed guidance only for the use of QSARs in assisting in the assessment of the risks for the environment.

If the QSARs which are explicitly described in this guidance document are used as described then there is no need for the rapporteur to supply additional information on the applied QSAR. As the field of (Q)SAR is continuously under development and as some predictive methods are not formulated in terms of formalised models, it is recognised that a rapporteur may wish to apply a (Q)SAR which is not explicitly recommended in this guidance document. When doing so, the rapporteur should consider the principles for its selection given in Section 3 and present in the comprehensive risk assessment report at least the information outlined in Appendix I on the (Q)SAR which has been used.

2 DEFINITIONS

(Q)SAR method:	A (Q)SAR method is the theory underlying a (Q)SAR, including the adequacy of the descriptor variables, the form of the model and the description of the activity which the model represents.
(Q)SAR model:	A (Q)SAR model is the quantification of the (Q)SAR method through for example the derivation of a mathematical equation describing the activity for a specific class of substances.
Domain of a (Q)SAR:	The domain of a (Q)SAR is the group of substances for which the model is valid. This group of substances can be defined by structural rules, mechanistic information and/or parameter ranges.
Reproducible:	A (Q)SAR is considered to be reproducible if it can be applied by all assessors independently and leads to the same results.
Training Set:	The training set is the set of data used to construct a (Q)SAR model.
Validation Set:	The validation set is the set of data which is used to validate the (Q)SAR model. The data in this set should not be included in the training set and should be chosen in the domain of the model, but independently of the training set.
$PNEC_{SAR}$:	The predicted no effect concentration using QSAR estimates for the $LC(EC)_{50}$ or NOEC instead of experimental data. The $PNEC_{SAR}$ is derived similarly to the derivation of the PNEC based on experimental ecotoxicity data, i.e. the same assessment factors are applied to the $L(E)C_{50}$ or the NOEC.

3 GENERAL PRINCIPLES FOR THE SELECTION AND USE OF (Q)SARS

3.1 INTRODUCTION

The development of a (Q)SAR is based on the assumption that chemical substances which reach and interact with a target site by the same mechanism do so because of their similar chemical properties. Since different mechanisms of interaction usually will depend on different properties, different (Q)SARs must be generally developed for each mode of action. Some (Q)SARs are developed using quantitative data in order to predict a quantitative parameter. Such methods are referred to as QSARs. The general principles described in this section apply to the whole range of predictive methods.

There are basically two types of predictive methods:

- formalised methods (e.g. QSARs);
- expert judgement.

Formalised methods are methods which can be subjected to validation, applied objectively by one assessor and are both reproducible and transparent to other assessors. They are based on mathematical formula and/or fixed rules. Critical evaluation of the models should be carried out, including the evaluation of the appropriateness and validity of the descriptor variables, the evaluation of the form of the models and the methods used to construct the models. These models should be applied critically acknowledging the limitations of the model, such as which chemicals are within the domain of the model. Other models may be used, but for models which are not included in this document, the information as outlined in Appendix I concerning the model which is used within the risk assessment process should be made available to the other assessors in order to ensure transparency and reproducibility.

Methods based on expert judgement are methods which only an "expert" can apply, as they rely on the expert's experience and intuition. They are generally non-quantitative methods based on structural similarity and/or analogues and have usually not undergone statistical treatment and validation. These methods should be used with extra caution, as they rely on the judgement and experience of the individual rapporteur and hence they may not be reproducible by the other assessors. Therefore, when a method based on expert judgement is used, sufficient information as outlined in Appendix I should be made available to the other assessors to ensure transparency.

Since there is no universal measure for structural similarity and since the measure of similarity between two substances is highly dependent on the endpoint and chemical class under consideration, the criteria used to draw a conclusion based on an analogue or a specific similarity in structure should be clearly stated.

A method based on expert judgement can be developed into a formalised method, through formalising the hypothesis used to produce the predictions, then collecting sufficient data and thereafter performing a statistical analysis with validation to construct the model. It is therefore clear that a sharp division between formalised methods and methods based on expert judgement does not exist and that usually the roots of a formalised model have been in a series of rules based on expert judgement.

The endpoint predicted by a (Q)SAR model have an outcome which is either:

- continuous;
- discrete.

Formalised methods can be of both types. Methods which are based on expert judgement are generally discrete outcome methods, as they generally have non-quantitative outcomes of the "positive" or "negative" type.

It is recommended that, in general, (Q)SAR estimates are to be used in a conservative manner, i.e., that (Q)SAR estimates should generally be used in the case where the estimate gives an indication of concern for man or the environment.

For a (Q)SAR to be used within the risk assessment process, it is necessary that the endpoint estimated is compatible with an endpoint used in the risk assessment. If such compatibility exists, then the (Q)SAR can be used for the purposes listed below:

Use I: to assist in data evaluation.

Use II: to contribute to the decision making process on whether further testing is necessary to clarify an endpoint of concern and, if further testing is needed, to optimise the testing strategies, where appropriate;

Use III: establishing (input) parameters which are necessary to conduct the exposure and/or effects assessment.

Independently of the above three uses, (Q)SAR methods can assist in

Use IV: identifying effects which may be of potential concern on which test data are not available.

The four uses are fundamentally different. Uses I, II and IV provides the assessor with the option of using (Q)SAR, whereas the assessor must use (Q)SAR within Use III if test data are not available.

Uses I, II and IV differ fundamentally in that Use I is applied in the situations where both experimental data and (Q)SAR estimates exist for the endpoint, whereas Uses II and IV are applied in cases where no experimental data are available for a given endpoint and where the estimate is used within and outside the testing strategies, respectively. The purpose for which a particular (Q)SAR is used will depend on the manner in which the model has been constructed, the evaluation of the model, the state of validation and to what extent the (Q)SAR can be applied. Several of these factors are independent of both the endpoint under consideration and the proposed use of the (Q)SAR. These general criteria are given in the next sub-section. The factors which are specific for the use but still independent of the endpoint are given in the sub-sections thereafter.

3.2 GENERAL CRITERIA FOR SELECTING (Q)SARS FOR USE WITHIN THE RISK ASSESSMENT PROCESS

A (Q)SAR is considered to be acceptable for a particular use within the risk assessment process, if:

- the (Q)SAR applied is valid;
- the estimate possesses the necessary accuracy for the intended use.

3.2.1 Evaluation of the validity of (Q)SARs

In order for a (Q)SAR to be considered valid, it must have been constructed in a sound scientific manner. It is not possible to set up strict criteria for determining if a (Q)SAR is valid, since such criteria will be strongly dependent on such factors as the endpoint under consideration, the method used to generate the (Q)SAR and the domain of the (Q)SAR.

However, it is possible to list a set of factors which should be considered when a method is evaluated with regard to its validity. These factors are given below. The (Q)SAR method to be used as a supporting tool in carrying out a risk assessment should meet all these validity criteria. Several of the criteria are based on considerations which need to be taken into account when using of QSARs, but, nevertheless, they should also be considered for any general (Q)SAR methods which are used.

3.2.1.1 Endpoint

The exact endpoint being modelled should be described. If it is a multiple response endpoint (e.g. the degradation rate at four different durations) and all the data are used, then this should be considered in the model (dependence between the different results). It is also useful, if the experimental error can be judged, that is if the standard deviation of the experimental error of the measurements used in the training set is given. A check should be carried out for variance stability (i.e. whether the experimental error is constant over the range of the model). It should also be clearly stated in which units the endpoint results are measured, and if applicable, if nominal or actual concentrations have been recorded.

3.2.1.2 Test method

The test method used as the basis for development of the (Q)SAR should be clearly described or referenced (e.g. details of the test species - age, sex, number etc. or tested soil type should be given). It should be checked if the test methods used to generate the training set follow an acceptable protocol (for example a test method in Annex V of Council Directive 67/548/EEC or an OECD Test Guideline). For a given test in a testing strategy, for which a (Q)SAR is under consideration for use as a supporting tool in conducting the risk assessment (see Section 3.3.2), it should be checked if the test protocol for the training set is comparable with the test protocol for the given test in the strategy.

3.2.1.3 Model

The model should reflect the underlying process described by the (Q)SAR, for example the physico-chemical and/or the biological interactions. The technique used to generate the model

should be stated clearly (methodology, statistical package, etc.) and should be appropriate. For example if linear regression was used on discrete descriptor variables (for example the number of chlorine atoms or a zero-one valued variable) then the model can provide inaccurate results. Also a discussion addressing the assumptions inherent in the technique used to generate the model should be included. For example, standard linear regression assumes variance stability and that the independent variables are measured with no error. It should be checked, if the model has been properly validated (see also Section 3.2.2).

3.2.1.4 Descriptors

The descriptor variables used in the model should be well defined and not intercorrelated and should be reproducible. The accuracy of the determination of the descriptor variables should be available as should be the data used to generate the descriptor variables. It should be stated how many (and which) variables were considered when developing the (Q)SAR and how many (and which) variables are present in the final (Q)SAR. The exact source of the data used for the descriptor variables should be given. If these data originate from experimental tests, then the same considerations as under "endpoint", "test medium" and "test method" above should be applied. If they are theoretical or calculated variables their relevance should be considered.

3.2.1.5 Domain of definition of the model

The exact domain of definition of the model should be stated. That is the exact structural rules defining the group of substances for which the model is valid, as well as the ranges of the model parameters for which the model is valid, should be given. The definition of such group(s) can be classical definitions (epoxides etc.) and/or that of an objective similarity measure, for example a collection of parameters or descriptor variables (not necessarily only those used in the (Q)SAR itself) of the substances are within specific ranges. Special attention should be given to the way in which this domain has been constructed. If it is mainly defined by "exclusion rules" rather than "inclusion rules", then this could be an indication that the domain has been defined after the model building, based on a test set for which some substances (now excluded) performed poorly.

3.2.1.6 Validity

The method used for generating the training set should be given. Preferably statistical design should be used to generate this set of data. Statistical design methodologies are objective methods, which ensure maximum variance in the descriptor variables of the training set and thus produces a training set which spans the domain of definition of the model. It should be checked if explanations have been given for removing "outliers" from the training set. This explanation may be, for example the identification of a mechanistic explanation (i.e. the outlier has a different mode of action). If outliers have been removed then the reason for doing so should be checked for consistency with the definition of the domain of the model.

3.2.1.7 Accuracy

It should be checked if the correlation coefficient for the model is given as well as overall statistics judging the overall validity and accuracy of the model. These statistics should include the estimated standard deviation of the prediction errors, the statistics describing the significance

of the model as a whole and the significance of the individual variables in the model as well as estimates (and if appropriate the estimated standard deviation) of the model parameters.

3.2.2 Evaluation of the accuracy of (Q)SARs for intended use

The accuracy of a (Q)SAR must be sufficient for the intended use, but the required level for adequate accuracy depend on both the use of the (Q)SAR and the endpoint under consideration. The accuracy of a model can, for example, be evaluated by determining the standard error of the estimation method or the "success" rate and by itemising and determining the "failure" rate. There may, however, be (Q)SARs where only indications for the occurrence of an effect (i.e. positive predictions) could be considered as being "accurate" and these may be used in the risk assessment. Negative predictions for toxicological endpoints should be subject to expert assessment. The extent to which they may contribute to the risk assessment will be influenced by the type of outcome (continuous or discrete) and must be evaluated on a case-by-case basis taking into account also all other available relevant data.

At a minimum, the accuracy of a (Q)SAR can be judged if a quantitative estimate can be given for the probability of categorising a substance wrongly in the case of a discrete outcome (Q)SAR and for the probable estimation error in the case of a continuous outcome (Q)SAR.

If only these statistics are given, then it is essential that the assumptions inherent in the technique used to generate the model are satisfied.

A good indication of the predictability of the model can be achieved through the presence of cross-validation studies. The simplest is the cross-validated correlation coefficient. If this coefficient and the correlation coefficient are approximately the same, then the model can be used for predicting with the accuracy indicated within the defined domain.

Other, more complex, cross validation techniques exist, which will give information on the predictability and correctness of the model. One such technique is the application of a bootstrap argument to simulate the robustness of the model and the model statistics. The main assumption behind a bootstrap argument is that the training set is representative of the set of substances in the domain of the model. This can be checked by means of for example statistical design. A random sample with replacement of the training set containing for example 50% of the substances is taken. The model is recalculated using this bootstrap training set. This procedure is repeated many (e.g. several hundred) times. If the parameter estimates are close to those of the repeated bootstrap parameter estimates and if the variability of the bootstrap parameter estimates are small, then the model is robust and the accuracy of the model can be deduced.

Finally, it should be checked whether an external validation set was used to evaluate the model. Such a validation gives the necessary information needed for judging the accuracy of the model.

The accuracy must be considered to be sufficient for the intended use. The requirements for an adequate accuracy are depended on both the use of the (Q)SAR and on the endpoint under consideration. A valid (Q)SAR possessing the adequate accuracy is considered acceptable for the intended use.

3.3 USE OF ACCEPTABLE (Q)SARS

Guidance is given below on how to use acceptable (Q)SAR estimates established by applying valid and accurate models. As a general rule, (Q)SAR estimates should be used only in a conservative manner in the risk assessment process. Particular care should be taken to exclude the possibility of reaching a conclusion on the risk to man and environment where that conclusion may have been markedly influenced towards a relatively lower risk by the use of (Q)SAR estimates.

3.3.1 Use I: data evaluation

The assessor may use acceptable (Q)SARs as a supporting tool when evaluating the adequacy of available experimental data. For this type of use, (Q)SARs on base-set endpoints and parameters and on datapoints beyond the base-set requirements can be used. Normally, (Q)SARs will be used in helping to decide whether data from available tests are suitable for use in the risk assessment when the validity of the test is not obvious, e.g. incomplete information on the test is available and/or the test differs in some respects from the current test guidelines and the generally accepted standards. However, existing experimental data should not be disregarded unless they can be shown clearly to be invalid or unsuitable for use in the risk assessment (see also Chapter 2, Section 3.2 and Chapter 3, Section 3.2.1).

The way in which the (Q)SAR is used for data evaluation is dependent on the type of outcome of the (Q)SAR.

Although the degree of accuracy of the (Q)SAR for data evaluation is dependent on the endpoint being modelled, a general guideline for the quantification of the accuracy for a continuous outcome (Q)SAR is that 95% of the data should be included in the confidence interval given by the accuracy. The (Q)SAR can then be used for data evaluation by comparing the difference between the estimate and the experimental value with the accuracy of the (Q)SAR. If the difference is greater than the expected accuracy then there could be reason to believe that either the (Q)SAR estimate or the experimentally derived value is inaccurate. Both possibilities should be considered, using expert judgement, before a decision is taken on the validity of a particular test.

For discrete outcome (Q)SARs (e.g. an estimate for a mutagenicity screening test), it is recommended that the accuracy of correctly predicting the property of the substance should be 95% in order to use the prediction for data evaluation. The (Q)SAR can then be used for data evaluation by comparing the (Q)SAR prediction with the experimentally derived result. If the two outcomes differ then there could be reason to believe that either the (Q)SAR prediction or the experimentally derived result is inaccurate. Both possibilities should be considered before a decision is taken on the validity of the experimental data. When several studies are available with differing results for a particular endpoint, (Q)SAR predictions may contribute to the weight of evidence for the outcome used in the risk assessment.

3.3.2 Use II: decision for further testing / testing strategies

This section discusses in detail only the use of (Q)SAR methods as a supporting tool in the risk assessment with regard to the aquatic environment. (Q)SARs may, however, be used as a tool in the decision making process in relation to potential further testing for mammalian toxicity (see Section 5 and Chapter 2).

If the PEC/PNEC ratio being established on the basis of tests on aquatic organisms is greater than one, the assessor shall judge taking into account inter alia data on structurally analogous substances if further information and/or testing are required to clarify the concern or if risk reduction measures are necessary. The assessor will then need to decide whether further data on exposure or ecotoxicity would allow a refinement of the PEC/PNEC ratio and would influence the risk characterisation result (see Chapter 3, Section 4.1).

Before requesting any further testing it is recommended that all available relevant data are considered, including all relevant estimates established by applying acceptable QSARs. QSAR estimates can be derived for tests according to Annex VIII of Directive 67/548/EEC. Based on these resulting estimates a $PEC/PNEC_{SAR}$ ratio is established. The $PEC/PNEC_{SAR}$ shall be used only as a supporting tool for the decision to be taken with regard to the two possible results of the environmental risk assessment as described above and, if further testing is necessary, to optimise the testing strategy. However, the QSAR estimates shall not be used for any revision of the PEC/PNEC ratio (see Chapter 3, Sections 3.2.1.2 and 4).

If, on the basis of the $PEC/PNEC_{SAR}$ taking into account (Q)SAR estimates for Annex VIII tests it is not likely that further testing would lead to a refinement and lowering of the PEC/PNEC ratio and no further refinement of the PEC is possible, then further testing should not be requested.

If, however, a refinement of the PEC/PNEC ratio is possible and further tests are required to clarify the concern for the aquatic environment, QSAR estimates may be used to facilitate the choice of the most appropriate test to reach clarification. For example, the NOECs for the different species under consideration should be estimated by applying accepted QSARs and comparing the results. The long-term test should then normally be conducted on the species which showed the lowest estimated NOEC.

The PEC/PNEC ratio will subsequently be revised using the test result obtained.

QSAR estimates for acute aquatic effects may also be used for the decision on any further action within the risk assessment. This may be the case, for instance, if for a species the long-term test is available while a (valid) acute test on the same species is missing. In that case it would normally not be requested to conduct the missing base-set test. In order to decide on the adequate assessment factor for establishing the PNEC and to identify the most sensitive species if further testing would have to be conducted, QSAR estimates on the missing acute effect should then assist in taking these decisions.

Figure 1 illustrates schematically the stepwise process within Use II. A more specific guidance of how to apply the QSAR estimates is given in Section 4 for the recommended QSARs.

3.3.3 Use III: establishing specific parameters

The use of acceptable (Q)SARs for the estimation of specific (input) parameters needed in the risk assessment, in particular in the exposure assessment, differs from the above two uses, as in order to be able to derive the PEC, QSARs must be used where measured data are not available.

In Chapter 3, several general (Q)SARs which can be used in particular for exposure assessment are mentioned.

3.3.4 Use IV: identifying data gaps on effects of potential concern

Acceptable (Q)SARs can be used in relation to preliminary assessment of endpoints which are not part of the base-set and for which information may not be available. These (Q)SAR estimates may indicate potential risks to man or the environment. Whether these estimates should give rise to any actions by the rapporteur should be considered on a case by case basis and in the light of all the available data, both on effects and on the actual or potential exposure scenarios.

