ISSN 0378-6978

# Official Journal

## of the European Communities

L 225

**Volume 44**

**21 August 2001**

English edition

# Legislation

Contents



**Price: EUR 59,50**

([1]) Text with EEA relevance.

I

*(Acts whose publication is obligatory)*

# COMMISSION DIRECTIVE 2001/59/EC

## of 6 August 2001

## adapting to technical progress for the 28th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances

**(Text with EEA relevance)**

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Directive 67/548/EEC of 27 June 1967 on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances ([1]), as last amended by Commission Directive 2000/33/EC ([2]), and in particular Article 28 thereof,

Whereas:

(1) Annex I to Directive 67/548/EEC contains a list of dangerous substances, together with particulars of the classification and labelling of each substance. Present scientific and technical knowledge has shown that the list of dangerous substances in that Annex should be adapted to technical progress. Specifically, Tables A and B in the Foreword to Annex I require inclusion of the Finnish and Swedish nomenclature. Certain language versions of the Directive require technical corrections in specific sections of the Foreword to Annex I. It is useful to publish an updated and recast version of the Foreword to Annex I. Furthermore, the list itself should be updated to include notified new substances and further existing substances; the identity, nomenclature, classification, labelling and/or concentration limits for certain substances should be amended to reflect increased technical knowledge; the entries for three substances should be deleted from the list, since they are covered by other entries.

(2) Annex II to Directive 67/548/EEC contains a list of symbols and indications of danger for dangerous substances and preparations. Annex III to Directive 67/548/EEC contains a list of phrases indicating the nature of special risks attributed to dangerous substances and preparations. Annex IV to Directive 67/548/EEC contains a list of the phrases indicating the safety advice concerning dangerous substances and preparations. Annexes II, III and IV require inclusion of the Finnish and Swedish wordings. Certain language versions of the Directive require technical corrections in specific sections of Annexes II, III and IV. It is useful to publish updated and recast versions of Annexes II, III and IV.

(3) Article 1 of European Parliament and Council Directive 1999/33/EC ([3]) permitted Sweden from 1 January 1999 until 31 December 2000 to require the use of the additional R-phrase R340, not listed in Annex III, for substances classified as carcinogenic, category 3, instead of R-phrase R40. Member State experts have agreed to revise the text of R-phrase R40 to refer to carcinogenic, category 3 substances. A new R-phrase R-68 should be added to Annex III, containing the original text of R-phrase R40 for classification and labelling of mutagenic category 3 and harmful substances listed in Annex I. The classification and labelling and concentration limit references in Annex I that include R40 should therefore be revised for such mutagenic category 3 and harmful substances.

(4) Annex V to Directive 67/548/EEC lays down the methods for the determination of the physicochemical properties, toxicity and ecotoxicity of substances and preparations. It is necessary to adapt that Annex to technical progress. It is appropriate to reduce to a minimum the number of animals used for experimental purposes, in accordance with Council Directive 86/609/EEC ([4]). Chapter B.1 should therefore be deleted, since alternative methods, using fewer animals, are available. Due regard should be given to methods recognised and recommended by competent international organisations. The methods for subchronic oral toxicity in Chapters B.26 and B.27 should be revised accordingly and Chapters C.14 to C.20, on

([1]) OJ 196, 16.8.1967, p. 1.
([2]) OJ L 136, 8.6.2000, p. 90.
([3]) OJ L 199, 30.7.1999, p. 57.
([4]) OJ L 358, 18.12.1986, p. 1.

environmental toxicity should be added to Annex V. Certain language versions require technical corrections to specific sections of Annex V.

(5) Annex VI to Directive 67/548/EEC contains a guide to the classification and labelling of dangerous substances and preparations. It is necessary to adapt that Annex to technical progress. Certain language versions of the Directive require technical corrections in specific sections of Annex VI. Specific sections require publication in Finnish and Swedish. It is useful to publish an updated and recast version of Annex VI, particularly including reference to Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations ([1]).

(6) In accordance with the provisions of Directive 67/548/EEC, any new substance placed on the market should be notified to the competent authorities of the Member States by means of a notification containing certain information including a technical dossier. For new substances supplied and then consumed in a chemical reaction which are strictly controlled (intermediates with limited exposure), it is technically justifiable and appropriate to define a reduced test package (RTP). Current technical progress can guarantee minimum exposure for man and the environment through rigorous containment of the process.

(7) The technical dossier should contain a test package for intermediates with limited exposure which would supply the information necessary to evaluate their foreseeable risk for man and the environment. Annex VII should specify the content of this technical dossier and Annex VIII should detail additional tests and studies that may be required for intermediates with limited exposure marketed in higher volumes.

(8) The criteria for the notification of intermediates with limited exposure may need to be revised in the light of technical progress and experience gained with such notifications made in accordance with the new specific requirements laid down in this Directive.

(9) The measures provided for in this Directive are in accordance with the opinion of the Committee on the Adaptation to Technical Progress of the Directives for the Elimination of Technical Barriers to Trade in Dangerous Substances and Preparations,

HAS ADOPTED THIS DIRECTIVE:

*Article 1*

Directive 67/548/EEC is hereby amended as follows:

1. Annex I is amended as follows:

   (a) Tables A and B in the foreword to Annex I shall include the Finnish and Swedish nomenclature. Certain language versions of the Directive shall include technical corrections in specific sections of the Foreword and Tables A and B. The Foreword including Tables A and B is replaced by Annex 1A to this Directive.

   (b) The corresponding entries are replaced by the entries in Annex 1B to this Directive.

   (c) The entries in Annex 1C to this Directive are inserted.

   (d) The entries in Annex 1D to this Directive are deleted.

   (e) The entries shown in Annex 1E to this Directive are amended by replacing classification references to 'Muta. Cat. 3; R40' by 'Muta. Cat. 3; R68' and by replacing labelling references to R40 by R68.

   (f) The entries shown in Annex 1F to this Directive are amended by replacing classification references to 'Xn; R40' by 'Xn; R68' and by replacing labelling references to R40 by R68.

   (g) The entry shown in Annex 1G to this Directive is amended by replacing concentration limit references to 'Xn; R40/20/21/22' by 'Xn; R68/20/21/22'.

   (h) The entry shown in Annex 1H to this Directive is amended by replacing concentration limit references to 'Xn; R20/21/22-40/20/21/22' by 'Xn; R20/21/22-68/20/21/22'.

   (i) The entries shown in Annex 1I to this Directive are amended by replacing classification references to 'Muta. Cat. 3; R40' by 'Muta. Cat. 3; R68'.

   (j) The entries shown in Annex 1J to this Directive are amended by replacing classification references to 'Muta. Cat. 3; R40' by 'Muta. Cat. 3; R68' and by adding R68 to the label.

2. Annex II shall include the Swedish and Finnish versions and technical corrections to certain language versions. Annex II is therefore replaced by Annex 2 to this Directive.

3. Annex III shall include the Swedish and Finnish versions and technical corrections to certain language versions. Annex III is therefore replaced by Annex 3 to this Directive.

4. Annex IV shall include the Swedish and Finnish versions and technical corrections to certain language versions. Annex IV is therefore replaced by Annex 4 to this Directive.

([1]) OJ L 200, 30.7.1999, p. 1.

5. Annex V is amended as follows:

(a) Chapter B.1 is deleted.

(b) The title of the English version of Chapter B13/14 is replaced by the text in Annex 5A.

(c) The last sentence of the French version of paragraph 1.4.2.2 of Chapter B.39 is replaced by the text in Annex 5B.

(d) The equation in the last sentence of section 1.7.1.6 of the English version of Chapter B.41 is replaced by the text in Annex 5C.

(e) The test method for subchronic oral toxicity tests in rodents is amended in accordance with Annex 5D to this Directive, which replaces Chapter B.26.

(f) The test method for subchronic oral toxicity tests in non-rodents is amended in accordance with Annex 5E to this Directive, which replaces Chapter B.27.

(g) The seven new test methods for environmental toxicity in Annex 5F to this Directive are included in Part C.

6. Annex VI shall include the Swedish and Finnish versions, technical corrections to certain language versions and further detailed technical updates. Annex VI is therefore replaced by Annex 6 to this Directive.

7. Annex VII.A shall include a technical dossier containing a test package for intermediates with limited exposure, supplying the information necessary to evaluate their foreseeable risk for man and the environment. Annex VII.A is therefore amended as follows:

(a) the text in Annex 7A to this Directive is inserted before section 0 of Annex VII.A;

(b) the text in Annex 7B to this Directive is inserted at the end of Annex VII.A.

8. Annex VIII shall include additional tests and studies that may be required for intermediates with limited exposure marketed in higher volumes. Annex VIII is therefore amended as follows:

(a) the text in Annex 8A to this Directive is inserted between 'Level 1' and 'Physicochemical studies' of Annex VIII;

(b) the text in Annex 8B to this Directive is inserted between 'Level 2' and 'Toxicological studies' of Annex VIII.

*Article 2*

1. Member States shall adopt and publish before 30 July 2002 the laws, regulations and administrative provisions necessary to comply with this Directive. They shall forthwith inform the Commission thereof.

2. Member States shall apply the laws, regulations and administrative provisions referred to in paragraph 1:

(a) as from 30 July 2002 or an earlier date for dangerous substances;

(b) as from 30 July 2002 for preparations not within the scope of Council Directive 91/414/EEC [1] or European Parliament and Council Directive 98/8/EC [2];

(c) as from 30 July 2004 for preparations within the scope of Directive 91/414/EEC or Directive 98/8/EC.

They shall forthwith inform the Commission thereof.

When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

3. Member States shall communicate to the Commission the main provisions of national law which they adopt in the field covered by this Directive and a correlation table between this Directive and the national provisions adopted.

*Article 3*

This Directive shall enter into force on the third day following its publication in the *Official Journal of the European Communities*.

*Article 4*

This Directive is addressed to the Member States.

Done at Brussels, 6 August 2001.

*For the Commission*

Margot WALLSTRÖM

*Member of the Commission*

[1] OJ L 230, 19.8.1991, p. 1.
[2] OJ L 123, 24.4.1998, p. 1.

*ANNEX 1A*

## FOREWORD TO ANNEX I

### Introduction

Annex I is an index of dangerous substances for which harmonised classification and labelling have been agreed at Community level in accordance with the procedure laid down in Article 4(3) of this Directive.

### Numbering of entries

Entries in Annex I are listed according to the atomic number of the element most characteristic of the substance's properties. A list of the chemical elements, arranged according to atomic number is shown in Table A. Organic substances, because of their variety, have been placed in the usual classes, as shown in Table B.

The index number for each substance is in the form of a digit sequence of the type ABC-RST-VW-Y, where:

— ABC is either the atomic number of the most characteristic chemical element (preceded by one or two zeros to make up the sequence) or the usual class number for organic substances,

— RST is the consecutive number of the substance in the series ABC,

— VW denotes the form in which the substance is produced or placed on the market,

— Y is the check-digit calculated in accordance with the ISBN (International Standard Book Number) method.

As an example, the index number for sodium chlorate is 017-005-00-9.

For dangerous substances in the European Inventory of Existing Commercial Chemical Substance (Einecs) (OJ C 146A, 15.6.1990), the Einecs number is included. This number is a seven-digit system of the type XXX-XXX-X which starts at 200-001-8.

For dangerous substances notified under the provisions of this Directive, the number of the substance in the European List of Notified Substance (Elincs) is included. This number is a seven-digit system of the type XXX-XXX-X which starts at 400-010-9.

For dangerous substances in the list of 'No-longer polymers' (Document, Office for Official Publications of the European Communities, 1997. ISBN 92-827-8995-0) the 'No-longer polymer' number is included. This number is a seven-digit system of the type XXX-XXX-X which starts at 500-001-0.

The Chemical Abstracts Service (CAS) number is also included to assist identification of the entry. It should be noted that the Einecs number includes both anhydrous and hydrated forms of a substance, and there are frequently different CAS numbers for anhydrous and hydrated forms. The CAS number included is for the anhydrous form only, and therefore the CAS number shown does not always describe the entry as accurately as the Einecs number.

Einecs, Elincs, 'No-longer polymer' or CAS numbers are not usually included for entries which comprise more than four individual substances.

### Nomenclature

Wherever possible, dangerous substances are designated by their Einecs, Elincs or 'No-longer polymer' names. Other substances not listed in Einecs, Elincs or the list of 'No-longer polymers' are designated using an internationally recognised chemical name (e.g. ISO, IUPAC). An additional common name is included in some cases.

Impurities, additives and minor components are normally not mentioned unless they contribute significantly to the classification of the substance.

Some substances are described as a mixture of A and B. These entries refer to one specific mixture. In some cases where it is necessary to characterise the substance put on the market, the proportions of the main substances in the mixture are specified.

Some substances are described with a specific percentage purity. Substances containing a higher content of active material (e.g. an organic peroxide) are not included in the Annex I entry and may have other hazardous properties (e.g. explosive). Where specific concentration limits are shown, these apply to the substance or substances shown in the entry. In particular, in the case of entries which are mixtures of substances or substances described with a specific percentage purity, the limits apply to the substance as described in Annex I and not the pure substance.

Article 23(2)(a) requires that for substances appearing in Annex I, the name of the substance to be used on the label should be one of the designations given in the Annex. For certain substances, additional information has been added in square brackets in order to help identify the substance. This additional information need not be included on the label.

Certain entries contain a reference to impurities. An example is index No 607-190-00-X: methyl acrylamidomethoxyacetate (containing ≥ 0,1 % acrylamide). In these cases the reference in brackets forms part of the name, and must be included on the label.

Certain entries refer to groups of substances. An example is index No 006-007-00-5: 'hydrogen cyanide (salts of …) with exception of complex cyanides such as ferrocyanides, ferricyanides and mercuric oxycyanide'. For individual substances covered by these entries, the Einecs name or another internationally recognised name must be used.

**Format of entries**

The following information is given for each substance in Annex I:

(a) *the classification:*

(i) the process of classification consists of placing a substance in one or more categories of danger (as defined in Article 2(2) of Council Directive 92/32/EEC (OJ L 154, 5.6.1992, p. 1)) and assigning the qualifying risk phrase or phrases. The classification has consequences not only for labelling but also for other legislation and regulatory measures on dangerous substances;

(ii) the classification for each category of danger is normally presented in the form of an abbreviation representing the category of danger together with the appropriate risk phrase or phrases. However, in some cases (i.e. substances classified as flammable, sensitising and some substances classified as dangerous for the environment) the risk phrase alone is used;

(iii) the abbreviation for each of the categories of danger is shown below:

— explosive: E

— oxidising: O

— extremely Flammable: F+

— highly Flammable: F

— flammable: R10

— very toxic: T+

— toxic: T

— harmful: Xn

— corrosive: C

— irritant: Xi

— sensitising: R42 and/or R43

— carcinogenic: Carc. Cat. ([1])

— mutagenic: Muta. Cat. ([1])

— toxic for reproduction: Repr. Cat. ([1])

— dangerous for the environment: N or/and R52, R53, R59;

(iv) additional risk phrases which have been assigned to describe other properties (see sections 2.2.6 and 3.2.8 of the labelling guide) are shown although they are not formally part of the classification;

([1]) The category of carcinogen, mutagen or toxic for reproduction (i.e. 1, 2 or 3) is shown as appropriate.

(b) *the label*, including:

(i) the letter assigned to the substance in accordance with Annex II (see Article 23(2)(c)). This acts as an abbreviation for the symbol and for the indication of danger (if these are assigned);

(ii) the risk phrases, denoted as a series of numbers preceded by the letter R indicating the nature of the special risks, in accordance with Annex III (see Article 23(2)(d)). The numbers are separated by either:

— a dash (-) to denote separate statements concerning special risks (R), or

— an oblique stroke (/) to denote a combined statement, in a single sentence, of the special risks as set out in Annex III;

(iii) the safety phrases denoted as a series of numbers preceded by the letter S indicating the recommended safety precautions, in accordance with Annex IV (see Article 23(2)(e)). Again the numbers are separated by either a dash or an oblique stroke; the significance of recommended safety precautions are set out in Annex IV. The safety phrases shown apply only to substances; for preparations, phrases are selected according to the usual rules.

Note that for certain dangerous substances and preparations sold to the general public certain S-phrases are mandatory.

S1, S2 and S45 are obligatory for all very toxic, toxic and corrosive substances and preparations sold to the general public.

S2 and S46 are obligatory for all other dangerous substances and preparations sold to the general public other than those that have only been classified as dangerous for the environment.

Safety phrases S1 and S2 are shown in brackets in Annex I and can only be omitted from the label when the substance or preparation is sold for industrial use only;

(c) *the concentration limits* and associated classifications necessary to classify dangerous preparations containing the substance in accordance with Directive 1999/45/EC.

Unless otherwise shown, the concentration limits are a percentage by weight of the substance calculated with reference to the total weight of the preparation.

Where no concentration limits are given, the concentration limits to be used when applying the conventional method of assessing health hazards are those in Annex II, and when applying the conventional method of assessing environmental hazards are those in Annex III of European Parliament and Council Directive 1999/45/EC (OJ L 200, 30.7.1999, p. 1).

**General explanatory notes**

*Groups of substances*

A number of group entries are included in Annex I. In these cases, the classification and labelling requirements will apply to all substances covered by the description if they are placed on the market, insofar as they are listed in Einecs or Elincs. Where a substance that is covered by a group entry occurs as an impurity in another substance, the classification and labelling requirements described in the group entry shall be taken into account in the labelling of the substance.

In some cases, there are classification and labelling requirements for specific substances that would be covered by the group entry. In such cases a specific Annex I entry will be present for the substance and the group entry will be annotated with the phrase 'except those specified elsewhere in this Annex'.

In some cases, individual substances may be covered by more than one group entry. Lead oxalate (Einecs No 212-413-5) is for instance covered by the entry for lead compounds (index No 082-001-00-6) as well as for salts of oxalic acid (607-007-00-3). In these cases, the labelling of the substance reflects the labelling for each of the two group entries. In cases where different classifications for the same hazard are given, the classification leading to the more severe classification is used for the label of the particular substance (see section on Note A below).

Entries in Annex I for salts (under any denomination) cover both anhydrous and hydrous forms unless specifically specified otherwise.

*Substances with an Elincs number*

In Annex I, substances with an Elincs number have been notified under the provisions of this Directive. A producer or importer who has not previously notified these substances must refer to the provisions of this Directive if he intends to place these substances on the market.

**Explanation of the notes relating to the identification, classification and labelling of substances**

*Note A:*

The name of the substance must appear on the label in the form of one of the designations given in Annex I (see Article 23(2)(a)).

In Annex I, use is sometimes made of a general description such as '… compounds' or '… salts'. In this case, the manufacturer or any other person who markets such a substance is required to state on the label the correct name, due account being taken of the chapter entitled 'Nomenclature' of the Foreword:

Example: for $BeCl_2$ (Einecs No 232-116-4): beryllium chloride.

The Directive also requires that the symbols, indications of danger, R- and S-phrases to be used for each substance shall be those shown in Annex I (Article 23(2)(c), (d) and (e)).

For substances belonging to one particular group of substances included in Annex I, the symbols, indications of danger, R- and S-phrases to be used for each substance shall be those shown in the appropriate entry in Annex I.

For substances belonging to more than one group of substances included in Annex I, the symbols, indications of danger, R- and S-phrases to be used for each substance shall be those shown in both the appropriate entries given in Annex I. In cases where two different classifications are given in the two entries for the same hazard, the classification reflecting the more severe hazard classification is used.

Example:

for substance AB - no individual entry in Annex I:

Annex I group entry for compounds of A:

Repr. Cat. 1; R61 Repr. Cat. 3; R62 Xn; R20/22 R33 N; R50-53

Annex I group entry for compounds of B:

Carc. Cat.1; R45 T; R23/25 N; R51-53

Classification of substance AB thus becomes:

Carc. Cat. 1; R45 Repr. Cat. 1; R61 Repr. Cat. 3; R62 T; R23/25 R33 N; R50-53.

*Note B:*

Some substances (acids, bases, etc.) are placed on the market in aqueous solutions at various concentrations and, therefore, these solutions require different labelling since the hazards vary at different concentrations.

In Annex I entries with Note B have a general designation of the following type: 'nitric acid …%'.

In this case the manufacturer or any other person who markets such a substance in aqueous solution must state the percentage concentration of the solution on the label.

Example: nitric acid 45 %.

Unless otherwise stated, it is assumed that the percentage concentration is calculated on a weight/weight basis.

The use of additional data (e.g. specific gravity, degrees Baumé) or descriptive phrases (e.g. fuming or glacial) is permissible.

*Note C:*

Some organic substances may be marketed either in a specific isomeric form or as a mixture of several isomers.

In Annex I, a general designation of the following type is sometimes used: 'xylenol'.

In this case the manufacturer or any other person who markets such a substance must state on the label whether the substance is a specific isomer (a) or a mixture of isomers (b).

Example: (a) 2,4-dimethylphenol

(b) xylenol (mixture of isomers).

*Note D:*

Certain substances which are susceptible to spontaneous polymerisation or decomposition are generally placed on the market in a stabilised form. It is in this form that they are listed in Annex I to this Directive.

However, such substances are sometimes placed on the market in a non-stabilised form. In this case, the manufacturer or any person who places such a substance on the market must state on the label the name of the substance followed by the words 'non-stabilised'.

Example: methacrylic acid (non-stabilised).

*Note E:*

Substances with specific effects on human health (see Chapter 4 of Annex VI) that are classified as carcinogenic, mutagenic and/or toxic for reproduction in categories 1 or 2 are ascribed Note E if they are also classified as very toxic (T+), toxic (T) or harmful (Xn). For these substances, the risk phrases R20, R21, R22, R23, R24, R25, R26, R27, R28, R39, R68 (harmful), R48 and R65 and all combinations of these risk phrases shall be preceded by the word 'Also'.

| | | |
|---|---|---|
| Examples: | R45-23 | 'May cause cancer. Also toxic by inhalation' |
| | R46-27/28 | 'May cause heritable genetic damage. Also very toxic in contact with skin and if swallowed'. |

*Note F:*

This substance may contain a stabiliser. If the stabiliser changes the dangerous properties of the substance, as indicated by the label in Annex I, a label should be provided in accordance with the rules for the labelling of dangerous preparations.

*Note G:*

This substance may be marketed in an explosive form in which case it must be evaluated using the appropriate test methods and a label should be provided reflecting its explosive property.

*Note H:*

The classification and label shown for this substance applies to the dangerous property(ies) indicated by the risk phrase(s) in combination with the category(ies) of danger shown. The requirements of Article 6 of this Directive on manufacturers, distributors and importers of this substance apply to all other aspects of classification and labelling. The final label shall follow the requirements of section 7 of Annex VI of this Directive.

This note applies to certain coal- and oil-derived substances and to certain entries for groups of substances in Annex I.

*Note J:*

The classification as a carcinogen need not apply if it can be shown that the substance contains less than 0,1 % w/w benzene (Einecs No 200-753-7). This note applies only to certain complex coal- and oil-derived substances in Annex I.

*Note K:*

The classification as a carcinogen need not apply if it can be shown that the substance contains less than 0,1 % w/w 1,3-butadiene (Einecs No 203-450-8). If the substance is not classified as a carcinogen, at least the S-phrases (2-)9-16 should apply. This note applies only to certain complex oil-derived substances in Annex I.

*Note L:*

The classification as a carcinogen need not apply if it can be shown that the substance contains less than 3 % DMSO extract as measured by IP 346. This note applies only to certain complex oil-derived substances in Annex I.

*Note M:*

The classification as a carcinogen need not apply if it can be shown that the substance contains less than 0,005 % w/w benzo[a]-pyrene (Einecs No 200-028-5). This note applies only to certain complex coal-derived substances in Annex I.

*Note N:*

The classification as a carcinogen need not apply if the full refining history is known and it can be shown that the substance from which it is produced is not a carcinogen. This note applies only to certain complex oil-derived substances in Annex I.

*Note P:*

The classification as a carcinogen need not apply if it can be shown that the substance contains less than 0,1 % w/w benzene (Einecs No 200-753-7).

When the substance is classified as a carcinogen, Note E shall also apply.

When the substance is not classified as a carcinogen at least the S-phrases (2-)23-24-62 shall apply.

This note applies only to certain complex oil-derived substances in Annex I.

*Note Q:*

The classification as a carcinogen need not apply if it can be shown that the substance fulfils one of the following conditions:

— a short term biopersistence test by inhalation has shown that the fibres longer than 20 μm have a weighted half-life less than 10 days, or

— a short term biopersistence test by intratracheal instillation has shown that the fibres longer than 20 μm have a weighted half-life less than 40 days, or

— an appropriate intra-peritoneal test has shown no evidence of excess carcinogenicity, or

— absence of relevant pathogenicity or neoplastic changes in a suitable long term inhalation test.

*Note R:*

The classification as a carcinogen need not apply to fibres with a length weighted geometric mean diameter less two standard geometric errors greater than 6 μm.

*Note S:*

This substance may not require a label according to Article 23 (see section 8 of Annex VI).

**Explanation of the notes relating to the labelling of preparations**

The significance of the notes that appear to the right of the concentration limits is as follows:

*Note 1:*

The concentration stated or, in the absence of such concentrations, the general concentrations of Directive 1999/45/EC are the percentages by weight of the metallic element calculated with reference to the total weight of the preparation.

