RIVM report 601200001/2003

Inventory of revisions in the EC Technical Guidance Documents (TGDs) on risk assessment of chemicals.

Luit, RJ, RB Beems, J van Benthem, CWM Bodar, JGM van Engelen, EM Hulzebos, H van Loveren, L Maślankiewicz, AH Piersma, MEJ Pronk, MAJ Rennen (TNO), THM Sijm, PGPC Zweers.

This investigation has been performed by order and for the account of the Directorate General for Environmental Protection, Directorate for Chemicals, External Safety and Radiation Protection, within the framework of project M/601200, risk assessment tools.

RIVM, P.O. Box 1, 3720 BA Bilthoven, telephone: 31 - 30 - 274 91 11; telefax: 31 - 30 - 274 29 71

Acknowledgements

The contributions of the co-authors are gratefully acknowledged.

Human health (chapter 2) section 3.11 was written by dr. RB Beems, section 3.10 by dr. J van Benthem, section 3.5 by dr. JGM van Engelen, section 2.3 by drs. EM Hulzebos, section 3.8 by dr. H van Loveren, section 3.6 and 3.7 by L Maślankiewicz, section 3.12 by dr. AH Piersma, section 3.8 by ir. MEJ Pronk, section 2.2 by drs. MAJ Rennen (TNO Nutrition and Food Research Institute) and section 1, 2.1, 3.1, 3.2, 3.3 and 3.4 by ir. RJ Luit.
Environment (chapter 3) section 3, 5 and 6 were written by dr. CWM Bodar, section 4 by dr.THM Sijm and section 1 and 2 by ir. PGPC Zweers.
Chapter 1 and 7 were written by ir. RJ Luit.

Abstract

This report presents the results of an inventory made by the Dutch National Institute for Public Health and the Environment (RIVM) listing all relevant changes in the EC Technical Guidance Documents (TGDs) in support of risk assessment for newly notified substances, existing substances and biocides. For this purpose the newly revised TGDs (available on August 1, 2002) were compared with the 'old' 1996 TGDs. RIVM risk assessments and risk assessment procedures, along with the software tool, EUSES (European Union System for the Evaluation of Substances), will be adapted on the basis of this report.

Contents

Samenvatting

Dit rapport beschrijft de resultaten van een inventarisatie, die is uitgevoerd door het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) van de veranderingen in de "EC Technical Guidance Documents" (TGD's) voor de ondersteuning bij het maken van risicobeoordelingen van nieuw kennisgegeven stoffen, bestaande stoffen en biociden.

De TGD's (voor het eerst gepubliceerd in 1996) zijn onderworpen aan een herzieningsprocedure op basis van de ervaringen die zijn opgedaan door de EU lidstaten en de industrie bij de beoordeling van circa 100 prioritaire bestaande stoffen en enkele honderden nieuwe stoffen. Tevens zijn de TGD's uitgebreid met de vereisten voor de risicobeoordeling van biociden. In het jaar 2000 zijn voor aparte secties van de TGD's EU werkgroepen van start gegaan met als doel de gewenste veranderingen in kaart te brengen. Dit proces heeft uiteindelijk geresulteerd in aangepaste TGD's. Deze "final draft" documenten zijn geaccordeerd door de Competente Autoriteiten (CA's) van de EU lidstaten. De "final draft" documenten die op 1 augustus 2002 beschikbaar waren op de beschermde internetpagina van het Europees Chemicaliën Bureau (ECB) zijn door het RIVM gebruikt voor de huidige inventarisatie. De documenten zijn onveranderd gebleven tot aan de publicatie van het huidige rapport in November 2002.

Het doel van dit project was het maken van een overzicht van alle relevante wijzigingen die zijn doorgevoerd in de nieuwe TGD's in vergelijking met de versie uit 1996. Het overzicht is bedoeld als startpunt om op eenvoudige wijze te kunnen overgaan tot aanpassing van de (procedures voor de) risicobeoordeling van nieuwe stoffen, bestaande stoffen en biociden en de herziening van de software ter ondersteuning van de risicobeoordeling, EUSES (European Union System for the Evaluation of Substances). Beoordelaars en deskundigen van het RIVM hebben de inventarisatie gemaakt van juli tot en met september 2002.

Summary

This report presents the results of an inventory made by the Dutch National Institute for Public Health and the Environment (RIVM) on the revisions of the EC Technical Guidance Documents (TGDs) in support of the risk assessment for newly notified substances, existing substances and biocides.

The TGDs (first published in 1996) have been subject to review taking into account the experience gained by the EU member states and industry with evaluating approximately 100 priority existing substances and several hundreds of new substances. Furthermore, the TGDs were extended to the additional needs of the risk assessment of biocides. In 2000, several EU working groups started discussions on the changes to be implemented in the separate sections of the TGDs. This process has finally resulted in revised TGDs. The Competent Authorities (CAs) of the EU member states came to an agreement on these 'final draft' documents. The 'final draft' documents, available on August 1, 2002, on the protected European Chemicals Bureau (ECB) website, were used for the current inventory. The documents remained unchanged until the finalisation of the current report in November 2002.

The objective of this project was to prepare an overview of all relevant changes in the new version of the TGDs compared to the 1996 version. As such, the overview is meant to be a starting point for an adaptation of the risk assessments and risk assessment procedures for new substances, existing substances and biocides along with an update of the software tool supporting the risk assessment, EUSES (European Union System for the Evaluation of Substances). Assessors and experts from the RIVM performed this inventory from July to September 2002.

Introduction to the report

The EC Technical Guidance Documents (TGDs) supporting the risk assessment legislation for newly notified substances (Commission Directive 93/67/EEC) and existing substances (Commission Regulation No. 1488/94), published in 1996, have been subject to a process of change. The TGDs provide technical and scientific support for member states and industry in assessing the risks of new and existing chemical substances to humans (workers, consumers, man indirectly exposed via the environment) and the environment (aquatic and terrestrial, micro-organism and predators). In recent years the guidance was further refined taking into account the experience gained in the EU member states and industry with approximately 100 existing substances and several hundreds of new notified substances. Furthermore, it was extended to the needs of the risk assessment of biocides. New insights were discussed in separate EU working groups of national experts starting in 2000. Working groups were formed to deal with the separate issues of human health exposure assessment (worker- and consumer exposure), human health effects assessment (toxicokinetics, acute toxicity, sensitisation, repeated-dose toxicity, mutagenicity, carcinogenicity and reproductive toxicity), environmental exposure assessment, environmental effects assessment and risk assessment for the marine environment. Working groups on human health risk characterisation (non-threshold endpoints/effects and threshold endpoints/effects) are due to start in the final quarter of 2002.

This process has finally resulted in revised TGDs. The Competent Authorities (CAs) of the EU member states came to an agreement on these ‘final draft’ documents. The National Institute for Public Health and the Environment (RIVM) used the ‘final draft’ documents available on the protected European Chemicals Bureau (ECB) website on August 1, 2002 for the current inventory. The documents remained unchanged until the finalisation of the current report in November 2002.

In the Netherlands the Chemical Substances Bureau is responsible for co-ordinating the activities concerning the evaluation of potential hazards and risks of new and existing substances for man and the environment. The RIVM Centre for Substances and Risk Assessment (CSR) advises the Chemical Substances Bureau with respect to these potential hazards and risks of new and existing substances. Occupational hazard and risk assessments are prepared by the Netherlands Organisation for Applied Scientific Research (TNO). Changes in the TGDs may affect the (procedures for) risk assessment currently performed. Furthermore, the software tool EUSES (European Union System for the Evaluation of Substances) that facilitates risk assessments in the framework of the TGDs has to be updated following the revision of the TGDs. Therefore, the current project was initiated with the objective to prepare an overview of all relevant changes in the new version of the TGDs compared to the 1996 version in order to be able to adapt risk assessments and risk assessment procedures.

Risk assessors and experts from the RIVM performed the inventory from July to September 2002. The report lists all relevant changes in the new TGDs compared to the 1996 TGDs. Whenever a certain issue is thought to require future adaptation of EUSES, this is specifically highlighted in the report. The structure of the document is similar to the structure of the TGDs itself. Hence, the report can be easily consulted as a working document in combination with the newly published TGDs.

Chapter 1: General introduction

1 General information

Legislative background on biocidal active compounds is added. It is noted that the environmental risk assessment (exposure, effects and risk characterisation) and the human health effects assessment of biocidal active substances will follow the methodologies described in the present TGDs. The human exposure assessment is dealt with in a separate guidance document (expected in 2002) and the guidance for risk characterisation shall be given in the TNsG for Annex I inclusion.

2 General principles of risk assessment

- Possible results of the risk assessment for biocides are added.
- Competent authority advice is added concerning including or excluding (certain parts of) the assessment for priority existing chemicals that are also subject to evaluation under other community legislation.

3 Procedures for preparing the risk assessments

3.1 Notified new substances

No changes

3.2 Priority existing substances

No changes

3.3 Biocidal active substances

New paragraph containing detailed information on the procedure for preparing a risk assessment for biocides, data requirements, risk assessment report format (still under discussion) and consultation. Reference is made to Biocides Directive 98/8/EC, the associated Technical Notes for Guidance (TNsG) and the ECB homepage.

Appendix I
With reference to Directive 67/548/EEC the Annex VIIA list of base set testing requirements is added.
Appendix II
Newly added list of abbreviations.

Chapter 2: Risk assessment for human health

1 General introduction to risk assessment for human health

No changes

2 Exposure assessment

2.1 Introduction

2.1.1 Core principles of human exposure assessments

This section is rewritten and shortened but similar in content to section 2.1 of TGD 1996.

2.1.2 Combined exposure

- This section is rewritten but similar in content to section 2.1 par. 6 of TGDs 1996.
- A new paragraph is shortly addressing the issue of combined exposure (e.g. workers may be exposed in their private lives (as consumers) as well). No specific guidance presented, however. A case-by-case approach is recommended.

2.2 Assessment of workplace exposure

The main differences between TGDs 1996 and TGDs 2002 with respect to worker exposure assessment are as follows:

1. In the 1996 TGDs, the exposure assessment was described as being based on a basic assessment. The EASE model developed by HSE UK was used to derive this basic assessment. Measured data was then compared with modelled data in deriving exposure levels. The revised TGDs state that measured data, once it fulfils certain quality requirements, is to be given priority over modelled data in the exposure assessment process. The methods that may be used to derive exposure levels - in order of preference are - use of measured data, analogous data and modelled data. Where sufficient measured data of a high quality and representative of the scenario under consideration, is available, the EASE model need not be used.
2. The deterministic model previously used for drumming of liquids is no longer relevant and has been removed.
3. Greater attention is now given to a qualitative description of uncertainties in the exposure assessment process.
4. The stance on conducting exposure assessment and personal protective equipment (PPE) use has not changed. Exposure is still assessed assuming the absence of PPE except under certain circumstances. This is consistent with previous practice.