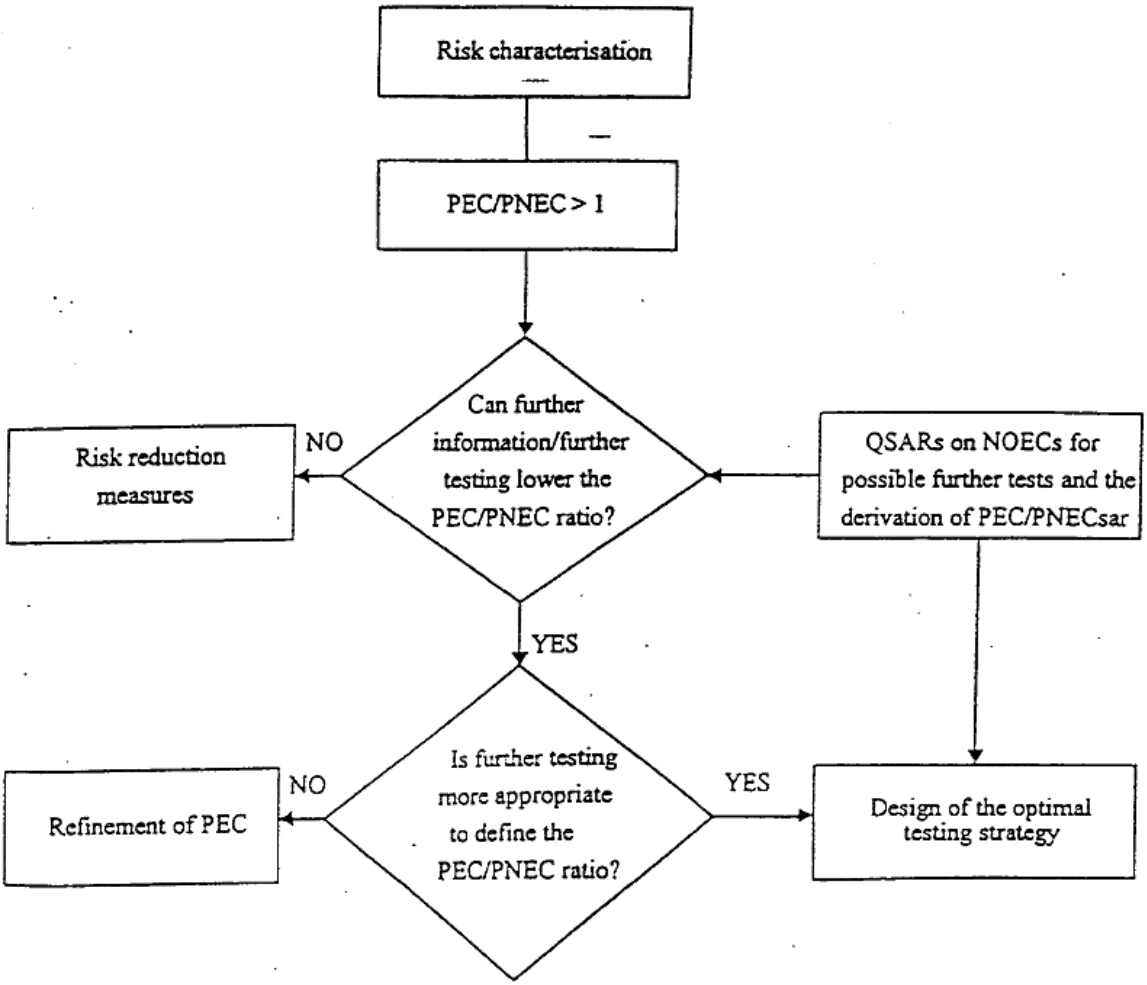

Figure 1 Use of QSARs as a supporting tool in the risk characterisation for the aquatic environment (see also detailed description of the risk characterisation for environmental compartments in Section 4.1 of Chapter 3).

4 SPECIFIC GUIDANCE ON THE USE OF (Q)SARS IN ENVIRONMENTAL RISK ASSESSMENT

Recommended QSARs for the following areas are included in this chapter: acute toxicity to fish (96-hour LC50), Daphnia (48-hour EC50) and algae (72-96-hour EC50), long-term toxicity to fish (NOEC, 28-day study) and to Daphnia (NOEC, 21-day study), *n*-octanol-water partition coefficient (logKow[1]), sorption (Koc), Henry's Law Constant (H), bioconcentration (BCF fish and worms), biodegradation (not ready biodegradable), photolysis ($kdeg_{air}$) and hydrolysis ($khydr_{water}$).

4.1 AQUATIC EFFECTS

4.1.1 Introduction

The environmental risk assessment procedure for the aquatic compartment focuses on acute and long-term effects for fish, Daphnia and algae. Experimentally determined data on short-term toxicity are required for the base-set. The availability of long-term toxicity data will vary from substance to substance. The QSARs can be used for data evaluation. Furthermore, they can assist in the decision whether further testing is needed and how to optimise the testing strategy.

Currently, reliable QSARs are available for chemicals that act by a non-specific mode of action (non-polar narcosis as well as polar narcosis). Regarding non-polar narcosis, QSARs are recommended for fish (short and long term), Daphnia (short and long term) and algae (short term). With respect to polar narcosis, QSARs are recommended for fish (short term) and Daphnia (short term). No QSARs have been recommended for substances that act by more specific modes of action.

4.1.2 Description of QSARs

4.1.2.1 Non-polar narcosis

The mechanism of non-polar narcosis is primarily related to the hydrophobicity of the substance, and is also referred to as "minimum toxicity" or "base-line toxicity".

In absence of specific toxic mechanisms, the internal effect concentrations are almost constant.

A compound will then be as toxic as predicted by its hydrophobicity, due to the relation with bioconcentration (McCarthy and MacKay, 1993).

Compilations of QSARs for this class of chemicals can be found in several publications, reports or computer programs from different organisations or research groups in the US and Europe (Könemann, 1981a; Veith et al., 1983; Russom et al., 1991; IUCT, 1992; OECD, 1992; Van Leeuwen et al., 1992; Clements and Nabholz, 1994). The following models have been selected and recalculated in a recent evaluation of QSARs for ecotoxicity (Verhaar et al., 1995).

[1] logKow is used in this document, which is equivalent to logPow.

Table 1 QSARs for non-polar narcosis (base-line toxicity, minimum toxicity)

Species	Endpoint	Equation + statistics	Reference
Fish			
Pimephales promelas	96-h LC50 mol · l^{-1}	log LC50 = -0.85 logKow - 1.39 n=58, r^2=0.94, Q^2=0.93, s.e.=0.36	Verhaar et al., 1995
Brachydanio rerio P. promelas	28-32-d NOEC ELS test, mol · l^{-1}	log NOEC = -0.90 logKow - 2.30 n=27, r^2=0.92, Q^2=0.91, s.e.=0.33	Verhaar et al., 1995
Daphnia			
Daphnia magna	48-h EC50 immobilis. mol · l^{-1}	log EC50 = -0.95 logKow - 1.32 n=49, r^2=0.95, Q^2=0.94, s.e.=0.34	Verhaar et al., 1995
Daphnia magna	16-d NOEC, growth, reproduct. mol · l^{-1}	log NOEC = -1.05 logKow - 1.85 n=10, r^2=0.97, Q^2=0.95, s.e.=0.39	Verhaar et al., 1995
Algae			
Selenastrum capricornutum	72-96-h EC50 growth, mol · l^{-1}	log EC50 = -1.00 logKow - 1.23 n=10, r^2=0.93, Q^2=n.d., s.e.=0.17	Van Leeuwen et al., 1992

n is the number of data, r^2 is the correlation coefficient, Q^2 is the cross-validated r^2 and s.e. is the standard error of estimate.

The models are generated by linear regression analysis. The data on which the models are based have been critically evaluated. The experimental data were generated according to OECD test guidelines or comparable methods.

In the cases where nominal concentrations were reported, a critical evaluation of these data was carried out. LogKow values were used as X-variable. The Kow values of the test set cover the domain of the models.

4.1.2.2 Polar narcosis

Besides the QSARs available for chemicals which act by non-polar narcosis, there is one other class of chemicals for which QSARs are relatively well established. This class consists out of more polar chemicals such as esters, phenols and anilines (Schultz et al., 1986; Veith and Broderius, 1986). The mode of action of these compounds is also not very specific, but they are significantly more toxic than predicted by non-polar narcosis. Therefore, several specific QSARs have been developed for these compounds. Mechanistic studies from Bradbury et al. have supported the distinction between polar and non-polar narcosis (McKim et al., 1987; Bradbury et al., 1990). In a recent evaluation of QSARs for polar narcosis, the following equations have been selected and recalculated (Verhaar et al., 1995).

Table 2 QSARs for polar narcosis (excess toxicity to non-polar narcosis).

Species	Endpoint	Equation + statistics	Reference
Fish			
Pimephales promelas	96-h LC50 mol · l^{-1}	log LC50 = -0.73 logKow - 2.16 n=86, r^2=0.90, Q^2=0.90, s.e.=0.33	Verhaar et al., 1995
Daphnia			
Daphnia magna	48-h EC50 immobilis. mol · l^{-1}	log EC50 = -0.56 logKow - 2.79 n=37, r^2=0.77, Q^2=0.73, s.e.=0.37	Verhaar et al., 1995

n is the number of data, r^2 is the correlation coefficient, Q^2 is the cross-validated r^2 and s.e. is the standard error of estimate.

The models are calculated with linear regression analysis. The fish toxicity data were taken from several publications (Könemann and Musch, 1981b; Saarikoski and Viluksela, 1982; Benoit-Guyod et al., 1984; Hall and Kier, 1984; Hermens et al., 1984; Roberts, 1986; Schultz et al., 1986; Veith and Broderius, 1986; Deneer et al., 1987; Newsome et al., 1991) and the data for *Daphnia magna* were collected from publications by Devillers and Chambon (1986), Vighi and Calamari (1987) and Nendza and Klein (1990). LogKow values are used as X-variable. The Kow values of the test set cover the domain of the models.

4.1.3 Domain

The models for chemicals acting by non-polar narcosis are valid in the logKow range of 1-6. The structural domain of the models include aliphatic and aromatic hydrocarbons, halogenated aliphatic and aromatic hydrocarbons, ethers, alcohols etc. A detailed definition of the domain is given by Verhaar et al. (1992 and 1995).

The models for chemicals acting by polar narcosis are valid in the logKow range of 1-6. Classes of chemicals which act by polar narcosis include aromatic nitro compounds, anilines and phenols. A detailed definition of the domain has been described by Verhaar et al. (1992 and 1995). Aliphatic amines are also included in this class. Although most aliphatic amines are ionised at a pH of 7, they have been included in the model because they perfectly fit the model. However, it should be realised that the uptake of ionised chemicals is complex and therefore, it can not be excluded that aliphatic amines somehow accidentally fit the model.

4.1.4 Accuracy

For 95% of the training set used to construct the models for non-polar narcotics the predicted value using the model was within a factor of three (i.e. 0.5 log units) of the measured value. A similar accuracy, i.e. a factor of three (i.e. 0.5 log units) between the estimated and observed values of the training set, was reached for the NOEC models. The QSAR models were not externally validated by using a training and validation set, but the model directly describes the mechanistic understanding of the toxicity. Furthermore, the large number of studies which all point in the same direction provides at the least an implicit validation.

4.2 *N*-OCTANOL-WATER PARTITION COEFFICIENT

4.2.1 Introduction

The log *n*-octanol-water partition coefficient (logKow) is a measure of the hydrophobicity of a chemical. As such, logKow is a key parameter in the assessment of environmental fate. Many distribution processes are driven by logKow, e.g. sorption to soil and sediment, partitioning into air and bioconcentration.

The determination of the *n*-octanol-water partition coefficient (Kow) is a requirement of the minimum data set to be submitted for notified new and priority existing substances. As the experimental determination of the Kow is not always possible, in special cases which are outlined in the test protocol of Annex V (Directive 67/548/EEC) a QSAR derived Kow may be used without generating experimental data for those substances for which measurement is inappropriate. However, extreme caution should be taken with the use of QSARs for substances where the determination is not possible. The most obvious example is the use of QSAR to calculate logKow of surfactants. QSARs can also assist to allow the evaluation of the data submitted in order to determine which Kow value(s) shall be used for the risk assessment. In this section, three models are discussed for the estimation of logKow.

4.2.2 Description of QSARs

Numerous QSARs have been and continue to be developed for the estimation of Kow. Commonly used methods are based on fragment constants. The fragmental approaches are based on a simple addition of the lipohilicity of the individual molecular fragments of a given molecule. Three commercially available PC programs are discussed in this section: CLOGP, LOGKOW, and AUTOLOGP.

4.2.2.1 CLOGP

CLOGP (Daylight Chemical Information Systems) was initially developed for use in drug design. The model is based on the Hansch and Leo calculation procedure (Hansch and Leo, 1979). This procedure comprises two parts. The summation of fragmental values of each of the composing atoms or groups is followed by the application of correction values concerned with e.g. chain length, ring size, branching, and unsaturation.

4.2.2.2 LOGKOW

LOGKOW (Syracuse Research Corporation (SRC)) is also based on a group contribution method developed by SRC. The method uses structural fragments and correction factors. The fragments are relatively simple in comparison to CLOGP. The correction factors include the ortho interaction in benzenes and fragments which are developed based on existing fragments and correction factors.

For example -NH-NH-: the fragment NH is used twice and additionally a correction factor for the whole group -NH-NH- is included.

The actual version contains 130 fragments values f and 235 correction factors c and is based on a training set of 2,351 substances (r=0.991).

4.2.2.3 AUTOLOGP

AUTOLOGP (Devillers et al., 1995a) has been derived from a heterogeneous set of 800 substances collected from literature. The substances are described by means of the autocorrelation method (Broto and Devillers, 1990), using the fragmental constants of Rekker and Manhold (1992), resulting in 66 atomic and group contributions. These contributions are subsequently used to compute an autocorrelation vector H. After calculation of the first 12 components of the autocorrelation vector H, a stepwise regression analysis is performed resulting in the final model with 4 components.

4.2.3 Domain

First the domains are characterised in terms of chemical structures. Secondly, the domain is described in terms of logKow ranges. The following results are based on experience gained in the practical use of the programs. CLOGP version 3.54, LOGKOW (version 1.35a) and AUTOLOGP (version 2.11) were used for defining the domains. The advises concerning the applicabilities of the programs apply only to the program versions mentioned above.

4.2.3.1 Structural domains

CLOGP (Daylight Chemical Information Systems) calculates logKow for organic compounds containing C, H, N, O, Hal, P, and/or S. LogKow for salts and for compounds with formal charges cannot be calculated (except for nitro compounds and nitrogen oxides). The calculation of logKow for ionisable substances, like phenols, amines and carboxylic acids represents the neutral or unionised form. For such substances it should be noted that this value will be pH dependent. Inherent to the fragment approach, it is clear that logKow cannot be calculated for simple compounds containing only above mentioned atoms, if the corresponding fragment is missing in the database.

This is the case for e.g. formaldehyde, formic acid, and maleinic acid anhydride. For more complex structures containing phosphorus or sulphur only some structure types may be calculated. Some examples for compound classes/substructures which cannot be calculated are summarised in the following:

Oxygen compounds:	C(aromatic)-C=C-C=O;
Nitrogen compounds:	N-N=O; C-NH-C(=O)O; tertiary amines;
Phosphorus compounds:	most thiophosphate compounds (some special types of thiophosphates may be calculated); phosphoric acid halides; phosphites; phosphines;
Sulphur compounds:	sulphinic acids; thio urea (some derivatives may be calculated); OS(=O)O

LOGKOW (Syracuse Research Corporation) calculates logKow for organic compounds containing the following atoms:

C, H, N, O, Hal, Si, P, S, Se, Li, Na, K, and/or Hg. LogKow for salts cannot be calculated except for compounds like organic hydrochlorides, organic sodium and potassium salts and quaternary ammonium salts. The results for these salts should be considered carefully because they are only valid for the undissociated species. LogKow for compounds with formal charges (like nitrogenoxides and nitro compounds) can also be calculated. The calculation of logKow for ionisable substances, like phenols, amines and carboxylic acids represents the neutral or unionised form. For such substances it should be noted that this value will be pH dependent.

AUTOLOGP calculates logKow values for organic chemicals (Devillers et al., 1995a). The logKow of any organic chemical containing C, H, N, O, Hal, P, and S can be calculated. The logKow values of salts cannot be calculated. Also, some compounds with formal charges (such as nitrogen oxides) cannot be calculated yet, with the exception of nitro compounds. The logKow values of ionisable chemicals like phenols, amines and carboxylic acids can be calculated although pH-dependencies should be noted. Improvements are in progress in order to extend the applicability of AUTOLOGP.

4.2.3.2 Domains in logKow ranges

The domains of the respective models can also be described in terms of the logKow range of their applicability.

In general, the programs CLOGP and LOGKOW result in clear estimates in the region of logKow 0-5. The mean square error of the calculated values equals 0.076 in case of CLOGP and 0.086 in case of LOGKOW. Estimates for compounds with logKow outside this region are generally less accurate. Estimates for logKow around 10 or above should be considered rather as qualitative than quantitative calculations.

For compounds with logKow < 0, CLOGP seems to give better estimates (this is based on 108 compounds), for compounds with logKow > 5 LOGKOW seems to give better estimates (based on 75 compounds) (Müller and Klein, 1994). In case of AUTOLOGP there does not exist as much experiences gained in practical use as for the other two programs. According to the presently available informations AUTOLOGP results in accurate values especially for highly lipophilic substances (logKow > 5) like PCBs, PAHs, PCDDs (Poly Chlorinated Dibenzo-*p*-Dioxins) and PCDFs (Poly Chlorinated DibenzoFurans).

4.2.4 Accuracy

A validation based on more than 6,000 compounds not included in the training set was performed by Meylan and Howard (1995) for the LOGKOW method.

Another validation study has been performed including both CLOGP and LOGKOW. The validation used 1,166 compounds from the “Starlist”. It considered mainly simple organic molecules, but also pesticides and more complex molecules were included (Müller and Klein, 1994). Based on the mean square error (experimental/estimated) for the 1,166 compounds, compound classes could be identified, for which one of the models CLOGP or LOGKOW gave significantly better results than the other. Recommendations for simple compound classes are summarised in **Table 3**.

Due to the lack of experiences concerning the practical use of AUTOLOGP it is not possible to give definite pieces of advice for the applicability of the program for different compound classes.

Based on the available data the mean square error of calculated values for aliphatic hydrocarbons seems to be in the same order of magnitude as for the programs CLOGP and LOGKOW (see **Table 3**). The same applies for compounds consisting of C,H,O; compounds consisting of C,H,N; compounds consisting of C,H,N,O; hydroxy compounds, acids and nitro compounds. In case of aromatic hydrocarbons and pesticides AUTOLOGP seems to result in more accurate values with lower mean square errors than the other programs.

Finally, it should be noted, that occasionally the calculations by the different programs result in large differences (several orders of magnitude) of the estimates, which is an indication that the estimates are inaccurate.

Table 3 LogKow models: recommendations for specific chemical classes (Müller and Klein, 1994)

Compound class	Number of compounds	Recommended model	Mean square error of the values calculated with the recommended model
aliphatic hydrocarbons	95	both, CLOGP better	0.076
aromatic hydrocarbons	61	both, CLOGP better	0.079
aliphatic chlorinated hydrocarbons	220	LOGKOW	0.151
aromatic chlorinated hydrocarbons	130	LOGKOW	0.194
organic compounds containing only C,H,O like ethers etc.	274	both	0.078 a), 0.062 b)
organic compounds containing only C,H,N like amines, pyridines etc.	138	both	0.064 a), 0.080 b)
organic compounds containing only C,H,S like thioethers etc.	11	both	0.007 a), 0.014 b)
organic compounds containing only C,H,N,O	216	both	0.058 a), 0.079 b)
hydroxy compounds	214	both	0.099 a), 0.087 b)
acids	84	both	0.147 a), 0.179 b)
nitro compounds	114	both	0.075 a), 0.084 b)
P compounds	49	(CLOGP) c)	0.284
S compounds	104	(both) c)	0.253 a), 0.389 b)
PS compounds, mainly thiophosphates	34	LOGKOW	0.099

a) mean square errors concerning the values calculated with CLOGP
b) mean square errors concerning the values calculated with LOGKOW
c) mean square error was rather large

4.2.4.1 Outliers

Based on 1166 compounds, 37 outliers could be identified (i.e. deviation between estimated logKow and experimental logKow > 1).