*Note 2:*

The concentration of isocyanate stated is the percentage by weight of the free monomer calculated with reference to the total weight of the preparation.

*Note 3:*

The concentration stated is the percentage by weight of chromate ions dissolved in water calculated with reference to the total weight of the preparation.

*Note 4:*

Preparations containing these substances have to be classified as harmful with R65 if they meet the criteria in section 3.2.3 in Annex VI.

*Note 5:*

The concentration limits for gaseous preparations are expressed as volume per volume percentage.

*Note 6:*

Preparations containing these substances have to be assigned R67 if they meet the criteria in section 3.2.8 in Annex VI.

This note will no longer apply from the date on which the criteria for the use of R67 provided for in Directive 1999/45/EC enter into force.

TABLA A — TABEL A — TABELLE A — ΠΙΝΑΚΑΣ A — TABLE A — TABLEAU A — TABELLA A — TABEL A — TABELA A — TABELL A — TAULUKKO A

**Lista de los elementos químicos clasificados por su número atómico (Z)**
**Liste over grundstoffer, ordnet efter deres atomvægt (Z)**
**Liste der chemischen Elemente, geordnet nach der Ordnungszahl (Z)**
**Κατάλογος χημικών στοιχείων ταξινομημένων σύμφωνα με τον ατομικό τους αριθμό (Z)**
**List of chemical elements listed according to their atomic number (Z)**
**Liste des éléments chimiques classés selon leur numéro atomique (Z)**
**Elenco degli elementi chimici ordinati secondo il loro numero atomico (Z)**
**Lijst van chemische elementen, gerangschikt naar atoomgewicht (Z)**
**Lista dos elementos químicos ordenados segundo o seu número atómico (Z)**
**Lista över grundämnen, ordnade efter deras atomnummer (Z)**
**Alkuaineiden luettelo järjestysluvun mukaan (Z)**

| Z | Symbol | DE | DA | EL | EN | ES | FR | IT | NL | PT | SV | FI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | Wasserstoff | Hydrogen (brint) | Υδρογόνο | Hydrogen | Hidrógeno | Hydrogène | Idrogeno | Waterstof | Hidrogénio | Väte | Vety |
| 2 | He | Helium | Helium | Ήλιο | Helium | Helio | Hélium | Elio | Helium | Hélio | Helium | Helium |
| 3 | Li | Lithium | Lithium | Λίθιο | Lithium | Litio | Lithium | Litio | Lithium | Lítio | Litium | Litium |
| 4 | Be | Beryllium | Beryllium | Βηρύλλιο | Beryllium | Berilio | Béryllium (Glucinium) | Berillio | Beryllium | Berílio | Beryllium | Beryllium |
| 5 | B | Bor | Bor | Βόριο | Boron | Boro | Bore | Boro | Boor | Boro | Bor | Boori |
| 6 | C | Kohlenstoff | Carbon (kulstof) | Άνθρακας | Carbon | Carbono | Carbone | Carbonio | Koolstof | Carbono | Kol | Hiili |
| 7 | N | Stickstoff | Nitrogen | Άζωτο | Nitrogen | Nitrógeno | Azote | Azoto | Stikstof | Azoto | Kväve | Typpi |
| 8 | O | Sauerstoff | Oxygen (ilt) | Όξυγόνο | Oxygen | Oxígeno | Oxygène | Ossigeno | Zuurstof | Oxigénio | Syre | Happi |
| 9 | F | Fluor | Fluor | Φθόριο | Fluorine | Flúor | Fluor | Fluoro | Fluor | Flúor | Fluor | Fluori |
| 10 | Ne | Neon | Neon | Νέον | Neon | Neón | Néon | Neon | Neon | Néon | Neon | Neon |
| 11 | Na | Natrium | Natrium | Νάτριο | Sodium | Sodio | Sodium | Sodio | Natrium | Sódio | Natrium | Natrium |
| 12 | Mg | Magnesium | Magnesium | Μαγνήσιο | Magnesium | Magnesio | Magnésium | Magnesio | Magnesium | Magnésio | Magnesium | Magnesium |
| 13 | Al | Aluminium | Aluminium | Αργίλιο | Aluminium | Aluminio | Aluminium | Alluminio | Aluminium | Alumínio | Aluminium | Alumiini |
| 14 | Si | Silicium | Silicium | Πυρίτιο | Silicon | Silicio | Silicium | Silicio | Silicium | Silício | Kisel | Pii |
| 15 | P | Phosphor | Phosphor | Φώσφορος | Phosphorus | Fósforo | Phosphore | Fosforo | Fosfor | Fósforo | Fosfor | Fosfori |
| 16 | S | Schwefel | Svovl | Θείο | Sulphur | Azufre | Soufre | Zolfo | Zwavel | Enxofre | Svavel | Rikki |
| 17 | Cl | Chlor | Chlor | Χλώριο | Chlorine | Cloro | Chlore | Cloro | Chloor | Cloro | Klor | Kloori |
| 18 | Ar | Argon | Argon | Αργό | Argon | Argón | Argon | Argon | Argon | Árgon | Argon | Argon |
| 19 | K | Kalium | Kalium | Κάλιο | Potassium | Potasio | Potassium | Potassio | Kalium | Potássio | Kalium | Kalium |
| 20 | Ca | Calcium | Calcium | Ασβέστιο | Calcium | Calcio | Calcium | Calcio | Calcium | Cálcio | Kalcium | Kalsium |

| Z | Symbol | DE | DA | EL | EN | ES | FR | IT | NL | PT | SV | FI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 21 | Sc | Scandium | Scandium | Σκάνδιο | Scandium | Escandio | Scandium | Scandio | Scandium | Escândio | Skandium | Skandium |
| 22 | Ti | Titan | Titan | Τιτάνιο | Titanium | Titanio | Titane | Titanio | Titaan | Titânio | Titan | Titaani |
| 23 | V | Vanadium | Vanadium | Βανάδιο | Vanadium | Vanadio | Vanadium | Vanadio | Vanadium | Vanádio | Vanadin | Vanadiini |
| 24 | Cr | Chrom | Chrom | Χρώμιο | Chromium | Cromo | Chrome | Cromo | Chroom | Crómio | Krom | Kromi |
| 25 | Mn | Mangan | Mangan | Μαγγάνιο | Manganese | Manganeso | Manganèse | Manganese | Mangaan | Manganês | Mangan | Mangaani |
| 26 | Fe | Eisen | Jern | Σίδηρος | Iron | Hierro | Fer | Ferro | IJzer | Ferro | Järn | Rauta |
| 27 | Co | Kobalt | Cobalt | Κοβάλτιο | Cobalt | Cobalto | Cobalt | Cobalto | Kobalt | Cobalto | Kobolt | Koboltti |
| 28 | Ni | Nickel | Nikkel | Νικέλιο | Nickel | Níquel | Nickel | Nichel | Nikkel | Níquel | Nickel | Nikkeli |
| 29 | Cu | Kupfer | Kobber | Χαλκός | Copper | Cobre | Cuivre | Rame | Koper | Cobre | Koppar | Kupari |
| 30 | Zn | Zink | Zink | Ψευδάργυρος | Zinc | Cinc | Zinc | Zinco | Zink | Zinco | Zink | Sinkki |
| 31 | Ga | Gallium | Gallium | Γάλλιο | Gallium | Galio | Gallium | Gallio | Gallium | Gálio | Gallium | Gallium |
| 32 | Ge | Germanium | Germanium | Γερμάνιο | Germanium | Germanio | Germanium | Germanio | Germanium | Germânio | Germanium | Germanium |
| 33 | As | Arsen | Arsen | Αρσενικό | Arsenic | Arsénico | Arsenic | Arsenico | Arseen | Arsénio | Arsenik | Arseeni |
| 34 | Se | Selen | Selen | Σελήνιο | Selenium | Selenio | Sélénium | Selenio | Selenium | Selénio | Selen | Seleeni |
| 35 | Br | Brom | Brom | Βρώμιο | Bromine | Bromo | Brome | Bromo | Broom | Bromo | Brom | Bromi |
| 36 | Kr | Krypton | Krypton | Κρυπτό | Krypton | Criptón | Krypton | Krypton | Krypton | Krípton | Krypton | Krypton |
| 37 | Rb | Rubidium | Rubidium | Ρουβήδιο | Rubidium | Rubidio | Rubidium | Rubidio | Rubidium | Rubídio | Rubidium | Rubidium |
| 38 | Sr | Strontium | Strontium | Στρόντιο | Strontium | Estroncio | Strontium | Stronzio | Strontium | Estrôncio | Strontium | Strontium |
| 39 | Y | Yttrium | Yttrium | Ύττριο | Yttrium | Itrio | Yttrium | Ittrio | Yttrium | Ítrio | Yttrium | Yttrium |
| 40 | Zr | Zirkon | Zirconium | Ζιρκόνιο | Zirconium | Circonio | Zirconium | Zirconio | Zirkonium | Zircónio | Zirkonium | Zirkonium |

| Z | Symbol | DE | DA | EL | EN | ES | FR | IT | NL | PT | SV | FI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 41 | Nb | Niob | Niobium | Νιόβιο | Niobium | Niobio | Niobium | Niobio | Niobium | Nióbio | Niob | Niobium |
| 42 | Mo | Molybdän | Molybden | Μολυβδένιο | Molybdenum | Molibdeno | Molybdène | Molibdeno | Molybdeen | Molibdénio | Molybden | Molybdeeni |
| 43 | Tc | Technetium | Technetium | Τεχνήτιο | Technetium | Tecnecio | Technetium | Tecnezio | Technetium | Tecnécio | Teknetium | Teknetium |
| 44 | Ru | Ruthenium | Ruthenium | Ρουθήνιο | Ruthenium | Rutenio | Ruthénium | Rutenio | Ruthernium | Ruténio | Rutenium | Rutenium |
| 45 | Rh | Rhodium | Rhodium | Ρόδιο | Rhodium | Rodio | Rhodium | Rodio | Rodium | Ródio | Rodium | Rodium |
| 46 | Pd | Palladium | Palladium | Παλλάδιο | Palladium | Paladio | Palladium | Palladio | Palladium | Paládio | Palladium | Palladium |
| 47 | Ag | Silber | Sølv | Άργυρος | Silver | Plata | Argent | Argento | Zilver | Prata | Silver | Hopea |
| 48 | Cd | Cadmium | Cadmium | Κάδμιο | Cadmium | Cadmio | Cadmium | Cadmio | Cadmium | Cádmio | Kadmium | Kadmium |
| 49 | In | Indium | Indium | Ίνδιο | Indium | Indio | Indium | Indio | Indium | Índio | Indium | Indium |
| 50 | Sn | Zinn | Tin | Κασσίτερος | Tin | Estaño | Étain | Stagno | Tin | Estanho | Tenn | Tina |
| 51 | Sb | Antimon | Antimon | Αντιμόνιο | Antimony | Antimonio | Antimoine | Antimonio | Antimoon | Antimónio | Antimon | Antimoni |
| 52 | Te | Tellur | Telur | Τελλούριο | Tellurium | Telurio | Tellure | Tellurio | Telluur | Telúrio | Tellur | Telluuri |
| 53 | I | Jod | Jod | Ιώδιο | Iodine | Yodo | Iode | Iodio | Jood | Iodo | Jod | Jodi |
| 54 | Xe | Xenon | Xenon | Ξένο | Xenon | Xenón | Xénon | Xenon | Xenon | Xénon | Xenon | Ksenon |
| 55 | Cs | Caesium | Cæsium | Καίσιο | Caesium | Cesio | Césium | Cesio | Cesium | Césio | Cesium | Cesium |
| 56 | Ba | Barium | Barium | Βάριο | Barium | Bario | Baryum | Bario | Barium | Bário | Barium | Barium |
| 57 | La | Lanthan | Lanthan | Λανθάνιο | Lanthanum | Lantano | Lanthane | Lantanio | Lanthaan | Lantânio | Lantan | Lantaani |
| 58 | Ce | Cer | Cerium | Δημήτριο | Cerium | Cerio | Cérium | Cerio | Cerium | Cério | Cerium | Cerium |
| 59 | Pr | Praseodym | Praseodym | Πρασεοδύμιο | Praseodymium | Praseodimio | Praséodyme | Praseodimio | Praseodymium | Praseodímio | Praseodym | Praseodyymi |
| 60 | Nd | Neodym | Neodym | Νεοδύμιο | Neodymium | Niodimio | Néodyme | Neodimio | Neodymium | Neodímio | Neodym | Neodyymi |

| Z | Symbol | DE | DA | EL | EN | ES | FR | IT | NL | PT | SV | FI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 61 | Pm | Promethium | Promethium | Προμήθειο | Promethium | Prometio | Prométhium | Promezio | Promethium | Promécio | Prometium | Prometium |
| 62 | Sm | Samarium | Samarium | Σαμάριο | Samarium | Samario | Samarium | Samario | Samarium | Samário | Samarium | Samarium |
| 63 | Eu | Europium | Europium | Ευρώπιο | Europium | Europio | Europium | Europio | Europium | Európio | Europium | Europium |
| 64 | Gd | Gadolinium | Gadolinium | Γαδολίνιο | Gadolinium | Gadolinio | Gadolinium | Gadolinio | Gadolinium | Gadolínio | Gadolinium | Gadolinium |
| 65 | Tb | Terbium | Terbium | Τέρβιο | Terbium | Terbio | Terbium | Terbio | Terbium | Térbio | Terbium | Terbium |
| 66 | Dy | Dysprosium | Dysprosium | Δυσπρόσιο | Dysprosium | Disprosio | Dysprosium | Disprosio | Dysprosium | Disprósio | Dysprosium | Dysprosium |
| 67 | Ho | Holmium | Holmium | Όλμιο | Holmium | Holmio | Holmium | Olmio | Holmium | Hólmio | Holmium | Holmium |
| 68 | Er | Erbium | Erbium | Έρβιο | Erbium | Erbio | Erbium | Erbio | Erbium | Érbio | Erbium | Erbium |
| 69 | Tm | Thulium | Thulium | Θούλιο | Thulium | Tulio | Thulium | Tulio | Thulium | Túlio | Tulium | Tulium |
| 70 | Yb | Ytterbium | Ytterbium | Υττέρβιο | Ytterbium | Iterbio | Ytterbium | Itterbio | Ytterbium | Itérbio | Ytterbium | Ytterbium |
| 71 | Lu | Lutetium | Lutetium | Λουτήτιο | Lutetium | Lutecio | Lutécium | Lutezio | Lutetium | Lutécio | Lutetium | Lutetium |
| 72 | Hf | Hafnium | Hafnium | Άφνιο | Hafnium | Hafnio | Hafnium | Afnio | Hafnium | Háfnio | Hafnium | Hafnium |
| 73 | Ta | Tantal | Tantal | Ταντάλιο | Tantalum | Tántalo | Tantale | Tantalio | Tantaal | Tântalo | Tantal | Tantaali |
| 74 | W | Wolfram | Wolfram | Βολφράμιο (Τουγκοτένιο) | Tungsten | Volframio | Tungstène | Tungsteno | Wolfram | Tungsténio | Wolfram | Volframi |
| 75 | Re | Rhenium | Rhenium | Ρήνιο | Rhenium | Renio | Rhénium | Renio | Renium | Rénio | Rhenium | Renium |
| 76 | Os | Osmium | Osmium | Όσμιο | Osmium | Osmio | Osmium | Osmio | Osmium | Ósmio | Osmium | Osmium |
| 77 | Ir | Iridium | Iridium | Ιρίδιο | Iridium | Iridio | Iridium | Iridio | Iridium | Irídio | Iridium | Iridium |
| 78 | Pt | Platin | Platin | Λευκόχρυσος | Platinum | Platino | Platine | Platino | Platinum | Platina | Platina | Platina |
| 79 | Au | Gold | Guld | Χρυσός | Gold | Oro | Or | Oro | Goud | Ouro | Guld | Kulta |
| 80 | Hg | Quecksilber | Kviksølv | Υδράργυρος | Mercury | Mercurio | Mercure | Mercurio | Kwik | Mercúrio | Kvicksilver | Elohopea |

| Z | Symbol | DE | DA | EL | EN | ES | FR | IT | NL | PT | SV | FI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 81 | Tl | Thallium | Thalium | Θάλλιο | Thallium | Talio | Thallium | Tallio | Thallium | Tálio | Tallium | Tallium |
| 82 | Pb | Blei | Bly | Μόλυβδος | Lead | Plomo | Plomb | Piombo | Lood | Chumbo | Bly | Lyijy |
| 83 | Bi | Wismuth | Bismuth | Βισμούθιο | Bismuth | Bismuto | Bismuth | Bismuto | Bismuth | Bismuto | Vismut | Vismutti |
| 84 | Po | Polonium | Plonium | Πολώνιο | Polonium | Polonio | Polonium | Polonio | Polonium | Polónio | Polonium | Polonium |
| 85 | At | Astat | Astat | Αστάτιο | Astatine | Astato | Astate | Astato | Astaat | Astato | Astat | Astatiini |
| 86 | Rn | Radon | Radon | Ραδόνιο | Radon | Radón | Radon | Radon | Radon | Rádon | Radon | Radon |
| 87 | Fr | Francium | Francium | Φράγκιο | Francium | Francio | Francium | Francio | Francium | Frâncio | Francium | Frankium |
| 88 | Ra | Radium | Radium | Ράδιο | Radium | Radio | Radium | Radio | Radium | Rádio | Radium | Radium |
| 89 | Ac | Actinium | Actinium | Ακτίνιο | Actinium | Actinio | Actinium | Attinio | Actinium | Actínio | Aktinium | Aktinium |
| 90 | Th | Thorium | Thorium | Θόριο | Thorium | Torio | Thorium | Torio | Thorium | Tório | Torium | Torium |
| 91 | Pa | Protactinium | Protactinium | Πρωτακτίνιο | Protactinium | Protactinio | Protactinium | Protoattinio | Protactinium | Protactínio | Protaktinium | Protaktinium |
| 92 | U | Uran | Uran | Ουράνιο | Uranium | Uranio | Uranium | Uranio | Uranium | Urânio | Uran | Uraani |
| 93 | Np | Neptunium | Neptunium | Νεπτούνιο (Ποσειδώνιο) | Neptunium | Neptunio | Neptunium | Nettunio | Neptunium | Neptúnio | Neptunium | Neptunium |
| 94 | Pu | Plutonium | Plutonium | Πλουτώνιο | Plutonium | Plutonio | Plutonium | Plutonio | Plutonium | Plutónio | Plutonium | Plutonium |
| 95 | Am | Americium | Americium | Αμερίκιο | Americium | Americio | Américium | Americio | Americium | Amerício | Americium | Amerikium |
| 96 | Cm | Curium | Curium | Κιούριο | Curium | Curio | Curium | Curio | Curium | Cúrio | Curium | Curium |
| 97 | Bk | Berkelium | Berkelium | Μπερκέλιο | Berkelium | Berquelio | Berkélium | Berkelio | Berkelium | Berquélio | Berkelium | Berkelium |
| 98 | Cf | Californium | Californium | Καλιφόρνιο | Californium | Californio | Californium | Californio | Californium | Califórnio | Californium | Kalifornium |
| 99 | Es | Einsteinium | Einsteinium | Αϊνστάνιο | Einsteinium | Einstenio | Einsteinium | Einstenio | Einsteinium | Einsteinio | Einsteinium | Einsteinium |
| 100 | Fm | Fermium | Fermium | Φέρμιο | Fermium | Fermio | Fermium | Fermio | Fermium | Férmio | Fermium | Fermium |
| 101 | Md | Mendelevium | Mendelevium | Μεντελέβιο | Mendelevium | Mendelevio | Mendélévium | Mendelevio | Mendelevium | Mendelévio | Mendelevium | Mendelevium |
| 102 | No | Nobelium | Nobelium | Νομπέλιο | Nobelium | Nobelio | Nobélium | Nobelio | Nobelium | Nobélio | Nobelium | Nobelium |
| 103 | Lw | Lawrentium | Lawrentium | Λαυρένσιο | Lawrencium | Laurencio | Lawrencium | Lawrencio | Laurentium | Laurêncio | Lawrentium | Lawrensium |

TABLA B — TABEL B — TABELLE B — ΠΙΝΑΚΑΣ B — TABLE B — TABLEAU B — TABELLA B — TABEL B — TABELA B — TABELL B — TAULUKKO B

**Clasificación especial para las sustancias orgánicas**
**Særlig inddeling af organiske stoffer**
**Spezielle Anordnung für die organischen Stoffe**
**Ειδική ταξινόμηση των οργανικών ουσιών**
**Special classification for organic substances**
**Classification particulière aux substances organiques**
**Classificazione speciale per le sostanze organiche**
**Speciale indeling voor de organische stoffen**
**Classificação especial para as substâncias orgânicas**
**Särskild indelning av organiska ämnen**
**Erityisryhmät orgaanisille aineille**

601 Hidrocarburos
Carbonhydrider (kulbrinter)
Kohlenwasserstoffe
Υδρογονάνθρακες
Hydrocarbons
Hydrocarbures
Idrocarburi
Koolwaterstoffen
Hidrocarbonetos
Kolväten
Hiilivedyt

602 Hidrocarburos halogenados
Halogensubstituerede carbonhydrider
Halogen-Kohlenwasserstoffe
Αλογονοπαράγωγα υδρογονανθράκων
Halogenated hydrocarbons
Dérivés halogénés des hydrocarbures
Derivati idrocarburi alogenati
Gehalogeneerde koolwaterstoffen
Hidrocarbonetos halogenados
Halogenerade kolväten
Halogenoidut hiilivedyt

603 Alcoholes y derivados
Alkoholer og deres derivater
Alkohole und ihre Derivate
Αλκοόλες και παράγωγά τους
Alcohols and their derivatives
Alcools et dérivés
Alcoli e derivati
Alcoholen en derivaten
Álcoois e derivados
Alkoholer och deras derivat
Alkoholit ja niiden johdannaiset

604 Fenoles y derivados
Phenoler og deres derivater
Phenole und ihre Derivate
Φαινόλες και παράγωγά τους
Phenols and their derivatives
Phénols et dérivés
Fenoli e derivati
Fenolen en derivaten
Fenóis e derivados
Fenoler och deras derivat
Fenolit ja niiden johdannaiset

605 Aldehídos y derivados
Aldehyder og deres derivater
Aldehyde und ihre Derivate
Αλδεΰδες και παράγωγά τους
Aldehydes and their derivatives
Aldéhydes et dérivés
Aldeidi e derivati
Aldehyden en derivaten
Aldeídos e derivados
Aldehyder och deras derivat
Aldehydit ja niiden johdannaiset

606 Cetonas y derivados
Ketoner og deres derivater
Ketone und ihre Derivate
Κετόνες και παράγωγά τους
Ketones and their derivatives
Cétones et dérivés
Chetoni e derivati
Ketonen en derivaten
Cetonas e derivados
Ketoner och deras derivat
Ketonit ja niiden johdannaiset

607 Ácidos orgánicos y derivados
Organiske syrer og deres derivater
Organische Säuren und ihre Derivate
Οργανικά οξέα και παράγωγά τους
Organic acids and their derivatives
Acides organiques et dérivés
Acidi organici e derivati
Organische zuren en derivaten
Ácidos orgânicos e derivados
Organiska syror och deras derivat
Orgaaniset hapot ja niiden johdannaiset

608 Nitrilos
Nitriler
Nitrile
Νιτρίλια
Nitriles
Nitriles
Nitrili
Nitrillen
Nitrilos
Nitriler
Nitriilit

609
Derivados nitrados
Nitroforbindelser
Nitroverbindungen
Νιτροενώσεις
Nitro compounds
Dérivés nitrés
Nitroderivati
Nitroverbindingen
Derivados nitrados
Kväveföreningar
Nitroyhdisteet

610
Derivados cloronitrados
Chlornitroforbindelser
Chlornitroverbindungen
Χλωρονιτροενώσεις
Chloronitro compounds
Dérivés chloronitrés
Cloronitro derivati
Chloornitroverbindingen
Derivados cloronitrados
Klornitroföreningar
Kloorinitroyhdisteet

611
Derivados azoicos y azoxi
Azoxy- og azoforbindelser
Azoxy- und Azoverbindungen
Αζωξυ- και αζω-ενώσεις
Azoxy- and azo compounds
Dérivés azoxy et azoïques
Azossi- e azoderivati
Azoxy- en azoverbindingen
Derivados azoxi e azóicos
Azoxi- och azoföreningar
Atsoksi- ja atsoyhdisteet

612
Derivados aminados
Aminer
Aminoverbindungen
Αμινοενώσεις
Amine compounds
Dérivés aminés
Aminoderivati
Aminoverbindingen
Derivados aminados
Aminer
Amiiniyhdisteet

613
Bases heterocíclicas y derivados
Heterocykliske baser og deres derivater
Heterocyclische Basen und ihre Derivate
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Heterocyclic bases and their derivatives
Bases hétérocycliques et dérivés
Basi eterocicliche e derivati
Heterocyclische basen en hun derivaten
Bases heterocíclicas e derivados
Heterocykliska baser och deras derivat
Heterosykliset emäkset ja niiden johdannaiset