2.3 Consumer exposure assessment

2.3.1 Introduction

This section is similar to section 2.3.1 par 2 of TGDs 1996. A general overview of the consumer exposure is added.

2.3.2 Scope of the consumer exposure assessment

2.3.2.1 Definitions

New is that:
Exposures to substances not directly related to consumer products need to be described as part of the consumer exposure assessment, such as exposure to paint after painting by professionals, exposure to residential air, exposure to substances in public areas such as swimming pools.

2.3.2.2 Legislative considerations

This section is rewritten but similar to section 2.3.1 par 5 of the TGDs 1996. Communication, with the agencies of the other frameworks considering consumer exposure, is strongly advised.

2.3.2.3 Considerations regarding the assessment of reasonable worst-case situations

- Some thought is given to the normal use and foreseeable misuse of products and which need to be considered.
- The second paragraph is on aggregated exposure and is similar to section 2.3.1 par 7 of TGDs 1996.
- The last paragraph is on exposed sub-groups. These are also discussed in section 2.3.6.2 and section 2.3.6.5 par. 2. The latest discussions on this issue are (not discussed in this revised TGDs):
  - When children are differently exposed than the general public a separate assessment should be performed, including the anthropometric data for children e.g. exposure to toys or hand-to-mouth contact after spraying biocides.
  - However if they are exposed as other members of the public, a separate assessment is not necessary (TMII-02, minutes styrene, existing chemicals).

2.3.3 Types of consumer exposure

This whole section is new.

2.3.3.1 Routes of exposure

Exposure routes are discussed.

2.3.3.2 Primary and secondary exposure

A distinction is made for users and bystanders (primary and secondary, respectively). Primary exposure also includes the exposure for bystanders in the parameters use duration and total duration. However, there may be cases that the user is a professional (painting or biocide application) and that only the bystander exposure needs to be calculated.

2.3.3.3 Phases of activity
All the phases of use of a consumer product are described. The exposure to a substance in a product during these uses needs to be added. For example, painting may include mixing two types of paint, inhalation exposure during and after painting, dermal exposure via splashes but also cleaning the brush and equipment.

2.3.4 Data needs and sources
This section is similar to section 2.3.2.1 of TGDs 1996.

2.3.4.1 Data for the initial screening
This section is similar to section 2.3.2.2 of TGDs 1996.

2.3.4.2 Data for a realistic quantitative exposure assessment
This section is similar to section 2.3.2.1 of TGDs 1996.

2.3.5 Initial screening
This section is similar to section 2.3.3 of TGDs 1996.

2.3.6 Quantitative exposure assessment

2.3.6.1 Scenario building
- This section is similar to section 2.3.5 of TGDs 1996.
- If worker exposure is similar to consumer exposure then the exposure assessment should be similar with regard to concentration data, for example for cleaning agents and adhesives for carpets. This is stated in the last paragraph of this section.

2.3.6.2 Highly exposed or more vulnerable (sub-)populations
See section 2.3.2.3 above for the latest discussion.

2.3.6.3 Check for realism
The text in section 2.3.5 of TGDs 1996 is partly used here.

2.3.6.4 Aggregated consumer exposure
This section is similar to section 2.3.1 last paragraph of TGDs 1996. Fragrances in household products are an example for which aggregated exposures can be an issue.

2.3.6.5 Outcome of the quantitative exposure assessment
The units of the exposure estimates that need to be forwarded to the risk characterisation are included. The different types of sub-groups are more outlined than in the 1996 TGDs.

2.3.7 Use of measured data in the exposure assessment
Similar to 2.1.1 of TGDs 1996. In this section is added that the quality of the measured data need to be evaluated carefully.

2.3.8 Influence of personal protective equipment
This section is new. The exposure assessment should normally not include the use of personal protective equipment.

2.3.9 Improvement of the exposure assessment

- This section is rewritten but basically similar to section 2.3.5 par. 6 and 7.
- In this section more realistic exposure calculations are proposed. Sophisticated models are mentioned including time dependent processes of migration and release of a substance from a matrix adsorption, desorption and disappearance from the medium (e.g. due to ventilation). This extra information needs only to be considered if the realistic worst-case causes concern. Often this improvement will already be integrated in performing the quantitative exposure assessment.

2.4 Exposure of man via environment

This section has not yet been revised. A working group will probably start in 2003.

3 Effects assessment

3.1 Introduction

- The discouragement (from an ethical point of view) of using studies with human volunteers is emphasised. Results should only be used in certain justified cases (exemplified).
- Tonnage independent data requirements for biocides are briefly mentioned with reference to Directive 98/8 and de TNsG in support of Directive 98/8.

3.2 Evaluation of data

3.2.1 Completeness of data

For detailed guidance on data requirements for biocides reference is made to the Biocidal Products Directive 98/8 and the publications on the web page of the Commission http://ecb.jrc.it/biocides.

3.2.2 Adequacy of the data

3.2.2.1 Reliability of test data

The reporting of purity/impurities and the origin of the test substance is added as additional reliability check for test reports.

3.2.2.2 Human data

- The submission of controlled studies in human volunteers is restricted to ‘very rare justified cases’ (not specified).
- Additional note for biocides: experimental human toxicity studies must not be conducted specifically for the purpose of inclusion in Annex I, IA or IB of the Biocidal Products Directive.

3.2.2.3 In vitro data
No changes

3.2.2.4 Relevance of data
One sentence added on the relevance of alternative (non-animal) tests. According to the ECVAM the validation procedure should focus on both the scientific relevance and the predictive relevance. In general, results of in vitro tests provide supplementary information.

3.2.2.5 (Quantitative) structure-activity relationships ((Q)SARs)
No changes

3.3 Exposure route and duration

3.3.1 Introduction
A definition of route-to-route extrapolation is added.

3.3.2 Route of exposure
No changes

3.3.3 Route-to-route extrapolation
- Guidance on the use of route-to-route extrapolation is added. Two aspects are brought to attention: the nature of the effect (the concept only applies for systemic effects) and the importance of toxicokinetics.
- It is noted that the reliability of current methodologies for route-to-route extrapolation is unknown.
- For the evaluation of local effects after repeated exposure, only results from toxicity studies performed with the route under consideration can be used.

3.3.3.1 Approximate dermal NAEL from oral NOAEL
Extrapolation of dermal NAEL from oral NOAEL should be treated with caution. Additional remark: in case data on dermal absorption are available, and/or in case data from dermal absorption studies exist, the available information should be used in the light of Annex IVB of section 3.5, including the use of default values of 10 and 100% dermal absorption. (EUSES)[1]

3.3.3.2 Approximate inhalation NAEL from oral NOAEL
- Additional sentence: the use of the inhalation LC50 and the oral LD50 for the estimation of the inhalation NAEL from the oral NOAEL remains uncertain despite the required similar cause of death.
- Additional remark: Since standard acute LD50/LC50 tests will probably not be available in the future, the alternative approach of converting an oral repeated NOAEL to an approximate inhalation NAEL using physiological parameters will gain relevance,

[1] (EUSES): European Union System for the Evaluation of Substances (software tool in support of the TGD). The note indicates that a change in EUSES is foreseen for the point of interest.

especially for new substances. No further guidance is presented here; reference is made to sections 3.5 and 3.6.

3.3.4 Duration of exposure
No changes

3.4 Dose-response assessment

- Additional guidance on the use of experimental NOAEL and LOAEL:
  - NOAEL and LOAEL depend on the experimental study design;
  - The shape of the dose-response curve should be taken into account in the risk characterisation stage. A steep curve yields a more reliable parameter while a shallow curve increases the uncertainty in the NOAEL/LOAEL.
- The benchmark dose concept as alternative for dose-response assessment is more thoroughly described:
  - The concept is briefly explained;
  - Advantages (all experimental data are used, independent of (spacing between) predefined dose levels and better use of sample size) and disadvantages (probably less reliable in case data are derived from classical (EU Annex V or OECD) toxicity studies) are discussed;
  - Future developments needed (optimisation of study design, predefinition of critical effect sizes for each parameter, development of data type dependent dose-response analyses);
  - For the time being determination of NOAEL is mandatory for EU risk assessments;
  - Benchmark dose concept can be used parallel to the NOAEL approach;
  - In case only a LOAEL can be established benchmark modelling is considered preferable over LOAEL-NOAEL extrapolation;
  - Reference is made to US-EPA benchmark dose software that is available from the US-EPA Internet site (www.epa.gov.ncea.bmds.htm). (EUSES)
- Acute toxicity: biocide legislation uses acute reference doses. For detailed description reference is made to the TNsG (2002). (EUSES)
- Skin sensitisation: Local lymph node assay facilitates categorisation (weak, moderate, and strong) of sensitisers since the test design includes multiple concentrations.

3.5 Toxicokinetics

The chapter on toxicokinetics has been enlarged substantially. Although in principle almost all aspects were present in the 1996 version, this was more or less in a bullet-form, whereas in the present text more guidance is given. In addition, very useful information is collected in Appendix IV A (Predicting toxicokinetics in the absence of experimental toxicokinetic data) and B (Dermal absorption). These appendices provide both default values for dermal exposure and guidance. (EUSES)

3.5.1 Introduction
The introduction is extended, and the role of toxicokinetic studies in the interpretation of toxicological findings and the risk assessment is illustrated.

3.5.2 Definitions
The definition of toxicokinetics is more explicitly formulated.

3.5.3 Objectives for investigating the toxicokinetics of a substance
Although in principle the objectives in 1996 were the same, in the present guidance more attention is paid to the reasons to obtain these parameters (e.g. absorption, bioavailability, biotransformation etc.), in the context of the toxicological profile of the compound and the risk assessment process.

Information derived from toxicokinetic studies is extended with:
- information on the formation of reactive metabolites and possible species differences;
- half life and potential for accumulation under repeated or continuous exposure;
- information on enterohepatic circulation.

3.5.4 Data requirements
Biocide requirements are included.

3.5.5 Types of studies to be used in risk assessment
- This chapter has been added. In the 1996 version titles were ‘data to be used in risk assessment’ and ‘ evaluation of the available data’.
- General: in the 1996 version a lot of information that can be derived from the base data set (log Pow, particle size, QSAR, etc) is listed; however, without guidance on the interpretation of this data. As already stated above, in the present document detailed guidance is provided in the text, and especially in the appendix. One aspect that was only briefly mentioned in the 1996 version is dermal absorption. In the present document extensive guidance on the interpretation of in vitro and in vivo data on dermal absorption is given.

3.5.5.1 Introduction
No changes

3.5.5.2 Predictive and modelling approaches (QSAR/SAR)
See 3.5.5. Guidance in the appendix.

3.5.5.3 In vitro approaches
Information in this paragraph has been updated. Examples are more detailed, and references are provided.

3.5.5.4 Animal studies
Information is provided with respect to e.g. data sampling, non-linearity. Valuable references are provided.