Outliers for CLOGP (25 outliers) are 10 highly chlorinated/fluorinated halocarbons (including compounds with experimental logKow < 6); 6 phosphoric/thiophosphoric acid esters; 4 pesticides with uncommon substructures; 2 highly lipophilic compounds; dibromodulcitol (hydrophilic compound with 4 OH-groups) and triallylamine cortisonacetate (steroid). Outliers for LOGKOW (16 outliers) are 5 highly chlorinated/brominated halocarbons (with

experimental logKow > 6); 4 thioureas/thioacetamid; 2 highly lipophilic compounds; 2 phosphoric acid esters; 2 pesticides with uncommon substructures; theophyllin (uncommon six-membered ring, hydrophilic compound, CLOGP uses a special fragment value for this type of ring).

4.3 SOIL AND SEDIMENT SORPTION

4.3.1 Introduction

The sorption to soil and sediment components is a determining factor for the mobility of chemicals. This property accounts for the distribution among soil, sediment and water phases, as well as for volatilisation from soil surfaces, and influences the chemicals bioavailability and hence e.g. its transformation by soil microbes. The extent of sorption to soil and sediment is governed by a variety of physico-chemical properties of both the soil and the contaminant. The heterogeneous soil chemistry and physics due to the variant proportions of the major components - mineral and organic matter, water, air and (micro)organisms - account for the differences in the binding capacity of different soils. The relevant parameters comprise organic carbon content, clay content, humidity, pH-value, cation exchange capacity, temperature, etc.

The underlying processes of sorption may be due to Van der Waals interactions, hydrophobic interactions, hydrogen bonding, charge transfer interactions, ligand exchange and ion bonding, direct and induced ion-dipole and dipole-dipole interactions and covalent binding.

The sorption of non-polar substances, generally to the organic matter of the soil or sediment can be regarded as a distribution process between the polar phase of the soil water and the organic phase of the soil components. The equilibrium constant of this partitioning between solid and solution phases constitutes the adsorption coefficient for soil and sediments. The sorption coefficient is defined as follows:

$$Kd = \frac{\textit{Concentration of chemical sorbed to soil or sediment}}{\textit{Mean concentration of chemical in aqueous solution}} \quad \text{at steady state} \quad (1)$$

Due to the different composition of soils, their sorption capacity varies considerably and hence the adsorption coefficients measured for the same compound may extend over several orders of magnitude. Therefore, a normalisation to the organic carbon fraction (%OC/100), the principal interaction site for hydrophobic compounds, is used to reduce the variance of sorption coefficients measured in different soils and to arrive at a carbon normalised partition coefficient (Koc).

$$Koc = Kd \cdot (100 / \%OC) \quad (2)$$

Several methods exist to determine Koc experimentally. However, if no measured Koc is available, QSARs may be used to estimate Koc. QSARs may also be used for the data evaluation. In the next section QSARs for the sorption of specific chemical classes are described.

4.3.2 Description of QSARs

Several compilations of QSAR models for soil sorption are published in the literature. The OECD (1993) has made an evaluation of QSARs for soil sorption. Most of the models, as

described in the OECD report, are based on the *n*-octanol-water partition coefficient (Kow). The influence of Kow is logical because hydrophobic interactions are the most dominant type of interactions between non-polar organic chemicals and the soil organic carbon. On the other hand, however, it is also obvious that chemicals with more polar groups may interact with the soil via more specific (electronic type) interactions. In those cases, Kow will not be the only crucial parameter in the estimation of Koc. Because of this, different models are developed and proposed for different classes of chemicals (Bockting et al., 1993; OECD, 1993) , instead of searching for one model for all organic chemicals. Most of these class specific models are still based on Kow. These same arguments have led to the development of the system of Meylan et al. (1992a) which used fragment contributions. Ionisation may also influence the sorption behaviour of organic chemicals (Schellenberg et al., 1984) and some authors use information on pKa as additional information in their models (Bintein and Devillers, 1994).

It may be obvious that there is not one single model which will accurately predict soil sorption coefficients and that different models should be used depending on to which class of chemicals a particular compound belongs. This reasoning was also the starting point for a recent overview prepared by Sabljic and Güsten (1995) in the framework of an international project funded by the EC. They chose a similar approach as in the OECD report but included more different classes and they defined the chemical domain in a rather extensive manner. An overview of the models is given in **Table 4**. 19 Models have been developed for different chemicals classes.

The models are based on linear regression analysis and logKow as descriptor variable. It should be noted that all models are developed assuming an equilibrium state. For certain classes of chemicals, e.g. anilines and carbamates, this assumption is not correct, because the sorption to soil is irreversible due to the formation of bonded residues. Improvements of the more specific models is certainly feasible if parameters for more specific interactions are taking into account.

4.3.3 Domain

An extensive description of the domain is given in **Table 5**. The description is made in terms of chemical structures as well as in terms of logKow ranges.

4.3.4 Accuracy

The standard errors of the estimates ($\pm 2\sigma$ range = 95%) range from 0.35 to 1.0 log units for the different models. The standard errors are indicated in **Table 4** for each model. A cross-validation has not been performed yet. External validation is not possible, because all available data have been used to generate the models (Sabljic and Güsten, 1995).

Table 4 QSARs for soil and sediment sorption for different chemical classes (Sabljic and Güsten, 1995)

Chemical class	Equation	Statistics
Predominantly hydrophobics	logKoc = 0.81 logKow + 0.10	n=81, r^2=0.89, s.e.=0.45
Nonhydrophobics	logKoc = 0.52 logKow + 1.02	n=390,r^2=0.63,s.e.=0.56
Phenols, anilines, benzo-nitriles, nitrobenzenes	logKoc = 0.63 logKow + 0.90	n=54, r^2=0.75, s.e.=0.40
Acetanilides, carbamates, esters, phenylureas, phosphates, triazines, triazoles, uracils	logKoc = 0.47 logKow + 1.09	n=216,r^2=0.68,s.e.=0.43
Alcohols, organic acids	logKoc = 0.47 logKow + 0.50	n=36, r^2=0.72, s.e.=0.39
Acetanilides	logKoc = 0.40 logKow + 1.12	n=21, r^2=0.51 s.e.=0.34
Alcohols	logKoc = 0.39 logKow + 0.50	n=13, r^2=0.77, s.e.=0.40
Amides	logKoc = 0.33 logKow + 1.25	n=28, r^2=0.46, s.e.=0.49
Anilines	logKoc = 0.62 logKow + 0.85	n=20, r^2=0.82, s.e.=0.34
Carbamates	logKoc = 0.37 logKow + 1.14	n=43, r^2=0.58, s.e.=0.41
Dinitroanilines	logKoc = 0.38 logKow + 1.92	n=20, r^2=0.83, s.e.=0.24
Esters	logKoc = 0.49 logKow + 1.05	n=25, r^2=0.76, s.e.=0.46
Nitrobenzenes	logKoc = 0.77 logKow + 0.55	n=10, r^2=0.70, s.e.=0.58
Organic acids	logKoc = 0.60 logKow + 0.32	n=23, r^2=0.75, s.e.=0.34
Phenols, benzonitriles	logKoc = 0.57 logKow + 1.08	n=24, r^2=0.75, s.e.=0.37
Phenylureas	logKoc = 0.49 logKow + 1.05	n=52, r^2=0.62, s.e.=0.34
Phosphates	logKoc = 0.49 logKow + 1.17	n=41, r^2=0.73, s.e.=0.45
Triazines	logKoc = 0.30 logKow + 1.50	n=16, r^2=0.32, s.e.=0.38
Triazoles	logKoc = 0.47 logKow + 1.41	n=15, r^2=0.66, s.e.=0.48

n is the number of data, r^2 is the correlation coefficient, s.e. is the standard error of estimate

Table 5 Domain of the sorption models (Sabljic and Güsten, 1995)

Model	X-variable domain Log Kow in log units	Chemical domain	Substituents or Warnings
Hydrophobics	1 - 7.5	All Chemicals with C, H, F, Cl, Br, and I atoms	
Nonhydrophobics	(-2.0) - 8.0	All Chemicals that are not classified as Hydrophobics	**Overestimated** n-Alkyl Alcohols (0.9 log units Organic Acids (0.55 log units **Underestimated** Amino-PAHs (1-2 log units Aliphatic Amines (1-2 log units Alkyl Ureas (1.0-1.5 log units
Phenols	1.0 - 5.0	Phenols Anilines Benzonitriles Nitrobenzenes	Cl, Br, CH_3, OH, NO_2, CH_3O Cl, Br, CH_3, CF_3, CH_3O, N-Me Chlorinated Cl, Br, NH_2
Agricultural	(-1.0) - 8.0	Acetanilides Carbamates Esters Phenylureas Phosphates Triazines Uracils	
Alcohols, acids	(-1.0) - 5.0	Alcohols Organic Acids	Alkyl, Phenalkyl, OH All
Acetanilides	0.9 - 5.0	Anilides	CH_3O, Cl, Br, NO_2, CF_3, CH_3
Alcohols	(-1.0) - 5.0	Alcohols	Alkyl, Phenalkyl, OH
Amides	(-1.0) - 4.0	Acetamides Benzamides	F, Cl, Br, CH_3O, Alkyl NO_2, N-Me
Anilines	1.0 - 5.1	Anilines	Cl, Br, CF_3, CH_3, N-Me, N, N-di-Me
Carbamates	(-1.0) - 5.0	Carbamates	Alkyl, Alkenyl, Cl, Br, N-Me, CH_3O
Dinitroanilines	0.5 - 5.5	Dinitroanilines	CF_3, Alkyl-SO_2, NH_2SO_2, CH_3, t-Bu
Esters	1.0 - 8.0	Phthalates Benzoates Phenylacetates Hexanoates Heptanoates Octanoates	alkyl, phenyl, Cl alkyl, phenyl, NO_2,OH,Cl,NH2 alkyl, phenalkyl alkyl alkyl alkyl
Nitrobenzenes	1.0 - 4.5	Nitrobenzenes	Cl, Br, NH_2
Organic Acids	(-0.5) - 4.0	Organic Acids	All
Phenols	0.5 - 5.5	Phenols	Cl, Br, NO_2, CH_3, CH_3O, OH
		Benzonitriles	Cl
Phenylureas	0.5 - 4.2	Phenylureas	CH_3, CH_3O, F, Cl, Br, Cyclo-alkyls, CF_3, PhO
Phosphates	0.0 - 6.5	All Phosphates	
Triazines	1.5 - 4.0	Triazines	Cl, CH_3O, CH_3S, NH_2, N-Alkyl
Triazoles	(-1.0) - 5.0	Triazoles	Alkyl, CH_3O, F, Cl, CF_3, NH_2

* The precision of estimates is higher for the less hydrophobic chemicals and lower for the more hydrophobic chemicals. For chemicals with the logKow data from 1 to 4 the spread of residuals is from 0.2 to 0.5 log units and for the chemicals with the logKow data from 4 to 7.5 the spread of residuals is from 0.6 to 1.0 log units.

4.4 HENRY'S LAW CONSTANT

4.4.1 Introduction

The partitioning of an organic chemical between water and air is a physical property that is described by the Henry's Law Constant, H. The magnitude of H provides an indication of which of the two phases, water and air, a chemical will tend to partition in at equilibrium. Chemicals with low values of H will tend to partition into the aqueous phase. Since air and water are the major "compartments" of most model ecosystems and water is considered to act as the link between all of the compartments, knowledge of the value of H is very important in assessing the environmental risks associated with a chemical.

The Henry's Law Constant is expressed either as the ratio of the partial pressure in the vapour phase and the concentration in water (H ($Pa \cdot m^3 \cdot mol^{-1}$)), or as the ratio of the concentrations in air and water (H', dimensionless).

$$H = P / C_w \quad \text{or} \tag{3}$$

$$H' = C_a / C_w \tag{4}$$

where, P = partial pressure, C_W = concentration in water and C_a = concentration in air.

Since the concentration and the partial pressure in air are related by the ideal gas law, the dimensioned and dimensionless versions of Henry's Law Constant are related:

$$H' = H / RT \tag{5}$$

where, R= the gas constant and T= the environmental temperature (º K).

If no experimentally determined Henry's Law Constants are available, H can be calculated from the ratio of the vapour pressure and the water solubility. Alternatively, QSARs can be used to estimate the Henry's Law Constant. In this section, a group contribution model is described for the estimation of H.

4.4.2 Description of QSARs

There is a relatively small range of approaches that are used to estimate the Henry's Law Constant and these are reviewed in a recent report (Cousins et al., 1995). The most important approaches are:

- ratio of water solubility to vapour pressure;
- estimation using connectivity indices;
- estimation using group and bond contribution methods.

The first method for estimating H is not strictly a QSAR method as it uses the water solubility and vapour pressure. Since both water solubility and vapour pressure can be calculated by QSAR methods, then this approach might in some circumstances be a QSAR based method. The method is limited to substances of low water solubility ($< 1.0\ mol \cdot l^{-1}$). If QSAR calculated values are used for Pv and/or Sw, then the respective uncertainties must be considered.

The second method is based on a combination of connectivity indices and calculated polarisability (Nirmalakhandan and Speece, 1988). A relatively narrow range of chemical types was used to develop the model, so it is not widely applicable.

The third approach is based on group and bond contribution methods. Two methods have been reported (Hine and Mokerjee, 1975) for estimating H directly from molecular structure, using group contributions and bond contributions respectively.

This approach has been further developed into SRC's "HENRY" Program (Meylan and Howard, 1991 and 1992b) and is here described in further detail.

The HENRY model was derived from a training set of 345 compounds of divers structural types. The technique used was least squares fit to determine the best fit for each contribution value used in linear equation for log Kair-water calculation. The model is commercially available as a PC program (Syracuse Research Corporation).

Experimentally measured log Kair-water values were used, when available, for deriving the bond contribution values and correction factors using the method of Hine and Mookerjee (1975) and Benson and Buss (1958). Otherwise the Henry's Law Constant was calculated by dividing the vapour pressure (VP) by the water solubility (WS) and the result converted to a log Kair-water value. For miscible compounds or the compounds with water solubility > 1 $mol \cdot l^{-1}$ the VP/WS method is not valid. The data were retrieved from US Department of Agriculture's pesticide Properties Database (1992); Syracuse Research Corporations Environmental Fate Database; 194 literature references. The units are in $atm \cdot cu \cdot m \cdot mol^{-1}$ (or unitless H).

The number of initial descriptors was 87 bond contribution values and 102 group contribution values.

Other methods that have been published are either very limited in the range of structural types of chemicals to which they are applicable, or use a combination of structure derived and experimentally measured parameters in the derived QSAR. This means that they are not particularly useful for the estimation of H for novel or existing substances.

4.4.3 Domain

The SRC's HENRY program is useful for estimating H for highly miscible or highly soluble compounds and has the advantage that it can be used to estimate for a large variety of compounds using the library of bond and group contribution values. Since it uses compound class specific correction terms in addition to bond/group contribution, care should be taken when using the methods for compounds with unconsidered fragments.

Classes of chemicals to which the model is applicable are alkanes, alkenes, alkynes, acids, alcohols, epoxides, ketones, amines, halomethanes, halopropanes, halobutanes, and other haloalkanes, haloalcohols, haloalkenes, nitriles, nitrogen containing compounds, sulphur containing compounds, five membered aromatics, pyridines, and pyrazines, benzene and alkylated benzenes, other aromatics, halogenated benzenes, anilines, phenols, biphenyls, PAHs.

4.4.3.1 Limitations

Compounds with large structures which include many different types of bonds and groups may have significant inaccuracies in their estimations. In some cases bond and group contribution

methods may differ by as much as 2 orders of magnitude. In these cases averaging two divergent values is reasonable. When H is lower than 10^{-21} numbers may be unrealistically low.

4.4.4 Accuracy

Bond contribution values used in the HENRY program were derived by SRC using a data set of 345 chemicals having either experimentally derived Henry's Law Constants or reliable vapour pressure or water solubility's (194 references). A correlation coefficient of 0.94 was determined for the relationship between known Henry's Law Constants and Henry's Law Constants predicted by the bond contribution method for the 345 chemicals set.

The bond contribution method was also tested against a validation set of 74 diverse and structurally complex compounds with known H values that were not used to derive the bond contribution values. The correlation coefficient for the test was 0.965 with a standard deviation of 0.475 log units.

4.5 BIOCONCENTRATION FACTOR - FOR AQUATIC ORGANISMS

4.5.1 Introduction

Bioconcentration by aquatic organisms is an important factor in the environmental risk assessment process. The bioconcentration factor is defined as the ratio between the concentration of the chemical in biota and the concentration in water at equilibrium.

The bioconcentration factor can also be calculated by the ratio of the first order uptake and elimination rate constants, a method that does not require equilibrium conditions. The bioconcentration factor can be measured experimentally directly. A number of test guidelines are available for the direct measurement of bioconcentration, of which OECD 305E is the most widely applied. This guideline has recently been revised (OECD, 1994) and replaces the previous versions OECD 305A-E. The assessment of the BCF is necessary for chemicals which are, based on base-set data, considered to have a logKow greater than 3.

In this sub-section models are described to be used for the estimation of BCF from logKow. A linear model is recommended for logKow up to 6 and a non-linear model for logKow values from 6 to 10.

4.5.2 Description of QSARs

Numerous QSAR models have been reported for the prediction of BCF. Most models are based on logKow (ECETOC, 1995). In general QSARs based on water solubility are no less accurate than those based on logKow when compared with the accuracy of the endpoint (Davies and Dobbs, 1984). The mechanistic basis for the relationship with logKow is the analogy between the partition process between the lipid phase of fish and water**,** and the partition process between *n*-octanol and water. The simplest form of the relationship between BCF and Kow is the linear relationship:

$$BCF = a \cdot Kow \qquad (6)$$

where *a* represents the lipid fraction of the fish, actually ranging from 0.02 to 0.20.

There are several types of relationships between logKow and BCF reported in the literature. The three most common types are the linear, the bilinear or the non-linear dependency of BCF on logKow. The three approaches agree on the shape of the curve relating logKow to BCF for logKow less than 6, whereas they differ on the shape for logKow for values above 6. In general, no quantitative estimation can be made on BCF if logKow is larger than 10.

4.5.2.1 QSARs for substances with logKow < 6

It is generally agreed that a linear relationship exists for chemicals which are not biotransformed with logKow < 6. Many examples of such models have been published in literature (Veith et al., 1979 and 1980; Könemann and Van Leeuwen, 1980; MacKay, 1982; Nendza, 1991; Bintein et al., 1993). Recently, a validation study has been performed on linear and non-linear BCF models (Devillers et al., 1995b). From this study, it was concluded that for chemicals with logKow < 6, the different models yielded equivalent results. For example, the linear model developed by Veith et al. (1979) can be used for the prediction of BCF of substances with logKow < 6.

Table 6 QSAR for BCF for substances with logKow < 6

Equation	Statistics	Reference
linear equation logKow < 6 log BCF = 0.85 logKow - 0.70	 n=55, r^2=0.90	 Veith et al., 1979

n is the number of data, r^2 is the correlation coefficient

The linear model generated by Veith et al. (1979) is based on BCF data for fathead minnows (*Pimephales promelas*). LogKow is used as descriptor variable.

4.5.2.2 QSARs for substances with LogKow > 6

For chemicals with logKow values exceeding approximately 6, it is well established that a linear model of bioconcentration is inaccurate (Bintein et al., 1993). In the logKow range above 6, the measured log BCF data tend to decrease with increasing logKow. Several explanations for this breakdown of linearity can be given. Conceptual explanations of non-linearity mainly refer to either biotransformation, reduced membrane permeation kinetics or reduced biotic lipid solubility for large molecules. Other factors consider experimental artefacts, such as equilibrium not being reached and reduced bioavailability due to sorption to organic matter in the aqueous phase. These experimental artefacts lead to an underestimation of the bioconcentration factor.