614
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Glycoside und Alkaloide
Γλυκοζίτες και αλκαλοειδή
Glycosides and alkaloids
Glucosides et alcaloïdes
Glucosidi e alcaloidi
Glycosiden en alkaloïden
Glicósidos e alcalóides
Glykosider och alkaloider
Glykosidit ja alkaloidit

615
Cianatos e isocianatos
Cyanater og isocyanater
Cyanate und Isocyanate
Κυανικές και ισοκυανικές ενώσεις
Cyanates and isocyanates
Cyanates et isocyanates
Cianati e isocianati
Cyanaten en isocyanaten
Cianatos e isocianatos
Cyanater och isocyanater
Syanaatit ja isosyanaatit

616
Amidas y derivados
Amider og deres derivater
Amide und ihre Derivate
Αμίδια και παράγωγά τους
Amides and their derivatives
Amides et dérivés
Ammidi e derivati
Amiden en derivaten
Amidas e derivados
Amider och deras derivat
Amidit ja niiden johdannaiset

617
Peróxidos orgánicos
Organiske peroxider
Organische Peroxide
Οργανικά υπεροξείδια
Organic peroxides
Peroxydes organiques
Perossidi organici
Organische peroxiden
Peróxidos orgânicos
Organiska peroxider
Orgaaniset peroksidit

647
Enzimas
Enzymer
Enzyme
Ένζυμα
Enzymes
Enzymes
Enzimi
Enzymen
Enzimas
Enzymer
Entsyymit

648
Sustancias complejas derivadas del carbón
Komplekse kulderivater
Aus Kohle abgeleitete komplexe Stoffe
Σύμπλοκες ουσίες παραγόμενες από άνθρακα
Complex substances derived from coal
Substances complexes dérivées du charbon
Sostanze complesse derivate dal carbone
Complexe steenkoolderivaten
Substâncias complexas derivadas do carvão
Komplexa kolderivat
Monimutkaiset hiilijohdannaiset

649
Sustancias complejas derivadas del petróleo
Komplekse oliederivater
Aus Erdöl abgeleitete komplexe Stoffe
Σύμπλοκες ουσίες παραγόμενες από πετρέλαιο
Complex substances derived from petroleum
Substances complexes dérivées du pétrole
Sostanze complesse derivate dal petrolio
Complexe aardoliederivaten
Substâncias complexas derivadas do petróleo
Komplexa oljederivat
Monimutkaiset öljyjohdannaisetgo 1

650 Sustancias diversas
Diverse stoffer
Verschiedene Stoffe
Διάφορες ουσίες
Miscellaneous substances
Substances diverses
Sostanze diverse
Diversen
Substâncias diversas
Diverse ämnen
Muut aineet