3.5.5.5 Studies in Man
No changes

3.5.6 Assessment of the data
New chapter, see 3.5.6. Aspects that need attention with respect to analytical method, timing of blood samples and experimental conditions for in vitro systems are described.

3.5.7 Use of toxicokinetic data in risk assessment
New chapter. Provides information on various aspects in the ADME- process, and how this information can be used in risk assessment.

3.5.8 PBTK-Modelling
New chapter. Gives some information on PBTK-modelling.

3.6 Acute toxicity

3.6.1 Introduction

3.6.1.1 Definition of acute toxicity
Introduction of the value of integrating the outputs of testing for skin irritation and acute toxicity.

3.6.1.2 Objectives of investigating the potential for substance-induced acute toxicity
- An objective on classification and labelling is added.
- General objective to move away from the induction of lethality in animal tests.

3.6.1.3 Information which would be obtained from Annex V tests for acute toxicity
- New tests for the acute toxicity testing are listed.
- Standard acute oral toxicity test (LD50, B1) has been removed from Annex V and will be removed from the OECD guidelines as well.
- Information on what should be determined in each test (including new ones) is given.

3.6.2 Data to be used in the effects assessment

3.6.2.1 Minimum data requirements
In general completely new chapter. Minimum data requirements and testing strategies for new, existing substances and biocides are given. For new substances a decision-tree is introduced, based on integration of information from acute toxicity testing with that from skin and eye irritation and skin sensitisation, physico-chemical and SAR properties and exposure profile. This aims at avoiding unnecessary testing by giving better consideration to the need for testing via the inhalation and dermal route. Instructions on how to use this scheme (e.g. for corrosive substances) and explanations are given. If applicable, the testing strategy for new substances could be followed for existing substances. For biocides reference also made to the TNsG. In principal, all tests must be conducted using EU-Annex V methods or corresponding OECD guidelines.

3.6.2.2 Data which may already be available
No changes.

3.6.3 Evaluation of the available data

3.6.3.1 New substances including new biocidal substances
No changes.

3.6.3.2 Existing substances including existing active biocidal substances
No changes.

3.6.4 Assessment of the dose-response relationship
Additional information on toxic signs other than from acute toxicity studies may be also used for characterisation of acute toxicity.

3.6.5 The degree of uncertainty in studies of acute toxicity
Minor changes (subjective effects for humans).

3.7 Irritation and corrosivity

3.7.1 Introduction

3.7.1.1 Definitions of irritation and corrosivity
Introduction with an additional explanation on the definition of irritation.

3.7.1.2 Objectives of investigating the potential for substance-induced irritation or corrosion
No changes.

3.7.1.3 Information which would be obtained from Annex V testing methods for irritation
The need to examine the corrosive/severely irritating substances with in vitro/ex vivo methods before any attempt of animal testing is emphasised.

3.7.2 Data to be used in the effects assessment

3.7.2.1 Minimum data requirements
Use of methods other than those specified in Annex V for **existing substances** may be accepted on a case-by-case basis (according to the 'old' 1996 TGDs Annex V methods for existing substances were not obligatory).

3.7.2.2 Data which may already be available
No changes.

3.7.3 Evaluation of the available data

3.7.3.1 New substances
No changes.

3.7.3.2 Existing substances
No changes.

3.7.4 Assessment of the dose-response relationship
No changes.

3.7.5 The degree of uncertainty in studies of irritation and corrosivity
No changes

3.8 Sensitisation

3.8.1 Introduction

3.8.1.1 Scope of the guidance
The scope of the guidance is on chemical-induced diseases that are presumed to be allergic in nature, such as asthma, rhinitis, allergic contact dermatitis, urticaria, and food allergies.

3.8.1.2 Definitions of skin and respiratory sensitisation
- The definition of sensitisation has been expanded to 'the characteristic adverse health effect of exposure via the skin or by inhalation', such as allergic contact dermatitis or asthma (or related respiratory symptoms such as rhinitis).
- The notion is added that, whereas skin sensitisation specifies an allergic mechanism of action, respiratory allergy and asthma do not necessarily do so.

3.8.1.3 Objectives of investigating the potential to cause allergic contact dermatitis or respiratory hypersensitivity.
The objectives have essentially not been changed. The adjuvant technique is no longer mentioned as the preferred test.

3.8.1.4 Information which would be obtained from internationally acceptable tests
- The murine local lymph node assay (LLNA) is now included as an accepted method for assessing skin sensitising capacity.
- For respiratory sensitisation, there is still no validated test. The guidance mentions to take into account possible structural alerts, physical properties, the likelihood to be inhaled, and known (not necessarily respiratory) sensitising properties of the compound.

3.8.2 Data to be used in the effects assessment

3.8.2.1 Minimum data requirements
- In addition to minimum data requirements described in EU annex V for new chemicals, for existing chemicals there is more flexibility allowed, while for biocidal actives and products tests according to the annex V are not required if the active substance is classified as a sensitiser, or where the preparation contains a sensitiser.
- There are no minimum requirements for respiratory sensitisers.

3.8.2.2 Data which may already be available
For animal data, the LLNA is now mentioned more pronouncedly as a validated test. For respiratory sensitisation, cytokine fingerprinting is now mentioned, in addition to structure-activity relationships and structural alerts.

3.8.3 Evaluation of the available data

It is now stated that for new substances tests conducted using Annex V methods are adequate.

3.8.3.1 Human data

- The quality of epidemiological data is added as a criterion.
- Also the conduction of bronchial provocation is further elaborated.

3.8.3.2 Predictive assays

- Removed from revised TGDs: adjuvant tests are generally more sensitive.
- For guinea pig assays it is now advised to look for signs of systemic toxicity.
- In case of doubtful results with guinea pig tests, re-challenge is advised.
- The murine local lymph node assay (LLNA) is now included as an accepted assay and criteria for execution are mentioned.

3.8.4 Assessment of the dose-response relationship

3.8.4.1 Measurement of dose-response

There is evidence that dose-response relationships for sensitisation exist. However, it is usually difficult to obtain information on dose-response relationships from human data or guinea pig tests, where only one concentration is tested. Dose response relationships can be derived from the murine local lymph node assay (LLNA).

3.8.4.2 Measurement of potency

This paragraph is new, and indicates that from dose-response information provided by the LLNA, the dose estimated to cause a 3-fold increase in the local lymph node proliferative response may be used as a measure of relative potency. In addition, the percentage of guinea pigs reacting positively may also indicate relative potency.

3.8.5 The degree of uncertainty in studies of sensitisation

New considerations have been added:

- Well conducted human studies can provide valuable information on skin sensitisation, but it should be realised that diagnostic tests are carried out to see if a patient is sensitised to a specific agent, and not to determine whether the agent can cause sensitisation;
- Guinea pig tests may be difficult to interpret when irritancy or staining occurs as a result of challenge;
- The use of adjuvant in the guinea pig maximisation test may lower the threshold and lead to false positives. Also the LLNA has occasionally given false positives;
- On the other hand, also false negatives are encountered. Where tests rely on topical application only, false negatives may occur when the substance fails to be absorbed into the skin. Careful consideration should therefore be given to the vehicle used;
- It is mentioned that major uncertainties remain in our understanding why a substance is an allergen or not, and what makes a chemical a skin or a respiratory sensitiser.

3.9 Repeated dose toxicity

3.9.1 Introduction

3.9.1.1 Definition of repeated dose toxicity
Next to the definition of repeated dose toxicity, new definitions for local effect and for systemic effect are added.

3.9.1.2 Objectives of investigating the potential of substances to induce repeated dose toxicity
No changes

3.9.2 Data to be used in the effects assessment

3.9.2.1 Minimum data requirements
This section is expanded, addressing separately the minimum data requirements for new substances (with modified test requirements for closed system intermediates), existing substances (with a need to address differences or parameters not covered in studies not conducted according to EU Annex V or corresponding OECD guideline) and biocides (with reference to the TNsG). In principle, the tests should be conducted following the latest version of the appropriate EU Annex V method or OECD guideline.

3.9.2.2 Data which may already be available
Under 'human data' the conduct of human volunteer studies is declared ethically undesirable and therefore strongly discouraged.

3.9.3 Evaluation of the available data
- It is indicated that the critical effect can be a local as well as a systemic effect.
- A section is added on the use of a standard set of default values (given in Appendix VI of the revised TGDs) in order to calculate a NOAEL or LOAEL in mg/kg/day in case necessary data are either not available or inadequate. Deviations from this standard set need to be documented and justified.

3.9.4 Assessment of the dose-response relationship
This subchapter now also addresses local effects: when clearly identified a N(L)OAEL should be established for these effects in addition to N(L)OAELs for systemic effects, when not observed or not investigated this should be mentioned.

3.9.5 The degree of uncertainty in studies on repeated dose toxicity
No changes

3.9.6 The testing strategy
Short introduction only. The text of the original section 3.9.6 of the 1996 TGDs has been relocated to 3.9.6.2-3.9.6.4 (see below).

3.9.6.1 The objective of this part of the guidance
This section contains the minimum data requirements for new substances (updated), existing substances (no change) and biocides (new, with reference to the TNsG).

3.9.6.2 General Principles
See section 3.9.6.4.

3.9.6.3 Preliminary considerations
See section 3.9.6.4.

3.9.6.4 Considerations for initial 28- or 90 day toxicity testing
Aside from some minor editorial changes, these three sections (3.9.6.2-3.9.6.4) comprise the text given in sections 3.9.6 ('When testing is required: general principles'), 3.9.8.1 ('Preliminary considerations') and 3.9.8.2 ('Base-set 28-day studies or a 90-day study in place of 28-day study') of the 1996 TGDs, together with a new paragraph on exemptions from testing in section 3.9.6.2 and updated information on OECD test guidelines 407/408 in section 3.9.6.4.

3.9.6.5 Immediate further testing
See section 3.9.6.6.

3.9.6.6 (Sub)chronic toxicity studies
The text in section 3.9.8.3 ('Further testing') of the 1996 TGDs has been rearranged into two sections (3.9.6.5 and 3.9.6.6), with some minor editorial changes and information on biocides included.

3.9.6.7 Specific system/organ toxicity
General aspects
No changes
Neurotoxicity
The text of this section has been rearranged, expanded and updated as to definitions, structure-activity considerations, testing (guidelines, interpretation of effects, WHO/FAO recommendations on 'Interpretation of Cholinesterase Inhibition') and testing strategy. For developmental toxicants a reference is made to chapter 3.12.6.7 of the revised TGDs.
Immunotoxicity
This section has also been expanded and updated as to definitions, testing (guidelines, indications for immunotoxicity) and further testing.
Effects on the endocrine system
This is a new section, with working definitions for endocrine disrupters and a reference to chapter 3.12 of the revised TGDs.
Overload phenomena and pulmonary fibrosis
No changes

3.10 Mutagenicity

3.10.1 Introduction
No changes

3.10.1.1 Definitions of mutagenicity and genotoxicity
Some minor, predominantly linguistic changes have been made.

3.10.1.2 Objectives of investigating the potential for substance-induced mutagenicity and genotoxicity

- Next to minor, predominantly linguistic changes, a definition for 'genotoxic carcinogens' is added.
- Section 3.10.1.3 of the 1996 TGDs is removed. The original text is partly copied into other chapters of the revised TGDs.