Similar care should be taken in evaluating a prediction of BCF for logKow above 6, as in evaluating experimental data. It is clear that a QSAR can never model an end-point with a higher level of accuracy than the accuracy of the experimental data itself. It should therefore be considered that the experimental data on BCF have a much higher level of uncertainty for high logKow values than for lower values.

Several approaches have been used to model BCF above logKow of 6. The plateau relationship (Spacie and Hamelink, 1982) can be seen as an approach which always overestimates the BCF, which generally takes all uncertainties, i.e., both the uncertainty inherent from the experimental test and the uncertainty inherent from the estimation model, into account. There is no mechanistic basis underlying this approach. A bilinear model was developed by Nendza (1991), who took the data with the highest BCF for a given logKow and a mathematical description of the worst-case situation was derived. This model is built in such a way that it will always predict a conservative value for BCF. An alternative bilinear model has been developed by Bintein et al (1993), which accurately fits the experimental data. Although this model fits the available experimental data accurately (Devillers et al., 1995b), it does not necessarily take the possible experimental artefacts into account.

Taking these uncertainties into consideration, a conservative non-linear approach is recommended for the prediction of BCF at logKow > 6. The choice for a conservative approach, implies that this is not necessarily the best model from statistical point of view. The polynomial relationship developed by Connell and Hawker (1988) can be used for this purpose. This model is generated in such a way, that the influence of non-equilibrium conditions has been eliminated. The polynomial equation is derived by the addition of two polynomial relationships for the estimation of the uptake and elimination rate constants respectively. Because the statistical validity of the polynomial relationship is questionable (Zoetemeijer, 1993; Bintein et al., 1995), the model has been recalculated, resulting in a significant parabolic relationship (**Table 7**).

Table 7 QSAR for BCF for substances with logKow > 6

Equation	Statistics	Reference
polynomial equation logKow > 6 $\log BCF = 6.9 \cdot 10^{-3} (logKow)^4 - 1.85 \cdot 10^{-1} (logKow)^3 + 1.55 (logKow)^2 - 4.18 logKow + 4.79$	n=45, r^2=n.a.	Connell and Hawker, 1988
parabolic equation logKow > 6 $\log BCF = -0.20 logKow^2 + 2.74 logKow - 4.72$	n=43, r^2=0.78	recalculated from Connell and Hawker, 1988

n is the number of data, r^2 is the correlation coefficient

The polynomial model (Connell and Hawker, 1988) is based on experimental data for several fish species (*Poecilia reticulata, Carassius auratus, Oncorhynchus mykiss, Pimephales promelas*) collected from literature (Neely, 1974; Könemann and Van Leeuwen, 1980; Bruggeman et al., 1981 and 1984; Muir et al., 1985; Opperhuizen et al., 1985 and 1986).

It considers persistent chemicals, mainly chlorinated hydrocarbons with a logKow range of 3.4 - 9.8. The parabolic relationship is based on the same data-set. Two data points have been removed from the original set, because the elimination rate constants were not available. LogKow is used as descriptor variable in both models.

On a case by case basis the risk-assessor may choose to use another relationship in particular if logKow > 6, e.g. for pigments, in order to take account of substance specific concerns which may play a role in the experimental determination of BCF.

4.5.3 Domain

The models can be used to derive estimates for neutral, non-polar and non-ionised chemicals. These type of chemicals are usually biotransformed relatively slowly. They are not applicable to ionic substances, partly ionised chemicals and organometallics.

Linear equations are applicable in the logKow range of 1-6. Non-linear equations are appropriate above logKow of 6. LogKow = 6, is an appropriate switch point for the recommended linear and parabolic model, because they cross at a logKow value of 6.05 (corresponding log BCF = 4.44 for both models). The upper limit of the models is around logKow of 10. Due to the lack of experimental logKow and BCF values above this value, estimates above logKow of 10 should be considered rather as qualitative than quantitative.

4.5.4 Accuracy

The linear model has been validated externally recently, using BCF data for 267 substances (Devillers et al., 1995b). The root mean square error of the predictions was 0.58 for logKow < 6.

The BCFs for substances with logKow > 6 should be used with care: The experimental determination of BCF for these substances is difficult, leading to relatively large experimental uncertainties. The QSAR estimates generated for these substances should be regarded with the same restrictions as the experimental data.

4.6 BIOCONCENTRATION FACTOR - FOR TERRESTRIAL ORGANISMS

4.6.1 Introduction

For the assessment of secondary poisoning in the terrestrial food chain the bioconcentration factor in worms is necessary. In analogy to the aquatic compartment, the bioconcentration factor for worms is defined as:

$$BCFworm = Cworm / C(pore)water \quad \text{at steady state} \quad (7)$$

No harmonised test procedures exist for the determination of the bioconcentration factor in terrestrial systems. The concentration in worms and porewater can be measured directly.

However, the direct measurement of the concentration in porewater is complicated. As Csoil and Cporewater are related through the Koc (Koc = Csoil(oc) / Cporewater), it follows that the BCFworm can also be calculated using the concentration in soil and the soil-water partition coefficient:

$$BCFworm = Cworm \cdot Koc / Csoil(oc) \quad \text{at steady state} \quad (8)$$

Alternatively, the BCFworm can be estimated using QSARs.

4.6.2 Description of QSARs

As discussed in Section 4.5, well established QSARs exist for the bioconcentration factor for aquatic organisms (e.g. Veith et al., 1979). Similarly, QSARs have been developed for benthic organisms living in aquatic sediments (e.g. Markwell et al., 1989). The basic assumption underlying this approach is the validity of the equilibrium partitioning theory. The equilibrium partitioning theory has been shown to be applicable to numerous substances under varying conditions in sediment (Di Toro et al., 1991). Its use in the terrestrial soil is however limited. For example, van Gestel and Ma (1988) determined the BCF in two species of earthworms for five chlorophenols and found a relationship with logKow. Connell and Markwell (1990) used these data, together with other BCF values reported in literature, and developed a model based on logKow (**Table 8**). This model is further discussed in this section.

Table 8 QSAR for BCF in earthworms

Equation	Statistics	Reference
log BCF = 1.0 logKow - 0.6	n=100, r^2=0.91	Connell and Markwell, 1990

n is the number of data, r^2 is the correlation coefficient

Data on the bioaccumulation of pesticides were collected from literature. If necessary, the concentration in porewater was calculated from the concentration in soil using the soil-water partition coefficient. If no organic carbon content of soil was reported, an organic carbon content of 4% was assumed.

4.6.3 Domain

The model has been generated on data of pesticides with a logKow range of 1 to 6. The BCF - logKow relationship applies generally to neutral organic substances which are not easily biotransformed. The relationship is not valid for ionised substances and organometallics.

4.6.4 Accuracy

Due to the lack of experimental data an external validation is not possible. The uncertainties in the model are substantial, due to the different sources and due to the assumptions made for the generation of the training set. The main assumption considers 4% organic carbon in the soil, if not reported.

On the other hand, the model is in agreement with the equilibrium partitioning theory and the model provides estimates in the same order of magnitude as similar models derived for worms in sediment. Therefore, it can be concluded that the model can be used to derive a first estimation of the bioconcentration factor in worms in the terrestrial compartment.

4.7 BIODEGRADATION

4.7.1 Introduction

Biodegradation is a function jointly of the intrinsic properties of the substance and of environmental conditions.

The biodegradability of a substance is therefore defined and determined within the limitations of the test methods laid down in Annex V to Council Directive 67/548/EEC and categorised as ready and inherent biodegradation tests, and simulation tests.

Tests on Ready biodegradability are in the base-set and data will therefore be supplied for all notified new and priority existing substances. However, for many existing substances, the experimental data have been derived under modified test conditions which complicates the interpretation of test results. Furthermore, data from several studies may have different results (Painter, 1992). (Q)SAR estimates may give additional information when evaluating the experimental data. Furthermore, (Q)SARs may assist in the decision on the strategy for further testing.

In this section, a model is recommended for the distinction between ready and not-ready biodegradable substances.

4.7.2 Description of QSARs

Several evaluation studies have been performed on biodegradation models, including qualitative as well as (semi) quantitative models. In an OECD report, 78 different SARs for biodegradation were presented and validated with more than 700 experimental data (Degner et al., 1993b). More recently, a literature search on SARs for biodegradation was performed including literature published until 1994 (Langenberg et al., 1994; Rorije et al., 1995a). In this study, 84 models were evaluated. The main conclusion in both studies was that only a few models provided an acceptable level of agreement between estimated and experimental data. The development of biodegradation models is restricted by the quality and quantity of the experimental biodegradation data. The rate and extent of biodegradation needs to be better determined and understood in experimental and environmental systems, prior to developing reliable QSARs for biodegradability. This is clearly an area for further consideration. The information presented below is based on the mentioned studies (Degner et al., 1993b; Langenberg et al., 1994; Rorije et al., 1995a).

Group contribution methods seem to be the most applied and successful way of modelling biodegradation. These models are based on a direct link between molecular structure and biodegradability and have therefore the possibility of straightforward interpretation. On the assumption that molecular fragments may have an enhancing or retarding effect on biodegradability, weighted molecular fragments are used as model descriptors.

Widely applicable group contribution models are the multiple linear and non-linear regression models incorporated in the Biodegradation Probability Program (BPP) (Howard et al., 1992a; Howard and Meylan, 1992b; Boethling et al., 1994). Although objections can be made against the form of the models, the accuracy and statistics, they can be used with certain restrictions. BPP gives a qualitative estimate for the probability of slow or fast aerobic biodegradation of an organic chemical in the presence of mixed populations of environmental microorganisms. The

models are based on miscellaneous experimental data, which have been evaluated on consistency. The relationships in BPP use 36 structural fragments and the molecular weight as model descriptors.

4.7.3 Domain

The BIODEG models are applicable to those chemicals that contain at least one of the molecular fragments in their molecule. Due to the incorporation of molecular weight, the models are theoretically not restricted to certain chemical classes. However the authors state that predictions will be of little value for compounds not containing one of the 36 structural fragments.

4.7.4 Accuracy

The multiple linear (BPP1) and non-linear (BPP2) models have been validated externally with MITI I test data (n=304) (Pederson et al., 1994). The differences between the performance of BPP1 and BPP2 are small. The evaluation turned out that the prediction "not ready degradable" is highly accurate (correct > 90% for both BPP1 and BPP2), however the prediction "ready degradable" is frequently not in agreement with experimental data obtained by the MITI I test. Therefore it is recommended to use the results of BPP only in a conservative way. If the program predicts fast biodegradation, this estimate should not be taken under consideration. However, if the program predicts slow biodegradation this can be used as a confirmation of not readily biodegradable.

4.8 PHOTOLYSIS IN ATMOSPHERE

4.8.1 Introduction

The atmospheric residence time of a chemical is determined by its Henry Law's Constant, wet and dry deposition and photodegradation. Photodegradation is one of the major transformation processes for many organic chemicals in the troposphere.

Kinetic rate constants for photolysis are necessary for the modelling of fate in the environmental risk assessment process. Kinetic rate constants may be extrapolated from experimentally determined half lives. Standardised (OECD or EC) test procedures are not available. QSARs can be used as a first estimation in the absence of experimental data. Furthermore QSARs can be used for the evaluation of experimental data. The models developed by Atkinson et al. (1988) are described in this section.

4.8.2 Description of QSARs

Models for the prediction of photodegradation rates were recently 48 QSAR models estimating reaction rate constants of organic chemicals with tropospheric radicals were evaluated in (Güsten and Sabljic, 1995). The models that performed well in the validation, were based on the group contribution method, first vertical ionisation energies, and global and local electronic properties. The Atkinson's group contribution method was evaluated positively in both studies reviewed (Degner et al., 1993a; Güsten and Sabljic, 1995).

The models developed by Atkinson (1988) estimate the reaction rate constant for the reaction of an organic chemical with hydroxyl radicals. The reaction rates of four relevant processes are estimated separately and it is assumed that the overall hydroxyl reaction rate constant can be calculated by summing the rate constants of the individual reactions:

- H-atom abstraction from C-H and O-H bonds;
- addition of hydroxyl radicals to C-C double and triple bonds;
- addition of hydroxyl radicals to aromatic rings;
- reactions with N, S or P.

$$k_{total} = k_{H\text{-}abstr} + k_{add\ (C=C)} + k_{add\ (arom)} + k_{N,S,P} \quad (9)$$

The models use the group contribution method. Thirteen parameters for reaction centres and 71 substituent constants are used as model descriptors. The model is available as a computerised program (Syracuse Research Corporation).

4.8.3 Domain

Atkinson's models are principally applicable to those substances, containing at least one of the model descriptors.

Large deviations have been observed for the following chemical classes (Müller and Klein, 1991): haloalkanes with 3 halogens on the same carbon atom, phosphates, small heterocyclic rings (epoxides and aziridines), nitroalkanes and aromatics which are not benzene derivatives.

4.8.4 Accuracy

The computerised version of Atkinson's models has been subjected to external validation using 370 compounds (Müller and Klein, 1991). For more than 90% of the compounds, the estimated and calculated rate constants differ less than a factor of 3 (0.48 log units). The larger deviations are observed primarily for the chemical classes mentioned under Section 4.8.3.

4.9 PHOTOLYSIS IN WATER

Photolysis in pure water may significantly contribute to the overall degradation process, particularly for those substances that are not biodegraded. However in natural waters, the extent of photolysis is usually significantly reduced due to the presence of organic matter. Furthermore, photolysis is highly dependent on geographic and seasonal fluctuations in field conditions.

QSARs for chemical degradation in the aqueous phase have been reviewed recently in the framework of an international project funded by the EC (Rorije and Peijnenburg, 1995b). No models for direct photolysis in the aqueous phase were selected by the authors of this study. It was stated that the models found in literature were either to limited or not mechanistically explained for. Therefore no models for direct photolysis in water are recommended currently.

4.10 HYDROLYSIS

4.10.1 Introduction

The persistence of a chemical in the aquatic environment is amongst others dependent on the chemical reactions between the compound and water. Only a limited number of chemical classes is potentially hydrolysable (Degner et al., 1993a).

As for photolysis, there is a need for kinetic rate constants of hydrolysis for a proper environmental risk assessment. A standardised test procedure (OECD 111 or EC C7) is available for the determination of hydrolysis as a function of pH. QSARs can be used if experimentally measured data are not available or for the evaluation of experimental data. In this section, 5 QSARs for specific chemical classes are described.

4.10.2 Description of QSARs

QSARs for abiotic degradation processes in the aqueous phase have been evaluated recently by Rorije and Peijnenburg (1995b). The text in this section is based on this review. The literature search resulted in a total of 68 quantitative models for abiotic degradation, from which 31 models describe hydrolysis. The other models describe oxidation reactions, reduction reactions and photolysis in water. The hydrolysis models have been evaluated according to the selection criteria described in "Overview of structure-activity relationships for environmental endpoints, Part1" (ed: Hermens et al., 1995), resulting in the selection of 5 hydrolysis models. The selected models apply to brominated alkanes, esters, carbamates and para-substituted benzonitriles.

The most important descriptors in the hydrolysis models, are the Hammett and Taft sigma constants. The second most important parameter is Taft's steric substituent constant Es, which is often used together with the Hammett and Taft sigma constants. A short description of the models is given in the next section. An overview of the model equations is given in **Table 9**.

4.10.2.1 Brominated alkanes (Vogel and Reinhard, 1986)

This model describes hydrolysis in the aquatic environment. The model is based on linear regression and uses Taft's polar sigma (I) constant as descriptor.

4.10.2.2 Esters (Drossman et al., 1988)

The model describes alkaline hydrolysis in water at 25°C. The model is based on multiple linear regression and uses Hammett and Taft substituent constants: sigma, sigma* and Es.

4.10.2.3 Carbamates (Drossman et al., 1988)

Two models are selected for carbamates, which differ in the structure of the carbamates to which they apply. Both models describe alkaline hydrolysis in water at 25°C.

The models are also based on multiple linear regression and use Hammett and Taft substituent constants sigma, sigma* and Es.

4.10.2.4 Benzonitriles (Masunaga et al., 1993)

The technique used is stepwise forward regression (least squares), which started with a number of 7 initial descriptors and ended with 1 final descriptor: the Hammett sigma (para) constant.

Table 9 QSARs for the estimation of hydrolysis rates for specific chemical classes

Chemical class	Equation and statistics	Reference
brominated alkanes	log k(i)/k(o) = -11.9 x sigma(I) n=16 r^2=0.77	Vogel and Reinhard, 1986
esters	log k = 0.98 (Es)R + 0.25(Es)R' + 2.24(sigma*)R + 2.24(sigma*)R' + 2.09(sigma)x + 1.21(sigma)x' + 2.69 n=103 r^2=0.974	Drossman et al., 1988
carbamates, I	log k = 2.39(sigma*)R1,R2 + 0.96(sigma)X1 + 7.97(sigma*)R3 + 2.81(sigma)X2 - 0.275 n=62 r^2=0.973	Drossman et al., 1988
carbamates, II	log k = 7.99(sigma*)R3 + 0.31(sigma)X2 + 3.14(Es)R1,R2 + 0.442 n=18 r^2=0.903	Drossman et al., 1988
benzonitriles	log k = 1.64 x sigma(para) - 1.37, n=14 r^2=0.858	Masunaga et al., 1993

n is the number of data, r^2 is the correlation coefficient

4.10.3 Domain

The model for brominated alkanes (Vogel and Reinhard, 1986) applies to linear and branched bromoalkanes with phenyl, chloro and bromo substituents. The parameter K(i) is the pseudo first order alkaline hydrolysis rate constant, and K(o) is the corresponding constant for CH_3-Br hydrolysis.

The model for esters (Drossman et al., 1988) is developed for alkyl/aryl - alkyl/aryl esters (X-C(=)-O-X, where X can be an alkyl or phenyl substituent).

Two models have been selected for carbamates (Drossman et al., 1988), which differ in the structure of the carbamates to which they apply. The first model (carbamates I) is developed for carbamates, X1R1N(R2)C(O)OR3X2, where R2=hydrogen, R1=alkyl or phenyl and R3=alkyl or phenyl. The second model (carbamates II) applies to carbamates with three alkyl or phenyl substituents, X1R1N(R2)C(O)OR3X2, where R1, R2 and R3 = alkyl or phenyl. The last model (Masunaga, 1993) applies to para-substituted benzonitriles.

4.10.4 Accuracy

The described models have not been cross validated nor externally validated. External validation will be performed in future (Hermens, 1995).

5 USE OF (Q)SARS IN HUMAN HEALTH RISK ASSESSMENT

(Q)SAR may be used as a contributing factor for the risk assessment for human health for certain purposes and for certain endpoints (see Chapter 3: Technical Guidance on Risk Assessment for Human Health). Most (Q)SARs which are used for toxicity endpoints are of the "expert judgement" type (see Sections 1.1 and 3.1). At the current stage it is not possible to recommend any defined (Q)SARs for human health endpoints. Section 3 outlines the general framework in which (Q)SAR can be applied for these endpoints. If the assessor uses any available (Q)SARs, of "expert judgement" type or "formalised methods" (e.g. QSAR) for toxicity endpoints, then the relevant information outlined in Appendix I should be provided in the comprehensive risk assessment report together with any other pertinent information, in order to assure transparency and facilitate acceptability.

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Appendix I Reporting on (Q)SAR models

1. Introduction

If the rapporteur uses a (Q)SAR which is not recommended in this document, it is recommended in order to assure transparency and homogeneity in the risk assessment process that a minimal set of information on the model used should be presented.