*ANNEX 1B*

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to prepara-tions |
|---|---|---|---|---|---|---|---|---|
| 004-002-00-2 | beryllium compounds with the exception of aluminium beryllium silicates, and with those specified elsewhere in this Annex | A<br>E | — | — | Carc. Cat. 2; R49<br>T+; R26<br>T; R25-48/23<br>Xi; R36/37/38<br>R43<br>N; R51-53 | T+; N<br>R: 49-25-26-36/37/38-43-48/23-51/53<br>S: 53-45-61 | | |
| 006-015-00-9 | diuron (ISO)<br>3-(3,4-dichlorophenyl)-1,1-dimethylurea | | 206-354-4 | 330-54-1 | Carc. Cat. 3; R40<br>Xn; R22-48/22<br>N; R50-53 | Xn; N<br>R: 22-40-48/22-50/53<br>S: (2-)13-22-23-37-46-60-61 | | |
| 006-024-00-8 | proxan-sodium (ISO)<br>sodium O-isopropyldithiocarbonate | | 205-443-5 | 140-93-2 | Xn; R22<br>Xi; R38<br>N; R51-53 | Xn; N<br>R: 22-38-51/53<br>S: (2-)13-61 | | |
| 006-032-00-1 | monolinuron (ISO)<br>3-(4-chlorophenyl)-1-methoxy-1-methylurea | | 217-129-5 | 1746-81-2 | Xn; R22-48/22<br>N; R50-53 | Xn; N<br>R: 22-48/22-50/53<br>S: (2-)22-60-61 | | |
| 006-041-00-0 | dimethylcarbamoyl chloride | E | 201-208-6 | 79-44-7 | Carc. Cat. 2; R45<br>T; R23<br>Xn; R22<br>Xi; R36/37/38 | T<br>R: 45-22-23-36/37/38<br>S: 53-45 | C ≥ 25 %: T; R45-22-23-36/37/38<br>20 % ≤ C < 25 %: T; R45-20-36/37/38<br>3 % ≤ C < 20 %: T; R45-20<br>0,001 % ≤ C < 3 %: T; R45 | |
| 006-069-00-3 | thiophanate-methyl (ISO)<br>1,2-di-(3-methoxycarbonyl-2-thioureido)benzene | | 245-740-7 | 23564-05-8 | Muta. Cat. 3; R68<br>Xn; R20<br>R43<br>N; R50-53 | Xn; N<br>R: 20-43-50/53-68<br>S: (2-)36/37-46-60-61 | | |
| 007-015-00-1 | O-ethylhydroxylamine | | 402-030-3 | 624-86-2 | F; R11<br>T; R23/24/25-48/23<br>Xi; R36<br>R43<br>N; R50 | F; T; N<br>R: 11-23/24/25-36-43-48/23-50<br>S: (1/2-)16-26-36/37/39-45-60-61 | | |
| 009-014-00-1 | lead hexafluorosilicate | E | 247-278-1 | 25808-74-6 | Repr. Cat. 1; R61<br>Repr. Cat. 3; R62<br>Xn; R20/22<br>R33<br>N; R50-53 | T; N<br>R: 61-62-20/22-33-50/53<br>S: 53-45-60-61 | | 1 |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to prepara-tions |
|---|---|---|---|---|---|---|---|---|
| 013-002-00-1 | aluminium powder (stabilised) | | 231-072-3 | — | F; R15<br>R10 | F<br>R: 10-15<br>S: (2-)7/8-43 | | |
| 015-003-00-2 | calcium phosphide<br>tricalcium diphosphide | | 215-142-0 | 1305-99-3 | F; R15/29<br>T+; R28<br>N; R50 | F; T+; N<br>R: 15/29-28-50<br>S: (1/2-)22-43-45-61 | | |
| 015-004-00-8 | aluminium phosphide | | 244-088-0 | 20859-73-8 | F; R15/29<br>T+; R28<br>R32<br>N; R50 | F; T+; N<br>R: 15/29-28-32-50<br>S: (1/2-)3/9/14-30-36/37-45-61 | | |
| 015-005-00-3 | magnesium phosphide<br>trimagnesium diphosphide | | 235-023-7 | 12057-74-8 | F; R15/29<br>T+; R28<br>N; R50 | F; T+; N<br>R: 15/29-28-50<br>S: (1/2-)22-43-45-61 | | |
| 015-006-00-9 | trizinc diphosphide<br>zinc phosphide | | 215-244-5 | 1314-84-7 | F; R15/29<br>T+; R28<br>R32<br>N; R50-53 | F; T+; N<br>R: 15/29-28-32-50/53<br>S: (1/2-)3/9/14-30-36/37-45-60-61 | | |
| 015-019-00-X | dichlorvos (ISO)<br>2,2-dichlorovinyl dimethyl phosphate | | 200-547-7 | 62-73-7 | T+; R26<br>T; R24/25<br>R43<br>N; R50 | T+; N<br>R: 24/25-26-43-50<br>S: (1/2-)28-36/37-45-61 | | |
| 015-106-00-2 | hexamethylphosphoric triamide<br>hexamethylphosphoramide | | 211-653-8 | 680-31-9 | Carc. Cat. 2; R45<br>Muta. Cat. 2; R46 | T<br>R: 45-46<br>S: 53-45 | C ≥ 0,1 %: T; R45-46<br>0,01 % ≤ C < 0,1 %: T; R45 | |
| 015-121-00-4 | edifenphos (ISO)<br>*O*-ethyl *S*,*S*-diphenyl phosphorodithioate | | 241-178-1 | 17109-49-8 | T; R23/25<br>Xn; R21<br>R43<br>N; R50-53 | T; N<br>R: 21-23/25-43-50/53<br>S: (1/2-)36/37-45-60-61 | | |
| 015-137-00-1 | pyrazophos (ISO)<br>*O*,*O*-diethyl *O*-(6-ethoxycarbonyl-5-methylpyrazolo[2,3-a] pyrimidin-2-yl) phosphorothioate | | 236-656-1 | 13457-18-6 | Xn; R20/22<br>N; R50-53 | Xn; N<br>R: 20/22-50/53<br>S: (2-)36/37-46-60-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to prepara-tions |
|---|---|---|---|---|---|---|---|---|
| 015-156-00-5 | methyl 3-[(dimethoxyphosphinothioyl) oxy]methacrylate [1]<br>methacrifos (ISO) [2]<br>methyl (*E*)-3-[(dimethoxyphosphinothioyl)oxy] methacrylate [2] | | 250-366-2 [1]<br>- [2] | 30864-28-9 [1]<br>62610-77-9 [2] | Xn; R22<br>R43<br>N; R50-53 | Xn; N<br>R: 22-43-50/53<br>S: (2-)36/37-60-61 | | |
| 015-157-00-0 | phosphonic acid [1]<br>phosphorous acid [2] | | 233-663-1 [1]<br>237-066-7 [2] | 10294-56-1 [1]<br>13598-36-2 [2] | Xn; R22<br>C; R35 | C<br>R: 22-35<br>S: (1/2-)26-36/37/39-45 | | |
| 016-002-00-X | barium sulphide | | 244-214-4 | 21109-95-5 | R31<br>Xn; R20/22<br>N; R50 | Xn; N<br>R: 20/22-31-50<br>S: (2-)28-61 | | |
| 016-003-00-5 | barium polysulphides | | 256-814-3 | 50864-67-0 | R31<br>Xi; R36/37/38<br>N; R50 | Xi; N<br>R: 31-36/37/38-50<br>S: (2-)28-61 | | |
| 016-004-00-0 | calcium sulphide | | 243-873-5 | 20548-54-3 | R31<br>Xi; R36/37/38<br>N; R50 | Xi; N<br>R: 31-36/37/38-50<br>S: (2-)28-61 | | |
| 016-005-00-6 | calcium polysulphides | | 215-709-2 | 1344-81-6 | R31<br>Xi; R36/37/38<br>N; R50 | Xi; N<br>R: 31-36/37/38-50<br>S: (2-)28-61 | | |
| 016-011-00-9 | sulphur dioxide | | 231-195-2 | 7446-09-5 | T; R23<br>C; R34 | T<br>R: 23-34<br>S: (1/2-)9-26-36/37/39-45 | C ≥ 20 %: T; R23-34<br>5 % ≤ C < 20 %: C; R20-34<br>0,5 % ≤ C < 5 %: Xi; R36/37/38 | 5 |
| 020-002-00-5 | calcium cyanide | | 209-740-0 | 592-01-8 | T+; R28<br>R32<br>N; R50-53 | T+; N<br>R: 28-32-50/53<br>S: (1/2-)7/8-23-36/37-45-60-61 | | |
| 027-001-00-9 | cobalt | | 231-158-0 | 7440-48-4 | R42/43<br>R53 | Xn<br>R: 42/43-53<br>S: (2-)22-24-37-61 | | |
| 027-002-00-4 | cobalt oxide | | 215-154-6 | 1307-96-6 | Xn; R22<br>R43<br>N; R50-53 | Xn; N<br>R: 22-43-50/53<br>S: (2-)24-37-60-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to prepara-tions |
|---|---|---|---|---|---|---|---|---|
| 027-003-00-X | cobalt sulphide | | 215-273-3 | 1317-42-6 | R43<br>N; R50-53 | Xi; N<br>R: 43-50/53<br>S: (2-)24-37-60-61 | | |
| 028-003-00-2 | nickel monoxide | | 215-215-7 | 1313-99-1 | Carc. Cat. 1; R49<br>R43<br>R53 | T<br>R: 49-43-53<br>S: 53-45-61 | | |
| 028-004-00-8 | nickel dioxide | | 234-823-3 | 12035-36-8 | Carc. Cat. 1; R49<br>R43<br>R53 | T<br>R: 49-43-53<br>S: 53-45-61 | | |
| 028-005-00-3 | dinickel trioxide | | 215-217-8 | 1314-06-3 | Carc. Cat. 1; R49<br>R43<br>R53 | T<br>R: 49-43-53<br>S: 53-45-61 | | |
| 028-006-00-9 | nickel sulphide | | 240-841-2 | 16812-54-7 | Carc. Cat. 1; R49<br>R43<br>N; R50-53 | T; N<br>R: 49-43-50/53<br>S: 53-45-60-61 | | |
| 028-007-00-4 | nickel subsulphide<br>trinickel disulphide | | 234-829-6 | 12035-72-2 | Carc. Cat. 1; R49<br>R43<br>N; R51-53 | T; N<br>R: 49-43-51/53<br>S: 53-45-61 | | |
| 028-008-00-X | nickel dihydroxide | | 235-008-5 | 12054-48-7 | Carc. Cat. 3; R40<br>Xn; R20/22<br>R43<br>N; R50-53 | Xn; N<br>R: 20/22-40-43-50/53<br>S: (2-)22-36-60-61 | | |
| 034-001-00-2 | selenium | | 231-957-4 | 7782-49-2 | T; R23/25<br>R33<br>R53 | T<br>R: 23/25-33-53<br>S: (1/2-)20/21-28-45-61 | | |
| 048-010-00-4 | cadmium sulphide | | 215-147-8 | 1306-23-6 | Carc. Cat. 3; R40<br>T; R48/23/25<br>Xn; R22<br>R53 | T<br>R: 22-40-48/23/25-53<br>S: (1/2-)22-36/37-45-61 | C ≥ 10 %: T; R22-40-48/23/25<br>1 % ≤ C < 10 %: Xn; R40-48/20/22<br>0,1 % ≤ C < 1 %: Xn; R48/20/22 | 1 |
| 050-003-00-6 | fentin acetate (ISO)<br>triphenyltin acetate | | 212-984-0 | 900-95-8 | Carc. Cat. 3; R40<br>Repr. Cat. 3; R63<br>T+; R26<br>T; R24/25-48/23<br>Xi; R37/38-41<br>N; R50-53 | T+; N<br>R: 24/25-26-37/38-40-41-48/23-50/53-63<br>S: (1/2-)26-28-36/37/39-45-60-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 050-004-00-1 | fentin hydroxide (ISO)<br>triphenyltin hydroxide | | 200-990-6 | 76-87-9 | Carc. Cat. 3; R40<br>Repr. Cat. 3; R63<br>T+; R26<br>T; R24/25-48/23<br>Xi; R37/38-41<br>N; R50-53 | T+; N<br>R: 24/25-26-37/38-40-41-48/23-50/53-63<br>S: (1/2-)26-28-36/37/39-45-60-61 | | |
| 050-013-00-0 | trioctyltin compounds, with the exception of those specified elsewhere in this Annex | A | — | — | Xi; R36/37/38<br>R53 | Xi<br>R: 36/37/38-53<br>S: (2-)61 | C ≥ 1 %: Xi; R36/37/38 | 1 |
| 078-001-00-0 | tetrachloroplatinates with the exception of those specified elsewhere in this Annex | A | — | — | T; R25<br>Xi; R41<br>R42/43 | T<br>R: 25-41-42/43<br>S: (2-)22-26-36/37/39-45 | | |
| 078-005-00-2 | hexachloroplatinates with the exception of those specified elsewhere in this Annex | A | — | — | T; R25<br>Xi; R41<br>R42/43 | T<br>R: 25-41-42/43<br>S: (1/2-)22-26-36/37/39-45 | | |
| 081-001-00-3 | thallium | | 231-138-1 | 7440-28-0 | T+; R26/28<br>R33<br>R53 | T+<br>R: 26/28-33-53<br>S: (1/2-)13-28-45-61 | | |
| 092-001-00-8 | uranium | | 231-170-6 | 7440-61-1 | T+; R26/28<br>R33<br>R53 | T+<br>R: 26/28-33-53<br>S: (1/2-)20/21-45-61 | | |
| 601-004-01-8 | butane (containing ≥ 0,1 % butadiene (203-450-8)) [1]<br>isobutane (containing ≥ 0,1 % butadiene (203-450-8)) [2] | C<br>S | 203-448-7 [1]<br>200-857-2 [2] | 106-97-8 [1]<br>75-28-5 [2] | F+; R12<br>Carc. Cat. 1; R45<br>Muta. Cat. 2; R46 | F+; T<br>R: 45-46-12<br>S: 53-45 | | |
| 601-005-00-6 | 2,2-dimethylpropane<br>neopentane | | 207-343-7 | 463-82-1 | F+; R12<br>N; R51-53 | F+; N<br>R: 12-51/53<br>S: (2-)9-16-33-61 | | |
| 601-007-00-7 | hexane, mixture of isomers (containing < 5 % *n*-hexane (203-777-6)) | C | — | — | F; R11<br>Xn; R65<br>Xi; R38<br>R67<br>N; R51-53 | F; Xn; N<br>R: 11-38-51/53-65-67<br>S: (2-)9-16-29-33-61-62 | | 4<br>6 |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to prepara-tions |
|---|---|---|---|---|---|---|---|---|
| 601-013-00-X | 1,3-butadiene<br>buta-1,3-diene | D | 203-450-8 | 106-99-0 | F+; R12<br>Carc. Cat. 1; R45<br>Muta. Cat. 2; R46 | F+; T<br>R: 45-46-12<br>S: 53-45 | | |
| 601-041-00-2 | dibenz[*a*,*h*]anthracene | | 200-181-8 | 53-70-3 | Carc. Cat. 2; R45<br>N; R50-53 | T; N<br>R: 45-50/53<br>S: 53-45-60-61 | C ≥ 0,01 %: T; R45 | |
| 602-027-00-9 | trichloroethylene<br>trichloroethene | | 201-167-4 | 79-01-6 | Carc. Cat. 2; R45<br>Muta. Cat. 3; R68<br>R67<br>Xi; R36/38<br>R52-53 | T<br>R: 45-36/38-52/53-67<br>S: 53-45-61 | | 6 |
| 602-037-00-3 | α-chlorotoluene<br>benzyl chloride | E | 202-853-6 | 100-44-7 | Carc. Cat. 2; R45<br>T; R23<br>Xn; R22-48/22<br>Xi; R37/38-41 | T<br>R: 45-22-23-37/38-41-48/22<br>S: 53-45 | | |
| 602-073-00-X | 1,4-dichlorobut-2-ene | E | 212-121-8 | 764-41-0 | Carc. Cat. 2; R45<br>T+; R26<br>T; R24/25<br>C; R34<br>N; R50-53 | T+; N<br>R: 45-24/25-26-34-50/53<br>S: 53-45-60-61 | C ≥ 25 %: T+; R45-24/25-26-34<br>10 % ≤ C < 25 %: T+; R45-21/22-26-34<br>7 % ≤ C < 10 %: T+;<br>R45-21/22-26-36/37/38<br>5 % ≤ C < 7 %: T;<br>R45-21/22-23-36/37/38<br>3 % ≤ C < 5 %: T; R45-21/22-23<br>1 % ≤ C < 3 %: T; R45-23<br>0,1 % ≤ C < 1 %: T; R45-20<br>0,01 % ≤ C < 0,1 %: T; R45 | |
| 602-076-00-6 | 2,3,4-trichlorobut-1-ene | | 219-397-9 | 2431-50-7 | Carc. Cat 3; R40<br>T; R23<br>Xn; R22<br>Xi; R36/37/38<br>N; R50-53 | T; N<br>R: 22-23-36/37/38-40-50/53<br>S: (1/2-)36/37-45-60-61 | C ≥ 25 %: T; R22-23-36/37/38-40<br>20 % ≤ C <25 %: Xn; R20-36/37/38-40<br>3 % ≤ C < 20 %: Xn; R20-40<br>0,1 % ≤ C < 3 %: Xn; R40 | |
| 602-084-00-X | 1,1-dichloro-1-fluoroethane | | 404-080-1 | 1717-00-6 | R52-53<br>N; R59 | N<br>R: 52/53-59<br>S: 59-61 | | |
| 603-014-00-0 | 2-butoxyethanol<br>ethylene glycol monobutyl ether<br>butyl cellosolve | | 203-905-0 | 111-76-2 | Xn; R20/21/22<br>Xi; R36/38 | Xn<br>R: 20/21/22-36/38<br>S: (2-)36/37-46 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to prepara-tions |
|---|---|---|---|---|---|---|---|---|
| 603-024-00-5 | 1,4-dioxane | D | 204-661-8 | 123-91-1 | F; R11-19<br>Carc. Cat. 3; R40<br>Xi; R36/37<br>R66 | F; Xn<br>R: 11-19-36/37-40-66<br>S: (2-)9-16-36/37-46 | | |
| 603-038-00-1 | allyl glycidyl ether<br>allyl 2,3-epoxypropyl ether<br>prop-2-en-1-yl 2,3-epoxypropyl ether | | 203-442-4 | 106-92-3 | R10<br>Carc. Cat. 3; R40<br>Muta. Cat. 3; R68<br>Repr. Cat. 3; R62<br>Xn; R20/22<br>Xi; R37/38-41<br>R43<br>R52-53 | Xn<br>R: 10-20/22-37/38-40-41-43-52/53-62-68<br>S: (2-)24/25-26-36/37/39-61 | | |
| 603-039-00-7 | butyl glycidyl ether<br>butyl 2,3-epoxypropyl ether | | 219-376-4 | 2426-08-6 | R10<br>Carc. Cat. 3; R40<br>Muta. Cat. 3; R68<br>Xn; R20/22<br>Xi; R37<br>R43<br>R52-53 | Xn<br>R:<br>10-20/22-37-40-43-52/53-68<br>S: (2-)24/25-36/37-61 | | |
| 603-044-00-4 | dicofol (ISO)<br>2,2,2-trichloro-1,1-bis (4-chlorophenyl)ethanol | | 204-082-0 | 115-32-2 | Xn; R21/22<br>Xi; R38<br>R43<br>N; R50-53 | Xn; N<br>R: 21/22-38-43-50/53<br>S: (2-)36/37-60-61 | | |
| 603-046-00-5 | bis (chloromethyl) ether<br>oxybis(chloromethane) | E | 208-832-8 | 542-88-1 | R10<br>Carc. Cat. 1; R45<br>T+; R26<br>T; R24<br>Xn; R22 | T+<br>R: 45-10-22-24-26<br>S: 53-45 | C ≥ 25 %: T+; R45-22-24-26<br>7 % ≤ C < 25 %: T+; R45-21-26<br>3 % ≤ C < 7 %: T; R45-21-23<br>1 % ≤ C < 3 %: T; R45-23<br>0,1 % ≤ C < 1 %: T; R45-20<br>0,001 % ≤ C < 0,1 %: T; R45 | |
| 603-049-00-1 | chlorfenethol (ISO)<br>1,1-bis (4-chlorophenyl) ethanol | | 201-246-3 | 80-06-8 | Xn; R22<br>N; R51-53 | Xn; N<br>R: 22-51/53<br>S: (2-)36-61 | | |
| 603-055-00-4 | propylene oxide<br>1,2-epoxypropane<br>methyloxirane | E | 200-879-2 | 75-56-9 | F+; R12<br>Carc. Cat. 2; R45<br>Muta. Cat. 2; R46<br>Xn; R20/21/22<br>Xi; R36/37/38 | F+; T<br>R:<br>45-46-12-20/21/22-36/37/38<br>S: 53-45 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to prepara-tions |
|---|---|---|---|---|---|---|---|---|
| 603-065-00-9 | resorcinol diglycidyl ether<br>1,3-bis(2,3-epoxypropoxy)benzene | | 202-987-5 | 101-90-6 | Carc. Cat. 3; R40<br>Muta. Cat. 3; R68<br>Xn; R21/22<br>Xi; R36/38<br>R43<br>R52-53 | Xn<br>R:<br>21/22-36/38-40-43-52/53-68<br>S: (2-)23-36/37-61 | | |
| 603-067-00-X | phenyl glycidyl ether<br>2,3-epoxypropyl phenyl ether<br>1,2-epoxy-3-phenoxypropane | E | 204-557-2 | 122-60-1 | Carc. Cat. 2; R45<br>Muta. Cat. 3; R68<br>Xn; R20<br>Xi; R37/38<br>R43<br>R52-53 | T<br>R: 45-20-37/38-43-52/53<br>S: 53-45-61 | | |
| 603-085-00-8 | bronopol (INN)<br>2-bromo-2-nitropropane-1,3-diol | | 200-143-0 | 52-51-7 | Xn; R21/22<br>Xi; R37/38-41<br>N; R50 | Xn; N<br>R: 21/22-37/38-41-50<br>S: (2-)26-37/39-61 | | |
| 603-091-00-0 | *exo*-1-methyl-4-(1-methylethyl)-7-oxabicyclo[2.2.1]heptan-2-ol | | 402-470-6 | 87172-89-2 | Xn; R22<br>Xi; R41 | Xn<br>R: 22-41<br>S: (2-)26-39 | | |
| 604-011-00-7 | 2,4-dichlorophenol | | 204-429-6 | 120-83-2 | T; R24<br>Xn; R22<br>C; R34<br>N; R51-53 | T; N<br>R: 22-24-34-51/53<br>S: (1/2-)26-36/37/39-45-61 | | |
| 604-021-00-1 | sodium 2-biphenylate<br>2-phenylphenol, sodium salt | | 205-055-6 | 132-27-4 | Xn; R22<br>Xi; R37/38-41<br>N; R50 | Xn; N<br>R: 22-37/38-41-50<br>S: (2-)22-26-61 | | |
| 604-038-00-4 | 4-chloro-3,5-dimethylphenol [1]<br>chloroxylenol [2] | | 201-793-8 [1]<br>215-316-6 [2] | 88-04-0 [1]<br>1321-23-9 [2] | Xn; R22<br>Xi; R36/38<br>R43 | Xn<br>R: 22-36/38-43<br>S: (2-)24-37 | | |
| 605-008-00-3 | acrylaldehyde<br>acrolein<br>prop-2-enal | D | 203-453-4 | 107-02-8 | F; R11<br>T+; R26<br>T; R24/25<br>C; R34<br>N; R50 | F; T+; N<br>R: 11-24/25-26-34-50<br>S: 23-26-28-36/37/39-45-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to prepara-tions |
|---|---|---|---|---|---|---|---|---|
| 605-009-00-9 | crotonaldehyde [1]<br>2-butenal [1]<br>(*E*)-2-butenal [2]<br>(*E*)-crotonaldehyde [2] | | 224-030-0 [1]<br>204-647-1 [2] | 4170-30-3 [1]<br>123-73-9 [2] | F; R11<br>Muta. Cat. 3; R68<br>T+; R26<br>T; R24/25<br>Xn; R48/22<br>Xi; R37/38-41<br>N; R50 | F; T+; N<br>R: 11-24/25-26-37/38-41-48/22-50-68<br>S: (1/2-)26-28-36/37/39-45-61 | | |
| 607-004-00-7 | trichloroacetic acid | | 200-927-2 | 76-03-9 | C; R35<br>N; R50-53 | C; N<br>R: 35-50/53<br>S: (1/2-)26-36/37/39-45-60-61 | C ≥ 10 %: C; R35<br>5 % ≤ C < 10 %: C; R34<br>1 % ≤ C < 5 %: Xi; R36/37/38 | |
| 607-005-00-2 | TCA-sodium (ISO)<br>sodium trichloroacetate | | 211-479-2 | 650-51-1 | Xi; R37<br>N; R50-53 | Xi; N<br>R: 37-50/53<br>S: (2-)46-60-61 | | |
| 607-035-00-6 | methyl methacrylate<br>methyl 2-methylprop-2-enoate<br>methyl 2-methylpropenoate | D | 201-297-1 | 80-62-6 | F; R11<br>Xi; R37/38<br>R43 | F; Xi<br>R: 11-37/38-43<br>S: (2-)24-37-46 | | |