3.10.2 Data to be used in the effects assessment

3.10.2.1 Minimum data requirements

- Since this TGDs are valid for new chemicals, existing chemicals and biocides, this paragraph is divided in 'new and existing chemicals' and 'biocides'.
- Although the exceptions to this requirement are not changed, the guidance in the case of exceptions, and particular when further testing is needed, is extended.
- The minimum requirements for biocides are added.

3.10.2.2 Data that may already be available

- This paragraph is predominantly aggravated on genotoxicity data obtained in tests other than those mentioned in Annex V to Directive 67/548/EC.
- It is important that the validity and usefulness of each of the data sets to the overall assessment of genotoxicity should be individually assessed.

3.10.3 Evaluation of the available data

- The content of this paragraph is hardly changed. The order of the different items ('conflicting results' vs. 'particular points when evaluating negative test results') has been turned.
- A paragraph on conflicting results from the same test has been added.
- The interpretation of human data and their relevance has been sharpened.

3.10.4 Assessment of the dose-response relationship

- Although the default assumption for genotoxic chemicals is a linear dose-response relationship, attention is given to mechanisms that lead to a non-linear or threshold relationship.
- It is indicated when the determination of experimental dose-effect relationships is of importance.
- The Lowest Observed Effect Dose (LOED) is introduced which may give an indication of the mutagenic potency of a compound and which may be a helpful tool in risk assessment.
- Sections 3.10.5 and 3.10.6 of the 1996 TGDs are removed. The original text is partly copied into other chapters of the revised TGDs.

3.10.5 The testing strategy

3.10.5.1 The objective of the testing strategy

- The message of this paragraph did not change; however, the wording is more to the point.
- There is less attention paid to the tonnage triggered testing requirements.
- The core data requirements for biocides are added.
- The general follow up procedure of the testing strategy (figure 2 and table 4 of the 1996 TGDs) is now summarised in table 5 and consist of seven different decision levels.

3.10.5.2 Preliminary considerations

- Previous section 3.10.8.1
- It is stated that animal tests are needed in case of specific metabolic pathways that can not be stimulated *in vitro*.
- The importance of toxicokinetic and toxicodynamic properties of test compounds is stressed. These properties should be considered before undertaking animal experiments because systemic unavailability may make animal experiments technically impossible.
- A substance giving an equivocal test result should be reinvestigated immediately.
- Tests need not to be performed if it is technically impossible to do so or if systemic availability to the target tissue is not guaranteed. However, alternative methods may be used when necessary provided that they are scientifically justified (former 3.10.5).

3.10.5.3 Base-level testing

- Previous section 3.10.8.1 'Testing for substances supplied at 1 tpa or more'.
- For base level testing, which still requires two tests: a gene mutation test in bacteria and an *in vitro* mammalian cell test capable of detecting chromosomal aberrations, it is now possible to choose between three tests: the *in vitro* chromosome aberration test, the mouse lymphoma test and the *in vitro* micronucleus test.
- The importance of aneuploidy is now distinguished; therefore, if a test compound is a suspected aneugen the mouse lymphoma assay should not be used.
- For compounds with a significant toxicity for bacteria, the *in vitro* gene mutation test in mammalian cells is an alternative.

3.10.5.4 Requirement for testing beyond the base level. Introductory comments

Previous section 3.10.8.4 'Requirement for further testing post 1 tpa'.

3.10.5.5 Substances which are negative in the base-level tests

- Previous section 3.10.8.5: 'Substances which are negative in both of the tests specified at the 1 tpa supply level'.
- It is stated that substances, which are negative in the base level tests, are non-genotoxic.
- The importance of aneugens is again stressed. Putative aneuploidy of a substance can be a reason for further testing since it can only be detected at base-level when a gene mutation test in bacteria is combined with an *in vitro* micronucleus test. Any other combination of base-level tests does not allow detection of aneuploidy.
- The timing and extent of further testing will depend largely on the intended use of the substance, the extent of expected human exposure and on supply level.
- By allowing the flexible approach for further testing the possibility is offered to consider less commonly used tests (*in vitro* UDS), different metabolic activation systems or *in vivo* genotoxicity tests.

3.10.5.6 Substances for which an in vitro test is positive

- Previous sections 3.10.8.6: 'Substances for which the *in vitro* cytogenetics test triggered at the 1 tpa supply level is positive' and 3.10.8.7: 'Substances for which the base set bacterial gene mutation test is positive'.
- When from the base set tests exclusively the bacterial gene mutation test is positive, the decision for further testing has to be made on a case by case basis. Particularly the level of human exposure can be decisive.
- Of highest importance is the remark that 'A particular *in vivo* test should be conducted only when it can be reasonably expected from all the properties of the test substance and the proposed test protocol that the specific target tissue will be adequately exposed to the test substance and/or its metabolites'. Therefore it is reported that 'before undertaking any *in vivo* testing, a review of the *in vitro* test results and all available information on the toxicokinetic and toxicodynamic profile of the test substance is needed'. If these data are not available investigation of toxicokinetics should be performed. In this way the number of animal experiments without exposure of target tissue will be radically reduced.
- Two *in vivo* tests are recommended: a rodent bone marrow cytogenetic assay and a rat liver UDS test. Which test is the most appropriate one to conduct has to be decided from earlier experiments (*in vitro* data) together with expert judgement; clastogenicity *in vitro* should be followed by a rodent bone marrow cytogenetic assay whereas the UDS test is the best choice after *in vitro* indications for gene mutations.
- Under certain conditions (e.g. no systemic availability) it is justified to select alternative tests (Comet assay or gene mutation assay with transgenic animals). Expert judgement is necessary to choose the appropriate one.
- If the first *in vivo* test is negative, the need for a second *in vivo* test should, necessary in the 1996 TGDs, be considered

3.10.5.7 Substances that give positive results in an in vivo test for genotoxic effects in somatic cells

- Previous section 3.10.8.8: 'Substances which are positive in an *in vivo* test for genotoxic effects in somatic cells'.
- For substances, which are genotoxic in somatic cells, expert judgement is needed to consider whether there is sufficient information to conclude that the substance poses a genotoxic hazard to germ cells. If so, further testing is not necessary but the substance is a germ cell genotoxin. If the appraisal is inconclusive further testing is required immediately.
- Next to international recognised test systems, alternative methods like the Comet assay or the gene mutation assay with transgenic animals can be used.
- Substances, which point to a clastogenic effect in germ cells, have to be studied further for differentiation between clastogenicity and aneuploidy unless this was already adequately established.

3.11 Carcinogenicity

3.11.1 Introduction

3.11.1.1 Definition of carcinogenicity

- The definition of carcinogenicity has been extended. Previously defined as substances that 'induce cancer or increase its incidence', it now also includes explicitly the induction of benign tumours in addition to malignant tumours (cancer) and increased malignancyor shortened time of tumour occurrence in addition to increased incidence. The types of studies from which carcinogens may be identified are added.
- New insights in the mechanism of carcinogenesis, e.g. role of cell death rate, have been included in the description of the cancer process.
- The definition of genotoxic carcinogens is adopted from section 3.10.1.
- Although an effect threshold cannot be identified for genotoxic carcinogens, it is recognised that for certain genotoxic carcinogens it is possible to define no-effect levels for the underlying non-carcinogenic effect.

3.11.1.2 Objectives of investigating the potential of substance-induced carcinogenicity

- It is more clearly stated that the objective of investigating the carcinogenicity of substances is 'to identify potential human carcinogens' and to differentiate carcinogens from non-carcinogens. Additional investigations are aimed upon the mode of action, the presence or absence of a threshold dose and the relevance of the finding to humans.
- The importance of the actual exposure level in the evaluation process is shortly addressed.

3.11.2 Data to be used in the effects assessment

3.11.2.1 Minimum data requirements

Requirements for biocides have been added.

3.11.2.2 Data which may already be available

- Data from short and medium term carcinogenicity tests with transgenic mice and other short-term models, studies on cell transformation and intercellular gap junction communication and studies on mechanism of action have been added.
- When human data of sufficient quality are available, they are preferable to animal data since no interspecies extrapolation is necessary and exposure scenarios are likely to be more realistic.

3.11.3 Evaluation of the available data

- The chapter on animal data is extended and data from carcinogenicity studies and evidence from other experimental data are discussed separately and more comprehensively than in the 1996 version of the TGDs.
- The importance of the mode of action, expert judgement and weight of evidence approach is stressed.
- Epidemiological studies may provide indications on the relative sensitivity of humans as compared to animals.
- It is difficult to establish non-carcinogenicity based on a negative epidemiological study.

- Animal data: Several evaluation criteria and points of attention are discussed. Subjects include:
  - Observation time, time of tumour onset, differences in survival;
  - Route and method of administration;
  - Consistency of different studies;
  - Relevance to humans, with respect to mode of induction;
  - Tumours in tissues with no human counterpart;
  - Mechanisms of tumour induction known to be not relevant to humans;
  - Increase in only benign tumours or in tumours with a high spontaneous incidence;
  - Use of alternative carcinogenicity assays.
- Evidence from other experimental data, e.g. genotoxicity studies, repeated dose toxicity studies (occurrence of hyperplastic changes), immunotoxicity, structural alerts, toxicokinetic data and mechanisms of toxicity, are mentioned.
- In the summary the importance of an integrated evaluation of the different categories of data and expert judgement on the weight of evidence is stressed.

3.11.4 Assessment of the dose-response relationship

- The existence of a threshold for non-genotoxic carcinogens as well as some genotoxic compounds is addressed. Data are generally not suitable for mathematical modelling.
- A guide for dose-response assessment of non-genotoxic carcinogens is added.
- The chapter on the degree of uncertainty in studies on carcinogenicity is omitted. This subject is addressed in several other chapters.

3.11.5 The testing strategy

This chapter has been reshuffled and partly rewritten, resulting in a more logical order of subjects.

3.11.5.1 General principles

- An introduction to the testing strategy is given.
- The flow scheme is rewritten and a number of possible conclusions on testing strategy is summarised.

3.11.5.2 Substances of no current concern for carcinogenicity

Some editorial revisions.

3.11.5.3 Substances with indications of concern for carcinogenicity

- Some guidance is added for genotoxic compounds and compounds that are classified as category 1, 2 or 3 mutagens.
- Use of short and medium term tests and the results of semichronic and chronic toxicity tests is shortly commented.
- For non-genotoxic carcinogens investigations on the mode of action may clarify the relevance for humans.