This appendix contains a list of the minimal information which is recommended to be supplied by the rapporteur. The type of information to be provided is dependent on the type of the (Q)SAR method used.

2. Minimal information for a method based on a model

For methods based on a model the information recommended to be supplied is as follows:

General information
Reference:
Process modelled:
Domain of model:

Y-variable (dependent variable)
Species
    Type:
    Other information:
Test method
    Experimental procedure:
End-point modelled
    Type:
    Reliability:
    Data source:
    Units:

X-variable (independent variable)
Descriptors
    # of initial descriptors:
    List of initial descriptors:
    descriptors:
    # of final descriptors:
    List of final descriptors:
    descriptors:
    Data source:
    Other remarks:

Model
Samples:
    # initial compounds:
    # final compounds:
Presentation of data:
Design of training set:
Outliers:
Technique:

Model Statistics
r-squared:
q-squared (x-val):
External validation:
ratio #compounds/#descriptors(initial):
ratio #compounds/#descriptors(final):
Validation:
Range of validity:

Accuracy
Remarks

3. Minimal information for a method based on expert judgement

For methods not based on a model the information recommended to be supplied is as follows:

General information
Reference:
Process:
Type (Fragment, Analogue, other):
Specific information
List analogues:
List fragments:
known substances with property and same effect:
known substances with property and not same effect:

Chapter 5

USE CATEGORIES

CONTENTS

1 INTRODUCTION

In accordance with Directive 67/548/EEC and Regulation (EEC) No. 93/793 exposure related information must be provided for notified new substances and for priority existing substances. The information required for new substances is specified in the Annexes VII A, VII B and VII C to Directive 67/548/EEC. The minimum exposure data requirements for priority existing substances are those specified in Annex VII A, to which Article 9 (2) of Regulation 793/93 makes reference.

The exposure data to be provided for all notified new and priority existing substances include information on the (proposed) use(s), and the function(s) and (desired) effect(s) of the substance under consideration. When neither measured nor estimated exposure data are provided by the responsible industry (i.e. the notifier of a new substance respectively the manufacturer or importer of a priority existing substance), the information on use and function will be useful to competent authorities for developing exposure scenarios and assessment of human and environmental exposure levels.

Taking into account the uses and functions of substances notified during the first seven years of application of the notification scheme for new substances, a set of industrial categories and a set of function categories were developed and agreed for use by all competent authorities when summarising notification dossiers. After being used for one year, the sets of categories underwent some revision in response to comments arising from this practical experience.

In the context of the development of a priority setting and risk assessment scheme for existing substances additionally a set of main categories was agreed. All three types of categories are contained in the Harmonised Electronic Data SET (HEDSET) used for the collection of data on existing substances under Articles 3 and 4 of Regulation 793/93 to describe their use pattern as they are part of the IUCLID data set.

These sets of categories will also be useful for statistical analysis of the uses and functions of chemical substances in the European Union.

2 LISTS AND DESCRIPTIONS OF CATEGORIES

2.1 MAIN CATEGORY

The four main categories used for existing substances are intended to describe the exposure relevance of the use(s) of a substance. Similar information is also submitted for new substances with the Summary Notification Dossier under the item "Fields of application".

NOTE: The interpretation of the four main categories as used for assessment of exposure to workers and of exposure to the environment do differ slightly. The terms as used in the HEDSET apply mainly to releases into the environment. A detailed definition of the terms as used for the workplace assessment is to be found in Section 2.2 of Chapter 2: Risk Assessment for Human Health.

1 Use in closed systems

A substance should be assigned to this category if it remains within a reactor or is transferred from vessel through closed pipework and therefore accidental spillage is the only likely cause for human exposure or environmental contamination. Intermediates are restricted to the reaction vessel and its dedicated equipment. Isolated products are stored on-site or are transported under controlled conditions.

Where substances are used in closed systems but might be released into the environment after production, or where significant discharges into the environment cannot be excluded during production, the use pattern should be assigned to the "non-dispersive use" or the "wide dispersive use" categories.

The substances should be assigned to one of the following sub-categories:

1A Non-isolated intermediates
For substances restricted to the reaction vessel and its dedicated equipment.

1B Isolated intermediates
For intermediates stored on-site.

1C Isolated intermediates with controlled transport

NOTE: The categories 1A, 1B and 1C are also used to characterise different release scenarios for the estimation of emission to the environment during production, formulation and processing of a substance. Further specification is given in Section 2.3.3.3 and Appendix I of Chapter 3: Environmental Risk Assessment.

2 Use resulting in inclusion into or onto matrix

Use consisting of inclusion into or onto a matrix means all processes where substances are incorporated into products or articles from which release into the environment would not take place (environment) or is substantially curtailed (workplace).
Examples relevant for environmental exposure: Inclusion of plasticisers in plastics; additives such as pigments or dyes in plastic or fibres; catalysts in coating materials.
Examples relevant for occupational exposure: Dispersion of solids in water; use of raw material in pellets form; use of elastomer master batches.

3 Non-dispersive use

Non dispersive use refers to processes in which substances are used in such a way that only certain groups of workers, with the knowledge of the processes, come into contact with these substances.

These substances may also be discharged into the environment from point sources. Quantities discharged will be limited due to protective measures such as waste water treatment or filtration of air.

4 Wide dispersive use

Wide dispersive use refers to activities which deliver uncontrolled exposure.
Examples relevant for occupational exposure: Painting with paints; spraying of pesticides.
Examples relevant for environmental/consumer exposure: Use of detergents, cosmetics, disinfectants, household paints.

2.2 INDUSTRIAL CATEGORY: INDUSTRY IN WHICH THE SUBSTANCE IS USED

The 16 industrial categories listed below represent industrial use areas for chemicals. Some substances will be used in more than one industrial category.

For new substances these categories should be entered in the Summary Notification Dossier under the item “use category”. For existing substances the term “industrial category” is used in HEDSET and IUCLID.

1 Agricultural industry
e.g. Plant protection products; fertilisers.

2 Chemical industry: basic chemicals
e.g. Solvents; pH-regulating agents (acids, alkalis).

3 Chemical industry: chemicals used in synthesis
e.g. Intermediates (including monomers); process regulators.

4 Electrical/electronic engineering industry
e.g. Electrolytes; semiconductors.
Not: galvanics; electroplating agents.

5 Personal/domestic
e.g. Consumer products such as detergents (including additives); cosmetics; agricultural pesticides for domestic use.

6 Public domain
e.g. Professional products used in public areas as non-agricultural pesticides, cleaning agents, products used in offices such as correction fluids, printing inks.

7 Leather processing industry
e.g. Dyestuffs; tanning auxiliaries.

8 Metal extraction industry, refining and processing industry
e.g. Heat transferring agents.

9 Mineral oil and fuel industry
e.g. Gasoline; motor oil; gear oil; hydraulic fluid; colouring agents; fuel additives; antiknock agents; waste oil detoxification agents.

10 Photographic industry
e.g. Antifogging agents; sensitisers.

11 Polymers industry
e.g. Stabilisers; softeners; antistatic agents; dyestuffs.

12 Pulp, paper and board industry
e.g. Dyestuffs; toners.

13 Textile processing industry
e.g. Dyestuffs; flame retardants.

14 Paints, lacquers and varnishes industry
e.g. Solvents; viscosity adjusters; dyestuffs; pigments.

15 NEW SUBSTANCES: Engineering industry: civil and mechanical
e.g. Agents used in construction work; agents used in automobile, aircraft and ship building.
EXISTING SUBSTANCES: others
Substances not described elsewhere.

999 NEW SUBSTANCES: others
Substances not described elsewhere.

2.3 FUNCTION CATEGORY / USE CATEGORY

The 55 categories listed below represent various functional uses of substances. Some of them are subdivided into sub-categories where appropriate. For clarity, exclusions are indicated in some cases.

For new substances these categories should be entered in the Summary Notification Dossier under the item “desired effects”. In cases where a sub-category is selected, this entry should be added to the same item. For existing substances the term "use category" is used in HEDSET and IUCLID.

NOTE: Some of the categories below are representative of substances which normally do not fall under the scope of Directive 67/548/EEC or Regulation 793/93 (e.g. category 19, fertilisers and 41 pharmaceuticals). These categories have been included so that, for example, substances having multiple uses, or those for which new/further uses are found, can be accommodated.

1 Absorbents and adsorbents
Materials used to absorb or adsorb gases or liquids: filter material/media; molecular sieves; silica gel etc..

2 Adhesives, binding agents
Materials which are applied to two surfaces causing them to adhere: dispersion-based adhesives, hotmelt, resins for polymer-based hardening adhesives, solvent based adhesives.

3 Aerosol propellants
Compressed or liquefied gases within which substances are dissolved or suspended and expelled from a container upon discharge of the internal pressure through expansion of the gas.

4 Anti-condensation agents
Substances used to avoid condensation on surfaces and in the atmosphere: anti-dim agents, condensation removers.

5 Anti-freezing agents
Substances used to prevent and remove ice formation: antifreeze liquids, de-icing agents.

6 Anti-set-off and anti-adhesive agents
Substances used to prevent set-off and adhesion: spraying powder and anti-set-off additives for printing; oils and waxes for laths and shuttering; casting slip etc..

7 Anti-static agents
Substances used to prevent or reduce the tendency to accumulate electrostatic charges: anti-static additives; substances for surface treatment against static electricity.

8 Bleaching agents
Substances used to whiten or decolourise materials.

Not: cosmetics; photographic bleaches; optical brighteners.

9 Cleaning/washing agents and additives
Substances used to remove dirt or impurities from surfaces.

Sub-categories: detergents; soaps; dry cleaning solvents; optical brighteners in detergents.

10 Colouring agents
Substances used to impart their colour to other materials.

Sub-categories: dyestuffs; pigments (including toners); colour forming agents; fluorescent brighteners (but see below re detergents).

Not: cosmetics; food colours; photo-chemicals; optical brighteners used exclusively in detergents; reprographic agents.

11 Complexing agents
Substances used to combine with other substances (mainly metal ions) to form complexes.

12 Conductive agents
Materials used to conduct electrical current.

Sub-categories: electrolytes; electrode materials.

13 Construction materials additives
Substances used in building materials and constructional articles: wall construction materials; road surface materials, ceramic, metal, plastic and wooden construction materials.

14 Corrosion inhibitors
Substances used to prevent corrosion: corrosion inhibiting additives; rust preventives

15 Cosmetics
Substances used as components of cosmetic and toiletry formulations.

16 Dust binding agents
Substances used to control finely divided solid particles of powdered or ground materials to reduce their discharge into the air.

17 Electroplating agents
Substances used as a source for a layer of metal deposited on another surface; or that aid such a deposition.

18 Explosives
Substances or mixtures that are characterised by chemical stability but that may be made to undergo chemical change, rapidly producing a large quantity of energy and gas accompanied by bursting or expansion.

Sub-categories: blasting agents; detonators; incendiaries.

19 Fertilisers
Substances used to supply chemical elements needed for plant nutrition.

20 Fillers
Relatively inert, and normally non-fibrous, finely divided substances added to elastomers, plastics, paints, ceramics etc., usually to extend volume which may improve desired properties such as whiteness, lubricity, density or tensile strength.

21 Fixing agents
Substances used to interact with a dye on fibres to improve fastness.

22 Flame retardants and fire preventing agents
Substances incorporated into, or applied to the surface of, materials to slow down or prevent combustion.

23 Flotation agents
Substances used to concentrate and obtain minerals from ores: flotation oil; flotation depressants.

24 Flux agents for casting
Substances used to promote the fusing of minerals or prevent oxide formation.

25 Foaming agents
Substances used to form a foam or cellular structure in a plastic or rubber material: physically by expansion of compressed gases or vaporisation of liquid, or chemically by decomposition evolving a gas.

Sub-categories: chemical or physical blowing agents; frothers.

26 Food/feedstuff additives
Substances used in food or animal feedstuffs to produce or enhance taste, odour or colour or to improve conservation.

27 Fuels
Substances used to evolve energy in a controlled combustion reaction.

Sub-categories: gasoline; kerosine; gas oil; fuel oil; petroleum gas; non-mineral oil.

28 Fuel additives
Substances added to fuels.

Sub-categories: anti-fouling agents; antiknock agents; deposit modifiers; fuel oxidisers.

29 Heat transferring agents
Substances used to transmit or to remove heat from a material.

Sub-categories: cooling agents; heating agents.

30 Hydraulic fluids and additives
Fluids used for transmitting pressure.

31 Impregnation agents
Substances used to admix with solid materials, which retain their original form: impregnating agents for leather, paper, textile and wood.

Not: flame retardants; conserving agents; biocides.

32 Insulating agents
Agents used to prevent or inhibit the flow of electrical current, heat or light or the transmission of sound.

33 Intermediates
Substances used for synthesis of other chemicals.

Sub-categories: monomers; pre-polymers.

34 Laboratory chemicals
Substances used in laboratories for analytical purposes.

35 Lubricants and additives
Substances entrained between two surfaces and thereby used to reduce friction: oils; fats; waxes; friction reducing additives.

36 Odour agents

Substances used to produce, enhance or mask odour.

Not: food additives; cosmetics.

37 Oxidising agents
Substances that give up oxygen easily, remove hydrogen from other substances, or accept electrons in chemical reactions, and are used for such purposes.

38 Pesticides
Active ingredients and preparations containing one or more active ingredients, intended to protect plants or plant products against harmful organisms or prevent the action of such organisms, influence the life processes of plants, preserve plant products, destroy undesirable plants or destroy parts of plants.

Not: nutrients; fertilisers.

39 Pesticides, non-agricultural (Biocides)
Active substances and preparations containing one or more active substances, intended to destroy, deter, render harmless, prevent the action of or otherwise exert a controlling effect on any organism which has an unwanted presence for man, or a detrimental effect for man, his activities or the products he uses or produces; or for animals or for the environment.

Sub-categories: disinfectants, preservative products, pest control products, specialist biocides.

Not: plant protection products; veterinary products.

40 pH-regulating agents
Substances used to alter or stabilise the hydrogen ion concentration (pH): acids; alkalis; buffers.

41 Pharmaceuticals
Substances used as active ingredients in medicinal preparations.

Sub-categories: veterinary medicines

42 Photochemicals
Substances used to create a permanent photographic image.

Sub-categories: desensitisers; developers; fixing agents; photosensitive agents; sensitisers; anti-fogging agents; light stabilisers; intensifiers.

43 Process regulators
Substances used to regulate the speed of a (chemical) process.

Sub-categories: accelerators; activators; catalysts; inhibitors; siccatives; anti-siccatives; cross-linking agents; initiators; photo-initiators etc..

44 Reducing agents
Substances used to remove oxygen, hydrogenate or, in general, act as electron donors in chemical reactions.

45 Reprographic agents
Substances used to reproduce a permanent image.

Sub-categories: toner for photocopying machines; toner additives.

46 Semiconductors

Substances having resistivities that are between those of insulators and metals, and are usually changeable by light, heat or electrical or magnetic field, or generate electromotive force upon the incidence of radiant energy.

Sub-categories: semiconductors; photovoltaic agents.

47 Softeners
Substances used for softening materials to improve feel, to facilitate finishing processes or to impart flexibility or workability.

Sub-categories: coalescing agents; bates (leather technology); devulcanising agents; emollients; swelling agents; water softeners; plasticisers.

48 Solvents
Substances used to dissolve, thin, dilute and extract: extraction agents; solvents and thinners for paints, lacquers, adhesives and other materials.

49 Stabilisers
Substances used to prevent or slow down spontaneous changes in, and ageing of, materials.

Sub-categories: antioxidants; heat stabilisers; light stabilisers; scavengers; charge stabilisers.

50 Surface-active agents
Substances used to lower the surface and/or interfacial tension of liquids and promote cleaning, wetting, dispersion etc..

51 Tanning agents
Substances used for treating hides and skins.

52 Viscosity adjusters
Substances used to modify the flow characteristics of other substances, or mixtures, to which they are added.

Sub-categories: pour point depressants; thickeners; thixotropic agents; turbulence suppressors; viscosity index improvers.

53 Vulcanising agents
Substances added to rubber to aid and hasten vulcanisation: vulcanising accelerators and vulcanising assistants.

54 Welding and soldering agents
Materials used for welding and soldering; electrodes; flux; powdered metal; wire etc..

55/999 Others
Substances whose technical functions are not described elsewhere.

NOTE : The function category 55 is not used for new substances. For new substances function category "Others" is numbered 999.

Chapter 6

FORMAT FOR RISK ASSESSMENT REPORT

CONTENTS

1 INTRODUCTION

The risk assessments to be conducted for notified new and priority existing substances need, according to the EU legislation on risk assessment (Commission Directive 93/67/EEC for notified new substances and Commission Regulation (EC) No. 1488/94 for existing substances), to be described in a risk assessment report by the responsible Competent Authorities. The elements to be included in that report are listed in Annex V of both the Directive and the Regulation.

Similar reporting formats are used for both new and existing substances. This format described is compatible with the format used in the OECD existing substances program.

The risk assessment report should address all stages of the risk assessment with regard to all effects/properties and all human populations and environmental compartments to be considered according to Directive 93/67/EEC and Regulation 1488/94, including their conclusions/results. The report should also indicate the integrated conclusions/results in relation to the totality of risks posed by the substance and present the necessary explanations or justifications as required by Directive 93/67/EEC (Annex V) and Regulation 1488/94 (Annex V).

The report should be readily understandable and the principles applied and the conclusions being drawn should be transparent. The key data should be easily identifiable without the need for reference to the underlying data sets, i.e. the summary notification dossier for new substances laid down in the SNIF (Summary Notification Interchange Format) or the definitive IUCLID (International Uniform ChemicaL Information Database) data set. i.e., the report should be an stand-alone document. However, this does not mean that all information in the SNIF or IUCLID is repeated. Only those details which are relevant for the risk assessment should be presented.

In order to provide the sufficient flexibility to accommodate reports of varying length depending upon the substance under consideration and the extent and complexity of the data on which the assessment has been based, the format consists of a free-text field containing only the headings corresponding to the four stages of the risk assessment described in Directive 93/67/EEC and Regulation 1488/94 and appropriate sub-headings, as described below in Appendix I (new substances) and Appendix III (existing substances). Guidance on the elements which should be included in the free-text fields under the various headings is provided in Appendix II (new substances) and in Appendix IV (existing substances).

For existing substances, word templates for the risk assessment report and the summary are available at the ECB website (http://ecb.jrc.it/tgdoc). Technical details on how to use the template are provided in an explanatory note available at the same internet address.

2 RISK ASSESSMENT REPORT FOR NEW SUBSTANCES

The risk assessment report for notified new substances will be chapter 7 of the SNIF. A possible future publication of risk assessments has been discussed but no decision has been taken so far.

With regard to substances placed on the market in very low tonnages, it will often be the case that the exposure of certain populations or compartments can be ruled out and that a detailed exposure assessment and risk characterisation for these populations or compartments will be unnecessary. Then, this fact should only be shortly stated and justified. Also with regard to the effects assessment it may not be necessary or possible to conduct a (detailed) assessment and subsequently, a risk characterisation. This applies, if a) either the hazard identification has not led to classification and if there are no other grounds for concern or b) the test appropriate for hazard identification has not (yet) been conducted. While for a) the test(s) should be summarised with respect to the information relevant for classification purposes or those data which give rise for other grounds of concern should be presented, for b) the respective section may contain only a short statement and a brief justification why no effects assessment is necessary.

For certain data of Section 1 (general substance information) and Section 2 (general information on exposure) frequently agreements to maintain confidentiality need to be considered.