| 607-039-00-8 | 2,4-D (ISO)<br>2,4-dichlorophenoxyacetic acid | | 202-361-1 | 94-75-7 | Xn; R22<br>Xi; R37-41<br>R43<br>R52-53 | Xn<br>R: 22-37-41-43-52/53<br>S: (2-)24/25-26-36/37/39-46-61 | | |
| 607-040-00-3 | salts of 2,4-D | A | — | — | Xn; R22<br>Xi; R41<br>R43<br>N; R51-53 | Xn; N<br>R: 22-41-43-51/53<br>S: (2-)24/25-26-36/37/39-46-61 | | |
| 607-043-00-X | dicamba (ISO)<br>2,5-dichloro-6-methoxybenzoic acid<br>3,6-dichloro-2-methoxybenzoic acid | | 217-635-6 | 1918-00-9 | Xn; R22<br>Xi; R41<br>R52-53 | Xn<br>R: 22-41-52/53<br>S: (2-)26-61 | | |
| 607-061-00-8 | acrylic acid<br>prop-2-enoic acid | D | 201-177-9 | 79-10-7 | R10<br>Xn; R20/21/22<br>C; R35<br>N; R50 | C; N<br>R: 10-20/21/22-35-50<br>S: (1/2-)26-36/37/39-45-61 | C ≥ 25 %: C; R20/21/22-35<br>10 % ≤ C < 25 %: C; R35<br>5 % ≤ C < 10 %: C; R34<br>1 % ≤ C < 5 %: Xi; R36/37/38 | |
| 607-083-00-8 | 2,4-DB (ISO)<br>4-(2,4-dichlorophenoxy)butyric acid | | 202-366-9 | 94-82-6 | Xn; R22<br>N; R51-53 | Xn; N<br>R: 22-51/53<br>S: (2-)25-29-46-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to prepara-tions |
|---|---|---|---|---|---|---|---|---|
| 607-084-00-3 | salts of 2,4-DB | A | — | — | Xn; R22<br>Xi; R41<br>N; R51-53 | Xn; N<br>R: 22-41-51/53<br>S: (2-)26-29-39-46-61 | | |
| 607-088-00-5 | methacrylic acid<br>2-methylpropenoic acid | D | 201-204-4 | 79-41-4 | Xn; R21/22<br>C; R35 | C<br>R: 21/22-35<br>S: (1/2-)26-36/37/39-45 | C ≥ 25 %: C; R21/22-35<br>10 % ≤ C < 25 %: C; R35<br>5 % ≤ C < 10 %: C; R34<br>1 % ≤ C < 5 %: Xi; R36/37/38 | |
| 607-133-00-9 | monoalkyl or monoaryl or monoalkylaryl esters of acrylic acid with the exception of those specified elsewhere in this Annex | A | — | — | Xi; R36/37/38<br>N; R51-53 | Xi; N<br>R: 36/37/38-51/53<br>S: (2-)26-28-61 | C ≥ 10 %: Xi; R36/37/38 | |
| 607-134-00-4 | monoalkyl or monoaryl or monoalkyaryl esters of methacrylic acid with the exception of those specified elsewhere in this Annex | A | — | — | Xi; R36/37/38 | Xi<br>R: 36/37/38<br>S: (2-)26-28 | C ≥ 10 %: Xi; R36/37/38 | |
| 607-288-00-2 | tetrasodium (c-(3-(1-(3-(e-6-dichloro-5-cyanopyrimidin-f-yl(methyl)amino)propyl)-1,6-dihydro-2-hydroxy-4-methyl-6-oxo-3-pyridylazo)-4-sulfonatophenylsulfamoyl) phthalocyanine-a,b,d-trisulfonato(6-))nickelato II, where a is 1 or 2 or 3 or 4, b is 8 or 9 or 10 or 11, c is 15 or 16 or 17 or 18, d is 22 or 23 or 24 or 25 and where e and f together are 2 and 4 or 4 and 2 respectively | | 410-160-7 | 148732-74-5 | Xi; R36<br>R43<br>R52-53 | Xi<br>R: 36-43-52/53<br>S: (2-)22-26-36/37-61 | | |
| 607-300-00-6 | trisodium [2-(5-chloro-2,6-difluoropyrimidin-4-ylamino)-5-(b-sulfamoyl-c,d-sulfonatophthalocyanin-a-yl-*K*4,*N*29,*N*30,*N*31,*N*32-sulfonylamino)benzoato(5-)] cuprate(II) where a = 1,2,3,4 b = 8,9,10,11 c = 15,16,17,18 d = 22,23,24,25 | | 411-430-7 | — | Xi; R41<br>R43 | Xi<br>R: 41-43<br>S: (2-)26-36/37/39 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 608-001-00-3 | acetonitrile<br>cyanomethane | | 200-835-2 | 75-05-8 | F; R11<br>Xn; R20/21/22<br>Xi; R36 | F; Xn<br>R: 11-20/21/22-36<br>S: (1/2-)16-36/37 | | |
| 608-007-00-6 | ioxynil (ISO)<br>4-hydroxy-3,5-diiodobenzonitrile | | 216-881-1 | 1689-83-4 | Repr. Cat. 3; R63<br>T; R25<br>Xn; R21<br>N; R50-53 | T; N<br>R: 21-25-50/53-63<br>S: (1/2-)36/37-45-60-61 | | |
| 608-014-00-4 | chlorothalonil (ISO)<br>tetrachloroisophthalonitrile | | 217-588-1 | 1897-45-6 | Carc. Cat. 3; R40<br>N; R50-53 | Xn; N<br>R: 40-50/53<br>S: (2-)36/37-60-61 | | |
| 608-015-00-X | dichlobenil (ISO)<br>2,6-dichlorobenzonitrile | | 214-787-5 | 1194-65-6 | Xn; R21<br>N; R51-53 | Xn; N<br>R: 21-51/53<br>S: (2-)36/37-61 | | |
| 608-017-00-0 | bromoxynil octanoate (ISO)<br>2,6-dibromo-4-cyanophenyl octanoate | | 216-885-3 | 1689-99-2 | Repr. Cat. 3; R63<br>Xn; R21/22<br>N; R50-53 | Xn; N<br>R: 21/22-50/53-63<br>S: (2-)36/37-60-61 | | |
| 608-018-00-6 | ioxynil octanoate (ISO)<br>4-cyano-2,6-diiodophenyl octanoate | | 223-375-4 | 3861-47-0 | Repr. Cat. 3; R63<br>Xn; R22<br>N; R50-53 | Xn; N<br>R: 22-50/53-63<br>S: (2-)36/37-60-61 | | |
| 609-016-00-8 | dinitrophenol [1]<br>2,4(or 2,6)-dinitrophenol [2] | | 247-096-2 [1]<br>275-732-9 [2] | 25550-58-7 [1]<br>71629-74-8 [2] | T; R23/24/25<br>R33<br>N; R50-53 | T; N<br>R: 23/24/25-33-50/53<br>S: (1/2-)28-37-45-60-61 | | |
| 609-021-00-5 | sodium salt of DNOC [1]<br>sodium 4,6-dinitro-*o*-cresolate [1]<br>potassium salt of DNOC [2]<br>potassium 4,6-dinitro-*o*-cresolate [2] | | 219-007-7 [1]<br>- [2] | 2312-76-7 [1]<br>5787-96-2 [2] | T; R23/24/25<br>R33<br>N; R50-53 | T; N<br>R: 23/24/25-33-50/53<br>S: (1/2-)13-45-60-61 | | |
| 609-022-00-0 | ammonium salt of DNOC<br>ammonium 4,6-dinitro-*o*-tolyl oxide | | 221-037-0 | 2980-64-5 | T+; R26/27/28<br>R33<br>N; R50-53 | T+; N<br>R: 26/27/28-33-50/53<br>S: (1/2-)13-28-45-60-61 | | |
| 609-024-00-1 | binapacryl (ISO)<br>2-*sec*-butyl-4,6-dinitrophenyl-3-methylcrotonate | E | 207-612-9 | 485-31-4 | Repr. Cat. 2; R61<br>Xn; R21/22<br>N; R50-53 | T; N<br>R: 61-21/22-50/53<br>S: 53-45-60-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to prepara-tions |
|---|---|---|---|---|---|---|---|---|
| 609-026-00-2 | salts and esters of dinoseb, with the exception of those specified elsewhere in this Annex | A<br>E | — | — | R44<br>Repr. Cat. 2; R61<br>Repr. Cat. 3; R62<br>T; R24/25<br>Xi; R36<br>N; R50-53 | T; N<br>R: 61-62-24/25-36-44-50/53<br>S: 53-45-60-61 | | |
| 609-027-00-8 | dinocton<br>mixture of isomers: methyl 2-octyl-4,6-dinitrophenyl carbonate, methyl 4-octyl-2,6-dinitrophenyl carbonate | | — | 63919-26-6 | Xn; R22<br>N; R50-53 | Xn; N<br>R: 22-50/53<br>S: (2-)60-61 | | |
| 609-028-00-3 | dinex<br>2-cyclohexyl-4,6-dinitrophenol | | 205-042-5 | 131-89-5 | T; R23/24/25<br>N; R50-53 | T; N<br>R: 23/24/25-50/53<br>S: (1/2-)13-45-60-61 | | |
| 609-029-00-9 | salts and esters of dinex | A | — | — | T; R23/24/25<br>N; R50-53 | T; N<br>R: 23/24/25-50/53<br>S: (1/2-)13-45-60-61 | | |
| 609-032-00-5 | bromofenoxim (ISO)<br>3,5-dibromo-4-hydroxybenzaldehyde-*O*-(2,4-dinitrophenyl)-oxime | | 236-129-6 | 13181-17-4 | Xn; R22<br>N; R50-53 | Xn; N<br>R: 22-50/53<br>S: (2-)25-60-61 | | |
| 609-033-00-0 | dinosam<br>2-(1-methylbutyl)-4,6-dinitrophenol | | — | 4097-36-3 | T; R23/24/25<br>N; R50-53 | T; N<br>R: 23/24/25-50/53<br>S: (1/2-)13-45-60-61 | | |
| 609-034-00-6 | salts and esters of dinosam | A | — | — | T; R23/24/25<br>N; R50-53 | T; N<br>R: 23/24/25-50/53<br>S: (1/2-)13-45-60-61 | | |
| 609-042-00-X | pendimethalin (ISO)<br>*N*-(1-ethylpropyl)-2,6-dinitro-3,4-xylidine | | 254-938-2 | 40487-42-1 | R43<br>N; R50-53 | Xi; N<br>R: 43-50/53<br>S: (2-)24-29-37-60-61 | | |
| 609-045-00-6 | mixture of: 4,6-dinitro-2-(3-octyl) phenyl methyl carbonate and 4,6-dinitro-2-(4-octyl)phenyl methyl carbonate<br>dinocton-6 | | — | 8069-76-9 | Xn; R22<br>N; R50-53 | Xn; N<br>R: 22-50/53<br>S: (2-)60-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 609-046-00-1 | trifluralin (ISO)<br>(containing < 0,5 ppm NPDA)<br>α,α,α-trifluoro-2,6-dinitro-*N*,*N*-dipropyl-*p*-toluidine<br>(containing < 0,5 ppm NPDA)<br>2,6-dinitro-*N*,*N*-dipropyl-4-trifluoromethylaniline<br>(containing < 0,5 ppm NPDA)<br>*N*,*N*-dipropyl-2,6-dinitro-4-trifluoromethylaniline<br>(containing < 0,5 ppm NPDA) | | 216-428-8 | 1582-09-8 | Xi; R36<br>R43<br>N; R50-53 | Xi; N<br>R: 36-43-50/53<br>S: (2-)24-37-60-61 | | |
| 609-053-00-X | hydrazine trinitromethane | E | 414-850-9 | — | E; R3<br>O; R8<br>Carc. Cat. 2; R45<br>T; R23/25<br>R43 | E; T<br>R: 45-3-8-23/25-43<br>S: 53-45 | | |
| 611-003-00-7 | fenaminosulf (ISO)<br>sodium 4-dimethylaminobenzene-diazosulphonate | | 205-419-4 | 140-56-7 | T; R25<br>Xn; R21<br>R52-53 | T<br>R: 21-25-52/53<br>S: (1/2-)36/37-45-61 | | |
| 612-023-00-9 | phenylhydrazine [1]<br>phenylhydrazinium chloride [2]<br>phenylhydrazine hydrochloride [3]<br>phenylhydrazinium sulphate (2:1) [4] | E | 202-873-5 [1]<br>200-444-7 [2]<br>248-259-0 [3]<br>257-622-2 [4] | 100-63-0 [1]<br>59-88-1 [2]<br>27140-08-5 [3]<br>52033-74-6 [4] | Carc. Cat. 2; R45<br>Muta. Cat. 3; R68<br>T; R23/24/25-48/23/24/25<br>Xi; R36/38<br>R43<br>N; R50 | T; N<br>R: 45-23/24/25-36/38-43-48/23/24/25-50<br>S: 53-45-61 | | |
| 612-024-00-4 | *m*-toluidine<br>3-aminotoluene | | 203-583-1 | 108-44-1 | T; R23/24/25<br>R33<br>N; R50 | T; N<br>R: 23/24/25-33-50<br>S: (1/2-)28-36/37-45-61 | | |
| 612-027-00-0 | xylidines with the exception of those specified elsewhere in this Annex<br>dimethyl anilines with the exception of those specified elsewhere in this Annex | C | — | — | T; R23/24/25<br>R33<br>N; R51-53 | T; N<br>R: 23/24/25-33-51/53<br>S: (1/2-)28-36/37-45-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to prepara-tions |
|---|---|---|---|---|---|---|---|---|
| 612-077-00-3 | dimethylnitrosoamine<br>*N*-nitrosodimethylamine | E | 200-549-8 | 62-75-9 | Carc. Cat. 2; R45<br>T+; R26<br>T; R25-48/25<br>N; R51-53 | T+; N<br>R: 45-25-26-48/25-51/53<br>S: 53-45-61 | C ≥ 25 %: T+; R45-25-26-48/25<br>10 % ≤ C < 25 %: T+; R45-22-26-48/25<br>7 % ≤ C < 10 %: T+; R45-22-26-48/22<br>3 % ≤ C < 7 %: T; R45-22-23-48/22<br>1 % < C < 3 %: T; R45-23-48/22<br>0,1 % ≤ C < 1 %: T; R45-20<br>0,001 % ≤ C < 0,1 %: T; R45 | |
| 612-083-00-6 | 1-methyl-3-nitro-1-nitrosoguanidine | E | 200-730-1 | 70-25-7 | Carc. Cat. 2; R45<br>Xn; R20<br>Xi; R36/38<br>N; R51-53 | T; N<br>R: 45-20-36/38-51/53<br>S: 53-45-61 | C ≥ 25 %: T+; R45-20-36/38<br>20 % < C < 25 %: T+; R45-36/38<br>0,01 % ≤ C < 20 %: T; R45 | |
| 612-088-00-3 | simazine (ISO)<br>6-chloro-*N*,*N*′-diethyl-1,3,5-triazine-2,4-diamine | | 204-535-2 | 122-34-9 | Carc. Cat. 3; R40<br>N; R50-53 | Xn; N<br>R: 40-50/53<br>S: (2-)36/37-46-60-61 | | |
| 612-098-00-8 | nitrosodipropylamine | E | 210-698-0 | 621-64-7 | Carc. Cat. 2; R45<br>Xn; R22<br>N; R51-53 | T; N<br>R: 45-22-51/53<br>S: 53-45-61 | C > 25 %: T+; R45-22<br>0,001 % < C < 25 %: T; R45 | |
| 613-025-00-2 | cinerin I<br>3-(but-2-enyl)-2-methyl-4-oxocyclopent-2-enyl 2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate | | 246-948-0 | 25402-06-6 | Xn; R22<br>N; R50-53 | Xn; N<br>R: 22-50/53<br>S: (2-)60-61 | | |
| 613-026-00-8 | cinerin II<br>3-(but-2-enyl)-2-methyl-4-oxocyclopent-2-enyl 2,2-dimethyl-3-(3-methoxy-2-methyl-3-oxoprop-1-enyl) cyclopropanecarboxylate | | 204-454-2 | 121-20-0 | Xn; R22<br>N; R50-53 | Xn; N<br>R: 22-50/53<br>S: (2-)60-61 | | |
| 613-033-00-6 | 2-methylaziridine<br>propyleneimine | E | 200-878-7 | 75-55-8 | F; R11<br>Carc. Cat. 2; R45<br>T+; R26/27/28<br>Xi; R41<br>N; R51-53 | F; T+; N<br>R: 45-11-26/27/28-41-51/53<br>S: 53-45-61 | C ≥ 10 %: T+; R45-26/27/28-41<br>7 % ≤ C < 10 %: T+; R45-26/27/28-36<br>5 % ≤ C < 7 %: T; R45-23/24/25-36<br>1 % ≤ C < 5 %: T; R45-23/24/25<br>0,1 % ≤ C < 1 %: T; R45-20/21/22<br>0,01 % ≤ C < 0,1 %: T; R45 | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 613-042-00-5 | imazalil (ISO)<br>1-[2-(allyloxy)-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole | | 252-615-0 | 35554-44-0 | Xn; R20/22<br>Xi; R41<br>N; R50-53 | Xn; N<br>R: 20/22-41-50/53<br>S: (2-)26-39-60-61 | | |
| 613-044-00-6 | captan (ISO)<br>1,2,3,6-tetrahydro-*N*-(trichloromethylthio)phthalimide | | 205-087-0 | 133-06-2 | Carc. Cat. 3; R40<br>T; R23<br>Xi; R41<br>R43<br>N; R50 | T; N<br>R: 23-40-41-43-50<br>S: (1/2-)26-29-36/37/39-45-61 | | |
| 613-045-00-1 | folpet (ISO)<br>*N*-(trichloromethylthio)phthalimide | | 205-088-6 | 133-07-3 | Carc. Cat. 3; R40<br>Xn; R20<br>Xi; R36<br>R43<br>N; R50 | Xn; N<br>R: 20-36-40-43-50<br>S: (2-)36/37-46-61 | | |
| 613-068-00-7 | atrazine (ISO)<br>2-chloro-4-ethylamine-6-isopropylamine-1,3,5-triazine | | 217-617-8 | 1912-24-9 | Xn; R48/22<br>R43<br>N; R50-53 | Xn; N<br>R: 43-48/22-50/53<br>S: (2-)36/37-60-61 | | |
| 613-070-00-8 | propylenethiourea | | — | 2122-19-2 | Repr. Cat. 3; R63<br>Xn; R22<br>R52-53 | Xn<br>R: 22-52/53-63<br>S: (2-)36/37-46-61 | | |
| 613-090-00-7 | paraquat dichloride [1]<br>1,1-dimethyl-4,4′-bipyridinium dichloride [1]<br>paraquat dimethylsulfate [2]<br>1,1-dimethyl-4,4′-bipyridinium dimethyl sulphate [2] | | 217-615-7 [1]<br>218-196-3 [2] | 1910-42-5 [1]<br>2074-50-2 [2] | T+; R26<br>T; R24/25-48/25<br>Xi; R36/37/38<br>N; R50-53 | T+; N<br>R: 24/25-26-36/37/38-48/25-50/53<br>S: (1/2-)22-28-36/37/39-45-60-61 | | |
| 613-116-00-7 | tolylfluanid (ISO)<br>dichloro-*N*-[(dimethylamino) sulphonyl]fluoro-*N*-(*p*-tolyl) methanesulphenamide | | 211-986-9 | 731-27-1 | T; R23<br>Xn; R48/20<br>Xi; R36/37/38<br>R43<br>N; R50-53 | T; N<br>R: 23-36/37/38-43-48/20-50/53<br>S: (1/2-)24-26-37-38-45-60-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to prepara-tions |
|---|---|---|---|---|---|---|---|---|
| 615-005-00-9 | 4,4′-methylenediphenyl diisocyanate [1]<br>diphenylmethane-4,4′-diisocyanate [1]<br>2,2′-methylenediphenyl diisocyanate [2]<br>diphenylmethane-2,2′-diisocyanate [2]<br>*o*-(*p*-isocyanatobenzyl)phenyl isocyanate [3]<br>diphenylmethane-2,4′-diisocyanate [3]<br>methylenediphenyl diisocyanate [4] | C | 202-966-0 [1]<br>219-799-4 [2]<br>227-534-9 [3]<br>247-714-0 [4] | 101-68-8 [1]<br>2536-05-2 [2]<br>5873-54-1 [3]<br>26447-40-5 [4] | Xn; R20<br>Xi; R36/37/38<br>R42/43 | Xn<br>R: 20-36/37/38-42/43<br>S: (1/2-)23-36/37-45 | C ≥ 25 %: Xn; R20-36/37/38-42/43<br>5 % ≤ C < 25 %: Xn; R36/37/38-42/43<br>1 % ≤ C < 5 %: Xn; R42/43<br>0,1 % ≤ C < 1 %: Xn; R42 | 2 |
| 616-003-00-0 | acrylamide<br>prop-2-enamide | D<br>E | 201-173-7 | 79-06-1 | Carc. Cat. 2; R45<br>Muta. Cat. 2; R46<br>Repr. Cat. 3; R62<br>T; R25-48/23/24/25<br>Xn; R20/21<br>Xi; R36/38<br>R43 | T<br>R: 45-46-20/21-25-36/38-43-48/23/24/25-62<br>S: 53-45 | | |
| 616-004-00-6 | allidochlor (ISO)<br>*N*,*N*-diallylchloroacetamide | | 202-270-7 | 93-71-0 | Xn; R21/22<br>Xi; R36/38<br>N; R51-53 | Xn; N<br>R: 21/22-36/38-51/53<br>S: (2-)26-28-36/37/39-61 | | |
| 616-007-00-2 | diphenamid (ISO)<br>*N*,*N*-dimethyl-2,2-diphenylacetamide | | 213-482-4 | 957-51-7 | Xn; R22<br>R52-53 | Xn<br>R: 22-52/53<br>S: (2-)61 | | |
| 616-008-00-8 | propachlor (ISO)<br>2-chloro-*N*-isopropylacetanilide<br>*α*-chloro-*N*-isopropylacetanilide | | 217-638-2 | 1918-16-7 | Xn; R22<br>Xi; R36<br>R43<br>N; R50-53 | Xn; N<br>R: 22-36-43-50/53<br>S: (2-)24-37-60-61 | | |
| 616-009-00-3 | propanil (ISO)<br>3′,4′-dichloropropionanilide | | 211-914-6 | 709-98-8 | Xn; R22<br>N; R50 | Xn; N<br>R: 22-50<br>S: (2-)22-61 | | |
| 616-011-00-4 | *N*,*N*-dimethylacetamide | E | 204-826-4 | 127-19-5 | Repr. Cat. 2; R61<br>Xn; R20/21 | T<br>R: 61-20/21<br>S: 53-45 | C ≥ 25 %: T; R61-20/21<br>5 % ≤ C < 25 %: T; R61 | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to prepara-tions |
|---|---|---|---|---|---|---|---|---|
| 616-014-00-0 | 2-butanone oxime<br>ethyl methyl ketoxime<br>ethyl methyl ketone oxime | | 202-496-6 | 96-29-7 | Carc. Cat. 3; R40<br>Xn; R21<br>Xi; R41<br>R43 | Xn<br>R: 21-40-41-43<br>S: (2-)13-23-26-36/37/39 | | |
| 616-015-00-6 | alachlor (ISO)<br>2-chloro-2′,6′-diethyl-N-(methoxymethyl)acetanilide | | 240-110-8 | 15972-60-8 | Carc. Cat. 3; R40<br>Xn; R22<br>R43<br>N; R50-53 | Xn; N<br>R: 22-40-43-50/53<br>S: (2-)36/37/39-60-61 | | |
| 616-017-00-7 | cartap hydrochloride | | 239-309-2 | 15263-52-2 | Xn; R21/22<br>N; R50-53 | Xn; N<br>R: 21/22-50/53<br>S: (2-)36/37-60-61 | | |
| 616-018-00-2 | *N*,*N*-diethyl-*m*-toluamide<br>deet | | 205-149-7 | 134-62-3 | Xn; R22<br>Xi; R36/38<br>R52-53 | Xn<br>R: 22-36/38-52/53<br>S: (2-)61 | | |
| 616-020-00-3 | tebuthiuron (ISO)<br>1-(5-*tert*-butyl-1,3,4-thiadiazol-2-yl)-1,3-dimethylurea | | 251-793-7 | 34014-18-1 | Xn; R22<br>N; R50-53 | Xn; N<br>R: 22-50/53<br>S: (2-)37-60-61 | | |
| 616-021-00-9 | thiazfluron (ISO)<br>1,3-dimethyl-1-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)urea | | 246-901-4 | 25366-23-8 | Xn; R22<br>N; R50-53 | Xn; N<br>R: 22-50/53<br>S: (2-)60-61 | | |
| 616-025-00-0 | valinamide | | 402-840-7 | 20108-78-5 | Repr. Cat. 3; R62<br>Xi; R36<br>R43 | Xn<br>R: 36-43-62<br>S: (2-)26-36/37 | | |
| 650-013-00-6 | asbestos | E | —<br>—<br>—<br>—<br>—<br>—<br>— | 12001-28-4<br>132207-32-0<br>12172-73-5<br>77536-66-4<br>77536-68-6<br>77536-67-5<br>12001-29-5 | Carc. Cat. 1; R45<br>T; R48/23 | T<br>R: 45-48/23<br>S: 53-45 | | |