3.11.5.4 New substances

- Partly previous section 3.11.7.1.
- Expert judgement on the weight of evidence may lead to requirement of investigations on carcinogenicity at a lower level of tpa.

3.11.5.5 Existing substances
Editorial revision with emphasis on specific investigations on carcinogenicity in case of insufficient information.

3.11.5.6 Biocides
New chapter, not in 1996 TGDs.

3.11.6 The carcinogenicity test
Chapter is rewritten. The importance of selection of species and strain and route of exposure and of concurrent chronic toxicity testing is stressed.

3.12 Reproductive toxicity

3.12.1 Introduction
- In 3.12.1.2 two bulleted objectives were added, one on the relative susceptibility of pregnant versus non-pregnant animals, and another on the dose-response relationship of adverse effects on reproduction.
- In the ensuing text block a reference was added to a new section on maternal toxicity, which appears in 3.12.7.1.
- A new text block explains that germ cell mutagens and genotoxic carcinogens should not normally need reproductive toxicity testing and should be regarded as potentially toxic to reproduction.

3.12.2 Data to be used in the effects assessment
- This section was restructured.
- The default key data requirements for new and existing substances and biocides are now a two-generation study (OECD416) and developmental toxicity studies (OECD414) in two species. However, these key data requirements can be modified.
- For biocides, a new subheading was introduced.
- Note that the biocides regulation prefers the rabbit for the first developmental toxicity study, whereas for new and existing substances, the rat is usually first choice.
- An explanation is given why a 2-generation study is preferable to a one-generation study. (Because the latter has limitation in that post weaning development, maturation, and the reproductive capacity of the offspring are not assessed, and consequently some adverse effects may not be detected).

3.12.3 Evaluation of the available data
Only minor editorial changes were made to this section.

3.12.4 Assessment of the dose-response relationship
No changes

3.12.5 The degree of uncertainty in studies of effects on reproduction
No changes

3.12.6 The testing strategies

- From this section onward unto the end of the guidance on reproductive toxicity, major changes were carried through, first as a consequence of the preferred requirement of the OECD416 study, and second due to the introduction of the developmental neurotoxicity study (OECD426).
- A principle of the new strategy is that results of one study are evaluated before another study is initiated. The strategy seeks to ensure that the data requirements are met in the most efficient and human manner (3.12.6.1).
- The general principles in 3.12.6.2 contain only marginal editorial changes. Route of administration: Oral dosing is generally considered the most practical when conducting a two-generation study. For developmental toxicity studies the oral route using gavage is generally recommended.
- The testing sequence in 3.12.6.3 is new.
- The explanatory sections on new (3.12.6.4) and existing substances (3.12.6.5) and biocides (3.12.6.6) are new.
- Another new section (3.12.6.7) introduces the developmental neurotoxicity study (OECD426), its triggers, its possible outcomes, and possible further action.

3.12.7 Additional considerations

- This chapter is newly added to the guidance.
- It contains new detailed guidance on the role of maternal toxicity in developmental toxicity testing (3.12.7.1), reproductive toxicity via lactation (3.12.7.2), and a short section on endocrine disruption (3.12.7.3).
- The section on additional testing (3.12.7.4) was taken from the earlier version with minor modifications.

4 Risk characterisation

Not yet revised. Workgroup starts in 2002.

Chapter 3: Environmental risk assessment

1 General introduction

1.1 Background

- Active substances and substances of concern in a biocidal product are added as substances that require an environmental risk assessment.
- The risk assessment has been extended to the marine environment. (EUSES)
- Advice for how to conduct a PBT (persistence, bioaccumulation and toxicity) assessment has been added.
- Specifications of sources and references for data requirements for biocidal active substances are given.
- For emission scenario documents (ESDs) for environmental compartments for a number of use categories reference is made to chapter 7 (Part IV).

1.2 General principles of assessing environmental risks

- Three approaches which combine examination of both exposure as effects are distinguished:
  - Quantitative PEC/PNEC estimation;
  - Qualitative environmental risk assessment;
  - PBT-assessment.
- A (new) distinction has been made between inland and marine risk assessment. (EUSES)
- If uncertainties in carrying out the standard risk assessment become unacceptably high, methodologies are implemented in order to identify where exposure from emission sources should be minimised.
- The PBT-assessment has been developed to identify insufficient protection of environmental compartments/ targets.
- A table for the relationship between different targets of the risk characterisation for different marine compartments is inserted.

2 Environmental exposure assessment

2.1 Introduction

- To the stages of the life cycle of a substance, ‘service life’ has been added. (EUSES)
- Unintentional sources have been defined as emissions not covered by the life cycle (for guidance how to deal with these emissions reference is made to Appendix XIII).
- Assessment and testing of relevant metabolites and transformation products is under preparation for plant protection products, which can lead to modification of guidance.

- Formation of substances with a PBT or POP (persistent organic pollutant) profile is of special concern, which should be noted in the risk assessment.

2.1.1 Measured / calculated environmental concentrations

- The specific guidance given here for existing and new chemicals should also be applied in general for biocides.
- A distinction has been made between existing and new substances:
  - Existing substances: generic 'reasonable worst-case' exposure assessment to derive an environmental concentration. Measured data (site-specific or monitoring information) can be used to revise calculated concentrations (presented in a table for each (group of) production site(s)). In case of extrapolation of site-specific information to other sites, it has to be justified in the report;
  - In the case of new substances a generic assessment would normally be conducted. Under some circumstances a site-specific assessment is justified (indicated by the notifier) as it enables one to perform a full evaluation of risks. Any relevant changes that may affect the risk assessment have to be reported in writing by the notifier. The estimated environmental concentrations have to be reasonably applicable for a European-level risk assessment by replacing only some of the default data with site-specific data.

2.1.2 Relationship between PEClocal and PECregional

No changes

2.2 Measured data

No changes

2.2.1 Selection of adequate measured data

- Considerations for handling data under LOQ (limit of quantitation) on a case by case basis are added.
- OECD-quality criteria for use of existing data are added for two quality levels. Most important factors to be addressed are the analytical quality control and the representativeness of the sample.
- Special attention is given to substances enclosed within a matrix (e.g. polymers).
- Two aspects for consideration of representativeness have been added:
  - level of confidence;
  - whether the sampling sites represents a local or regional scenario.
- Guidance on how to handle outliers is added.
- A detailed description has been added for proper selection of the 90^{th} percentile (recommended) and other data for deriving a regional PEC.
- Other representative measured (emission) data have to be compiled as tables, for comparison with calculated PECs.
- A steady state (between production, occurrence and release) is required for use of the measured data for evaluation of the PECs.

2.2.2 Allocation of the measured data to a local or a regional scale

Measured concentrations in biota can be of use for environmental monitoring, especially for deriving a PEC_{biota}.

2.3 Model calculations

2.3.1 Introduction

- Fate of substances in waste incineration, landfills and/or recovery operations has been added. No changes in EUSES (See section 2.3.3.6 and 2.3.3.7).
- A sensitivity analysis has been added, which evaluates how critical the variation of the input parameter(s) is in relation to the result of the assessment (the conclusion). An alternative exposure assessment may be made taking into account the variation of the input parameters. If the analysis shows that the variation of the input parameters is critical in relation to the result of the assessment, further consideration is necessary of ways to improve the certainty of the input parameters.

2.3.2 Data for exposure models

Models for the extrapolation of vapour pressure and water solubility to the environmental temperature have been added. (EUSES)

2.3.3 Release estimation

See chapter 7 of this report for the changes in and additions to the emission scenario documents (i.e. five new environmental emission scenarios for biocides were added). (EUSES)

2.3.3.1 Life cycle of substances

- The schematic representation of the life cycle of a substance has been simplified:
  - Transport and storage have been mentioned, but no guidance is included for estimation of emissions.
  - Processing has been replaced by industrial/ professional use. (EUSES)
  - Disposal has been replaced by service life and waste disposal (including waste treatment and recovery processes). (EUSES)
  - A schematic representation of the waste life stages of a substance is added.

2.3.3.2 Types of emissions and sources

- A diffuse emission from articles during their service life has been added as a source of emission. No change of the release estimation (A-tables).
- Remarks have been added with respect to emissions related to the waste life stage, which may follow the market volume with a (great) delay in time.

2.3.3.3 Release estimation

- General guidelines for emission estimation (10% rule) have been more elaborately explained (See also section 2.3.8.1 and 2.3.8.7). It is mentioned that alternatively it can be decided to use other percentages or specific values as input for the regional model where this reflects a more realistic worst case. Similarly, this information can be used to set the fraction of the main source for the local exposure calculation. (EUSES)
- New remarks:

- A case-by-case assessment using expert judgement remains warranted;
- The few quantitative methods that have been developed for estimation of the emissions during the service life of articles containing the substance may be applied on a case-by-case basis.

2.3.3.4 Intermittent releases
No changes

2.3.3.5 Emissions during service life of long life articles
- Completely new paragraph!
- Long life articles are articles that have a service life longer than one year.
- Guidance on estimation/ calculation of emission of substances characterised by inherent properties such as low water solubility and low vapour pressure for both society and waste remaining in the environment. (EUSES)

2.3.3.6 Emissions from waste disposal
- Completely new paragraph!
- The major share of a substance remains in chemical products or articles at the end of their service life.
- The underlying criterion for considering emissions from the waste stage in the risk assessment of substances, is that the waste stage will contribute significantly to the overall human exposure or environmental concentration in comparison to the emissions from other stages of the life cycle. Considerations to establish whether this is the case are given in this paragraph. (EUSES)

2.3.3.7 Delayed releases from waste disposal and dilution in time
- Completely new paragraph!
- Factors that determine the delay in releases at the waste life stage are given. PECs are usually very low and in particular relevant for metals or organic substances that are persistent and toxic.

2.3.4 Characterisation of the environmental compartments
No changes

2.3.5 Partition coefficients
The remark has been added that for substances that also will be distributed in the environment as particles, the partitioning method may give an incorrect estimation of exposure to the different environmental compartments.

2.3.5.1 Adsorption to aerosol particles
As an alternative for vapour pressure the octanol-air partition coefficient can be used for estimation of the fraction of the substance associated with aerosol particles. (EUSES)

2.3.5.2 Volatilisation
No changes

2.3.5.3 Adsorption/desorption
- The following remarks are new:
  - For ionic substances, a measured adsorption coefficient is needed; (EUSES)

- For water soluble, highly adsorptive substances, the input of Kow to Simple Treat may lead to an overestimation of the aquatic exposure concentration (for proposal: See next bullet); (EUSES)
- In the absence of better adsorption/desorption data, the Zahn-Wellens elimination level can be used as an estimate of the extent of adsorption to sludge, and the 3h value is recommended. (EUSES)

2.3.6 Abiotic and biotic degradation rates

In general, the assessment of degradation processes should be based on data, which reflect the environmental conditions as realistic as possible. In this section some new criteria are given for doing so.