3 RISK ASSESSMENT REPORT FOR EXISTING SUBSTANCES

The risk assessment report submitted to the Commission for priority existing substances shall comprise:

- a comprehensive risk assessment report;
- a summary thereof; and
- the definitive data set including all relevant data for the risk assessment according to Article 6 and Annex V of the Risk Assessment Regulation 1488/94 on HEDSET or IUCLID.

ad (a): the comprehensive report is the report containing all detailed information on exposure and the effects of the priority substance and the discussion of their interpretation. This report is intended to present the necessary detailed information to decide on the results of the risk assessment. It will serve as the basis for the discussion in the technical meeting(s) on risk assessment and the committee under Article 15.

ad (b): the summary report should normally comprise between 5 and 15 pages. The summary report will also become part of the IUCLID database, as an attached file.

ad (c): the results of the report will be adopted by the committee and be published in the Official Journal.

ad (d): the complete data set comprising all relevant data for the risk assessment to be provided should be based on the HEDSET data submitted by industry (which are stored on IUCLID). While this IUCLID version contains all data available, only valid data should be included in a relevant/definitive data set. This definitive data set will therefore contain selected data from the original IUCLID which may, where necessary, be complemented or amended by the rapporteurs and which are supplemented by additional data (obtained by own literature research and possibly additional, more detailed exposure data received from industry under Article 9 of Regulation 793/93).

Annex III also describes the differences in content and detail between the comprehensive and the summary report.

3.1 DEFINITIVE DATA SET / IUCLID DATABASE

The IUCLID database, which consists of all data submitted by manufacturers and importers, is intended to include for each substance for which a risk assessment has been adopted at EU level the definitive data set and the risk assessment summary report. The definitive data set will be flagged. The definitive data set, the comprehensive risk assessment report and the risk assessment summary report are made available on the ECB website (http://ecb.jrc.it/).

The rapporteur for an existing substance should submit all relevant data for the risk assessment using a software which allows their uploading on IUCLID. It is therefore recommended that the definitive data set be submitted on HEDSET or the IUCLID software itself.

When preparing the definitive data set based on the complete IUCLID database, i.e. the compilation of all HEDSET submissions, the rapporteur needs to select the relevant data and/or summarise the available data. The HEDSET/IUCLID software and the OECD guidance documents for data entry provide the necessary technical facilities and guidance for doing so.

With regard to chapter 1 of the IUCLID, the definitive data set can either be a summary of the different submissions laid down in one "data sheet" or a compilation of different submissions presented in sequential "data sheets". As the definitive data set is made publicly available, confidentiality aspects need to be considered. The relevant confidentiality items are impurities, composition, production volumes, use pattern and (site specific) exposure information.

For chapters 2 - 5 of IUCLID: Where several valid studies are available for a given effect or a property, those different studies should be included in the definitive data set using multiple "data sheets". The same applies for monitoring data where it may be necessary to lay down multiple "data sheets" in order to describe the exposure for a population or an environmental compartment. However, for substances with a large amount of exposure data, it may be useful to present these data in the form of a summary, e.g. giving the range of concentrations determined by a monitoring programme over a certain period.

Appendix I New substances: Format for risk assessment report

0. OVERALL CONCLUSIONS/RESULTS OF THE RISK ASSESSMENT

Notification No.
CAS No.
ELINCS No.
Substance Name (IUPAC Name)
Trade Name
Generic Name

Overall conclusions of the risk assessment:

( ) i) No immediate concern for man and the environment
( ) ii) The substance is of concern, further information required at next tonnage threshold
( ) iii) The substance is of concern, further information required immediately
( ) iv) The substance is of concern, risk reduction recommendations required

Summary of conclusions

1. GENERAL SUBSTANCE INFORMATION

Identification of the substance
Purity/impurities, additives
Physico-chemical properties
Classification

2. GENERAL INFORMATION ON EXPOSURE

3. ENVIRONMENT

3.1. Environmental exposure

3.1.0. General discussion
3.1.1. Aquatic compartment (incl. sediment)
3.1.2. Atmosphere
3.1.3. Terrestrial compartment
3.1.4. Non compartment specific exposure relevant to the food chain (secondary poisoning)

3.2. Effects assessment: Hazard identification and Dose (concentration) - response (effect) assessment

3.2.1. Aquatic compartment (incl. sediment)
3.2.2. Atmosphere
3.2.3. Terrestrial compartment
3.2.4. Non compartment specific effects relevant to the food chain (secondary poisoning)

3.3. Risk characterisation

3.3.1. Aquatic compartment (incl. sediment)
3.3.2. Atmosphere
3.3.3. Terrestrial compartment
3.3.4. Non compartment specific effects relevant to the food chain (secondary poisoning)

4. HUMAN HEALTH

4.1. HUMAN HEALTH (TOXICITY)
(risk assessment concerning the potential toxic effects listed in Annex IA to Directive 93/67/EEC and Annex IA to Regulation 1488/94)

4.1.1. Exposure assessment

4.1.1.0. General discussion
4.1.1.1. Occupational exposure
4.1.1.2. Consumer exposure
4.1.1.3. Indirect exposure via the environment
(4.1.1.4. Combined exposure)

4.1.2. Effects assessment:
Hazard identification and Dose (concentration) - response (effect) assessment

4.1.2.1. Toxico-kinetics, metabolism and distribution
4.1.2.2. Acute toxicity
4.1.2.3. Irritation
4.1.2.4. Corrosivity
4.1.2.5. Sensitisation
4.1.2.6. Repeated dose toxicity
4.1.2.7. Mutagenicity
4.1.2.8. Carcinogenicity
4.1.2.9. Toxicity for reproduction

4.1.3. Risk characterisation
(with regard to the effects listed in Annex IA to Directive 93/67/EEC and Annex IA to Regulation 1488/94)

4.1.3.0. General aspects
4.1.3.1. Workers
4.1.3.2. Consumers
4.1.3.3. Man exposed indirectly via the environment
(4.1.3.4. Combined exposure)

4.2. HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)
(risk assessment concerning the properties listed in Annex IIA to Directive 93/67/EEC and Annex IIA to Regulation 1488/94)

4.2.1. Exposure assessment

4.2.1.1. Occupational exposure
4.2.1.2. Consumer exposure
4.2.1.3. Indirect exposure via the environment

4.2.2. Effects assessment:
Hazard identification and Dose (concentration) - response (effect) assessment

4.2.2.1 Explosivity
4.2.2.2 Flammability
4.2.2.3 Oxidising potential

4.2.3 Risk characterisation

4.2.3.1 Workers
4.2.3.2 Consumers
4.2.3.3 Man exposed indirectly via the environment

5. Conclusions / Results

6. References

Appendix II New substances: Guidance on how to complete the risk assessment

0. OVERALL CONCLUSIONS OF THE RISK ASSESSMENT

Notification No.
CAS No.
ELINCS No.
Substance Name (IUPAC Name)
Trade Name
Generic Name

When the risk assessment is part of the SNIF the above sections may be left blank (as the data will be transcribed directly from the SNIF).

Overall conclusions of the risk assessment:

( ) i) No immediate concern for man and the environment
( ) ii) The substance is of concern, further information required at next tonnage threshold
( ) iii) The substance is of concern, further information required immediately
( ) iv) The substance is of concern, risk reduction recommendations required

Summary of conclusions:

This section is intended to give a brief overview on the risk assessment by identifying the substance under consideration and summarising the overall conclusions of the risk assessment. The information to be presented here can be copied from Section 1 (substance identification) and from Section 5 (conclusions, possibly to be shortened) of the report.

Conclusion i) can be applied, if in relation to all potential adverse effects, human populations and environmental compartments, on the basis of all available information, the substance is of no immediate concern. If it is not obvious that the substance is of no immediate concern, e.g. if the substance is classified but the exposure to man and environment can be excluded, the reason for applying conclusion i) should be clarified.

If conclusion ii) and/or iii) applies in relation to one or more potential adverse effect(s), human population(s) or environmental compartment(s), a short description and justification of the further information required should be given.

If conclusion iv) applies in relation to one or more potential adverse effect(s), human population(s) or environmental compartment(s), a short description and justification of the recommendations for risk reduction should be given.

NB: The conclusions ii), iii) and/or iv) may apply at the same time in relation to more than one effect, human population and/or environmental compartment.

1. GENERAL SUBSTANCE INFORMATION

Identity of the substance

The substance should be identified by CAS-No, ELINCS-No, IUPAC name, trade name, generic name, molecular formula, structural formula and molecular weight.

When the risk assessment is a part of the SNIF this section may be left blank (as the data will be transcribed directly from the SNIF).

Purity/impurities, additives

Information on the composition of the substance and relevant additives should be stated, such as:

- degree of purity (range);
- identity and percentage of impurities;
- identity and percentage of necessary additives.

Only the impurities/additives that contribute to the label should be given.

When the risk assessment is a part of the SNIF this section may be left blank.

Physico-chemical properties

All physico-chemical properties which are relevant for the risk assessment should be presented. These should include at least:

- physical state (at ntp)
- melting-point
- boiling-point
- relative density
- vapour pressure
- surface tension
- water solubility
- partition coefficient n-octanol/water
- granulometry (where appropriate).

When the risk assessment is a part of the SNIF this section may be left blank.

Classification

The list of relevant R phrases together with the description of the categories of danger as given in Annex I to Directive 67/548/EEC should be stated. If the substance is not included in Annex I, the CA's proposal for classification should be given.

The CA's proposal should also be stated (in addition to the classification of Annex I), if the CA proposes on the basis of the hazard identification a revision of the classification.

If the hazard identification in relation to a particular effect or property has not led to classification but other grounds for concern (both predicted properties or exposure related) had been identified, those grounds for concern should be stated.

The following sub-headings should be introduced, as appropriate:

- classification according to Annex I;
- proposal of the competent authority;
- other grounds for concern.

2. GENERAL INFORMATION ON EXPOSURE

The intention of this section is to give a brief general introduction on exposure issues and to point out where exposures may occur.

A description of the elements relevant to the exposure assessment for the environment and for human populations should be set out here and should include, where available:

- information on production/import tonnages (individual and total in banded values);
- break down of use pattern/use categories/desired effects;
- form of marketed product(s);
- emission pattern/points of release considering the whole life cycle of the substance;
- breakdown/transformation products, if relevant;
- frequency and quantity of emissions, where relevant for general discussion;
- patterns of control (e.g. exposure limiting measures in place and/or applied).

If the exposure of the substance to man and/or environment can be excluded, this should be stated and justified here. The following sections may then be omitted.

3. ENVIRONMENT

3.1. Exposure assessment

3.1.0. General discussion

This section is intended to introduce briefly the exposure issue with regard to the environment considering, where necessary, any other grounds for concern. The elements relevant for deriving the PEC(s) (or, where a PEC cannot be derived, a qualitative evaluation of the exposure) for all three environmental compartments (incl. secondary poisoning) and the discussion of environmental fate and pathways and of the distribution in the environment should be presented here, comprising:

- statement of the compartment(s) of primary release;
- data on environmental fate and pathways and on the distribution and accumulation in the environment, e.g. data on biotic and abiotic degradation, adsorption/desorption, evaporation.

3.1.1. Aquatic compartment (incl. sediment)
3.1.2. Atmosphere
3.1.3. Terrestrial compartment
3.1.4. Non compartment specific exposure relevant to the food chain (secondary poisoning)

For each of the compartments and for secondary poisoning (i.e. for the aquatic compartment under 3.1.1., the terrestrial compartment under 3.1.2., the atmosphere under 3.1.3. and secondary poisoning under 3.1.4.) the specific exposure data on which the PEC(s) (or, where a PEC cannot be derived, a qualitative evaluation of the exposure) is (are) based should be briefly presented.

The resulting PEC(s) or the qualitative estimations should be stated at the end of each section of the discussion.

It may be necessary to derive more than one PEC for a given compartment to take account of different exposure scenarios. In these cases, it is necessary to identify and to justify the PEC(s) that should be used in the risk characterisation.

The specific exposure data mentioned above should comprise:

- relevant monitoring data, where available, including a brief description of the analytical method and detection limit;
- release estimation(s);
- information on specific sources of environmental exposure, e.g. sewage sludge application or landfilling for the terrestrial compartment, where available and relevant;
- measured data on waste water treatment, river flows, if appropriate (for the aquatic compartment);
- model calculations used to derive the PEC (the models applied should be identified and, if necessary, justified and the parameters used be described and justified).

Alternatively, for any compartment for which the exposure is negligible, the relevant section may contain only a short statement to that effect and a brief justification. This is particularly likely in relation to the terrestrial compartment or the atmosphere.

ad 3.1.1. Aquatic compartment: This section should include the discussion of the exposure in sediments.

3.2. Effects assessment:
Hazard identification and Dose (concentration) - response (effect) assessment

3.2.1. Aquatic compartment (incl. sediment)
3.2.2. Atmosphere
3.2.3. Terrestrial compartment
3.2.4. Non compartment specific effects relevant to the food chain
(secondary poisoning)

While it is not necessary to repeat the information given in the SNIF, the relevant information used to assess the hazards to each environmental compartment and, where necessary, to derive the PNECs should be briefly presented. I.e., the relevant test results and the relevant test conditions (e.g. test duration) should be recorded for each environmental compartment (and for secondary poisoning).

These data will comprise:

- acute data (LC/EC 50) for aquatic organisms: fish, daphnia, algae;

and possibly

- acute data for microorganisms, predators, sediment dwelling organisms, terrestrial organisms;
- long-term toxicity data (NOEC) for aquatic organisms, predators, sediment dwelling organisms, terrestrial organisms;
- data on biotic/abiotic effects in the atmosphere.

Where necessary, the data should be discussed and interpreted. The PNEC (or, where a PNEC cannot be derived, a qualitative estimation of the dose (concentration) - response (effect) relation) to be used in the risk characterisation should be stated for each compartment (and for secondary poisoning). The method used to derive the PNEC, including any assessment factors, should be described and briefly justified.

The effects assessment for each compartment (and for secondary poisoning) should be discussed under the relevant heading. For any compartment for which it is not necessary to conduct the effects assessment, the relevant section may contain only a short statement to that effect and a brief justification. This is particularly likely in relation to the terrestrial compartment, the atmosphere or secondary poisoning.

3.3. Risk characterisation

3.3.1. Aquatic compartment (incl. sediment)
3.3.2. Atmosphere
3.3.3. Terrestrial compartment
3.3.4. Non compartment specific effects relevant to the food chain (secondary poisoning)

The PEC/PNEC ratio for each environmental compartment (and for secondary poisoning) should be derived and the value stated. If it is not possible to derive a PEC/PNEC ratio, a qualitative comparison of effects with exposure data should be made. On the basis of the PEC/PNEC ratio or the qualitative comparison, the decision as to which of the conclusions i), ii) iii) or iv) applies, should be taken and stated for each environmental compartment and for secondary poisoning.

The risk characterisation for each compartment (and for secondary poisoning) should be discussed under the relevant heading. For any compartment for which the exposure is negligible or it is not necessary to conduct the risk characterisation, the relevant section may be left blank.

4. HUMAN HEALTH

4.1. HUMAN HEALTH (TOXICITY)
(risk assessment concerning the potential toxic effects listed in Annex IA to Directive 93/67/EEC)

4.1.1. Exposure assessment

4.1.1.0. General discussion

This section is intended to introduce briefly the exposure issue with regard to risk assessment concerning the potential toxic effects of Annex IA of Directive 93/67/EEC and any other grounds for concern. The elements relevant for the quantitative or qualitative estimation of the exposure levels for all populations potentially exposed to the substance should be presented here. It should also describe the routes of exposure, identify the populations potentially concerned and, where appropriate, the significance of the different stages of the life cycle of the substance for the exposure of the populations concerned.

4.1.1.1. Occupational exposure
4.1.1.2. Consumer exposure
4.1.1.3. Indirect exposure via the environment

For each human population (i.e. for workers under 4.1.1.1, consumers under 4.1.1.2 and man exposed indirectly via the environment under 4.1.1.3) the relevant exposure data on which the quantitative or qualitative estimation of the dose/concentration for each population/relevant sub-population is based should be presented. The resulting exposure level(s)/qualitative estimate(s) should be stated at the end of each section of the discussion.

It may be necessary to derive more than one exposure level for a given population to take account of different exposure scenarios. In these cases, it is necessary to identify and to justify the exposure level(s) that should be used in the risk characterisation.

The relevant exposure data mentioned above should comprise:

- relevant measured exposure data, where available;
- information on frequency and duration of exposure;
- information on specific sources of exposure, where available and relevant;
- information on specific exposed population(s), where available and relevant;
- model calculations used to derive the exposure level (the models applied should be identified and, if necessary, justified and the parameters used be described and justified).

For any population for which the exposure is negligible, the relevant section may contain only a short statement to that effect and a brief justification. This is particularly likely in relation to indirect exposure via the environment.

ad 4.1.1.3. Indirect exposure via the environment: Where the assessment of the indirect exposure of man via the environment has to be conducted, the outcome of the environmental exposure assessment relevant to the assessment of the indirect exposure should be stated and the estimates of food, water and air intake should be described and justified.

(4.1.1.4. Combined exposure

If populations are exposed to a substance under different circumstances (e.g. exposure at the workplace and exposure from consumer products/indirect exposure via the environment) the combined exposure should be stated.)

4.1.2. Effects assessment:
Hazard identification and Dose (concentration) - response (effect) assessment

4.1.2.1. Toxico-kinetics, metabolism and distribution

Information available on toxico-kinetics, metabolism and distribution which is relevant for the discussion on a (the) subsequent endpoint(s) should be described here.

4.1.2.2. Acute toxicity
4.1.2.3. Irritation
4.1.2.4. Corrosivity
4.1.2.5. Sensitisation
4.1.2.6. Repeated dose toxicity (sub-acute, sub-chronic, chronic)
4.1.2.7. Mutagenicity
4.1.2.8. Carcinogenicity
4.1.2.9. Toxicity for reproduction

While it is not necessary to repeat the information given in the SNIF, the relevant information used to assess the hazards of each effect to humans and to establish the dose (concentration) -

response (effect) relationship, should be briefly presented. I.e., the relevant test results and test conditions (e.g. test duration, route of administration) or other relevant data should be recorded. Where appropriate, the relevance of animal data/other data for the assessment of the toxicity to humans should be interpreted.

The data should be discussed and interpreted and, where possible, the N(L)OAEL should be identified. When it is not possible to identify a N(L)OAEL the qualitative dose-response relationship should be described.

The effects assessment for each endpoint should be discussed under the relevant heading. For any endpoint for which it is not necessary to conduct the effects assessment, the relevant section may contain only a short statement to that effect and a brief justification. .

ad 4.1.2.6. Repeated dose toxicity: this section shall consider the discussion of sub-acute, sub-chronic and chronic effects, where data are available.

4.1.3. Risk characterisation

4.1.3.0. General aspects

This section is intended to identify the effects and populations for which a risk characterisation is going to be presented, i.e. the effects which merit classification or which give grounds for concern and the exposures which are significant.

4.1.3.1. Workers
4.1.3.2. Consumers
4.1.3.3. Man exposed indirectly via the environment

The N(L)OAEL/exposure ratio for each relevant endpoint and population/sub-population should be derived and the value stated. If it is not possible to derive a N(L)OAEL/exposure ratio, a qualitative comparison of effects with exposure data should be made. On the basis of the N(L)OAEL/exposure ratio or the qualitative comparison, the decision as to which of the conclusions i), ii), iii) or iv) applies, should be taken and stated for each human population.

The risk characterisation for each population should be discussed under the relevant heading. For any population for which the exposure is negligible or it is not necessary to conduct the risk characterisation, the relevant section may be left blank.