*ANNEX 1C*

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 004-003-00-8 | beryllium oxide | E | 215-133-1 | 1304-56-9 | Carc. Cat. 2; R49<br>T+; R26<br>T; R25-48/23<br>Xi; R36/37/38<br>R43 | T+<br>R: 49-25-26-36/37/38-43-48/23<br>S: 53-45 | | |
| 007-025-00-6 | (4-hydrazinophenyl)-*N*-methylmethanesulfonamide hydrochloride | | 406-090-1 | 81880-96-8 | Muta. Cat. 3; R68<br>T; R25-48/25<br>R43<br>N; R50-53 | T; N<br>R: 25-43-48/25-68-50/53<br>S: (1/2-)22-36/37/39-45-60-61 | | |
| 007-026-00-1 | oxo-((2,2,6,6-tetramethylpiperidin-4-yl)amino)carbonylacetohydrazide | | 413-230-5 | 122035-71-6 | Xi; R41<br>R43 | Xi<br>R: 41-43<br>S: (2-)8-22-24-26-30-37/39 | | |
| 007-027-00-7 | 1,6-bis(3,3-bis((1-methylpentylidenimino) propyl)ureido)hexane | | 420-190-2 | — | Xn; R21/22<br>C; R34<br>R43<br>N; R50-53 | C; N<br>R: 21/22-34-43-50/53<br>S: (1/2-)7-26-36/37/39-45-60-61 | | |
| 013-008-00-4 | di-*n*-octylaluminium iodide | | 408-190-0 | 7585-14-0 | R14<br>F; R17<br>C; R34<br>N; R50-53 | F; C; N<br>R: 14-17-34-50/53<br>S: (1/2-)6-16-26-36/37/39-43-45-60-61 | | |
| 014-017-00-6 | flusilazole (ISO) bis(4-fluorophenyl)(methyl)(1*H*-1,2,4-triazol-1-ylmethyl)silane | E | — | 85509-19-9 | Carc. Cat. 3; R40<br>Repr. Cat. 2; R61<br>Xn; R22<br>N; R51-53 | T; N<br>R: 61-22-40-51/53<br>S: 53-45-61 | | |
| 014-018-00-1 | octamethylcyclotetrasiloxane | | 209-136-7 | 556-67-2 | Repr. Cat. 3; R62<br>R53 | Xn<br>R: 53-62<br>S: (2-)36/37-46-51-61 | | |
| 014-019-00-7 | a mixture of: 4-[[bis-(4-fluorophenyl)methylsilyl]methyl]-4*H*-1,2,4-triazole; 1-[[bis-(4-fluorophenyl)methylsilyl]methyl]-1*H*-1,2,4-triazole | E | 403-250-2 | — | Carc. Cat. 3; R40<br>Repr. Cat. 2; R61<br>Xn; R22<br>N; R51-53 | T; N<br>R: 61-22-40-51/53<br>S: 53-45-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 014-020-00-2 | bis(1,1-dimethyl-2-propynyloxy)dimethylsilane | | 414-960-7 | 53863-99-3 | Xn; R20 | Xn<br>R: 20<br>S: (2) | | |
| 014-021-00-8 | tris(isopropenyloxy)phenyl silane | | 411-340-8 | 52301-18-5 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 014-022-00-3 | reaction product of: (2-hydroxy-4-(3-propenoxy)benzophenone and triethoxysilane) with (hydrolysis product of silica and methyltrimethoxysilane) | | 401-530-9 | — | F; R11<br>T; R39/23/24/25<br>Xn; R20/21/22 | F; T<br>R: 11-20/21/22-39/23/24/25<br>S: (1/2-)16-29-36/37-45 | | |
| 014-023-00-9 | *α*,*ω*-dihydroxypoly(hex-5-en-1-ylmethylsiloxane) | | 408-160-7 | 125613-45-8 | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |
| 014-024-00-4 | 1-((3-(3-chloro-4-fluorophenyl)propyl)dimethylsilanyl)-4-ethoxybenzene | | 412-620-2 | 121626-74-2 | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |
| 014-025-00-X | 4-[3-(diethoxymethylsilylpropoxy)-2,2,6,6-tetramethyl]piperidine | | 411-400-3 | 102089-33-8 | Xn; R22-48/21<br>Xi; R38-41<br>R52-53 | Xn<br>R: 22-38-41-48/21-52/53<br>S: (2-)26-36/37/39-61 | | |
| 015-168-00-0 | fosthiazate (ISO)<br>(*RS*)-*S*-*sec*-butyl-*O*-ethyl-2-oxo-1,3-thiazolidin-3-ylphosphonothioate | | — | 98886-44-3 | T; R23/25-39<br>Xn; R21<br>Xi; R41<br>R43<br>N; R50-53 | T; N<br>R: 21-23/25-39-41-43-50/53<br>S: (1/2-)53-45-25-26-39-60-61 | | |
| 015-169-00-6 | tributyltetradecylphosphonium tetrafluoroborate | | 413-520-1 | — | Xn; R22-48/22<br>C; R34<br>R43<br>N; R50-53 | C; N<br>R: 22-34-43-48/22-50/53<br>S: (1/2-)26-28-36/37/39-45-60-61 | | |
| 015-170-00-1 | a mixture of: di-(1-octane-*N*,*N*,*N*-trimethylammonium) octylphosphate; 1-octane-*N*,*N*,*N*-trimethylammonium di-octylphosphate; 1-octane-*N*,*N*,*N*-trimethylammonium octylphosphate | | 407-490-9 | — | Xn; R21/22<br>C; R34 | C<br>R: 21/22-34<br>S: (1/2-)26-36/37/39-45 | | |
| 015-171-00-7 | *O*,*O*,*O*-tris(2(or 4)-$C_{9-10}$-isoalkylphenyl) phosphorothioate | | 406-940-1 | — | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 015-172-00-2 | a mixture of: bis(isotridecylammonium) mono(di-(4-methylpent-2-yloxy)thiophosphorothionylisopropyl)phosphate; isotridecylammonium bis(di-(4-methylpent-2-yloxy)thiophosphorothionylisopropyl) phosphate | | 406-240-6 | — | R10<br>C; R34<br>N; R51-53 | C; N<br>R: 10-34-51/53<br>S: (1/2-)23-26-28-36/37/39-45-61 | | |
| 015-173-00-8 | methyl [2-(1,1-dimethylethyl)-6-methoxypyrimidin-4-yl]ethylphosphonothioate | | 414-080-3 | 117291-73-3 | Xn; R22<br>N; R50-53 | Xn; N<br>R: 22-50/53<br>S: (2-)23-36-60-61 | | |
| 015-174-00-3 | 1-chloro-*N*,*N*-diethyl-1,1-diphenyl-1-(phenylmethyl)phosphoramine | | 411-370-1 | 82857-68-9 | T; R25<br>Xi; R41<br>N; R51-53 | T; N<br>R: 25-41-51/53<br>S: (1/2-)26-37/39-41-45-61 | | |
| 015-175-00-9 | *tert*-butyl (triphenylphosphoranylidene) acetate | | 412-880-7 | 35000-38-5 | T; R25<br>Xn; R48/22<br>Xi; R36<br>R43<br>N; R51-53 | T; N<br>R: 25-36-43-48/22-51/53<br>S: (1/2-)26-36/37/39-45-61 | | |
| 015-176-00-4 | *P*,*P*,*P*′,*P*′-tetrakis-(*o*-methoxyphenyl)propane-1,3-diphosphine | | 413-430-2 | 116163-96-3 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 015-177-00-X | ((4-phenylbutyl)hydroxyphosphoryl)acetic acid | | 412-170-7 | 83623-61-4 | Xn; R48/22<br>Xi; R41<br>R43 | Xn<br>R: 41-43-48/22<br>S: (2-)22-26-36/37/39 | | |
| 015-178-00-5 | (*R*)-α-phenylethylammonium (-)-(1*R*, 2*S*)-(1,2-epoxypropyl)phosphonate monohydrate | | 418-570-8 | 25383-07-7 | Repr. Cat. 3; R62<br>N; R51-53 | Xn; N<br>R: 62-51/53<br>S: (2-)22-36/37-61 | | |
| 015-179-00-0 | UVCB condensation product of: tetrakis-hydroxymethylphosphonium chloride, urea and distilled hydrogenated $C_{16-18}$ tallow alkylamine | | 422-720-8 | 166242-53-1 | Muta. Cat. 3; R68<br>Xn; R22-48/22<br>C; R34<br>R43<br>N; R50-53 | C; N<br>R: 22-34-43-48/22-68-50/53<br>S: (1/2-)26-36/37/39-45-60-61 | | |
| 016-063-00-2 | sodium metabisulphite | | 231-673-0 | 7681-57-4 | Xn; R22<br>Xi; R41<br>R31 | Xn<br>R: 22-31-41<br>S: (2-)26-39-46 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 016-072-00-1 | 3-amino-4-hydroxy-*N*-(2-methoxyethyl)-benzenesulfonamide | | 411-520-6 | 112195-27-4 | Xi; R41<br>R43<br>N; R51-53 | Xi; N<br>R: 41-43-51/53<br>S: (2-)24-26-37/39-61 | | |
| 016-073-00-7 | tetrakis(phenylmethyl)thioperoxydi(carbothioamide) | | 404-310-0 | 10591-85-2 | R53 | R: 53<br>S: 61 | | |
| 016-074-00-2 | 6-fluoro-2-methyl-3-(4-methylthiobenzyl)indene | | 405-410-7 | — | Xi; R38-41<br>R43<br>N; R51-53 | Xi; N<br>R: 38-41-43-51/53<br>S: (2-)26-36/37/39-61 | | |
| 016-075-00-8 | 2,2′-diallyl-4,4′-sulfonyldiphenol | | 411-570-9 | 41481-66-7 | R43<br>N; R51-53 | Xi; N<br>R: 43-51/53<br>S: (2-)24-37-61 | | |
| 016-076-00-3 | 2,3-bis((2-mercaptoethyl)thio)-1-propanethiol | | 411-290-7 | 131538-00-6 | Xn; R22-48/22<br>N; R50-53 | Xn; N<br>R: 22-48/22-50/53<br>S: (2-)23-24/25-36-60-61 | | |
| 016-077-00-9 | 2-chloro-*p*-toluenesulfochloride | | 412-890-1 | 42413-03-6 | C; R34<br>R43<br>R52-53 | C<br>R: 34-43-52/53<br>S: (1/2-)23-26-36/37/39-45-61 | | |
| 016-078-00-4 | 4-methyl-*N*,*N*-bis(2-(((4-methylphenyl)sulfonyl)amino)ethyl)benzenesulfonamide | | 413-300-5 | 56187-04-3 | R53 | R: 53<br>S: 61 | | |
| 016-079-00-X | *N*,*N*-bis(2-(*p*-toluenesulfonyloxy)ethyl)-*p*-toluenesulfonamide | | 412-920-3 | 16695-22-0 | R43<br>R53 | Xi<br>R: 43-53<br>S: (2-)24-37-61 | | |
| 016-080-00-5 | sodium 2-anilino-5-(2-nitro-4-(*N*-phenylsulfamoyl))anilinobenzenesulfonate | | 412-320-1 | 31361-99-6 | Xi; R41<br>R52-53 | Xi<br>R: 41-52/53<br>S: (2-)26-39-61 | | |
| 016-081-00-0 | hexahydrocyclopenta[*c*]pyrrole-1-(1*H*)-ammonium *N*-ethoxycarbonyl-*N*-(*p*-tolylsulfonyl)azanide | | 418-350-1 | — | Muta. Cat. 3; R68<br>Xn; R22<br>Xi; R36<br>R43<br>N; R51-53 | Xn; N<br>R: 22-36-43-68-51/53<br>S: (2-)26-36/37-61 | | |
| 016-082-00-6 | ethoxysulfuron 1-(4,6-dimethoxypyrimidin-2-yl)-3-(2-ethoxyphenoxysulfonyl)urea | | — | 126801-58-9 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 016-083-00-1 | acibenzolar-*S*-methyl benzo[1,2,3]thiadiazole-7-carbothioic acid *S*-methyl ester | | 420-050-0 | 135158-54-2 | Xi; R36/37/38<br>R43<br>N; R50-53 | Xi; N<br>R: 36/37/38-43-50/53<br>S: (2-)24/25-37-46-59-60-61 | | |
| 016-084-00-7 | prosulfuron 1-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)-3-[2-(3,3,3-trifluoropropyl)phenylsulfonyl]urea | | — | 94125-34-5 | Xn; R22<br>N; R50-53 | Xn; N<br>R: 22-50/53<br>S: (2-)60-61 | | |
| 016-085-00-2 | flazasulfuron 1-(4,6-dimethoxypyrimidin-2-yl)-3-(3-trifluoromethyl-2-pyridylsulfonyl)urea | | — | 104040-78-0 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 022-003-00-6 | bis ($\eta^5$-cyclopentadienyl)-bis(2,6-difluoro-3-[pyrrol-1-yl]-phenyl)titanium | | 412-000-1 | 125051-32-3 | F; R11<br>Repr. Cat. 3; R62<br>Xn; R48/22<br>N; R51-53 | F; Xn; N<br>R: 11-48/22-62-51/53<br>S: (2-)7-22-33-36/37-61 | | |
| 024-018-00-3 | sodium chromate | E | 231-889-5 | 7775-11-3 | Carc. Cat. 2; R49<br>Muta. Cat. 2; R46<br>T+; R26<br>T; R25<br>Xn; R21<br>Xi; R37/38-41<br>R43<br>N; R50-53 | T+; N<br>R: 49-46-21-25-26-37/38-41-43-50/53<br>S: 53-45-60-61 | C >≥ 7 %: T+; R49-46-21-25-26-37/38-41-43<br>0,5 % ≤ C < 7 %: T; R49-46-43<br>0,1 % ≤ C < 0,5 %: T; R49-46 | 3 |
| 025-004-00-X | bis(*N*,*N*′,*N*″-trimethyl-1,4,7-triazacyclononane)-trioxo-dimanganese (IV) di(hexafluorophosphate) monohydrate | | 411-760-1 | 116633-53-5 | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |
| 026-001-00-6 | (η-cumene)-(η-cyclopentadienyl)iron(II) hexafluoroantimonate | | 407-840-0 | 100011-37-8 | Xn; R22<br>Xi; R41<br>R52-53 | Xn<br>R: 22-41-52/53<br>S: (2-)22-26-39-61 | | |
| 026-002-00-1 | (η-cumene)-(η-cyclopentadienyl)iron(II) trifluoromethane-sulfonate | | 407-880-9 | 117549-13-0 | Xn; R22<br>R52-53 | Xn<br>R: 22-52/53<br>S: (2-)26-61 | | |
| 029-009-00-7 | phthalocyanine-*N*-[3-(diethylamino)propyl]sulfonamide copper complex | | 413-650-9 | 93971-95-0 | R52-53 | R: 52/53<br>S: 61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 029-010-00-3 | A mixture of compounds from (dodecakis(*p*-tolylthio)phthalocyaninato)copper(II) to (hexadecakis(*p*-tolylthio)phthalocyaninato)copper(II) | | 407-700-9 | 101408-30-4 | R43 | Xi<br>R: 43<br>S: (2-)24-37 | | |
| 029-011-00-9 | sodium [29*H*,31*H*-phthalocyaninato-(2-)-*N*29,*N*30,*N*31,*N*32]-((3-(*N*-methyl-*N*-(2-hydroxyethyl)amino) propyl)amino)sulfonyl-sulfonato, copper complex | | 412-730-0 | 150522-10-4 | C; R34 | C<br>R: 34<br>S: (1/2-)22-26-36/37/39-45 | | |
| 033-007-00-2 | *tert*-butylarsine | | 423-320-6 | 4262-43-5 | F; R17<br>T+; R26 | F; T+<br>R: 17-26<br>S: (1/2-)9-28-36/37-43-45 | | |
| 035-004-00-1 | 2-hydroxyethylammonium perbromide | | 407-440-6 | — | O; R8<br>Xn; R22<br>C; R35<br>R43<br>N; R50 | O; C; N<br>R: 8-22-35-43-50<br>S: (1/2-)3/7-14-26-36/37/39-45-60-61 | | |
| 042-004-00-5 | Reaction product of ammonium molybdate and C12-C24-diethoxylated alkylamine (1:5-1:3) | | 412-780-3 | — | Xi; R38<br>R43<br>N; R51-53 | Xi; N<br>R: 38-43-51/53<br>S: 24/25-37-61 | | |
| 050-020-00-9 | trioctylstannane | | 413-320-4 | 869-59-0 | T; R48/25<br>Xi; R38<br>R53 | T<br>R: 38-48/25-53<br>S: (1/2-)23-36/37-45-61 | | |
| 072-001-00-4 | hafnium tetra-*n*-butoxide | | 411-740-2 | 22411-22-9 | Xi; R41<br>R43 | Xi<br>R: 41-43<br>S: (2-)24/25-26-37/39 | | |
| 074-001-00-X | hexasodium dihydrogen-dodecawolframate | | 412-770-9 | 12141-67-2 | Xn; R22<br>Xi; R41<br>R52-53 | Xn<br>R: 22-41-52/53<br>S: (2-)22-26-39-61 | | |
| 074-002-00-5 | reaction products of tungsten hexachloride with 2-methylpropan-2-ol, nonylphenol and pentane-2,4-dione | | 408-250-6 | — | F; R11<br>Xn; R20<br>C; R34<br>R43<br>N; R50-53 | F; C; N<br>R: 11-20-34-43-50/53<br>S: (1/2-)16-26-29-33-36/37/39-45-60-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 601-052-00-2 | naphthalene | | 202-049-5 | 91-20-3 | Xn; R22<br>N; R50-53 | Xn; N<br>R: 22-50/53<br>S: (2-)36/37-60-61 | | |
| 601-053-00-8 | nonylphenol [1]<br>4-nonylphenol, branched [2] | | 246-672-0 [1]<br>284-325-5 [2] | 25154-52-3 [1]<br>84852-15-3 [2] | Xn; R22<br>C; R34<br>N; R50-53 | C; N<br>R: 22-34-50/53<br>S: (1/2-)26-36/37/39-45-60-61 | | |
| 601-054-00-3 | a mixture of isomers of: dibenzylbenzene; dibenzyl(methyl)benzene; dibenzyl(dimethyl)benzene; dibenzyl(trimethyl)benzene | | 405-570-8 | — | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 601-055-00-9 | a mixture of isomers of: mono-(2-tetradecyl)naphthalenes; di-(2-tetradecyl)naphthalenes; tri-(2-tetradecyl)naphthalenes | | 410-190-0 | 132983-41-6 | Xi; R36<br>R53 | Xi<br>R: 36-53<br>S: (2-)26-61 | | |
| 602-085-00-5 | 2-bromopropane | E | 200-855-1 | 75-26-3 | F; R11<br>Repr. Cat. 1; R60<br>Xn; R48/20<br>R66 | F; T<br>R: 60-11-48/20-66<br>S: 16-53-45 | | |
| 602-086-00-0 | trifluoroiodomethane<br>trifluoromethyl iodide | | 219-014-5 | 2314-97-8 | Muta. Cat. 3; R68 | Xn<br>R: 68<br>S: (2-)36/37 | | |
| 602-087-00-6 | 1,2,4-trichlorobenzene | | 204-428-0 | 120-82-1 | Xn; R22<br>Xi; R38<br>N; R50-53 | Xn; N<br>R: 22-38-50/53<br>S: (2-)23-37/39-60-61 | | |
| 602-088-00-1 | 2,3-dibromopropan-1-ol<br>2,3-dibromo-1-propanol | E | 202-480-9 | 96-13-9 | Carc. Cat. 2; R45<br>Repr. Cat. 3; R62<br>T; R24<br>Xn; R20/22<br>R52-53 | T<br>R: 45-20/22-24-52/53-62<br>S: 53-45-61 | | |
| 602-089-00-7 | 4-bromo-2-chlorofluorobenzene | | 405-580-2 | 60811-21-4 | Xn; R22<br>Xi; R38<br>N; R50-53 | Xn; N<br>R: 22-38-50/53<br>S: (2-)26-36/37-60-61 | | |
| 602-090-00-2 | 1-allyl-3-chloro-4-fluorobenzene | | 406-630-6 | 121626-73-1 | Xi; R38<br>N; R51-53 | Xi; N<br>R: 38-51/53<br>S: (2-)23-37-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 602-091-00-8 | 1,3-dichloro-4-fluorobenzene | | 406-160-1 | 1435-48-9 | Xn; R22-48/20/22<br>Xi; R38<br>N; R51-53 | Xn; N<br>R: 22-38-48/20/22-51/53<br>S: (2-)36/37-61 | | |
| 602-092-00-3 | 1-bromo-3,4,5-trifluorobenzene | | 418-480-9 | 138526-69-9 | R10<br>Carc. Cat. 3; R40<br>Xi; R38-41<br>N; R51-53 | Xn; N<br>R: 10-38-40-41-51/53<br>S: (2-)23-26-36/37/39-61 | | |
| 603-104-00-X | fenarimol (ISO)<br>2,4′-dichloro-α-(pyrimidin-5-yl)benzhydryl alcohol | | 262-095-7 | 60168-88-9 | Repr. Cat. 3; R62-63<br>R64<br>N; R51-53 | Xn; N<br>R: 51/53-62-63-64<br>S: (2-)36/37-61 | | |
| 603-105-00-5 | furan | E | 203-727-3 | 110-00-9 | F+; R12<br>R19<br>Carc. Cat. 2; R45<br>Muta. Cat. 3; R68<br>Xn; R20/22-48/22<br>Xi; R38<br>R52-53 | F+; T<br>R: 45-12-19-20/22-38-48/22-52/53<br>S: 53-45-61 | | |
| 603-139-00-0 | bis(2-methoxyethyl) ether | | 203-924-4 | 111-96-6 | R10<br>R19<br>Repr. Cat. 2; R60-61 | T<br>R: 60-61-10-19<br>S: 53-45 | | |
| 603-140-00-6 | 2,2′ -oxybisethanol<br>diethylene glycol | | 203-872-2 | 111-46-6 | Xn; R22 | Xn<br>R: 22<br>S: (2-)46 | | |
| 603-141-00-1 | a mixture of: dodecyloxy-1-methyl-1-[oxy-poly-(2-hydroxymethylethanoxy)]pentadecane; dodecyloxy-1-methyl-1-[oxy-poly-(2-hydroxymethylethanoxy)]heptadecane | | 413-780-6 | — | R52-53 | R: 52/53<br>S: 61 | | |
| 603-142-00-7 | 2-(2-(2-hydroxyethoxy) ethyl)-2-aza-bicyclo[2.2.1]heptane | | 407-360-1 | 116230-20-7 | Xn; R21/22-48/20<br>Xi; R38-41 | Xn<br>R: 21/22-38-41-48/20<br>S: (2-)26-36/37/39 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 603-143-00-2 | *R*-2,3-epoxy-1-propanol | E | 404-660-4 | 57044-25-4 | E; R2<br>Carc. Cat. 2; R45<br>Muta. Cat. 3; R68<br>Repr. Cat. 2; R60<br>T; R23<br>Xn; R21/22<br>C; R34 | E; T<br>R: 45-60-2-21/22-23-34<br>S: 53-45 | | |
| 603-144-00-8 | a mixture of: 2,6,9-trimethyl-2,5,9-cyclododecatrien-1-ol; 6,9-dimethyl-2-methylen-5,9-cyclododecadien-1-ol | | 413-530-6 | 111850-00-1 | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |
| 603-145-00-3 | 2-isopropyl-2-(1-methylbutyl)-1,3-dimethoxypropane | | 406-970-5 | 129228-11-1 | Xi; R38<br>N; R51-53 | Xi; N<br>R: 38-51/53<br>S: (2-)36/37-61 | | |
| 603-146-00-9 | 2-[(2-[2-(dimethyl-amino)ethoxy]ethyl)methylamino]ethanol | | 406-080-7 | 83016-70-0 | Xn; R22<br>C; R34<br>R52-53 | C<br>R: 22-34-52/53<br>S: (1/2-)23-26-36/37/39-45-61 | | |
| 603-147-00-4 | (-)-*trans*-4-(4′-fluorophenyl)-3-hydroxy-methyl-*N*-methylpiperidine | | 406-030-4 | 105812-81-5 | Xn; R22<br>Xi; R41<br>N; R51-53 | Xn; N<br>R: 22-41-51/53<br>S: (2-)22-24-26-37/39-61 | | |
| 603-148-00-X | 1,4-bis[(vinyloxy)methyl]cyclohexane | | 413-370-7 | 17351-75-6 | R43<br>N; R51-53 | Xi; N<br>R: 43-51/53<br>S: (2-)24-37-61 | | |
| 603-149-00-5 | a mixture of diastereoisomers of 1-(1-hydroxyethyl)-4-(1-methyl-ethyl)cyclohexane | | 407-640-3 | 63767-86-2 | Xi; R36/38<br>N; R51-53 | Xi; N<br>R: 36/38-51/53<br>S: (2-)26-37-61 | | |
| 603-150-00-0 | (+/−) *trans*-3,3-dimethyl-5-(2,2,3-trimethyl-cyclopent-3-en-1-yl)-pent-4-en-2-ol | | 411-580-3 | 107898-54-4 | Xi; R38<br>N; R50-53 | Xi; N<br>R: 38-50/53<br>S: (2-)24/25-37-60-61 | | |
| 603-151-00-6 | (+/−)-2-(2,4-dichlorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propan-1-ol | | 413-570-4 | - | R52-53 | R: 52/53<br>S: 61 | | |
| 603-152-00-1 | 2-(4-*tert*-butylphenyl)ethanol | | 410-020-5 | 5406-86-0 | Repr. Cat. 3; R62<br>Xn; R48/22<br>Xi; R41<br>N; R51-53 | Xn; N<br>R: 41-48/22-62-51/53<br>S: (2-)26-36/37/39-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 603-153-00-7 | 3-((2-nitro-4-(trifluoromethyl) phenyl)amino)propane-1,2-diol | | 410-010-0 | 104333-00-8 | Xn; R22<br>R52-53 | Xn<br>R: 22-52/53<br>S: (2-)22-61 | | |
| 603-154-00-2 | 1-[(2-*tert*-butyl)cyclohexyloxy]-2-butanol | | 412-300-2 | 139504-68-0 | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |
| 603-155-00-8 | reaction products of 2-(4,6-bis(2,4-dimethylphenyl)-1,3,5-triazin-2-yl)-5-hydroxyphenol with (($C_{10-16}$, rich in $C_{12-13}$ alkyloxy)methyl)oxyrane | | 410-560-1 | — | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 603-156-00-3 | 2-(2,4-dichlorophenyl)-2-(2-propenyl)oxirane | | 411-210-0 | 89544-48-9 | Xi; R38<br>R43<br>N; R50-53 | Xi; N<br>R: 38-43-50/53<br>S: (2-)24-37-60-61 | | |
| 603-157-00-9 | 6,9-bis(hexadecyloxymethyl)-4,7-dioxanonane-1,2,9-triol | | 411-450-6 | 143747-72-2 | R53 | R: 53<br>S: 61 | | |
| 603-158-00-4 | a mixture of 4 diastereoisomers of 2,7-dimethyl-10-(1-methylethyl)-1-oxaspiro[4.5]deca-3,6-diene | | 412-460-3 | — | Xi; R38<br>N; R51-53 | Xi; N<br>R: 38-51/53<br>S: (2-)37-61 | | |
| 603-159-00-X | 2-cyclododecylpropan-1-ol | | 411-410-8 | 118562-73-5 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 603-160-00-5 | 1,2-diethoxypropane | | 412-180-1 | 10221-57-5 | F; R11<br>R19 | F<br>R: 11-19<br>S: (2-)9-16-24-33 | | |
| 603-161-00-0 | 1,3-diethoxypropane | | 413-140-6 | 3459-83-4 | R10 | R: 10<br>S: (2-)9-24 | | |
| 603-162-00-6 | α[2-[[[(2-hydroxyethyl)methylamino]acetyl]amino]propyl]-γ-(nonylphenoxy)poly[oxo(methyl-1,2-ethanediyl)] | | 413-420-8 | 144736-29-8 | C; R34<br>R43<br>N; R51-53 | C; N<br>R: 34-43-51/53<br>S: (1/2-)26-28-36/37/39-45-61 | | |
| 603-163-00-1 | 2-phenyl-1,3-propanediol | | 411-810-2 | 1570-95-2 | Xi; R41 | Xi<br>R: 41<br>S: (2-)26-39 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 603-164-00-7 | 2-butyl-4-chloro-4,5-dihydro-5-hydroxymethyl-1-[2′-(2-triphenylmethyl-1,2,3,4-2*H*-tetrazol-5-yl)-1,1′-biphenyl-4-methyl]-1*H*-imidazole | | 412-420-5 | 133909-99-6 | R53 | R: 53<br>S: 61 | | |
| 603-165-00-2 | a mixture of: 4-allyl-2,6-bis(2,3-epoxypropyl)phenol; 4-allyl-6-[3-[6-[3-[6-[3-(4-allyl-2,6-bis(2,3-epoxypropyl)phenoxy)-2-hydroxypropyl]-4-allyl-2-(2,3-epoxypropyl)phenoxy]-2-hydroxypropyl]-4-allyl-2-(2,3-epoxypropyl)phenoxy]-2-hydroxypropyl]-2-(2,3-epoxypropyl)phenol; 4-allyl-6-[3-(4-allyl-2,6-bis(2,3-epoxypropyl)phenoxy)-2-hydroxypropyl]-2-(2,3-epoxypropyl)phenol; 4-allyl-6-[3-[6-[3-(4-allyl-2,6-bis(2,3-epoxypropyl)phenoxy)-2-hydroxypropyl]-4-allyl-2-(2,3-epoxypropyl)phenoxy]-2-hydroxypropyl]-2-(2,3-epoxypropyl)phenol | | 417-470-1 | — | Muta. Cat. 3; R68<br>R43 | Xn<br>R: 43-68<br>S: (2-)36/37 | | |
| 603-166-00-8 | (*R*)-1-chloro-2,3-epoxypropane | | 424-280-2 | 51594-55-9 | R10<br>Carc. Cat. 2; R45<br>T; R23/24/25<br>C; R34<br>R43 | T<br>R: 45-10-23/24/25-34-43<br>S: 53-45 | | |
| 604-012-00-2 | 4-chloro-*o*-cresol<br>4-chloro-2-methylphenol | | 216-381-3 | 1570-64-5 | T; R23<br>C; R35<br>N; R50 | T; C; N<br>R: 23-35-50<br>S: (1/2-)26-36/37/39-45-61 | C ≥ 25 %: T; C; R23-35<br>10 % ≤ C < 25 %: C; R20-35<br>5 % ≤ C < 10 %: C; R20-34<br>3 % ≤ C < 5 %: Xn; R20-36/37/38<br>1 % ≤ C < 3 %: Xi; R36/37/38 | |
| 604-056-00-2 | 2-(2-hydroxy-3,5-dinitroanilino)ethanol | | 412-520-9 | 99610-72-7 | F; R11<br>Repr. Cat. 3; R62<br>Xn; R22 | F; Xn<br>R: 11-22-62<br>S: (2-)22-33-36/37 | | |
| 604-057-00-8 | a mixture of: isomers of 2-(2*H*-benzotriazol-2-yl)-4-methyl-(*n*)-dodecylphenol; isomers of 2-(2*H*-benzotriazol-2-yl)-4-methyl-(*n*)-tetracosylphenol; isomers of 2-(2*H*-benzotriazol-2-yl)-4-methyl-5,6-didodecyl-phenol. *n* = 5 or 6 | | 401-680-5 | — | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 604-058-00-3 | 1,2-bis(3-methylphenoxy)ethane | | 402-730-9 | 54914-85-1 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 604-059-00-9 | 2-*n*-hexadecylhydroquinone | | 406-400-5 | — | Xn; R48/22<br>Xi; R38<br>R43<br>R53 | Xn<br>R: 38-43-48/22-53<br>S: (2-)22-36/37-61 | | |
| 604-060-00-4 | 9,9-bis(4-hydroxyphenyl)fluorene | | 406-950-6 | 3236-71-3 | Xi; R36-38<br>N; R50-53 | Xi; N<br>R: 36/38-50/53<br>S: (2-)26-37-60-61 | | |