2.3.6.1 Hydrolysis

Rates of hydrolysis determined in standard tests should be recalculated to reflect an average EU outdoor temperature; the equation has been given. (EUSES)

2.3.6.2 Photolysis in water

A remark has been added:

- In practice it is not possible to easily demonstrate significant photodegradation in water.

2.3.6.3 Photochemical reactions in the atmosphere

A remark has been added:

- Degradation in the atmosphere is an important process and it is essential to consider whether it can affect the outcome of environmental concentrations.

2.3.6.4 Biodegradation in a sewage treatment plant

A remark has been added:

- The assessment of biodegradability and/or removal in sewage treatment plants should preferably be based on results from tests simulating the conditions in treatment plants (OECD 303).
- When biodegradation rates have been determined in simulation tests, it should be considered to recalculate the degradation rates obtained to reflect an average EU outdoor temperature (See section 2.3.6.1, equation 25). (EUSES)

2.3.6.5 Biodegradation in surface water, sediment and soil

New remarks:

- The assessment of biodegradation should preferably be based on tests simulating the conditions in the relevant environmental compartments;
- Degradation rates from simulation tests often have to be corrected for (an average EU outdoor) temperature;
- If no test results from simulation tests are available, results from screening tests may be considered;
- Conditions of screening tests are very different from those of simulation tests, which has to be taken into account;
- For interpretation of degradation data reference is made to OECD Guidance Document for classification of chemicals hazardous for the aquatic environment;
- A degradation rate for surface water (or sediment) can be established from a simulation test for soil biodegradation, when there are no data available.

New simulation tests are:

- OECD 307'Aerobic and anaerobic transformation in soil';
- OECD 308 'Aerobic and anaerobic transformation aquatic sediment systems';
- New OECD guideline (2001d) 'Simulation test – Aerobic transformation in surface water'.

2.3.6.6 Overall rate constant for degradation in surface water

The remark is added that some simulation tests might in fact already include the effects of other degradation processes such as hydrolysis.

2.3.7 Elimination processes prior to the release to the environment

2.3.7.1 Wastewater treatment

- An interim figure of 80% for the connection rate (previously 70%) is proposed for the regional standard environment at the time of the revision of the TGDs. This figure is still increasing. (EUSES)
- From the table standard characteristics of a municipal sewage treatment plant the capacity of both the regional as well as the continental STP have been removed. Emissions from the regional and continental STP are calculated based on the release fractions from the local STP. (EUSES)
- The calculation of the STP concentration for evaluation of inhibition to micro-organisms has been extended:
  - The assumption for homogeneous mixing is elucidated, which implies that the dissolved concentration of a substance is equal to the effluent concentration;
  - The PEC derivation in case of intermittent release is handled in more detail, depending on the length of the discharge period. If the interval between two releases is shorter than one month, adaptation of the activated sludge is maintained and the PEC_{stp} can still be considered equal to $Clocal_{eff}$. (EUSES)

2.3.7.2 Waste disposal, including waste treatment and recovery

- Completely new paragraph!
- Guidance on how to identify specific concerns related to the waste life cycle stage of a substance, especially qualitative aspects, are considered:
  - Various types of waste streams are distinguished;
  - Information on use category and product category are essential as well as waste category and waste management/treatment category;
  - A realistic worst case scenario is the preferred approach;
  - Municipal waste incineration destroys organic substances, inorganic substances will be distributed by residues and/ or atmospheric deposition;
  - Waste incinerator residues will cause emissions due to leaching landfills or from recovered residues;
  - Releases from municipal landfills are reduced as much as possible nowadays, uncontrolled emissions are prevented;
  - The main routes of emission from landfills are leaching with water, transport with landfill gas and diffusion to the atmosphere;
  - The fate of a substance going into a landfill is mainly based on modelling (MOCLA);
  - Separation of waste components and recovery is often carried out for articles or chemical products at the end of their service life;

- Certain types of installations can be distinguished based on mechanical, chemical-physical or thermal treatment with each a specific emission, which has to be evaluated on a case-by-case basis.

2.3.8 Calculation of PECs

2.3.8.1 Introduction
Guidance on the estimation of releases during the service life of articles (2.3.3.5) and the waste life stage (2.3.3.6/2.3.7.2) has been added. (EUSES)

2.3.8.2 Calculation of PEClocal for the atmosphere
No changes

2.3.8.3 Calculation of PEClocal for the aquatic compartment
Some remarks are added:
- When a substance is predominantly released to surface water as particles this may lead to an overestimation of the PECsurface water and underestimation of the PECsediment.
- In a mixing zone of surface water higher concentrations of the substance will occur. In case of site-specific assessments the dilution factor applied to the local concentration in surface water should not be greater than 1000. (EUSES)

2.3.8.4 Calculation of PEClocal for sediment
See first remark of 2.3.8.3.

2.3.8.5 Calculation of PEClocal for the soil compartment
No changes

2.3.8.6 Calculation of concentration in groundwater
No changes

2.3.8.7 Calculation of PECregional
- In the proposed model parameters for the regional model an EU average connection percentage to STP has been changed into 80%.(EUSES)
- More recent versions of multimedia models do also contain global scales for different temperature regions. In this case the continents are embedded in the moderate scale leading to a (marginally) more accurate estimation of continental concentrations and more insight in the ultimate persistence of the chemical.

2.4 Summary of PECs derived

No changes

2.5 Decision on the environmental concentration used for risk characterisation

Some new considerations for making the decision what PEC (measured or calculated) to use are given.

3 Effects assessment

3.1 Introduction

Addition of (some) general text on endocrine disrupting effects and importance of paying attention to the mode of action of the chemical in the environmental part of the risk assessment.

3.2 Evaluation of data

3.2.1 Ecotoxicity data

No changes

3.2.1.1 Completeness of data

Addition of legal data requirements ('base set') for biocides.

3.2.1.2 Adequacy of data

No changes

3.2.2 Quantitative Structure-Activity Relationships

No changes

3.3 Effects assessment for the aquatic compartment

3.3.1 Calculation of PNEC

Part of previous section 3.3.1 is transferred to new section 3.3.1.1.

3.3.1.1 Calculation of PNEC using assessment factors

- New section (part of previous section 3.3.1). Mainly editorial changes. Addition of assessment factors to be used when using the statistical extrapolation method (Table 16).
- Guidance on what to do in case the short-term toxicity L(E)C50 is lower than the lowest long-term NOEC (and most sensitive short term tested species long-term tested species). In such case: PNEC = L(E)C50/100. (EUSES)

3.3.1.2 Calculation of PNEC using statistical extrapolation techniques

- New section (modification of previous Appendix V).
- The statistical extrapolation method may be used for the PNEC derivation if a large data set of long-term tests for different taxonomic groups is available. Detailed guidance on the use of this method is given (minimal species requirements, statistics etc.). (EUSES)

3.3.2 Effects assessment for substances with intermittent release

No changes

3.4 Effects assessment for micro-organisms in sewage treatment plants (STP)

- Guidance (new) on the use of results of different types of ready biodegradation tests for derivation of the $PNEC_{micro\text{-}organisms}$. The tested concentration at which toxicity to the inoculum can be ruled out with sufficient reliability may serve this purpose, including the use of an assessment factor (EUSES)
- Guidance (new) on the use of test data for protozoa, ciliates in particular, for deriving the $PNEC_{micro\text{-}organisms}$.
- Guidance (new) on the procedure for refining the $PNEC_{micro\text{-}organisms}$ if PEC/PNEC > 1 for STP. Distinction is made between industrial and domestic sewage sludge.

3.5 Effects assessment for the sediment

3.5.1 Introduction

No changes

3.5.2 Strategy for effects assessment for sediment organisms

- Part of previous section 3.5.2.
- Guidance on sediment testing. Log Kow 3 can be used as trigger for conducting sediment effects assessment
- In order to take uptake via ingestion into account (relevant for substances with log Kow >5) the PEC/PNEC ratio is increased by a factor of 10 rather than 'only' the PEC_{sed} as stated in the 1996 TGDs. Overall effect of this change is the same, only a matter of principle. (EUSES)

3.5.3 Calculation of PNEC using the equilibrium method

- Part of previous section 3.5.2.
- Equation (70) for calculating the $PNEC_{sed}$ on the basis of the equilibrium partitioning theory is changed: K_{susp}-water and RHO_{susp} instead of K_{sed}-water and RHO_{sed}. This is in conformity with the equilibrium partitioning PEC estimation for sediment. (EUSES)

3.5.4 Calculation of PNEC using assessment factors

- New section.
- Guidance on the use of assessment factors for the derivation of $PNEC_{sed}$ on the basis of long-term sediment toxicity tests is added. (EUSES)

3.6 Effects assessment for the terrestrial compartment

3.6.1 Introduction

No changes

3.6.2 Strategy for effects assessment for soil organisms

- Part of previous section 3.6.2.
- Reference is made to the Technical Notes of Directive 98/8 for the testing methodology for biocides.
- Addition of some background information on trophic levels of the terrestrial ecosystem. This information is used to define the representative types of soil tests.

3.6.2.1 Calculation of PNEC using the equilibrium partitioning method

In order to take uptake via ingestion into account (relevant for substances with log Kow >5) the PEC/PNEC ratio is increased by a factor of 10 rather than 'only' the PEC_{soil} in 1996 TGDs. Overall effect of this change is the same, only a matter of principle. (EUSES)

3.6.2.2 Calculation of PNEC using assessment factors

Addition of assessment factors to be used when using the statistical extrapolation method for the PNEC derivation (Table 20).

3.6.2.3 Calculation of PNEC using statistical extrapolation techniques

- New section.
- Guidance on the use of statistical extrapolation techniques when sufficient long-term data for soil are available.

3.7 Effects assessment for the air compartment

3.7.1 Biotic effects

- Extension of previous section 3.7.1.
- Some initial guidance on the use of plant fumigation tests for the derivation of a $PNEC_{plants\text{-}air}$. It is recognised that this is still a rather unexplored field. Case-by-case approach to be followed.

3.7.2 Abiotic effects

No changes

3.8 Assessment of secondary poisoning

3.8.1 Introduction
No changes

3.8.2 Indication of bioaccumulation potential
No changes

3.8.3 Effects assessment for bioaccumulation and secondary poisoning

3.8.3.1 General approach
- Introduction of the biomagnification factor (BMF) which addresses the indirect uptake of a chemical via food.
- Some guidance is added on the effects of genotoxic carcinogens on top-predators. In most cases difficult to link tumour incidence rates for genotoxic carcinogens to effects on populations (exception may be endangered species with long life cycle, like marine mammals).