(4.1.3.4. Combined exposure

If the consideration of a combined exposure is necessary, a N(L)OAEL/exposure ratio should be derived for each relevant endpoint or a qualitative comparison of effects with exposure data be made based on the combined exposure and the decision as to which of the conclusions i), ii), iii) or iv) applies, should be taken and stated.)

4.2. HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)
(risk assessment concerning the properties listed in Annex IIA to Directive 93/67/EEC)

4.2.1. Exposure assessment

4.2.1.1. Workers
4.2.1.2. Consumers
4.2.1.3. Man exposed indirectly via the environment
These sections may be left blank, if no specific exposure information is available.

4.2.2. Effects assessment: Hazard identification

4.2.2.1. Explosivity
4.2.2.2. Flammability
4.2.2.3. Oxidising potential

For each property, the relevant test result(s) should be recorded and the conclusions be drawn.

The assessment for each property should be discussed under the relevant heading. For any property for which it is not necessary to conduct the effects assessment, the relevant section may contain only a short statement to that effect and a justification.

4.2.3. Risk characterisation

4.2.3.1. Workers
4.2.3.2. Consumers
4.2.3.3. Man exposed indirectly via the environment

The likelihood that an adverse effect occurs under the conditions of use should be discussed and the results be stated. The decision as to which of the conclusions i), ii), iii) or iv) applies, should be taken and stated for each human population.

The risk characterisation for each population should be discussed under the relevant heading. For any population for which either the exposure is negligible or it is not necessary to conduct the risk characterisation, the relevant section may be left blank.

5. Conclusions

This section is intended to draw together the overall risk characterisation combining the environmental and human health sections on risk characterisation to give overall conclusions of the risk assessment. The justification of each of the possible conclusions:

i) No immediate concern for man and the environment

ii) The substance is of concern, further information required at next tonnage threshold

iii) The substance is of concern, further information required immediately

iv) The substance is of concern, risk reduction recommendations required

must be clearly set out, noting that more than one conclusion may apply and that each one may have more than one entry below it.

If conclusion i) applies in relation to all potential adverse effects, human populations and environmental compartments, a statement should be given that, on the basis of all available information, the substance is of no immediate concern. If it is not obvious that the substance is of no immediate concern, e.g. if the substance is classified but the exposure to man and environment can be excluded, the reason for applying conclusion i) should be clarified.

If conclusion ii) and/or iii) applies in relation to one or more potential adverse effect(s), human population(s) or environmental compartment(s), a description and justification of the further information required should be given. If conclusion iii) applies, a proposal should be made for the time limits within which that further information should be submitted.

If conclusion iv) applies in relation to one or more potential adverse effect(s), human population(s) or environmental compartment(s), a description and justification of the recommendations for risk reduction should be given.

(6. Summary of how integrated risk reduction recommendations have been developed in those cases where Article 3.6 of Directive 93/67/EEC applies)

(7. Summary of notifiers comments on initial risk assessment and of any relevant additional information in those cases where Article 3.5 of Directive 93/67/EEC applies)

Appendix III Existing substances: Format for risk assessment reports and summaries

Comprehensive report

O OVERALL RESULTS OF THE RISK ASSESSMENT

1 GENERAL SUBSTANCE INFORMATION

- 1.1 IDENTIFICATION OF THE SUBSTANCE
- 1.2 PURITY/IMPURITIES, ADDITIVES
- 1.3 PHYSICO-CHEMICAL PROPERTIES
- 1.4 CLASSIFICATION
  - 1.4.1 Current classification
  - 1.4.2 Proposed classification

2 GENERAL INFORMATION ON EXPOSURE

- 2.1 PRODUCTION
  - 2.1.1 Production processes
  - 2.1.2 Production capacity
- 2.2 USES
  - 2.2.1 Introduction
  - 2.2.2 Scenarios
- 2.3 TRENDS
- 2.4 LEGISLATIVE CONTROLS

3 ENVIRONMENT [2]

- 3.1 ENVIRONMENTAL EXPOSURE
  - 3.1.1 General discussion
  - 3.1.2 Environmental releases
    - 3.1.2.1 Release from production
    - 3.1.2.2 Release from formulation
    - 3.1.2.3 Release from industrial/professional use
    - 3.1.2.4 Release from private use
    - 3.1.2.5 Release from disposal
    - 3.1.2.6 Summary of releases
  - 3.1.3 Environmental fate
    - 3.1.3.1 Degradation in the environment
      - 3.1.3.1.1 Atmospheric degradation
      - 3.1.3.1.2 Aquatic degradation (incl. sediment)
      - 3.1.3.1.3 Degradation in soil
      - 3.1.3.1.4 Summary of environmental degradation

[2] A marine risk assessment report will be included when more experience has been obtained.

3.1.3.2 Distribution
3.1.3.2.1 Adsorption
3.1.3.2.2 Precipitation
3.1.3.2.3 Volatilisation
3.1.3.2.4 Distribution in wastewater treatment plants
3.1.3.3 Accumulation and metabolism
.1.4 Aquatic compartment (incl. sediment)
3.1.4.1 Calculation of predicted environmental concentrations (PEClocal)
3.1.4.1.1 Calculation of PEClocal for production
3.1.4.1.2 Calculation of PEClocal for formulation
3.1.4.1.3 Calculation of PEClocal for industrial/professional use
3.1.4.1.4 Calculation of PEClocal for private use
3.1.4.1.5 Calculation of PEClocal for disposal
3.1.4.2 Measured levels
3.1.4.3 Comparison between predicted and measured levels
3.1.5 Terrestrial compartment
3.1.5.1 Calculation of PEClocal
3.1.5.1.1 Calculation of PEClocal for production
3.1.5.1.2 Calculation of PEClocal for formulation
3.1.5.1.3 Calculation of PEClocal for industrial/professional use
3.1.5.1.4 Calculation of PEClocal for private use
3.1.5.1.5 Calculation of PEClocal for disposal
3.1.5.2 Measured levels
3.1.5.3 Comparison between predicted and measured levels
3.1.6 Atmosphere
3.1.6.1 Calculation of PEClocal
3.1.6.1.1 Calculation of PEClocal for production
3.1.6.1.2 Calculation of PEClocal for formulation
3.1.6.1.3 Calculation of PEClocal for industrial/professional use
3.1.6.1.4 Calculation of PEClocal for private use
3.1.6.1.5 Calculation of PEClocal for disposal
3.1.6.2 Measured levels
3.1.6.3 Comparison between predicted and measured levels
3.1.7 Secondary poisoning
3.1.8 Calculation of PECregional and PECcontinental

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT ASSESSMENT)
3.2.1 Aquatic compartment (incl. sediment)
3.2.1.1 Toxicity test results
3.2.1.1.1 Fish
3.2.1.1.2 Aquatic invertebrates
3.2.1.1.3 Algae
3.2.1.1.4 Microorganisms
3.2.1.1.5 Amphibians
3.2.1.2 Calculation of Predicted No Effect Concentration (PNEC)
3.2.1.3 Toxicity test results for sediment organisms
3.2.1.4 Calculation of Predicted No Effect Concentration (PNEC) for sediment organisms
3.2.2 Terrestrial compartment
3.2.2.1 Toxicity test results
3.2.2.1.1 Plants
3.2.2.1.2 Earthworm
3.2.2.1.3 Microorganisms
3.2.2.1.4 Other terrestrial organisms
3.2.2.2 Calculation of Predicted No Effect Concentration (PNEC)
3.2.3 Atmosphere
3.2.4 Secondary poisoning
3.2.4.1 Effect data
3.2.4.2 Calculation of PNECoral

3.3 RISK CHARACTERISATION
- 3.3.1 Aquatic compartment (incl. sediment)
- 3.3.2 Terrestrial compartment
- 3.3.3 Atmosphere
- 3.3.4 Secondary poisoning

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)
- 4.1.1 Exposure assessment
  - 4.1.1.1 General discussion
  - 4.1.1.2 Occupational exposure
    - 4.1.1.2.1 Occupational exposure from production
    - 4.1.1.2.2 Occupational exposure from formulation
    - 4.1.1.2.3 Occupational exposure from end uses
    - 4.1.1.2.4 Summary of occupational exposure
  - 4.1.1.3 Consumer exposure
    - 4.1.1.3.1 Exposure from uses
    - 4.1.1.3.2 Summary of consumer exposure
  - 4.1.1.4 Humans exposed via the environment
    - 4.1.1.4.1 Exposure via air
    - 4.1.1.4.2 Exposure via food and water
  - 4.1.1.5 Combined exposure
- 4.1.2 Effects assessment: Hazard identification and dose (concentration)- response (effect) assessment
  - 4.1.2.1 Toxicokinetics, metabolism and distribution
    - 4.1.2.1.1 Studies in animals
    - 4.1.2.1.2 Studies in humans
    - 4.1.2.1.3 Summary of toxicokinetics, metabolism and distribution
  - 4.1.2.2 Acute toxicity
    - 4.1.2.2.1 Studies in animals
    - 4.1.2.2.2 Studies in humans
    - 4.1.2.2.3 Summary of acute toxicity
  - 4.1.2.3 Irritation
    - 4.1.2.3.1 Skin
    - 4.1.2.3.2 Eye
    - 4.1.2.3.3 Respiratory tract
    - 4.1.2.3.4 Summary of irritation
  - 4.1.2.4 Corrosivity
  - 4.1.2.5 Sensitisation
    - 4.1.2.5.1 Studies in animals
    - 4.1.2.5.2 Studies in humans
    - 4.1.2.5.3 Summary of sensitisation
  - 4.1.2.6 Repeated dose toxicity
    - 4.1.2.6.1 Studies in animals
    - 4.1.2.6.2 Studies in humans
    - 4.1.2.6.3 Summary of repeated dose toxicity
  - 4.1.2.7 Mutagenicity
    - 4.1.2.7.1 Studies in vitro
    - 4.1.2.7.2 Studies in vivo
    - 4.1.2.7.3 Summary of mutagenicity
  - 4.1.2.8 Carcinogenicity
    - 4.1.2.8.1 Studies in animals
    - 4.1.2.8.2 Studies in humans
    - 4.1.2.8.3 Summary of carcinogenicity
  - 4.1.2.9 Toxicity for reproduction
    - 4.1.2.9.1 Effects on fertility
    - 4.1.2.9.2 Developmental toxicity
    - 4.1.2.9.3 Summary of toxicity for reproduction

- 4.1.3 Risk characterisation
  - 4.1.3.1 General aspects
  - 4.1.3.2 Workers
    - 4.1.3.2.1 Acute toxicity
    - 4.1.3.2.2 Irritation and corrosivity
    - 4.1.3.2.3 Sensitisation
    - 4.1.3.2.4 Repeated dose toxicity
    - 4.1.3.2.5 Mutagenicity
    - 4.1.3.2.6 Carcinogenicity
    - 4.1.3.2.7 Toxicity for reproduction
    - 4.1.3.2.8 Summary of risk characterisation for workers
  - 4.1.3.3 Consumers
    - 4.1.3.3.1 Acute toxicity
    - 4.1.3.3.2 Irritation and corrosivity
    - 4.1.3.3.3 Sensitisation
    - 4.1.3.3.4 Repeated dose toxicity
    - 4.1.3.3.5 Mutagenicity
    - 4.1.3.3.6 Carcinogenicity
    - 4.1.3.3.7 Toxicity for reproduction
    - 4.1.3.3.8 Summary of risk characterisation for consumers
  - 4.1.3.4 Humans exposed via the environment
    - 4.1.3.4.1 Exposure via air
    - 4.1.3.4.2 Exposure via food and water
    - 4.1.3.4.3 Summary of risk characterisation for exposure via the environment
  - 4.1.3.5 Combined exposure

- 4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)
  - 4.2.1 Exposure assessment
    - 4.2.1.1 Workers
    - 4.2.1.2 Consumers
    - 4.2.1.3 Humans exposed via the environment
  - 4.2.2 Effects assessment: Hazard identification
    - 4.2.2.1 Explosivity
    - 4.2.2.2 Flammability
    - 4.2.2.3 Oxidizing potential
  - 4.2.3 Risk characterisation
    - 4.2.3.1 Workers
    - 4.2.3.2 Consumers
    - 4.2.3.3 Humans exposed via the environment

5 RESULTS

- 5.1 INTRODUCTION

- 5.2 ENVIRONMENT

- 5.3 HUMAN HEALTH
  - 5.3.1 Human health (toxicity)
    - 5.3.1.1 Workers
    - 5.3.1.2 Consumer
    - 5.3.1.3 Humans exposed via the environment
    - 5.3.1.4 Combined exposure
  - 5.3.2 Human health (risks from physico-chemical properties)

6 REFERENCES

ABBREVIATIONS

Appendices

Summary report

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

1.2 PURITY/IMPURITIES, ADDITIVES

1.3 PHYSICO-CHEMICAL PROPERTIES

1.4 CLASSIFICATION

2 GENERAL INFORMATION ON EXPOSURE

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.2 EFFECTS ASSESSMENT

3.3 RISK CHARACTERISATION

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY0
- 4.1.1 Exposure assessment
- 4.1.2 Effects assessment
- 4.1.3 Risk characterisation

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

5 RESULTS

5.1 ENVIRONMENT

5.2 HUMAN HEALTH
- 5.2.1 Human health (toxicity)
- 5.2.2 Human health (risks from physico-chemical properties)

Note: Word templates and guidance documents are available on the ECB website at the following address: http://ecb.jrc.it/tgdoc.

Appendix IV Existing substances: Guidance on how to complete the risk assessment report and summary

Guidance to Content

0. OVERALL RESULTS OF THE RISK ASSESSMENT

This section is intended to give a brief overview on the risk assessment by identifying the substance under consideration and summarising the overall results of the risk assessment. The information to be presented here can be copied from Section 1 (substance identification) and from Section 5 (results, possibly to be shortened) of the report.

Structure

CAS Number:
EINECS Number:
IUPAC Name:

Overall results of the risk assessment (separate sections for environment and human health)

Conclusion (i) There is a need for further information and/or testing.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

(*Note: Only the appropriate conclusions should be kept*).

ad (i) If conclusion (i) applies in relation to one or more potential adverse effect(s), human population(s) or environmental compartment(s), a short description and justification of the further information and/or tests required should be given here and a proposal be made for the time limits within which that further information and/or the results of tests should be submitted.

ad (ii) If conclusion (ii) applies in relation to all potential adverse effects, human populations and environmental compartments, a statement should be given that, on the basis of all available information, at present no further information/testing on the substance is needed and that at present no risk reduction measures (beyond those being applied already), are necessary.

It should be indicated, if conclusion (ii) applies, because a) the substance does not show adverse effects and/or an exposure "of concern" or b) the risk reduction measures in place ensure that the substance does not pose a risk to man and environment.

ad (iii) If conclusion (iii) applies in relation to one or more potential adverse effect(s), human population(s) or environmental compartment(s), a statement of the effect(s), human population(s) and/or the environmental compartment(s) for which the risk needs to be reduced and a short explanation of that need should be given here.

NB: Conclusions (i) and (iii) may apply at the same time in relation to more than one effect, human population and/or environmental compartment.

1. GENERAL SUBSTANCE INFORMATION

1.1 Identification of the substance

The substance should be identified by CAS-No, EINECS-No, IUPAC (EINECS) name, molecular formula, structural formula, molecular weight.

1.2 Purity/impurities, additives

Information on the composition of the substance and relevant additives should be stated, such as:

- degree of purity (range);
- identity and percentage of impurities;
- identity and percentage of necessary additives.

In the comprehensive report detailed information should, where relevant, be presented, e.g. the description of different impurities arising from different manufacturing routes. The summary report should present the summarisation thereof.

1.3 Physico-chemical properties

All physico-chemical properties which are relevant for the risk assessment should be presented if possible in a table. These should include at least:

- physical state (at ntp);
- melting-point;
- boiling-point;
- relative density;
- vapour pressure;
- surface tension;
- water solubility;
- partition coefficient *n*-octanol/water;
- granulometry (where appropriate).

For the comprehensive report: Where several valid values are available reflecting the normal variability of test results, the rapporteur may give ranges of these values. Where the differences in the values may be due to different measurement techniques or in the nature and content of impurities (perhaps due to different routes of synthesis) these differences and the reasons for them should be made clear in deriving the validated physico-chemical data set listed above.

The summary report should normally present one value for each property or, where appropriate, a range. Where necessary, specific information on deviating values should be summarised.

1.4 Classification

For the comprehensive report: The list of relevant R phrases together with the description of the categories of danger as given in Annex I to Directive 67/548/EEC should be stated. If the substance is not included in Annex I, the rapporteur's proposal for classification should be given.

The rapporteur's proposal should also be stated (in addition to the classification of Annex I), if the rapporteur proposes on the basis of the hazard identification a revision of the classification.

The following subheadings should be introduced, as appropriate:

- classification according to Annex I;
- proposal of the rapporteur.

2 GENERAL INFORMATION ON EXPOSURE

The intention of this section is to give a general introduction on exposure issues and to point out where exposures may occur.

A description of the elements relevant to the exposure assessment for the environment and for human populations should be set out here and should include:

- information on production/import tonnages (total and related to regions);
- break down of use pattern/industrial categories/use categories;
- form of marketed product(s);
- emission pattern/points of release considering the whole life cycle of the substance;
- breakdown/transformation products, if relevant;
- frequency and quantity of emissions, where relevant for general discussion;
- patterns of control (e.g. exposure limiting measures in place and/or applied).

This section will consist partly of data that should be extractable from IUCLID (chapters 1.5, 1.7, 1.8, 1.9) and partly from discussion and interpretation, e.g. considering the life cycle and the significance of breakdown products. Hence, where there is some discussion the comprehensive report should present the details of this discussion which should be summarised in the summary report.

3 ENVIRONMENT

3.1 Exposure assessment

3.1.1 General discussion
3.1.2 Environmental releases
3.1.3 Environmental fate

These sections are intended to introduce the exposure issue with regard to the environment. The elements relevant for deriving the PEC(s) (or, where a PEC cannot be derived, a qualitative evaluation of the exposure) for all three environmental compartments (incl. secondary poisoning) and the discussion of environmental fate and pathways and of the distribution in the environment should be presented here, comprising:

- description of the quantitative releases to the environmental compartments for all relevant life-cycle steps;
- data on environmental fate and pathways and on the distribution and accumulation in the environment, e.g. data on biotic and abiotic degradation, adsorption/desorption, evaporation.

The discussion should be presented in the comprehensive report and should be summarised in the summary report.

3.1.4 Aquatic compartment (incl. sediment)
3.1.5 Terrestrial compartment
3.1.6 Atmosphere
3.1.7 Secondary poisoning
3.1.8 Calculation of PECregional and PECcontinental

For each of the compartments and for secondary poisoning (i.e. for the aquatic compartment under 3.1.4, the terrestrial compartment under 3.1.5, the atmosphere under 3.1.6 and secondary poisoning under 3.1.7) the specific exposure data on which the PEC(s) (or, where a PEC cannot be derived, a qualitative evaluation of the exposure) is (are) based should be presented. The resulting PEC(s) or the qualitative estimations should be stated at the end of each section of the discussion.

It may be necessary to derive more than one PEC for a given compartment to take account of different exposure scenarios. In these cases, it is necessary to identify and to justify the PEC(s) that should be used in the risk characterisation.

The PECs derived from measured exposure data and those derived from modelling for a given exposure scenario should be compared and the approaches used to derive them be validated and the result of the comparison be stated.

In the comprehensive report the exposure assessment should be discussed in detail for each compartment, presenting the monitoring data available and the model calculations applied and concluding on the PEC(s) to be used for the risk characterisation. The summary report should present the summary of this discussion.