| 604-061-00-X | a mixture of: 2-chloro-5-*sec*-tetradecylhydroquinones where *sec*-tetradecyl = 1-methyltridecyl; 1-ethyldodecyl; 1-propylundecyl; 1-butyldecyl; 1-pentylnonyl; 1-hexyloctyl | | 407-740-7 | — | Xi; R38<br>R43<br>R52-53 | Xi<br>R: 38-43-52/53<br>S: (2-)24-37-61 | | |
| 604-062-00-5 | 2,4-dimethyl-6-(1-methyl-pentadecyl)phenol | | 411-220-5 | — | Xi; R38<br>R43<br>N; R50-53 | Xi; N<br>R: 38-43-50/53<br>S: (2-)24-37-60-61 | | |
| 604-063-00-0 | 5,6-dihydroxyindole | | 412-130-9 | 3131-52-0 | Xn; R22<br>Xi; R41<br>N; R51-53 | Xn; N<br>R: 22-41-51/53<br>S: (2-)22-26-36/37/39-61 | | |
| 604-064-00-6 | 2-(4,6-diphenyl-1,3,5-triazin-2-yl)-5-((hexyl)oxy)-phenol | | 411-380-6 | 147315-50-2 | R53 | R: 53<br>S: 61 | | |
| 605-028-00-2 | ß-methyl-3-(1-methylethyl)-benzenepropanal | | 412-050-4 | 125109-85-5 | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |
| 605-029-00-8 | 2-cyclohexylpropanal | | 412-270-0 | 2109-22-0 | R43<br>N; R51-53 | Xi; N<br>R: 43-51/53<br>S: (2-)24-37-61 | | |
| 605-030-00-3 | 1-(*p*-methoxyphenyl)acetaldehyde oxime | | 411-510-1 | 3353-51-3 | R43 | Xi<br>R: 43<br>S: (2-)24-37 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 606-053-00-1 | flurtamone (ISO)<br>(*RS*)-5-methylamino-2-phenyl-4-(*α,α,α*-trifluoro-*m*-tolyl)furan-3(2*H*)-one | | — | 96525-23-4 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 606-054-00-7 | isoxaflutole (ISO)<br>5-cyclopropyl-1,2-oxazol-4-yl *α,α,α*-trifluoro-2-mesyl-*p*-tolyl ketone | | — | 141112-29-0 | Repr. Cat. 3; R63<br>N; R50-53 | Xn; N<br>R: 50/53-63<br>S: (2-)36/37-60-61 | | |
| 606-055-00-2 | 1-(2,3-dihydro-1,3,3,6-tetramethyl-1-(1-methylethyl)-1*H*-inden-5-yl)ethanone | | 411-180-9 | 92836-10-7 | Xn; R22-48/22<br>N; R51-53 | Xn; N<br>R: 22-48/22-51/53<br>S: (2-)24-36-61 | | |
| 606-056-00-8 | 4-chloro-3′,4′-dimethoxybenzophenone | | 404-610-1 | 116412-83-0 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 606-057-00-3 | 4-propylcyclohexanone | | 406-810-4 | 40649-36-3 | Xi; R38<br>R52-53 | Xi<br>R: 38-52/53<br>S: (2-)25-37-61 | | |
| 606-058-00-9 | 4′-fluoro-2,2-dimethoxyacetophenone | | 407-500-1 | 21983-80-2 | R43<br>R52-53 | Xi<br>R: 43-52/53<br>S: (2-)24-37-61 | | |
| 606-059-00-4 | 2,4-difluoro-*α*-(1*H*-1,2,4-triazol-1-yl) acetophenone hydrochloride | | 412-390-3 | 86386-75-6 | Xn; R22<br>Xi; R41<br>R43 | Xn<br>R: 22-41-43<br>S: (2-)22-26-36/37/39 | | |
| 606-060-00-X | a mixture of: *trans*-2,4-dimethyl-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-yl)-1,3-dioxolane; *cis*-2,4-dimethyl-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-yl)-1,3-dioxolane | | 412-950-7 | — | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 606-061-00-5 | (3-chlorophenyl)-(4-methoxy-3-nitrophenyl)methanone | | 423-290-4 | 66938-41-8 | Muta. Cat. 3; R68<br>N; R50-53 | Xn; N<br>R: 68-50/53<br>S: (2-)22-36/37-60-61 | | |
| 607-232-00-7 | pyridate (ISO)<br>*O*-(6-chloro-3-phenylpyridazin-4-yl) *S*-octyl thiocarbonate | | 259-686-7 | 55512-33-9 | Xi; R38<br>R43<br>N; R50-53 | Xi; N<br>R: 38-43-50/53<br>S: (2-)24-37-60-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 607-246-00-3 | allyl methacrylate<br>2-methyl-2-propenoic acid 2-propenyl ester | | 202-473-0 | 96-05-9 | R10<br>T; R23<br>Xn; R21/22<br>N; R50 | T; N<br>R: 10-21/22-23-50<br>S: (1/2-)36/37-45-61 | | |
| 607-304-00-8 | fluazifop-butyl (ISO)<br>butyl (*RS*)-2-[4-(5-trifluoromethyl-2-pyridyloxy)phenoxy]propionate | | 274-125-6 | 69806-50-4 | Repr. Cat. 2; R61<br>N; R50-53 | T; N<br>R: 61-50/53<br>S: 53-45-60-61 | | |
| 607-305-00-3 | fluazifop-*P*-butyl (ISO)<br>butyl (*R*)-2-[4-(5-trifluoromethyl-2-pyridyloxy)phenoxy]propionate | | — | 79241-46-6 | Repr. Cat. 3; R63<br>N; R50-53 | Xn; N<br>R: 50/53-63<br>S: (2-)29-36/37-46-60-61 | | |
| 607-306-00-9 | chlozolinate (ISO)<br>ethyl (*RS*)-3-(3,5-dichlorophenyl)-5-methyl-2,4-dioxo-oxazolidine-5-carboxylate | | 282-714-4 | 84332-86-5 | Carc. Cat. 3; R40<br>N; R51-53 | Xn; N<br>R: 40-51/53<br>S: (2-)36/37-61 | | |
| 607-307-00-4 | vinclozolin (ISO)<br>*N*-3,5-dichlorophenyl-5-methyl-5-vinyl-1,3-oxazolidine-2,4-dione | | 256-599-6 | 50471-44-8 | Carc. Cat. 3; R40<br>Repr. Cat. 2; R60-61<br>R43<br>N; R51-53 | T; N<br>R: 60-61-40-43-51/53<br>S: 53-45-61 | | |
| 607-308-00-X | esters of 2,4-D | A | — | — | Xn; R22<br>R43<br>N; R50-53 | Xn; N<br>R: 22-43-50/53<br>S: (2-)26-29-36/37-46-60-61 | | |
| 607-309-00-5 | carfentrazone-ethyl (ISO)<br>ethyl (*RS*)-2-chloro-3-[2-chloro-4-fluoro-5-[4-difluoromethyl-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl]phenyl]propionate | | — | 128639-02-1 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 607-310-00-0 | kresoxim-methyl (ISO)<br>methyl (*E*)-2-methoxyimino-[2-(*o*-tolyloxymethyl)phenyl]acetate | | — | 143390-89-0 | Carc. Cat. 3; R40<br>N; R50-53 | Xn; N<br>R: 40-50/53<br>S: (2-)36/37-60-61 | | |
| 607-311-00-6 | benazolin-ethyl<br>ethyl 4-chloro-2-oxo-2*H*-benzothiazole-3-acetate | | 246-591-0 | 25059-80-7 | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 607-312-00-1 | methoxyacetic acid | E | 210-894-6 | 625-45-6 | Repr. Cat. 2; R60-61<br>Xn; R22<br>C; R34 | T<br>R: 60-61-22-34<br>S: 53-45 | C ≥ 25 %: T; R60-61-22-34<br>10 % ≤ C < 25 %: T; R60-61-34<br>5 % ≤ C < 10 %: T; R60-61-36/37/38<br>0,5 % ≤ C < 5 %: T; R60-61 | |
| 607-313-00-7 | neodecanoyl chloride | | 254-875-0 | 40292-82-8 | T+; R26<br>Xn; R22<br>C; R34 | T+<br>R: 22-26-34<br>S: (1/2-)26-28-36/37/39-45 | C ≥ 25 %: T+; R22-26-34<br>10 % ≤ C < 25 %: T+; R26-34<br>7 % ≤ C < 10 %: T+; R26-36/37/38<br>5 % ≤ C < 7 %: T; R23-36/37/38<br>1 % ≤ C < 5 %: T; R23<br>0,1 % ≤ C < 1 %: Xn; R20 | |
| 607-314-00-2 | ethofumesate (ISO)<br>(+/−)-2-ethoxy-2,3-dihydro-3,3-dimethyl-benzofuran-5-yl methanesulfonate | | 247-525-3 | 26225-79-6 | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |
| 607-315-00-8 | glyphosate (ISO)<br>*N*-(phosphonomethyl)glycine | | 213-997-4 | 1071-83-6 | Xi; R41<br>N; R51-53 | Xi; N<br>R: 41-51/53<br>S: (2-)26-39-61 | | |
| 607-316-00-3 | glyphosate-trimesium<br>glyphosate-trimethylsulfonium | | - | 81591-81-3 | Xn; R22<br>N; R51-53 | Xn; N<br>R: 22-51/53<br>S: (2-)36/37-46-61 | | |
| 607-317-00-9 | bis(2-ethylhexyl) phthalate<br>di-(2-ethylhexyl) phthalate<br>DEHP | | 204-211-0 | 117-81-7 | Repr. Cat. 2; R60-61 | T<br>R: 60-61<br>S: 53-45 | | |
| 607-318-00-4 | dibutyl phthalate<br>DBP | | 201-557-4 | 84-74-2 | Repr. Cat. 2; R61<br>Repr. Cat. 3; R62<br>N; R50 | T; N<br>R: 61-50-62<br>S: 53-45-61 | | |
| 607-319-00-X | deltamethrin (ISO)<br>(*S*)-α-cyano-3-phenoxybenzyl (1*R*, 3*R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate | | 258-256-6 | 52918-63-5 | T; R23/25<br>N; R50-53 | T; N<br>R: 23/25-50/53<br>S: (1/2-)24-28-36/37/39-38-45-60-61 | | |
| 607-320-00-5 | bis[4-(ethenyloxy)butyl] 1,3-benzenedicarboxylate | | 413-930-0 | 130066-57-8 | R43<br>N; R50-53 | Xi; N<br>R: 43-50/53<br>S: (2-)24-37-60-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 607-321-00-0 | (*S*)-methyl-2-chloropropionate | | 412-470-8 | 73246-45-4 | R10<br>Xn; R48/22<br>Xi; R36 | Xn<br>R: 10-36-48/22<br>S: (2-)23-26-36 | | |
| 607-322-00-6 | 4-(4,4-dimethyl-3-oxo-pyrazolidin-1-yl)-benzoic acid | | 413-120-7 | 107144-30-9 | Xn; R22<br>N; R51-53 | Xn; N<br>R: 22-51/53<br>S: (2-)22-61 | | |
| 607-323-00-1 | 2-(1-(2-hydroxy-3,5-di-*tert*-pentyl-phenyl)ethyl)-4,6-di-*tert*-pentylphenyl acrylate | | 413-850-6 | 123968-25-2 | R53 | R: 53<br>S: 61 | | |
| 607-324-00-7 | a mixture of: *N*,*N*-di(hydrogenated alkyl C14-C18)phthalamic acid; dihydrogenated alkyl (C14-C18)amine | | 413-800-3 | — | R53 | R: 53<br>S: 61 | | |
| 607-325-00-2 | (*S*)-2-chloropropionic acid | | 411-150-5 | 29617-66-1 | Xn; R21/22<br>C; R35 | C<br>R: 21/22-35<br>S: (1/2-)23-26-28-36/37/39-45 | | |
| 607-326-00-8 | a mixture of: isobutyl hydrogen 2-(*α*-2,4,6-trimethylnon-2-enyl)succinate; isobutyl hydrogen 2-(*ß*-2,4,6-trimethylnon-2-enyl)succinate | | 410-720-0 | 141847-13-4 | Xi; R41<br>N; R51-53 | Xi; N<br>R: 41-51/53<br>S: (2-)26-39-61 | | |
| 607-327-00-3 | 2-(2-iodoethyl)-1,3-propanediol diacetate | | 411-780-0 | 127047-77-2 | Xn; R22<br>N; R51-53 | Xn; N<br>R: 22-51/53<br>S: (2-)36-61 | | |
| 607-328-00-9 | methyl 4-bromomethyl-3-methoxybenzoate | | 410-310-1 | 70264-94-7 | Xi; R38-41<br>R43<br>N; R50-53 | Xi; N<br>R: 38-41-43-50/53<br>S: (2-)26-36/37/39-60-61 | | |
| 607-329-00-4 | a mixture of: sodium 2-($C_{12-18}$-*n*-alkyl)amino-1,4-butandioate; sodium 2-octadecenyl-amino-1,4-butandioate | | 411-250-9 | — | R43 | Xi<br>R: 43<br>S: (2-)24-26-37/39 | | |
| 607-330-00-X | (*S*)-2,3-dihydro-1*H*-indole-2-carboxylic acid | | 410-860-2 | 79815-20-6 | Repr. Cat. 3; R62<br>Xn; R48/22<br>R43 | Xn<br>R: 43-48/22-62<br>S: (2-)22-25-26-36/37 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 607-331-00-5 | a mixture of: bis(2,2,6,6-tetramethyl-1-octyloxypiperidin-4-yl)-1,10-decanedioate; 1,8-bis[(2,2,6,6-tetramethyl-4-((2,2,6,6-tetramethyl-1-octyloxypiperidin-4-yl)-decan-1,10-dioyl)piperidin-1-yl)oxy]octane | | 406-750-9 | — | R53 | R: 53<br>S: 23-61 | | |
| 607-332-00-0 | cyclopentyl chloroformate | | 411-460-0 | 50715-28-1 | R10<br>T; R23<br>Xn; R22-48/22<br>Xi; R41<br>R43 | T<br>R: 10-22-23-41-43-48/22<br>S: (1/2-)26-36/37/39-45 | | |
| 607-333-00-6 | a mixture of: dodecyl *N*-(2,2,6,6-tetramethylpiperidin-4-yl)-*ß*-alaninate; tetradecyl *N*-(2,2,6,6-tetramethylpiperidin-4-yl)-*ß*-alaninate | | 405-670-1 | — | Xn; R22-48/22<br>C; R34<br>N; R50-53 | C; N<br>R: 22-34-48/22-50/53<br>S: (1/2-)26-36/37/39-45-60-61 | | |
| 607-334-00-1 | ethyl 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate | | 405-880-3 | 100501-62-0 | R43<br>R52-53 | Xi<br>R: 43-52/53<br>S: (2-)24-37-61 | | |
| 607-335-00-7 | methyl (*R*)-2-(4-(3-chloro-5-trifluoromethyl-2-pyridyloxy)phenoxy) propionate | | 406-250-0 | 72619-32-0 | Xn; R22<br>N; R50-53 | Xn; N<br>R: 22-50/53<br>S: (2-)60-61 | | |
| 607-336-00-2 | 4-methyl-8-methylenetricyclo[3,3,1.1$^{3,7}$]dec-2-yl acetate | | 406-560-6 | 122760-85-4 | Xi; R38<br>R43<br>N; R51-53 | Xi; N<br>R: 38-43-51/53<br>S: (2-)36/37-61 | | |
| 607-337-00-8 | di-*tert*-($C_{12-14}$)-alkylammonium 2-benzothiazolylthiosuccinate | | 406-052-4 | 125078-60-6 | R10<br>Xn; R22<br>Xi; R38-41<br>N; R51-53 | Xn; N<br>R: 10-22-38-41-51/53<br>S: (2-)26-37/39-61 | | |
| 607-338-00-3 | 2-methylpropyl 2-hydroxy-2-methylbut-3-enoate | | 406-235-9 | 72531-53-4 | Xi; R36/38 | Xi<br>R: 36/38<br>S: (2-)26-37 | | |
| 607-339-00-9 | 2,3,4,5-tetrachlorobenzoylchloride | | 406-760-3 | 42221-52-3 | Xn; R22<br>C; R34<br>R43 | C<br>R: 22-34-43<br>S: (1/2-)26-36/37/39-45 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 607-340-00-4 | 1,3-bis(4-benzoyl-3-hydroxyphenoxy)prop-2-yl acetate | | 406-990-4 | — | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |
| 607-341-00-X | (9*S*)-9-amino-9-deoxyerythromycin | | 406-790-7 | 26116-56-3 | Xi; R41<br>N; R50-53 | Xi; N<br>R: 41-50/53<br>S: (2-)26-39-60-61 | | |
| 607-342-00-5 | 4-chlorobutyl veratrate | | 410-950-1 | 69788-75-6 | R43<br>N; R51-53 | Xi; N<br>R: 43-51/53<br>S: (2-)24-37-61 | | |
| 607-343-00-0 | 4,7-methanooctahydro-1*H*-indene-diyldimethyl bis(2-carboxybenzoate) | | 407-410-2 | — | R53 | R: 53<br>S: 61 | | |
| 607-344-00-6 | a mixture of:<br>3-(*N*-(3-dimethylaminopropyl)-($C_{4-8}$)perfluoroalkylsulfonamido)propionic acid;<br>*N*-[dimethyl-3-($C_{4-8}$-perfluoroalkylsulfonamido)propylammonium propionate;<br>3-(*N*-(3-dimethyl-propylammonium)-($C_{4-8}$)perfluoroalkylsulfonamido)propionic acid propionate | | 407-810-7 | — | Xn; R48/22 | Xn<br>R: 48/22<br>S: (2-)21-22-36/37 | | |
| 607-345-00-1 | potassium 2-(2,4-dichlorophenoxy)-(*R*)-propionate | | 413-580-9 | 113963-87-4 | Xn; R22<br>Xi; R38-41<br>R43 | Xn<br>R: 22-38-41-43<br>S: (2-)24-26-37/39 | | |
| 607-346-00-7 | 3-icosyl-4-henicosylidene-2-oxetanone | | 401-210-9 | 83708-14-9 | R53 | R: 53<br>S: 61 | | |
| 607-347-00-2 | sodium (*R*)-2-(2,4-dichlorophenoxy)propionate | | 413-340-3 | 119299-10-4 | Xn; R22<br>Xi; R38-41<br>R43 | Xn<br>R: 22-38-41-43<br>S: (2-)22-26-36/37/39 | | |
| 607-348-00-8 | magnesium bis((*R*)-2-(2,4-dichlorophenoxy)propionate) | | 413-360-2 | — | Xn; R22<br>Xi; R38-41<br>R43 | Xn<br>R: 22-38-41-43<br>S: (2-)22-26-36/37/39 | | |
| 607-349-00-3 | mono-(tetrapropylammonium) hydrogen 2,2′-dithiobisbenzoate | | 411-270-8 | — | R52-53 | R: 52/53<br>S: 61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 607-350-00-9 | bis(4-(1,2-bis(ethoxycarbonyl)ethylamino)-3-methylcyclohexyl)methane | | 412-060-9 | 136210-32-7 | R43<br>R52-53 | Xi<br>R: 43-52/53<br>S: (2-)36/37-61 | | |
| 607-351-00-4 | methyl O-(4-amino-3,5-dichloro-6-fluoropyridin-2-yloxy)acetate | | 407-550-4 | 69184-17-4 | N; R51-53 | N<br>R: 51/53<br>S: 20/21-61 | | |
| 607-352-00-X | 4,4′-oxydiphthalic anhydride | | 412-830-4 | 1823-59-2 | R52-53 | R: 52/53<br>S: 61 | | |
| 607-353-00-5 | a mixture of: ethyl *exo*-tricyclo[5.2.1.$0^{2,6}$]decane-*endo*-2-carboxylate; ethyl *endo*-tricyclo[5.2.1.$0^{2,6}$]decane-*exo*-2-carboxylate | | 407-520-0 | 80657-64-3 | Xi; R38<br>N; R51-53 | Xi; N<br>R: 38-51/53<br>S: (2-)37-61 | | |
| 607-354-00-0 | ethyl 2-cyclohexylpropionate | | 412-280-5 | 2511-00-4 | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |
| 607-355-00-6 | *p*-tolyl 4-chlorobenzoate | | 411-530-0 | 15024-10-9 | R43<br>N; R50-53 | Xi; N<br>R: 43-50/53<br>S: (2-)24-37-60-61 | | |
| 607-356-00-1 | ethyl *trans*-2,2,6-trimethylcyclohexanecarboxylate | | 412-540-8 | — | Xi; R38<br>N; R51-53 | Xi; N<br>R: 38-51/53<br>S: (2-)37-61 | | |
| 607-357-00-7 | a mixture of: *trans*-4-acetoxy-4-methyl-2-propyl-tetrahydro-2*H*-pyran; *cis*-4-acetoxy-4-methyl-2-propyl-tetrahydro-2*H*-pyran | | 412-450-9 | 131766-73-9 | R43 | Xi<br>R: 43<br>S: (2-)24-37 | | |
| 607-358-00-2 | (1*S*,3*S*,5*R*,6*R*)-(4-nitrophenylmethyl)-1-dioxo-6-phenylacetamido-penam-3-carboxylate | | 412-670-5 | 54275-93-3 | R42 | Xn<br>R: 42<br>S: (2-)22 | | |
| 607-359-00-8 | (1*S*,4*R*,6*R*,7*R*)-(4-nitrophenylmethyl)3-methylene-1-oxo-7-phenylacetamido-cepham-4-carboxylate | | 412-800-0 | 76109-32-5 | R42 | Xn<br>R: 42<br>S: (2-)22 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 607-360-00-3 | sodium 3-acetoacetylamino-4-methoxytolyl-6-sulfonate | | 411-680-7 | 133167-77-8 | R43 | Xi<br>R: 43<br>S: (2-)24-37 | | |
| 607-361-00-9 | methyl (*R*)-2-(4-hydroxyphenoxy) propionate | | 411-950-4 | 96562-58-2 | Xi; R41<br>R52-53 | Xi<br>R: 41-52/53<br>S: (2-)26-39-61 | | |
| 607-362-00-4 | A mixture of: (3-methoxy)propylammonium/[tris-(2-hydroxyethyl)]ammonium 2-(2-(bis(2-hydroxyethyl)amino)ethoxycarbonylmethyl)hexadec-4-enoate; (3-methoxy)propylammonium/[tris-(2-hydroxyethyl)]ammonium 2-(2-(bis(2-hydroxyethyl)amino)ethoxycarbonylmethyl)tetradec-4-enoate; (3-methoxy)propylammonium/[tris-(2-hydroxyethyl)]ammonium 2-(3-methoxypropylcarbamoylmethyl)hexadec-4-enoate; (3-methoxy)propylammonium/[tris-(2-hydroxyethyl)]ammonium 2-(3-methoxypropylcarbamoylmethyl)tetradec-4-enoate | | 413-500-2 | — | Xi; R38-41<br>N; R51-53 | Xi; N<br>R: 38-41-51/53<br>S: (2-)26-37/39-61 | | |
| 607-363-00-X | methyl-3-methoxyacrylate | | 412-900-4 | 5788-17-0 | R43 | Xi<br>R: 43<br>S: (2-)24-37 | | |
| 607-364-00-5 | 3-phenyl-7-[4-(tetrahydrofurfuryloxy)phenyl]-1,5-dioxa-s-indacen-2,6-dione | | 413-330-9 | 134724-55-3 | R53 | R: 53<br>S: 61 | | |
| 607-365-00-0 | 2-(2-amino-1,3-thiazol-4-yl)-(Z)-2-methoxyiminoacetyl chloride hydrochloride | | 410-620-7 | 119154-86-8 | Xn; R22<br>C; R34<br>R43 | C<br>R: 22-34-43<br>S: (1/2-)22-26-36/37/39-45 | | |
| 607-366-00-6 | 3,5-dimethylbenzoyl chloride | | 413-010-9 | 6613-44-1 | C; R34<br>R43 | C<br>R: 34-43<br>S: (1/2-)26-36/37/39-45 | | |
| 607-367-00-1 | potassium bis(*N*-carboxymethyl)-*N*-methyl-glycinato-(2-)*N*,*O*,*O*,*N*)-ferrate-(1-) monohydrate | | 411-640-9 | 153352-59-1 | Xn; R22 | Xn<br>R: 22<br>S: (2-)37 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 607-368-00-7 | 1-(*N*,*N*-dimethylcarbamoyl)-3-*tert*-butyl-5-carbethoxymethylthio-1*H*-1,2,4-triazole | | 411-650-3 | 110895-43-7 | T; R23/25<br>N; R50-53 | T; N<br>R: 23/25-50/53<br>S: (1/2-)37-38-45-60-61 | | |
| 607-369-00-2 | a mixture of:<br>*trans*-(2*R*)-5-acetoxy-1,3-oxathiolane-2-carboxylic acid;<br>*cis*-(2*R*)-5-acetoxy-1,3-oxathiolane-2-carboxylic acid | | 411-660-8 | 147027-04-1 | Xn; R22<br>Xi; R38-41<br>R43 | Xn<br>R: 22-38-41-43<br>S: (2-)22-24-26-37/39 | | |
| 607-370-00-8 | 2-[[2-(acetyloxy)-3-(1,1-dimethyl-ethyl)-5-methylphenyl]methyl]-6-(1,1-dimethyl-ethyl)-4-methylphenol | | 412-210-3 | 41620-33-1 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 607-371-00-3 | 3-ethyl 5-methyl 4-(2-chlorophenyl)-1,4-dihydro-2-[2-(1,3-dihydro-1,3-dioxo-(2*H*)isoindol-2-yl)-ethoxymethyl]-6-methyl-3,5-pyridinedicarboxylate | | 413-410-3 | 88150-62-3 | R53 | R: 53<br>S: 61 | | |
| 607-372-00-9 | ethoxylated bis phenol A di-(norbornene carboxylate) | | 412-410-0 | — | R52-53 | R: 52/53<br>S: 61 | | |
| 607-373-00-4 | (+/−) tetrahydrofurfuryl (*R*)-2-[4-(6-chloroquinoxalin-2-yloxy)phenyloxy]propionate | E | 414-200-4 | 119738-06-6 | Muta. Cat. 3; R68<br>Repr. Cat. 2; R61<br>Repr. Cat. 3; R62<br>Xn; R22-48/22<br>N; R50-53 | T; N<br>R: 61-22-48/22-62-68-50/53<br>S: 53-45-60-61 | | |
| 607-374-00-X | 5-amino-2,4,6-triiodo-1,3-benzenedicarbonyldichloride | | 417-220-1 | 37441-29-5 | R43<br>N; R51-53 | Xi; N<br>R: 43-51/53<br>S: (2-)22-36/37-61 | | |
| 607-375-00-5 | a mixture of: *cis*-4-hydroxy-3-(1,2,3,4-tetrahydro-3-(4-(4-trifluoromethylbenzyloxy)phenyl)-1-naphthyl)coumarin; *trans*-4-hydroxy-3-(1,2,3,4-tetrahydro-3-(4-(4-trifluoromethylbenzyloxy)phenyl)-1-naphthyl)coumarin | | 421-960-0 | 90035-08-8 | T+; R26/27/28<br>T; R48/23/24/25<br>N; R50-53 | T+; N<br>R: 26/27/28-48/23/24/25-50/53<br>S: (1/2-)28-36/37/39-45-60-61 | | |
| 607-376-00-0 | benzyl 2,4-dibromobutanoate | | 420-710-8 | 23085-60-1 | Repr. Cat. 3; R62<br>Xi; R38<br>R43<br>N; R50-53 | Xn; N<br>R: 38-43-62-50/53<br>S: (2-)23-36/37-41-60-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 607-377-00-6 | *trans*-4-cyclohexyl-L-proline monohydrochloride | | 419-160-1 | 90657-55-9 | Repr. Cat. 3; R62<br>Xn; R22<br>Xi; R38-41<br>R43 | Xn<br>R: 22-38-41-43-62<br>S: (2-)22-26-36/37/39 | | |
| 607-378-00-1 | ammonium (Z)-α-methoxyimino-2-furylacetate | | 405-990-1 | 97148-39-5 | F; R11 | F<br>R: 11<br>S: (2-)22-43 | | |
| 608-026-00-X | 3-cyano-3,5,5-trimethylcyclohexanone | | 411-490-4 | 7027-11-4 | Xn; R22-48/22<br>R43<br>R52-53 | Xn<br>R: 22-43-48/22-52/53<br>S: (2-)36/37-61 | | |
| 608-027-00-5 | a mixture of: 3-(4-ethylphenyl)-2,2-dimethylpropanenitrile; 3-(2-ethylphenyl)-2,2-dimethylpropanenitrile; 3-(3-ethylphenyl)-2,2-dimethylpropanenitrile | | 412-660-0 | — | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |
| 608-028-00-0 | 4-(2-cyano-3-phenylamino)-acryloyloxymethyl-cyclohexyl-methyl 2-cyano-3-phenylamino)-acrylate | | 413-510-7 | 147374-67-2 | Xn; R48/20/21<br>R43<br>N; R51-53 | Xn; N<br>R: 43-48/20/21-51/53<br>S: (2-)36/37-61 | | |
| 608-029-00-6 | 1,2-dihydro-6-hydroxy-4-methyl-1-[3-(1-methylethoxy)propyl]-2-oxo-3-pyridinecarbonitrile | | 411-990-2 | 68612-94-2 | R43 | Xi<br>R: 43<br>S: (2-)24-37 | | |
| 608-030-00-1 | *N*-acetyl-*N*-[5-cyano-3-(2-dibutylamino-4-phenylthyazol-5-yl-methylene)-4-methyl-2,6-dioxo-1,2,3,6-tetrahydropyridin-1-yl]benzamide | | 412-340-0 | 147741-93-3 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 609-041-00-4 | 2,4-dinitrophenol | | 200-087-7 | 51-28-5 | T; R23/24/25<br>R33<br>N; R50 | T; N<br>R: 23/24/25-33-50<br>S: (1/2-)28-37-45-61 | | |
| 609-050-00-3 | 2,3-dinitrotoluene | E | 210-013-5 | 602-01-7 | Carc. Cat. 2; R45<br>Muta. Cat. 3; R68<br>Repr. Cat. 3; R62<br>T; R23/24/25<br>Xn; R48/22<br>N; R50-53 | T; N<br>R: 45-23/24/25-48/22-50/53-62<br>S: 53-45-60-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 609-051-00-9 | 3,4-dinitrotoluene | E | 210-222-1 | 610-39-9 | Carc. Cat. 2; R45<br>Muta. Cat. 3; R68<br>Repr. Cat. 3; R62<br>T; R23/24/25<br>Xn; R48/22<br>N; R51-53 | T; N<br>R: 45-23/24/25-48/22-51/53-62<br>S: 53-45-61 | | |
| 609-052-00-4 | 3,5-dinitrotoluene | E | 210-566-2 | 618-85-9 | Carc. Cat. 2; R45<br>Muta. Cat. 3; R68<br>Repr. Cat. 3; R62<br>T; R23/24/25<br>Xn; R48/22<br>R52-53 | T<br>R: 45-23/24/25-48/22-52/53-62<br>S: 53-45-61 | | |
| 609-054-00-5 | 2,3-dinitrophenol [1]<br>2,5-dinitrophenol [2]<br>2,6-dinitrophenol [3]<br>3,4-dinitrophenol [4]<br>salts of dinitrophenol [5] | | 200-628-7 [1]<br>206-348-1 [2]<br>209-357-9 [3]<br>209-415-3 [4]<br>- [5] | 66-56-8 [1]<br>329-71-5 [2]<br>573-56-8 [3]<br>577-71-9 [4]<br>- [5] | T; R23/24/25<br>R33<br>N; R51-53 | T; N<br>R: 23/24/25-33-51/53<br>S: (1/2-)28-37-45-61 | | |
| 609-055-00-0 | 2,5-dinitrotoluene | E | 210-581-4 | 619-15-8 | Carc. Cat. 2; R45<br>Muta. Cat. 3; R68<br>Repr. Cat. 3; R62<br>T; R23/24/25<br>Xn; R48/22<br>N; R51-53 | T; N<br>R: 45-23/24/25-48/22-51/53-62<br>S: 53-45-61 | | |