3.8.3.2 Calculation of BCF from log Kow
No changes

3.8.3.3 Experimentally derived BCF
No changes

3.8.3.4 Calculation of a predicted environmental concentration in food
- Previous section 3.8.3.6.
- New equation for the calculation of $PEC_{oral,\ fish}$ (addition of BMF). (EUSES)
- Default values for the BMF dependent on logKow or BCF. (EUSES)

3.8.3.5 Calculation of the predicted no-effect concentration (PNECoral)
- Merging of previous sections 3.8.3.4 and 3.8.3.5.
- Assessment factors are changed taking into account BW/DFI differences between wildlife and laboratory species. (EUSES)

3.8.3.6 Assessment of secondary poisoning via the aquatic food chain
- Previous section 3.8.3.7
- Some minor suggestions are given for further testing in case of potential risk secondary poisoning route.

3.8.3.7 Assessment of secondary poisoning via the terrestrial food chain
- Previous section 3.8.3.8.
- Major changes in calculation of BCF earthworm (new equations). (EUSES)

4 Environmental risk assessment – marine

4.1 Introduction

- This entire new section was not part of the 1996 version of the Technical Guidance Documents (TGDs).
- While the objectives of a marine environmental risk assessment should be similar to an inland environmental risk assessment, two extra concerns address the main differences between the two environments:
  a. The concern that hazardous substances may accumulate in parts of the marine environment and that:
     (i) the effects of such accumulation are unpredictable in the long-term;
     (ii) that such accumulation would be practically difficult to reverse;
  b. The concern that remote areas of the oceans should remain untouched by hazardous substances resulting from human activity, and that the intrinsic value of pristine environments should be protected.
- Of these additional concerns (a) above may be seen as the main concern. To meet these concerns, which principally relate to substances that are considered as Persistent, Bioaccumulative and Toxic (referred to as PBTs), or have other properties which give rise to a similar level of concern, an assessment approach will be detailed that will give special consideration to this new protection goal. The objective for these substances is the cessation of emissions in order to reduce their levels in the marine environment to the lowest level practically possible. In this context, the assessment of risk fulfils the purpose of determining how the above objective can be achieved; specifically, what are the sources, routes and pathways to the environment. This assessment will facilitate subsequent risk management decisions on the effectiveness of programmes and measures to reduce environmental levels.
- The structure of this section on marine risk assessment basically follows the structure of the inland environmental assessment. It starts with a section on exposure assessment where specific issues are highlighted relating to marine partitioning processes and marine degradation and where a description is given on how the predicted environmental concentration (PEC) for the local and regional situation should be derived. In the next section on marine effect assessment the specific procedures for the derivation of predicted no-effect concentrations (PNECs) for the aquatic compartment and for sediment are described. This section also deals with the assessment of possible effects through secondary poisoning via the food chain in the marine environment. The section ends with the PBT assessment that describes criteria for identification of persistent, bioaccumulative and toxic substances and includes testing strategies to obtain the necessary data for this identification. For the risk characterisation the reader is referred to section 3.5 of the revised TGDs.

4.2 Marine exposure assessment

4.2.1 Measured data

For this new section, reference is made to section 3.2.2 of the TGDs for the inland environment.

4.2.2 Partition coefficients

- This new section refers to section 3.2.3.5 of the TGDs for specific information on the derivation of the partitioning processes between air-aerosol, air-water, and solids-water in the various compartments. This section only highlights some specific issues related to the marine environmental conditions, i.e.
  - to consider the extent to which partition coefficients may differ between seawater and freshwater;
  - if no measured seawater data of equal reliability are available, freshwater data can be used for non-ionisable organic compounds without adjustment for the marine environment;
  - the procedure to correct partition coefficients for ionisable substances, as described in Appendix XI of the TGDs**,** may however be considered sufficiently reliable for marine conditions;
  - for inorganic chemicals such as metals, on a case-by-case basis, there may be sufficient information available to allow the relevant partition coefficient in seawater to be calculated from the freshwater data; otherwise, measurements under marine conditions may be necessary.

4.2.3 Marine degradation

4.2.3.1 Abiotic degradation

This new section tells that abiotic degradation (i.e. hydrolysis and photolysis) in marine environments should be assessed in a similar manner to abiotic degradation in freshwater environments except that the different physico-chemical conditions in marine environments should be taken into account.

4.2.3.2 Biotic degradation

- In this new section it is stated that the rate of biodegradation varies significantly between various marine environments.
- It tells that it is probable that biodegradation of xenobiotics occurs with the following relative rates: rate in estuaries = rate in coastal areas > rate in more distant marine environments.
- The assessment of the biodegradation in marine sediments should ideally be based on results from investigations simulating these conditions. If not available, other approaches may be used, e.g.:
  - An approach similar to the one used for freshwater sediments could be used.
  - Anaerobic screening tests may be performed using a sediment inoculum. Degradation rates must be derived by expert judgement.
  - If no degradation data from studies with sediment or soil are available, the use of data on degradation in water could be considered. The possibly very low bioavailability in the sediment of highly hydrophobic and/or poorly water-soluble substances should be taken into consideration as is done also for freshwater sediments.

4.2.3.3 Marine biodegradation simulation tests

This new section describes general conditions to carry out marine biodegradation simulation tests, the required expert judgement to evaluate the results, and refers to a number of standardised simulation test methods for various marine compartments.

4.2.3.4 Use of biodegradation screening test data

This new section describes the use of marine and freshwater biodegradation screening tests that can be used when marine biodegradation simulation test results are not available. The section also provides a table that converts screening test data into mineralisation half-lives (in days) for freshwater, estuaries and other marine environments. (EUSES)

4.2.4 Local Assessment

4.2.4.1 Introduction

This new section describes that aquatic concentrations are highest at the point of emission and that existing methodology is to be used to adequately assess risks. It further provides examples on various types of point sources for various marine local sites.

4.2.4.2 Calculation of PEClocal for the aquatic compartment

- This new section tells that for the marine environmental risk assessment calculating the local concentration in seawater must always be performed, whereas it was on a case-by-case basis in the 1996 TGDs. For a default assessment it is assumed that in a local setting, industrial effluents are not treated in a municipal biological STP, unless there is specific information available. Local dilution is assumed greater than in a river, i.e. an initial default value of 10 is assumed, which is increased taking into account tidal influences. Hence, a dilution factor for discharges to a coastal zone of 100 is assumed tentatively. (EUSES)
- The section provides new equations for calculating:
  - the local concentration in seawater, $Clocal_{seawater}$; (EUSES)
  - the annual average concentration in surface water (for later calculations for indirect exposure and secondary poisoning), $Clocal_{seawater,ann}$; (EUSES)
  - the local PEC that includes the regional background concentration, $PEClocal_{seawater}$; (EUSES)
  - the annual average local PEC that includes the regional background concentration, $PEClocal_{seawater,ann}$. (EUSES)
- Furthermore the section provides some guidance how to improve the exposure assessment.

4.2.4.3 Calculation of PEClocal for the sediment compartment.

This new section provides information how to calculate the PEClocal for the marine sediment compartment, from the $PEClocal_{seawater}$ and the properties of the suspended matter. The section provides the equation for $PEClocal_{sed.}$ (EUSES)

4.2.5 Regional assessment

This new section provides information how calculating the environmental concentrations on a regional scale, $PEC_{regional}$, of substances emitted from point and diffuse sources over a wide area. The region is defined as a coastal sea area for which a new 'coastal sea scenario' has been introduced. This scenario has been computerised by Van de Meent and colleagues in the summer of 2002 and needs to be implemented in a new version of SimpleBox. (EUSES)

4.3 Marine effects assessment

4.3.1 Effects assessment for the aquatic compartment

4.3.1.1 Introduction

This new section explains that conventionally freshwaters were the main protection goals, while now marine waters are protection goals as well. It is important using effects data from marine species, but since they will probably be scarce, it is agreed to use effects data from estuarine / marine species *in lieu* of freshwater species.

4.3.1.2 Evaluation of data

This new section explains that there are probably good reasons using freshwater and marine water data interchangeably.

4.3.1.3 Derivation of PNEC

This new section provides the arguments why a greater assessment factor is needed for the derivation of a PNEC for the marine environment than compared to similar sized databases on effects data for the freshwater environment. In addition, the section provides a table containing assessment factors and guidance on deriving the $PNEC_{water}$ for saltwater, based on the available data on effects, comprising of tests on both freshwater and marine water species. (EUSES)

4.3.2 Effects assessment for the sediment compartment

4.3.2.1 Introduction

This new section explains that it is especially highly hydrophobic substances, which may need to be assessed of risks for the benthic species. In addition, in particularly for marine sediments, effects assessment should be based on chronic toxicity tests. It is important using effects data from marine benthic species, but since they will probably be scarce, it is accepted to use effects data from estuarine / marine species *in lieu* of freshwater species.

4.3.2.2 Strategy for effects assessment for sediment organisms

This new section shows the strategy for which substances effects assessment is most likely needed to avoid unnecessary testing, as well the use of alternative methods to derive the $PNEC_{marine\_sediment}$, and the various ways how mixed information on effects from freshwater sediment, marine water sediment and equilibrium partitioning should be dealt with. For example, the section tells that for hydrophobic substances, the PEC/PNEC ratio is to be increased by a factor of 10 to include sediment ingestion.

4.3.2.3 Calculations of PNEC for marine sediment using the equilibrium method

This new section provides the equation to derive the $PNEC_{marine\_sediment}$ from information on the $PNEC_{saltwater}$ using the equilibrium partitioning method. (EUSES)

4.3.2.4 Calculation of PNEC for marine sediment using assessment factors154

This new section provides tables containing assessment factors and guidance on deriving the $PNEC_{marine\_sediment}$. One table provides assessment factors for derivation of the $PNEC_{marine\_sediment}$ from short-term toxicity tests, the other table from long-term sediment

toxicity test. Furthermore, the section provides a table with examples of sub-chronic and chronic toxicity tests with whole sediment. (EUSES)

4.3.3 Assessment of secondary poisoning

4.3.3.1 Introduction

This new section explains that, while the assessment of risks for marine and freshwater top predators is similar, the marine food chain may be longer and more complex. It is proposed to use a $PEC_{saltwater}$ that is based on the mean of the local and the regional concentrations for the assessment of the local situation, and for the regional situation to apply a spatially broader scale. (EUSES)

4.3.3.2 Assessment of bioaccumulation and secondary poisoning

This new section provides an assessment scheme, the calculation of the PEC in the food of predators, including the required equation, as well as a table to provide default biomagnification factors for organic substances with different log Kow or BCF values for fish. Two spatially different PECs are calculated, one for the local and regional scale for the first tier of predators, the other for the larger scale regional marine environment for the second tier of top-predators. Finally, the section provides guidance on how to deal with deriving $PNEC_{oral}$ values, which is similar to other media, as explained in section 3.3.8.3.5 of the revised TGDs. (EUSES)

4.3.3.3 Testing strategy

This new section provides guidance on how to further refine the PEC/PNEC-ratio when it indicates a risk at any trophic level.