For any compartment for which the exposure is negligible, the relevant section may contain only a short statement to that effect and a brief justification.

3.2 Effects assessment:
Hazard identification and Dose (concentration) - response (effect) assessment

3.2.1 Aquatic compartment (incl. sediment)
3.2.2 Terrestrial compartment
3.2.3 Atmosphere
3.2.4 Secondary poisoning

In the comprehensive report all information used to assess the hazards to each environmental compartment and to derive the PNECs should be presented: i.e., all relevant test results and the relevant test conditions (e.g. test duration) should be recorded for each environmental compartment (and for secondary poisoning) and referenced to the original papers. These data will comprise:

- acute data (LC/EC50) for aquatic organisms: fish, daphnia, algae;

and possibly

- acute data for microorganisms, predators, sediment dwelling organisms, terrestrial organisms;
- long-term toxicity data (NOEC) for aquatic organisms, predators, sediment dwelling organisms, terrestrial organisms;
- data on biotic/abiotic effects in the atmosphere.

The data should be discussed and interpreted and the PNEC (or, where a PNEC cannot be derived, a qualitative estimation of the dose (concentration) - response (effect) relation) to be used in the risk characterisation should be stated for each compartment (and for secondary poisoning). The method used to derive the PNEC, including any assessment factors, should be described and briefly justified.

The summary report should summarise the discussion on the effects assessment for each compartment and should include the statement of the PNEC.

The effects assessment for each compartment (and for secondary poisoning) should be discussed under the relevant heading.

3.3 Risk characterisation

3.3.1 Aquatic compartment (incl. sediment)
3.3.2 Terrestrial compartment
3.3.3 Atmosphere
3.3.4 Secondary poisoning

The PEC/PNEC ratio for each environmental compartment (and for secondary poisoning) should be derived and the value stated. If it is not possible to derive a PEC/PNEC ratio, a qualitative comparison of effects with exposure data should be made. On the basis of the PEC/PNEC ratio or the qualitative comparison, the decision as to which of the conclusions (i), (ii) or (iii) applies, should be taken and stated for each environmental compartment and for secondary poisoning.

Detailed discussion should be presented in the comprehensive report, summarised in the summary report.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)
(risk assessment concerning the potential toxic effects listed in Annex IA to Regulation 1488/94)

4.1.1 Exposure assessment

4.1.1.1 General discussion

This section is intended to introduce the exposure issue with regard to risk assessment concerning the potential toxic effects of Annex IA to Regulation 1488/94. The elements relevant for the quantitative or qualitative estimation of the exposure levels for all populations potentially exposed to the substance should be presented here. It should describe the routes of exposure, identify the populations potentially concerned and the significance of the different stages of the life cycle of the substance for the exposure of the populations concerned. It should also point out where exposure is not expected to occur.

The discussion should be presented in the comprehensive report and should be summarised in the summary report.

4.1.1.2 Occupational exposure
4.1.1.3 Consumer exposure
4.1.1.4 Humans exposed via the environment

For each human population (i.e. for workers under 4.1.1.2, consumers under 4.1.1.3 and humans exposed indirectly via the environment under 4.1.1.4) the relevant exposure data on which the quantitative or qualitative estimation of the dose/concentration for each population/relevant sub-population is based should be presented. The resulting exposure level(s)/qualitative estimate(s) should be stated at the end of each section of the discussion.

It may be necessary to derive more than one exposure level for a given population to take account of different exposure scenarios. In these cases, it is necessary to identify and to justify the exposure level(s) that should be used in the risk characterisation.

The relevant exposure data mentioned above should comprise:

- relevant measured exposure data, where available;
- information on frequency and duration of exposure;
- information on specific sources of exposure, where available and relevant;
- information on specific exposed population(s), where available and relevant;
- only for comprehensive report: model calculations used to derive the exposure level (the models applied should be identified and, if necessary, justified and the parameters used be described and justified).

The exposure levels derived from monitoring and those derived from modelling for a given population should be compared and the approaches used to derive them be validated and the result of the comparison be stated.

In the comprehensive report the exposure assessment should be discussed in detail for each population, presenting the measured data available and the model calculations applied and concluding on the exposure level(s) to be used for the risk characterisation. The summary report should present the summary of this discussion.

For any population for which the exposure is negligible, the relevant sections of the comprehensive and the summary report may contain only a short statement to that effect and a brief justification.

ad 4.1.1.4 Humans exposed via the environment: The outcome of the environmental exposure assessment relevant to the assessment of the indirect exposure of man via the environment should be stated and the estimates of food, water and air intake should be described and justified.

4.1.1.5 Combined exposure

If populations are exposed to a substance under different circumstances (e.g. exposure at the workplace and exposure from consumer products/indirect exposure via the environment) the combined exposure should be described in the comprehensive report and summarised in the summary report.

4.1.2 Effects assessment: Hazard identification and Dose (concentration) - response (effect) assessment

4.1.2.1 Toxicokinetics, metabolism and distribution

Information available on toxicokinetics, metabolism and distribution which is relevant for the discussion on a (the) subsequent endpoint(s) should be described here.

4.1.2.2 Acute toxicity
4.1.2.3 Irritation
4.1.2.4. Corrosivity
4.1.2.5. Sensitisation
4.1.2.6. Repeated dose toxicity (sub-acute, sub-chronic, chronic)
4.1.2.7. Mutagenicity
4.1.2.8. Carcinogenicity
4.1.2.9. Toxicity for reproduction

In the comprehensive report all information used to assess the hazards of each effect to humans and to derive, where possible, the N(L)OAEL should be presented. i.e., all relevant test results and test conditions (e.g. test duration, route of administration) or other relevant data, e.g. observations of human exposure, should be recorded and referenced to the original papers. The relevance of animal data/other data for the assessment of the toxicity to humans should be interpreted, particularly where only animal data are available. A synthesis of the discussion should be presented identifying, where possible, the N(L)OAEL or stating the qualitative dose-response relationship. For each effect, the justification for an existing classification and proposals for any changes should be easily identifiable. The summary report should summarise the assessment of each effect and should include the synthesis of the discussion.

It is recommended, particularly in the comprehensive report, to separate animal data, human data and other data (e.g. in vitro tests, data from analogous substances), and to introduce the sub-headings in the respective section(s):

- Studies in animals
- Studies in humans
- Other information
- Summary/Synthesis

The effects assessment for each endpoint should be discussed under the relevant heading.

ad 4.1.2.6 Repeated dose toxicity: this section shall consider the discussion of sub-acute, sub-chronic and chronic effects, where data are available.

4.1.3. Risk characterisation

4.1.3.1 General aspects

This section is intended to summarise the probable effects on humans, to identify those which were a cause for concern under differing circumstances of exposure and indicating where there was insufficient information to complete the assessment. The detailed argument should be presented in the comprehensive report with a summary for the summary report.

4.1.3.2 Workers
4.1.3.3 Consumers
4.1.3.4 Humans exposed via the environment

The N(L)OAEL/exposure ratio for each relevant endpoint and population/sub-population should be derived and the value stated. If it is not possible to derive a N(L)OAEL/exposure ratio, a qualitative comparison of effects with exposure data should be made. On the basis of the N(L)OAEL/exposure ratio or the qualitative comparison, the decision as to which of the conclusions (i), (ii) or (iii) applies, should be taken and stated for each human population.

Detailed discussion should be presented in the comprehensive report, summarised in the summary report.

4.1.3.5 Combined exposure

If the consideration of a combined exposure is necessary, a N(L)OAEL/exposure ratio should be derived for each relevant endpoint or a qualitative comparison of effects with exposure data be made based on the combined exposure and the decision as to which of the conclusions (i), (ii), or (iii) applies, should be taken and stated.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

(risk assessment concerning the properties listed in Annex IIA to Regulation 1488/94)

4.2.1 Exposure assessment

4.2.1.1 Workers
4.2.1.2 Consumers
4.2.1.3 Humans exposed via the environment

These sections may be left blank, if no specific exposure information is available.

4.2.2 Effects assessment: Hazard identification

4.2.2.1 Explosivity
4.2.2.2 Flammability
4.2.2.3 Oxidising potential

For each property, the relevant test result(s) should be recorded and the conclusions be drawn in the comprehensive report. A summary should be presented in the summary report.

The assessment for each property should be discussed under the relevant heading.

4.2.3 Risk characterisation

4.2.3.1 Workers
4.2.3.2 Consumers
4.2.3.3 Humans exposed via the environment

The likelihood that an adverse effect occurs under the conditions of use should be discussed and the results be stated.The decision as to which of the conclusions (i), (ii) or (iii) applies, should be taken and stated for each human population.

Detailed discussion should be presented in the comprehensive report, summarised in the summary report.

5. Results

This section is intended to draw together the overall risk characterisation combining the environmental and human health sections on risk characterisation to give overall results of the risk assessment. The justification of each of the possible results

Conclusion (i) There is need for further information and/or testing.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

must be clearly set out, noting that more than one result may apply and that each one may have more than one entry below it. Any relevant risk reduction measures in place should be considered when taking a decision on the result(s).

ad (i) If conclusion (i) applies in relation to one or more potential adverse effect(s), human population(s) or environmental compartment(s), a description and justification of the further information and/or tests required should be given here and a proposal be made for the time limits within which that further information and/or the results of tests should be submitted.

ad (ii) If conclusion (ii) applies in relation to all potential adverse effects, human populations and environmental compartments, a statement should be given that, on the basis of all available information, at present no further information/testing on the substance is needed and that at present no risk reduction measures (beyond those being applied already), are necessary.

It should be indicated, if conclusion (ii) applies, because a) the substance does not show adverse effects and/or an exposure "of concern" or b) the risk reduction measures in place ensure that the substance does not pose a risk to man and environment.

ad (iii) If conclusion (iii) applies in relation to one or more potential adverse effect(s), human population(s) or environmental compartment(s), a statement of the effect(s), human population(s) and/or the environmental compartment(s) for which the risk needs to be reduced and an explanation of that need should be given here.

6. References

The list of references of the original papers which can be copied from IUCLID should be presented. Only for comprehensive report.

Abbreviations Only for comprehensive report.

Guidance to format

Chapter Title is numbered and set at level 1 (Style *Heading 1*). Each chapter is further detailed in subsections (6 additional sub-levels to the highest level).

The first 4 sets of subheadings are numbered (from *Heading 2* to *Heading 5*) to be included in the table of contents. The second two headings (*Heading 8* and *Heading 9,* Headings 6 and 7 being already used for specific chapter titles) are not numbered but have different lettering (see description of styles below).

Should the information not be available, the subsection can be deleted.

Table 1 Page setup

Paper size (A4)	Width Height	21 cm 29.7 cm
Margins	Top Bottom Left Right Gutter Header Footer	2.5 cm 2.5 cm 2.5 cm 2.5 cm 0 1.27 cm 0.76 cm

Table 2 Text [1)]

Body Text (based on no style)	Font Size Style Language Style for following paragraph Alignment Paragraph Space after Widow/orphan control	Times New Roman 12 pt Regular English (UK) Body Text Justified Line spacing – single 9 pt
Body Text 2	Based on Body Text	+ Space After 0
Body Text 3 [2)]	Based on Body Text	+ Space After 7 pt / + Font size 10 pt

1) The core of the text is based on the *Body text* style.
2) Used in the Reference chapter and in the list of abbreviations

Table 3 Titles and headings

Chapters	**Style**	**Description**	
Included in the Table of contents (TOC)			
Chapter 1 to chapter 6	*Heading 1*	Based on no style Font Paragraph Tabs Language Numbering	Style for following paragraph: body text Times New Roman, 14 pt, bold, All caps Aligned left, Space after 10 pt, page break before, widow/orphan control, keep with next Left tab at 3,25 cm English UK Outline numbered, level 1, Starts at 1
Abbreviations	*Heading 6*	Based on Heading 1	No tabs, no numbering, Level 6
Appendix	*Heading 7*	Based on Heading 1	No tabs, no numbering, Not All caps, Level 7
Not in the TOC			
Chapter 0	*Chapter 0*	Based on no style	Same description as Heading 1, but numbering starts at 0
Contents (*used also on cover pages*)	*Title14pt*	Based on Heading 1	+ No tabs, no numbering
Subsections	**Style**	**Description**	
Numbered	*Heading 2*	Based on Heading 1	+ No page break before, Font 12 pt, Space before 18 pt, Level 2
	Heading 3	Based on Heading 2	+ Not All caps, Level 3
	Heading 4	Based on Heading 3	+ Level 4
	Heading 5	Based on Heading 4	+ Level 5
Not Numbered	*Heading 8*	Based on Body text	+ underline, Level 8
	Heading 9	Based on Body text	+ italics, Level 9

Table 4 Headers and footers

Style	**Information**	**Description**	
Header	Left aligned: publication type, substance name, CAS number Right Aligned: chapter title	Based on no style Font Paragraph Tabs Border	 Aria Narrow , 10 pt, Small caps Aligned Left Centred at 8 cm Right at 16 cm Bottom, single solid line ¾ pt width, spacing from text 2 pt
Footer	Left aligned: Rapporteur Centered: page number (font TNR 12) Right aligned: Name of the file	Based on header	+ No Border

Table 5 Footnotes

Style	**Information**	**Description**
Footnote text	Text in the footnote	Based on no style Times New Roman 10pt, regular, line spacing single
Footnote Reference	Number of footnote	Default paragraph font + 8pt +raised 3pt

Table 6 Tables

Style	Information	Description	
Caption	Title	Based on no style Font Paragraph	 Arial Narrow 10 pt bold Line spacing single, Left Aligned, Space before 12 pt, Space after 4.5 pt, Widow/orphan control
Table body	Text in table	Based on no style Font Paragraph	 Arial Narrow 9.5 pt regular Space before 3.5 pt, Space after 2.7 pt (might be modified for large tables)
Table heading	1st row	Based on table body	+ bold
Table note	After table	Based on no style Font Paragraph	 Arial Narrow 9.5 pt regular, condensed by 0.15 Space before 4.5 pt
Borders	outside inside	Line 1 ½ pt Line ¾ pt	

Table 7 Table of contents

Style	Information	Description	
TOC1	Numbering Level 1 (linked to Heading1)	Font Paragraph Tabs Numbering	Times New Roman, 10 pt, All caps Aligned left, Space before 12 pt Left 0.5 cm, Left 15.25 cm leader, Right 16 cm None
TOC2	Numbering Level 2	Based on TOC1	+ Indent at 0.5 cm, hanging 0.75 cm + Tabs at 1.25 cm, not at 0.5 cm
TOC3	Numbering Level 3	Based on TOC2	+ Not All Caps + Space before 0 pt / + Indent 1.25 cm, hanging 1 cm + Tabs at 2.25 cm, not at 1.25 cm
TOC4	Numbering Level 4	Based on TOC3	+ Indent 2.25 cm, hanging 1.25 cm / + Tabs at 3.5 cm, not at 2.25 cm
TOC5	Numbering Level 5	Based on TOC4	+ Indent 3.5 cm, hanging 1.5 cm + Tabs at 5 cm, not at 3.5 cm
TOC6		Based on TOC1	+ Tabs Not at 0.5 cm
TOC7		Based on TOC1	+ Tabs Not at 0.5 cm, Not All Caps

Table 8 Index of tables

Style	Description	
Table of figures	Font Paragraph Tabs	Times New Roman, 10 pt, Regular Aligned left, Line spacing single Left 15.25 leader, Right 16 no leader

References

(Harvard system or author-date system)

Reference citation in text : The system uses the author(s)' name(s) and date of publication in parentheses for each reference cited as it occurs in the text.

Single author

Smith (2002) was the first to propose the theory...
The theory was first proposed in 2002 (Smith, 2002).

When an author has published several cited documents in the same year, these are distinguished by adding lower case letters after the year within the brackets: Smith (2002a) …

Multiple authors (2 or 3)

Same work by 2 or 3 authors:
(Smith and Brown and Jones, 2002)
Smith and Brown and Jones (2002) were the first to propose…

If more than 1 reference is given at the same point in the text, they should be listed chronologically.
Smith (1998), Brown (1999) and Jones (2001)

Multiple authors (more than 3 authors)

Only the name of the 1st listed author is given, followed by the expression et al.
Smith et al. (2002) were the first to propose the theory….
The theory was…(Smith et al., 2002).

References list: All names will be given in Section 6. (references).

- The list of the full references is arranged alphabetically by author.
- When an item has no author it is cited by its title and ordered in the reference list in sequence by the most significant word of the title.
- All significant words in the book titles are capitalised (not in journal titles).
- The date appears after the author.
- The titles of the journals may be abbreviated (generally according to the style used in Index Medicus).

Standard Journal article

Author(s). (Year of publication). Article title. Title of journal, **Volume**, Issue number, Article pages.

Ahel M, Hršak D and Giger W (1994a). Aerobic transformation of short-chain alkylphenol polyethoxylates by mixed bacterial cultures. Arch. Environ. Contam. Toxicol. **26** (2), 540-548.

Ahel M, Giger W and Koch M (1994b). Behaviour of alkylphenol polyethoxylate surfactants in the aquatic environment - I. Occurrence and transformation in sewage treatment. Water Res. **28**, 1131-1142.

Books and other monographs

Author(s) (Year). Title. Editor(s), Publisher(s), Place of publication.

Flynn GL (1985). Percutaneous Absorption; Mechanisms-Methodology-Drug Delivery, Bronough R and Maibach HI (eds), Marcel Dekker Inc., New York, NY.

Chapter in a book

Snipes MB (1995). Pulmonary retention of particles and fibres: Biokinetics and effects of exposure concentrations. **In**: Concepts in Inhalation Toxicology. McClellan RO and Henderson RF (eds), Taylor & Francis, Washington, DC.

For reports produced by organisations or industry, the following information should be added to the reference (if available): Organisation/Company, Year of publication, year of completion of study, Document number, Project number.

Unpublished report should be referenced as such.

Examples

OECD (2000a). Draft Guidance Document for Neurotoxicity Testing. Organisation for Economic Cooperation and Development (OECD), Environment Directorate, OECD Environmental Health and Safety Publications Series on Testing and Assessment No 20. Paris.

OECD (2000b). Skin Absorption: *In Vivo* Method. Organisation for Economic Cooperation and Development (OECD), Environment Directorate, OECD Guideline for the Testing of Chemicals, Draft New Guideline 427, Paris.

IPCS (1986). Principles and Test Methods for the Assessment of Neurotoxicity Associated with Exposure to Chemicals. World Health Organixation (WHO), International Programme on Chemical Safety (IPCS), Environmental Health Criteria 60, Geneva.

US EPA (1996). Health Effect Test Guidelines. Dermal Penetration. US Environmental Protection Agency (EPA). Doc. EPA 712-C-96-350, Washington, DC.

Appendices

Appendices should be numbered using letters in the alphabetical order to facilitate the numbering of the tables (Ex.: Table A.1, Table A.2…) and to avoid any confusion with the tables of the main chapters.

The mission of the JRC is to provide customer-driven scientific and technical support for the conception, development, implementation and monitoring of EU policies. As a service of the European Commission, the JRC functions as a reference centre of science and technology for the Union. Close to the policy-making process, it serves the common interest of the Member States, while being independent of special interests, private or national.

European Commission – Joint Research Centre
Institute for Health and Consumer Protection
European Chemicals Bureau (ECB)

Technical Guidance Document on Risk Assessment
in support of

Commission Directive 93/67/EEC on Risk Assessment
for new notified substances

Commission Regulation (EC) No 1488/94 on Risk Assessment
for existing substances

Directive 98/8/EC of the European Parliament and of the Council
concerning the placing of biocidal products on the market

Part III

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