4.4 PBT-assessment

4.4.1 Introduction

This new section explains what the PBT-assessment is all about, i.e. it seeks to protect (marine) ecosystems where the risks are more difficult to estimate. The PBT-assessment consists of two steps: (a) identification of PBT-substances, and (b) an evaluation of sources, major emissions, and pathways to the marine environment to sufficiently establish the most appropriate and effective measures to reduce the releases to the marine environment.

4.4.2 PBT-criteria

This new section provides a table with the criteria to be used to decide if a substance must be regarded as a PBT-substance. The testing strategies to obtain the data that are necessary to decide whether a substance fulfils these criteria are given in the next sections. It must be noted that when a substance is identified as vPvB, information on toxicity is not really required. (EUSES)

4.4.3 Testing strategy for the P-criterion

4.4.3.1 Introduction

This new section describes the various types of information that can be used to estimate persistence in the marine environment as outlined in the next three sections.

4.4.3.2 Experimental data on persistence in the marine environment
This new section describes which test is most suitable for estimating persistence in the marine environment, i.e. the simulation test systems, and refers to section 3.4.2.3.3 of the revised TGDs for recommended simulation test methods for water and sediment. It further provides guidance for sampling inocula for the simulation tests.

4.4.3.3 Other experimental data
In this new section guidance is given which experimental test results can be used when no simulation test results are available. It also indicates how these experimental test results to be evaluated for the persistence assessment.

4.4.3.4 Data from biodegradation estimation models
In this new section guidance is given which models can be used when no simulation or experimental test results are available. It also indicates how these model results to be evaluated for the persistence assessment.

4.4.3.5 Summary of the P-assessment
This new section provides an overview table for persistence assignment based on the various types of information on degradation. Similar summaries of the T and B-assessment have not been specified. (EUSES)

4.4.4 Testing strategy for the B-criterion

4.4.4.1 Introduction
This new section describes the various types of information that can be used to estimate bioaccumulation in the marine environment as outlined in the next three sections. For bioconcentration, reference is made to section 3.3.8.2 of the revised TGDs.

4.4.4.2 Assessment of measured BCF data
This new section describes how bioconcentration (BCF) data to be interpreted for fulfilling the B-criterion, and refers to other guidance for the quality assessment of bioconcentration data.

4.4.4.3 Assessment of the potential for bioaccumulation
This new section describes how other data can be used to estimate bioaccumulation, such as model estimates and log Kow. Reference is made to section 3.3.8.3.2 for model estimates for BCF and Chapter 4 of the revised TGDs for log Kow.

4.4.4.4 Other information relevant for assessment of the B-criterion
This new section describes that other types of information than pointed out in sections 3.444.3 and 3.4.4.4.4 may be used to estimate bioaccumulation, e.g. specific laboratory or field tests. Special caution is provided not to simply use monitoring data.

4.4.5 Testing strategy for the T-criterion

4.4.5.1 Introduction
This new section describes the various types of information that can be used to estimate toxicity for the marine environment as outlined in the next three sections. It explains that

while chronic or long-term ecotoxicity data are preferred, these data are not always available and acute ecotoxicity data can be used. In addition, it also explains that mammalian toxicity data need to be evaluated as well.

4.4.5.2 Chronic effects data

This new section explains how long-term effects data to be evaluated for fulfilling the T-criterion.

4.4.5.3 Acute effects data (screening level)

This new section explains how acute effects data to be evaluated for fulfilling the T-criterion in absence of chronic effects data.

4.4.5.4 Estimated effects data

This new section describes how dealing with a lack of experimental toxicity data, i.e. when no acute or chronic toxicity data are available. The section refers to Chapter 4 of the revised TGDs for guidance on the use of QSARs.

5 Risk characterisation

5.1 Introduction

- Previous section 4.1.
- Addition of overview of PEC/PNEC ratios for marine risk assessment.
- The TGDs now make a clear distinction between a quantitative and a qualitative risk characterisation.

5.2 General premises for risk characterisation

No changes

5.3 Risk characterisation for existing substances

No changes

5.4 Risk characterisation for new substances

No changes

5.5 Risk Characterisation for biocides

New section on risk characterisation for biocides.

5.6 Qualitative risk characterisation

- Previous section 4.5.
- Qualitative risk characterisation, i.e. PBT assessment, may be relevant for remote marine area where quantitative risk characterisation cannot be carried out.

6 Testing strategies

6.1 Introduction

- New section.
- Reference is made to the testing strategy for PBT/vPvB chemicals.

6.2 Refinement of PEC

- Previous section 5.1.
- Some text on/references to the testing strategy for biocides.

6.2.1 Aquatic compartment

- Previous section 5.1.1.
- Reference is made to the use of simulation tests (rather than inherent biodegradation testing as suggested in 1996 TGDs) when PEC/PNEC > 1 and the substance is not ready biodegradable.
- Reference is made to available testing strategy on biodegradation for biocides.

6.2.2 Soil compartment

- Previous section 5.1.2.
- Reference is made to soil biodegradation simulation test OECD TG 307.

6.2.3 Air compartment

No changes

6.3 Refinement of PNEC: strategy for further testing

6.3.1 Introduction

No changes

6.3.2 Aquatic compartment

No changes

6.3.2.1 Introduction
No changes

6.3.2.2 Available long-term tests
- Previous section 5.2.2.2.
- Long-term fish testing

For both the embryo/sac-fry test and juvenile growth test reference is made now to 'official' OECD guidelines. In the 1996 TGDs these tests were still 'under construction'.
- Long-term Daphnia testing

14-Day Daphnia reproduction test is deleted.
- Algal testing

Text on algae toxicity testing has been revised. EbC50 (biomass growth) should not be used in effect assessment. If only EbC50 is available and primary data are available a re-analysis should be carried out to determine the ErC50 (growth rate). If primary data are lacking, it should be considered to perform a new algae study. Further guidance is given on the ErC50 or NOEC or ErC10 calculation if test shows technical shortcomings.

6.3.2.3 Decision table for further testing
No changes

6.3.3 Sediment compartment
- Completely new section.
- Detailed guidance on testing strategy for sediment. To be followed if no long-term test with sediment organisms is available and the PEC/PNEC ratio is established via the equilibrium partitioning method or from short-term tests shows concern for the sediment compartment.

6.3.4 Soil compartment
- Previous section 5.2.3.
- Detailed overview of the various standardised types of assays for microbes, invertebrates and plants to be possibly used in strategy for further soil testing.

Chapter 4: Use of (quantitative) structure activity relationships ((Q)SARs)

Not part of the TGDs-revision process.

Chapter 5: Use categories

Not part of the TGDs-revision process.

Chapter 6: Risk assessment report format

Not part of the TGDs-revision process.

Chapter 7: Emission scenario documents

- Five new EU environmental emission scenarios for biocides (Biocidal Product Types) are included. (EUSES)
- One new ESD is added for IC-15, rubber industry. (EUSES)
- The document refers to the OECD review process for future adaptations of existing ESDs.

IC-3 Chemical industry: Chemicals used in synthesis. (EUSES)
Assessment of the environmental release of intermediates
ESD extended with river flow data on rivers receiving wastewater form the chemicals industry in France and Germany (replaces data in former Annex 3 and 4).

IC-5 Personal/Domestic and IC-6 Public domain.
Assessment of the environmental release of soaps, fabric washing, dish cleaning and surface cleaning substances.
No changes

IC-7 Leather processing industry.
BPT-9: Biocides used as preservatives. (EUSES)
Assessment of the environmental release of chemicals from the leather processing industry.
Document extended with:
- elaborated description of the main processes;
- quantities used and release estimations at each stage of chemicals and biocides;
- branch-specific parameters;
- guidance and examples for emission calculation of industrial chemicals and biocides.

IC-8 Metal extraction industry, refining and processing industry. (EUSES)
Assessment of environmental release of chemicals used in metal cutting and -forming fluids.
Document has been completely rewritten and elaborated.

IC-10 Photographic industry. (EUSES)
Assessment of the environmental release of photochemicals.
Document has been completely rewritten and elaborated.

IC-12 Pulp, paper and board industry.
Assessment of the environmental release of chemicals used in the pulp, paper and board industry.
No changes

IC-13 Textile processing industry.
BPT-9 Biocides used as preservatives. (EUSES)
Assessment of environmental release of chemicals from the textile finishing industry.
Document has been completely rewritten and elaborated.

IC- 14 Paints, lacquers and varnished industry.
Assessment of environmental release of chemicals from the paints, lacquers and varnished industry.
No changes

IC-15 Others: Rubber industry. (EUSES)
Assessment of environmental release of chemicals in the rubber industry.
Completely new ESD.

BPT-6,7&9 Biocides used as preservatives in paper coating and finishing. (EUSES)
Assessment of the environmental release of biocides used in paper coating and finishing.
Completely new BPT.

BPT 22 Embalming and taxidermist fluids. (EUSES)
Assessment of environmental release of biocides in taxidermy and embalming processes.
Completely new BPT.

BPT 2 Private and public health area disinfectants and other biocidal products. (EUSES)
Assessment of environmental release of private and public health area disinfectants used for sanitary purposes and disinfectants for use in the medical sector.
Completely new BPT.

References

EC (1996). Technical Guidance Documents in support of the Commission Directive 93/67/EEC on risk assessment for new notified substances and the Commission Regulation (EC) 1488/94 on risk assessment for existing substances.

EC (2002). Technical Guidance Document on risk assessment in support of Commission Directive 93/67/EEC on risk assessment for new notified substances and Commission Regulation (EC) No 1488/94 on risk assessment for existing substances and Directive 98/8/EC of the European parliament and of the council concerning the placing of biocidal products on the market. Draft version, May 2002.

Appendix 1 Mailing list

1	Ministerie van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer Directie SAS, Mr. A.B. Holtkamp
2	Ministerie van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer Directeur-generaal Milieubeheer, Ir. J. van der Vlist
3	Dr. H. Roelfzema, VWS/GZB
4	Drs. A.A. Vijlbrief, SZW/A&O
5-34	Björn Hanssen, European Chemicals Bureau (ECB), Ispra (It)
35	Dr. F. M. Carpanini, ECETOC, Brussel, België
36-40	Monique Rennen, TNO-voeding, Zeist
41-43	P.F. Tanis, TSA Group Delft BV, Delft
44	Depot Nederlandse Publikaties en Nederlandse Bibliografie
45	Dr. ir. G. de Mik
46	Dr. W.H. Könemann
47	Dr. ir. M.N. Pieters
48	Drs. J.H. Canton
49	Dr. R. B. Beems
50	Dr. A. Opperhuizen
51	Dr. J. Struijs
52	Drs. D. de Zwart
53-62	Exemplaren voor CSR
63-72	Exemplaren voor SIR
73-84	Auteurs
85	SBC/Communicatie
86	Bureau Rapportenregistratie
87	Bibliotheek RIVM
88-97	Bureau Rapportenbeheer
98-107	Reserve exemplaren