| 609-056-00-6 | 2,2-dibromo-2-nitroethanol | | 412-380-9 | 69094-18-4 | E; R2<br>Carc. Cat. 3; R40<br>Xn; R22-48/22<br>C; R35<br>R43<br>N; R50-53 | E; C; N<br>R: 2-22-35-40-43-48/22-50/53<br>S: (1/2-)23-26-35-36/37/39-45-60-61 | C ≥ 10 %: C; R22-35-40-43-48/22<br>5 % ≤ C < 10 %: C; R34-40-43<br>1 % ≤ C < 5 %: Xn; R36/37/38-40-43 | |
| 609-057-00-1 | 3-chloro-2,4-difluoronitrobenzene | | 411-980-8 | 3847-58-3 | Xn; R22<br>C; R34<br>R43<br>N; R50-53 | C; N<br>R: 22-34-43-50/53<br>S: (1/2-)22-26-28-36/37/39-45-60-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 609-058-00-7 | 2-nitro-2-phenyl-1,3-propanediol | | 410-360-4 | 5428-02-4 | T; R39-48/25<br>Xn; R21/22<br>Xi; R41<br>R43<br>N; R51-53 | T; N<br>R: 21/22-39-41-43-48/25-51/53<br>S: 53-45-61 | | |
| 609-059-00-2 | 2-chloro-6-(ethylamino)-4-nitrophenol | | 411-440-1 | 131657-78-8 | Xn; R22<br>R43<br>N; R51-53 | Xn; N<br>R: 22-43-51/53<br>S: (2-)22-24-37/39-61 | | |
| 609-060-00-8 | 4-[(3-hydroxypropyl)amino]-3-nitrophenol | | 406-305-9 | 92952-81-3 | Xi; R38<br>N; R51-53 | Xi; N<br>R: 38-51/53<br>S: (2-)37-61 | | |
| 609-061-00-3 | (*E*,*Z*)-4-chlorophenyl(cyclopropyl)ketone O-(4-nitrophenylmethyl)oxime | | 406-100-4 | 94097-88-8 | R43<br>N; R50-53 | Xi; N<br>R: 43-50/53<br>S: (2-)24-37-60-61 | | |
| 609-062-00-9 | 2-bromo-2-nitropropanol | | 407-030-7 | 24403-04-1 | T; R24<br>Xn; R22-48/22<br>C; R34<br>R43<br>N; R50-53 | T; N<br>R: 22-24-34-43-48/22-50/53<br>S: (1/2-)26-36/37/39-45-60-61 | | |
| 609-063-00-4 | 2-[(4-chloro-2-nitrophenyl)amino]ethanol | | 413-280-8 | 59320-13-7 | Xn; R22<br>N; R51-53 | Xn; N<br>R: 22-51/53<br>S: (2-)22-61 | | |
| 611-053-00-X | 2,2′-azobis[2-methylpropionamidine] dihydrochloride | | 221-070-0 | 2997-92-4 | Xn; R22<br>R43 | Xn<br>R: 22-43<br>S: (2-)24-37 | | |
| 611-055-00-0 | C.I. Disperse Yellow 3<br>N-[4-[(2-hydroxy-5-methylphenyl)azo]phenyl]acetamide | | 220-600-8 | 2832-40-8 | Carc. Cat. 3; R40<br>R43 | Xn<br>R: 40-43<br>S: (2-)22-36/37-46 | | |
| 611-056-00-6 | C.I. Solvent Yellow 14<br>1-phenylazo-2-naphthol | | 212-668-2 | 842-07-9 | Carc. Cat. 3; R40<br>Muta. Cat. 3; R68<br>R43<br>R53 | Xn<br>R: 40-43-53-68<br>S: (2-)22-36/37-46-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 611-057-00-1 | 6-hydroxy-1-(3-isopropoxypropyl)-4-methyl-2-oxo-5-[4-(phenylazo)phenylazo]-1,2-dihydro-3-pyridinecarbonitrile | | 400-340-3 | 85136-74-9 | Carc. Cat. 2; R45<br>R53 | T<br>R: 45-53<br>S: 53-45-61 | | |
| 611-058-00-7 | (6-(4-hydroxy-3-(2-methoxyphenylazo)-2-sulfonato-7-naphthylamino)-1,3,5-triazin-2,4-diyl)bis[(amino-1-methylethyl)ammonium] formate | | 402-060-7 | 108225-03-2 | Carc. Cat. 2; R45<br>Xi; R41<br>N; R51-53 | T; N<br>R: 45-41-51/53<br>S: 53-45-61 | | |
| 611-059-00-2 | octasodium 2-(6-(4-chloro-6-(3-(*N*-methyl-*N*-(4-chloro-6-(3,5-disulfonato-2-naphthylazo)-1-hydroxy-6-naphthylamino)-1,3,5-triazin-2-yl)amino-methyl)phenylamino)-1,3,5-triazin-2-ylamino)-3,5-disulfonato-1-hydroxy-2-naphthylazo)naphthalene-1,5-disulfonate | | 412-960-1 | 148878-21-1 | Xi; R41<br>R43<br>R52-53 | Xi<br>R: 41-43-52/53<br>S: (2-)22-24-26-37/39-61 | | |
| 611-060-00-8 | a mixture of: sodium 5-[8-[4-[4-[4-[7-(3,5-dicarboxylatophenylazo)-8-hydroxy-3,6-disulfonatonaphthalen-1-ylamino]-6-hydroxy-1,3,5-triazin-2-yl]-2,5-dimethylpiperazin-1-yl]-6-hydroxy-1,3,5-triazin-2-ylamino]–1-hydroxy-3,6-disulfonato-naphthalen-2-ylazo]-isophthalate; ammonium 5-[8-[4-[4-[4-[7-(3,5-dicarboxylatophenylazo)-8-hydroxy-3,6-disulfonatonaphthalen-1-ylamino]-6-hydroxy-1,3,5-triazin-2-yl]-2,5-dimethylpiperazin-1-yl]-6-hydroxy-1,3,5-triazin-2-ylamino]-1-hydroxy-3,6-disulfonatonaphthalen-2-ylazo]-isophthalate; 5-[8-[4-[4-[4-[7-(3,5-dicarboxylatophenylazo)-8-hydroxy-3,6-disulfonatonaphthalen-1-ylamino]-6-hydroxy-1,3,5-triazin-2-yl]-2,5-dimethylpiperazin-1-yl]-6-hydroxy-1,3,5-triazin-2-ylamino]-1-hydroxy-3,6-disulfonaphthalen-2-ylazo]-isophthalic acid | | 413-180-4 | — | Xi; R41<br>R43<br>R52-53 | Xi<br>R: 41-43-52/53<br>S: (2-)22-24-26-37/39-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 611-061-00-3 | disodium 5-[5-[4-(5-chloro-2,6-difluoropyrimidin-4-ylamino)benzamido]-2-sulfonatophenylazo]-1-ethyl-6-hydroxy-4-methyl-2-oxo-3-pyridylmethylsulfonate | | 412-530-3 | — | Xi; R41<br>R43 | Xi<br>R: 41-43<br>S: (2-)22-24-26-37/39 | | |
| 611-062-00-9 | octasodium 2-(8-(4-chloro-6-(3-((4-chloro-6-(3,6-disulfonato-2-(1,5-disulfonatonaphthalen-2-ylazo)-1-hydroxynaphthalen-8-ylamino)-1,3,5-triazin-2-yl)aminomethyl)phenylamino)-1,3,5-triazin-2-ylamino)-3,6-disulfonato-1-hydroxynaphthalen-2-ylazo)naphthalene-1,5-disulfonate | | 413-550-5 | — | Xi; R38-41 | Xi<br>R: 38-41<br>S: (2-)22-26-37/39 | | |
| 611-063-00-4 | trisodium [4′-(8-acetylamino-3,6-disulfonato-2-naphthylazo)-4″-(6-benzoylamino-3-sulfonato-2-naphthylazo)-biphenyl-1,3′,3″,1′″-tetraolato-*O*,*O*′,*O*″,*O*′″]copper(II) | | 413-590-3 | — | Carc. Cat. 2; R45 | T<br>R: 45<br>S: 53-45 | | |
| 611-064-00-X | 4-(3,4-dichlorophenylazo)-2,6-di-*sec*-butyl-phenol | | 410-600-8 | 124719-26-2 | Xn; R48/22<br>Xi; R38<br>N; R50-53 | Xn; N<br>R: 38-48/22-50/53<br>S: (2-)23-25-36/37-60-61 | | |
| 611-065-00-5 | 4-(4-nitrophenylazo)-2,6-di-*sec*-butyl-phenol | | 410-610-2 | 111850-24-9 | Xn; R48/22<br>Xi; R36/38<br>R43<br>N; R50-53 | Xn; N<br>R: 36/38-43-48/22-50/53<br>S: (2-)23-26-36/37-60-61 | | |
| 611-066-00-0 | tetrasodium 5-[4-chloro-6-(*N*-ethyl-anilino)-1,3,5-triazin-2-ylamino]-4-hydroxy-3-(1,5-disulfonatonaphthalen-2-ylazo)-naphthalene-2,7-disulfonate | | 411-540-5 | 130201-57-9 | Xi; R41<br>R43<br>N; R51-53 | Xi; N<br>R: 41-43-51/53<br>S: (2-)22-24-26-37/39-61 | | |
| 611-067-00-6 | a mixture of: bis(tris(2-(2-hydroxy(1-methyl)ethoxy)ethyl)ammonium) 7-anilino-4-hydroxy-3-(2-methoxy-5-methyl-4-(4-sulfonatophenylazo)phenylazo)naphthalene-2-sulfonate; bis(tris(2-(2-hydroxy(2-methyl)ethoxy)ethyl)ammonium) 7-anilino-4-hydroxy-3-(2-methoxy-5-methyl-4-(4-sulfonatophenylazo)phenylazo)naphthalene-2-sulfonate | | 406-910-8 | — | Xn; R22<br>Xi; R41<br>R52-53 | Xn<br>R: 22-41-52/53<br>S: (2-)26-36/39-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 611-068-00-1 | tetrasodium 4-amino-3,6-bis(5-[4-chloro-6-(2-hydroxyethylamino)-1,3,5-triazin-2-ylamino]-2-sulfonatophenylazo)-5-hydroxynaphthalene-2,7-disulfonate | | 400-690-7 | 85665-98-1 | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |
| 611-069-00-7 | *N*,*N*-di-[poly(oxyethylene)-co-poly(oxypropylene)]-4-[(3,5-dicyano-4-methyl-2-thienyl)azo)]-3-methylaniline | | 413-380-1 | — | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |
| 611-070-00-2 | a mixture of: disodium (6-(4-anisidino)-3-sulfonato-2-(3,5-dinitro-2-oxidophenylazo)-1-naphtholato)(1-(5-chloro-2-oxidophenylazo)-2-naphtholato)chromate(1-); trisodium bis(5-(4-anisidino)-3-sulfonato-2-(3,5-dinitro-2-oxidophenylazo)-1-naphtholato)chromate(1-) | | 405-665-4 | — | R43<br>N; R50-53 | Xi; N<br>R: 43-50/53<br>S: (2-)24-37-60-61 | | |
| 611-071-00-8 | tris(tetramethylammonium) 5-hydroxy-1-(4-sulphonatophenyl)-4-(4-sulphonatophenylazo)pyrazole-3-carboxylate | | 406-073-9 | 131013-81-5 | T; R25<br>R52-53 | T<br>R: 25-52/53<br>S: (1/2-)37-45-61 | | |
| 611-072-00-3 | 2,4-bis[2,2′-[2-(*N*,*N*-dimethylamino)ethyloxycarbonyl]phenylazo]-1,3-dihydroxybenzene, dihydrochloride | | 407-010-8 | 118208-02-9 | Xn; R22<br>Xi; R41<br>N; R51-53 | Xn; N<br>R: 22-41-51/53<br>S: (2-)26-39-61 | | |
| 611-073-00-9 | dimethyl 3,3′-(*N*-(4-(4-bromo-2,6-dicyanophenylazo)-3-hydroxyphenyl)imino)dipropionate | | 407-310-9 | 122630-55-1 | R53 | R: 53<br>S: 61 | | |
| 611-074-00-4 | a mixture of: sodium/potassium (3-(4-(5-(5-chloro-2,6-difluoropyrimidin-4-ylamino)-2-methoxy-3-sulfonatophenylazo)-2-oxidophenylazo)-2,5,7-trisulfonato-4-naphtholato)copper(II); sodium/potassium (3-(4-(5-(5-chloro-4,6-difluoropyrimidin-2-ylamino)-2-methoxy-3-sulfonatophenylazo)-2-oxidophenylazo)-2,5,7-trisulfonato-4-naphtholato)copper(II) | | 407-100-7 | — | R43 | Xi<br>R: 43<br>S: (2-)22-24-37 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 611-075-00-X | a 2:1 mixture of: tris(3,5,5-trimethylhexylammonium) 4-amino-3-(4-(4-(2-amino-4-hydroxyphenylazo)anilino)-3-sulfonatophenylazo)-5,6-dihydro-5-oxo-6-phenylhydrazononaphthalene-2,7-disulfonate; tris(3,5,5-trimethylhexylammonium) 4-amino-3-(4-(4-(4-amino-2-hydroxyphenylazo)anilino)-3-sulfonatophenylazo)-5,6-dihydro-5-oxo-6-phenylhydrazononaphthalene-2,7-disulfonate | | 406-000-0 | — | Xi; R41<br>N; R51-53 | Xi; N<br>R: 41-51/53<br>S: (2-)26-39-61 | | |
| 611-076-00-5 | 3-(2,6-dichloro-4-nitrophenylazo)-1-methyl-2-phenylindole | | 406-280-4 | 117584-16-4 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 611-077-00-0 | dilithium disodium (5,5′-diamino-(μ-4,4′-dihydroxy-1:2-κ-2,O4,O4′,-3,3′-[3,3′-dihydroxy-1:2-κ-2-O3,O3′-biphenyl-4,4′-ylenebisazo-1:2-(*N*3,*N*4-*η*:*N*3′,*N*4′-*η*)]-dinaphthalene-2,7-disulfonato(8)))dicuprate(2-) | | 407-230-4 | 126637-70-5 | Xn; R22<br>R43 | Xn<br>R: 22-43<br>S: (2-)22-24-37 | | |
| 611-078-00-6 | (2,2′-(3,3′-dioxidobiphenyl-4,4′-diyldiazo)bis(6-(4-(3-(diethylamino)propylamino)-6-(3-(diethylammonio)propylamino)-1,3,5-triazin-2-ylamino)-3-sulfonato-1-naphtholato))dicopper(II) acetate lactate | | 407-240-9 | 159604-94-1 | R43<br>N; R51-53 | Xi; N<br>R: 43-51/53<br>S: (2-)22-24-37-61 | | |
| 611-079-00-1 | disodium 7-[4-chloro-6-(*N*-ethyl-*o*-toluidino)-1,3,5-triazin-2-ylamino]-4-hydroxy-3-(4-methoxy-2-sulfonatophenylazo)-2-naphthalenesulfonate | | 410-390-8 | — | Xi; R41 | Xi<br>R: 41<br>S: (2-)22-26-39 | | |
| 611-080-00-7 | sodium 3-(2-acetamido-4-(4-(2-hydroxybutoxy)phenylazo)phenylazo)benzenesulfonate | | 410-150-2 | 147703-65-9 | R43 | Xi<br>R: 43<br>S: (2-)22-24-37 | | |
| 611-081-00-2 | tetrasodium [7-(2,5-dihydroxy-KO2-7-sulfonato-6-[4-(2,5,6-trichloro-pyrimidin-4-ylamino)phenylazo]-(N1,N7-N)-1-naphthylazo)-8-hydroxy-KO8-naphthalene-1,3,5-trisulfonato(6-)]cuprate(II) | | 411-470-5 | 141048-13-7 | R43<br>R52-53 | Xi<br>R: 43-52/53<br>S: (2-)22-24-37-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 611-082-00-8 | a mixture of: pentasodium bis(1-(3(or 5)-(4-anilino-3-sulfonatophenylazo)-4-hydroxy-2-oxidophenylazo)-6-nitro-4-sulfonato-2-naphtholato)ferrate(1-); pentasodium [(1-(3-(4-anilino-3-sulfonatophenylazo)-4-hydroxy-2-oxidophenylazo)-6-nitro-4-sulfonato-2-naphtholato)-(5-(4-anilino-3-sulfonatophenylazo)-4-hydroxy-2-oxidophenylazo)-6-nitro-4-sulfonato-2-naphtholato]ferrate(1-) | | 407-570-3 | — | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |
| 611-083-00-3 | a mixture (1:1) of:<br>2-[*N*-ethyl-4-[(5,6-dichlorobenzothiazol-2-yl)azo]-*m*-toludino]ethyl acetate;<br>2-[*N*-ethyl-4-[(6,7-dichlorobenzothiazol-2-yl)azo]-*m*-toludino]ethyl acetate | | 411-560-4 | — | T; R48/25<br>R43<br>N; R51/53 | T; N<br>R: 43-48/25-51/53<br>S: (1/2-)22-36/37-R45-61 | | |
| 611-084-00-9 | a mixture of:<br>*N*-(4-chlorophenyl)-4-(2,5-dichloro-4-(dimethylsulfamoyl)phenylazo)-3-hydroxy-2-naphthalenecarboxamide; *N*-(4-chlorophenyl)-4-(2,5-dichloro-4-(methylsulfamoyl)phenylazo)-3-hydroxy-2-naphthalenecarboxamide | | 412-550-2 | — | R53 | R: 53<br>S: 61 | | |
| 611-085-00-4 | a mixture of: 3-cyano-5-(2-cyano-4-nitrophenylazo)-2-(2-hydroxyethylamino)-4-methyl-6-[3-(2-phenoxyethoxy)propylamino]pyridine; 3-cyano-5-(2-cyano-4-nitrophenylazo)-6-(2-hydroxyethylamino)-4-methyl-2-[3-(2-phenoxyethoxy)propylamino]pyridine; 3-cyano-5-(2-cyano-4-nitrophenylazo)-2--amino-4-methyl-6-[3-(3-hydroxypropoxy-)propylamino]pyridine;3-cyano-5-(2-cyano-4-nitrophenylazo)-6-amino-4-methyl-2-[3-(3--methoxypropoxy)propylamino]pyridine | | 411-880-4 | — | R43<br>N; R51-53 | Xi; N<br>R: 43-51/53<br>S: (2-)24-37-61 | | |
| 611-086-00-X | monolithium 5-[[2,4-dihydroxy-5-[(2-hydroxy-3,5-dinitrophenyl)azo]phenyl]azo]-2-naphthalenesulfonate], iron complex, monohydrate | | 411-360-7 | — | R52-53 | R: 52/53<br>S: 61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 611-087-00-5 | a mixture of: 3-((5-cyano-1,6-dihydro-1,4-dimethyl-2-hydroxy-6-oxo-3-pyridinyl)azo)-benzoyloxy-2-phenoxy-ethane; 3-((5-cyano-1,6-dihydro-1,4-dimethyl-2-hydroxy-6-oxo-3-pyridinyl)azo)-benzoyloxy-2-ethyloxy-2-(ethylphenol) | | 411-710-9 | — | R53 | R: 53<br>S: 61 | | |
| 611-088-00-0 | a mixture of: trilithium 4-amino-3-((4-((4-((2-amino-4-hydroxyphenyl)azo)phenyl)amino)-3-sulfophenyl)azo)-5-hydroxy-6-(phenylazo)naphthalene-2,7-disulfonate; trilithium 4-amino-3-((4-((4-((4-amino-2-hydroxyphenyl)azo)phenyl)amino)-3-sulfophenyl)azo)-5-hydroxy-6-(phenylazo)naphthalene-2,7-disulfonate | | 411-890-9 | — | Xn; R22<br>Xi; R41<br>R52-53 | Xn<br>R: 22-41-52/53<br>S: (2-)22-26-39-61 | | |
| 611-089-00-6 | 2-((4-(ethyl-(2-hydroxyethyl)amino)-2-methylphenyl)azo)-6-methoxy-3-methyl-benzothiazolium methylsulfate | | 411-100-2 | 136213-73-5 | Xn; R48/22<br>R43<br>N; R50-53 | Xn; N<br>R: 43-48/22-50/53<br>S: (2-)22-36/37-60-61 | | |
| 611-090-00-1 | 2,5-dibutoxy-4-(morpholin-4-yl)benzene-diazonium 4-methylbenzenesulfonate | | 413-290-2 | 93672-52-7 | F; R11<br>Xn; R22<br>Xi; R41<br>R43<br>R52-53 | F; Xn<br>R: 11-22-41-43-52/53<br>S: (2-)12-22-24-26-37/39-47-61 | | |
| 611-091-00-7 | sodium (1,0-1,95)/lithium (0,05-1) 5-((5-((5-chloro-6-fluoro-pyrimidin-4-yl)amino)-2-sulfonatophenyl)azo)-1,2-dihydro-6-hydroxy-1,4-dimethyl-2-oxo-3-pyridinemethylsulfonate | | 413-470-0 | 134595-59-8 | R43 | Xi<br>R: 43<br>S: (2-)22-24/25-37 | | |
| 611-092-00-2 | *tert*-(dodecyl/tetradecyl)-ammonium bis(3-(4-((5-(1,1-dimethyl-propyl)-2-hydroxy-3-nitrophenyl)azo)-3-methyl-5-hydroxy-(1*H*)pyrazol-1-yl)benzenesulfonamidato)chromate | | 413-210-6 | — | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |
| 611-093-00-8 | sodium 2-(4-(4-fluoro-6-(2-sulfoethylamino)-[1,3,5]triazin-2-ylamino)-2-ureidophenylazo)-5-(4-sulfophenylazo)benzene-1-sulfonate | | 410-770-3 | 146177-84-6 | R43 | Xi<br>R: 43<br>S: (2-)22-24-37 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 611-094-00-3 | a mixture (50:50) of:<br>2-[2-acetylamino-4-[*N*,*N*-bis[2-ethoxycarbonyloxy)ethyl]amino]phenylazo]-5,6-dichloro-1,3-benzothiazole;<br>2-[2-acetylamino-4-[*N*,*N*-bis[2-ethoxycarbonyloxy)ethyl]amino]phenylazo]-6,7-dichloro-1,3-benzotriazole | | 411-600-0 | 143145-93-1 | R53 | R: 53<br>S: 61 | | |
| 611-095-00-9 | hexasodium 1,1′-[(1-amino-8-hydroxy-3,6-disulfonate-2,7-naphthalenediyl)bis(azo(4-sulfonate-1,3-phenyl)imino[6-[(4-chloro-3-sulfonatophenyl)amino]-1,3,5-triazin-2,4-diyl]]]bis[3-carboxypyridinium] dihydroxide | | 412-240-7 | 89797-03-5 | N; R51-53 | N<br>R: 51/53<br>S: 22-61 | | |
| 611-096-00-4 | methyl *N*-[3-acetylamino)-4-(2-cyano-4-nitrophenylazo)phenyl]-*N*-[(1-methoxy)acetyl]glycinate | | 413-040-2 | 149850-30-6 | R43 | Xi<br>R: 43<br>S: (2-)22-24-37 | | |
| 611-097-00-X | a mixture of isomers of iron (1:2) complexes of a mixture of: isomers of: 1,3-dihydroxy-4-[(5-phenylaminosulfonyl)-2-hydroxyphenylazo]-*n*-(5-amino-sulfonyl-2-hydroxyphenylazo)benzene (*n* = 2,5,6); isomers of: 1,3-dihydroxy-4-[(5-phenylaminosulfonyl)-2-hydroxyphenylazo]-*n*-[4-(4-nitro-2-sulfophenylamino)phenylazo]benzene (*n* = 2,5,6) | | 414-150-3 | — | R43<br>N; R51-53 | Xi; N<br>R: 43-51/53<br>S: (2-)22-24-37-61 | | |
| 611-098-00-5 | tetrakis(tetramethylammonium)3,3′-(6-(2-hydroxyethylamino)1,3,5-triazine-2,4-diylbisimino(2-methyl-4,1-phenyleneazo))bisnaphthalene-1,5-disulfonate | | 405-950-3 | 131013-83-7 | T; R25<br>R52-53 | T<br>R: 25-52/53<br>S: (1/2-)37-45-61 | | |
| 612-160-00-4 | *p*-toluidine [1]<br>4-aminotoluene [1]<br>toluidinium chloride [2]<br>toluidine sulphate (1:1) [3] | | 203-403-1 [1]<br>208-740-8 [2]<br>208-741-3 [3] | 106-49-0 [1]<br>540-23-8 [2]<br>540-25-0 [3] | Carc. Cat. 3; R40<br>T; R23/24/25<br>Xi; R36<br>R43<br>N; R50 | T; N<br>R: 23/24/25-36-40-43-50<br>S: (1/2-)28-36/37-45-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 612-161-00-X | 2,6-xylidine<br>2,6-dimethylaniline | | 201-758-7 | 87-62-7 | Carc. Cat. 3; R40<br>Xn; R20/21/22<br>Xi; R37/38<br>N; R51-53 | Xn; N<br>R: 20/21/22-37/38-40-51/53<br>S: (2-)23-25-36/37-61 | | |
| 612-162-00-5 | dimethyldioctadecylammonium chloride<br>DODMAC | | 203-508-2 | 107-64-2 | Xi; R41<br>N; R50-53 | Xi; N<br>R: 41-50/53<br>S: (2-)24-26-39-46-60-61 | | |
| 612-163-00-0 | metalaxyl-M (ISO)<br>mefenoxam<br>(*R*)-2-[(2,6-dimethylphenyl)-methoxy-acetylamino]propionic acid methyl ester | | — | 70630-17-0 | Xn; R22<br>Xi; R41 | Xn<br>R: 22-41<br>S: (2-)26-39-46 | | |
| 612-164-00-6 | 2-butyl-2-ethyl-1,5-diaminopentane | | 412-700-7 | 137605-95-9 | Xn; R21/22-48/22<br>C; R34<br>R43<br>R52-53 | C<br>R: 21/22-34-43-48/22-52/53<br>S: (1/2-)26-36/37/39-45-61 | | |
| 612-165-00-1 | *N*,*N*′-diphenyl-*N*,*N*′-bis(3-methylphenyl)-(1,1′-diphenyl)-4,4′-diamine | | 413-810-8 | 65181-78-4 | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |
| 612-166-00-7 | a mixture of: *cis*-(5-ammonium-1,3,3-trimethyl)-cyclohexanemethylammonium phosphate (1:1);<br>*trans*-(5-ammonium-1,3,3-trimethyl)-cyclohexanemethylammonium phosphate (1:1) | | 411-830-1 | 114765-88-7 | Xi; R41<br>R43<br>R52-53 | Xi<br>R: 41-43-52/53<br>S: (2-)24-26-37/39-61 | | |
| 612-167-00-2 | 5-acetyl-3-amino-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine-hydrochloride | | 410-490-1 | — | Xn; R22-48/22<br>Xi; R41<br>R43<br>N; R51-53 | Xn; N<br>R: 22-41-43-48/22-51/53<br>S: (2-)22-26-36/37/39-61 | | |
| 612-168-00-8 | 3,5-dichloro-2,6-difluoropyridine-4-amine | | 220-630-1 | 2840-00-8 | Xn; R21/22<br>N; R51-53 | Xn; N<br>R: 21/22-51/53<br>S: (2-)36/37-61 | | |
| 612-170-00-9 | 4-chlorophenyl cyclopropyl ketone O-(4-aminobenzyl)oxime | | 405-260-2 | — | Xn; R22<br>R43<br>N; R50-53 | Xn; N<br>R: 22-43-50/53<br>S: (2-)24-37-60-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 612-171-00-4 | *N*,*N*,*N*′,*N*′-tetraglycidyl-4,4′-diamino-3,3′-diethyldiphenylmethane | | 410-060-3 | 130728-76-6 | Muta. Cat. 3; R68<br>R43<br>N; R51-53 | Xn; N<br>R: 43-68-51/53<br>S: (2-)36/37-61 | | |
| 612-172-00-X | 4,4′-methylenebis(*N*,*N*′-dimethylcyclohexanamine) | | 412-840-9 | 13474-64-1 | Xn; R22-48/22<br>C; R35<br>R52-53 | C<br>R: 22-35-48/22-52/53<br>S: (1/2-)26-36/37/39-45-61 | | |
| 612-173-00-5 | lithium 1-amino-4-(4-*tert*-butylanilino)anthraquinone-2-sulfonate | | 411-140-0 | 125328-86-1 | Xi; R41<br>R43<br>N; R51-53 | Xi; N<br>R: 41-43-51/53<br>S: (2-)22-26-36/37/39-61 | | |
| 612-174-00-0 | 4,4-dimethoxybutylamine | | 407-690-6 | 19060-15-2 | Xn; R22<br>C; R34<br>R43<br>R52-53 | C<br>R: 22-34-43-52/53<br>S: (1/2-)26-36/37/39-45-61 | | |
| 612-175-00-6 | 2-(O-aminooxy)ethylamine dihydrochloride | | 412-310-7 | 37866-45-8 | R43<br>R52-53 | Xi<br>R: 43-52/53<br>S: (2-)24-37-61 | | |
| 612-176-00-1 | polymer of 1,3-dibromopropane and *N*,*N*-diethyl-*N*′,*N*′-dimethyl-1,3-propanediamine | | 410-570-6 | 143747-73-3 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 612-177-00-7 | 2-naphthylamino-6-sulfomethylamide | | 412-120-4 | — | Xn; R48/22<br>R43<br>N; R51-53 | Xn; N<br>R: 43-48/22-51/53<br>S: (2-)22-36/37-61 | | |
| 612-178-00-2 | 1,4,7,10-tetraazacyclododecane disulfate | | 412-080-8 | 112193-77-8 | Xn; R22<br>Xi; R37-41<br>R52-53 | Xn<br>R: 22-37-41-52/53<br>S: (2-)26-36/37/39-61 | | |
| 612-179-00-8 | 1-(2-propenyl)pyridinium chloride | | 412-740-5 | 25965-81-5 | Xn; R22<br>R43 | Xn<br>R: 22-43<br>S: (2-)24-37 | | |
| 612-180-00-3 | 3-aminobenzylamine | | 412-230-2 | 4403-70-7 | Xn; R22<br>C; R34<br>N; R51-53 | C; N<br>R: 22-34-51/53<br>S: (1/2-)22-26-36/37/39-45-61 | | |
| 612-181-00-9 | 2-phenylthioaniline | | 413-030-8 | 1134-94-7 | R43<br>N; R51-53 | Xi; N<br>R: 43-51/53<br>S: (2-)24-37-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 612-182-00-4 | 1-ethyl-1-methylmorpholinium bromide | | 418-210-1 | 65756-41-4 | Muta. Cat. 3; R68 | Xn<br>R: 68<br>S: (2-)36/37 | | |
| 612-183-00-X | 1-ethyl-1-methylpyrrolidinium bromide | | 418-200-5 | 69227-51-6 | Muta. Cat. 3; R68 | Xn<br>R: 68<br>S: (2-)36/37 | | |
| 613-054-00-0 | thiabendazol (ISO)<br>2-(thiazole-4-yl)benzimidazole | | 205-725-8 | 148-79-8 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 613-163-00-3 | azimsulfuron (ISO)<br>1-(4,6-dimethoxypyrimidin-2-yl)-3-[1-methyl-4-(2-methyl-2*H*-tetrazol-5-yl)pyrazol-5-ylsulfonyl]urea | | — | 120162-55-2 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 613-164-00-9 | flufenacet (ISO)<br>*N*-(4-fluorophenyl)-*N*-isopropyl-2-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yloxy)acetamide | | — | 142459-58-3 | Xn; R22-48/22<br>R43<br>N; R50-53 | Xn; N<br>R: 22-43-48/22-50/53<br>S: (2-)13-24-37-60-61 | | |
| 613-165-00-4 | flupyrsulfuron-methyl-sodium (ISO)<br>methyl 2-[[(4,6-dimethoxypyrimidin-2-ylcarbamoyl)sulfamoyl]-6-trifluoromethyl]nicotinate, monosodium salt | | — | 144740-54-5 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 613-166-00-X | flumioxazin (ISO)<br>*N*-(7-fluoro-3,4-dihydro-3-oxo-4-prop-2-ynyl-2*H*-1,4-benzoxazin-6-yl)cyclohex-1-ene-1,2-dicarboxamide | | — | 103361-09-7 | Repr. Cat. 2; R61<br>N; R50-53 | T; N<br>R: 61-50/53<br>S: 53-45-60-61 | | |
| 613-167-00-5 | a mixture of: 5-chloro-2-methyl-2*H*-isothiazol-3-one [EC No 247-500-7] and 2-methyl-2*H*-isothiazol-3-one [EC No 220-239-6] (3:1)<br>a mixture of: 5-chloro-2-methyl-4-isothiazolin-3-one [EC No 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC No 220-239-6] (3:1) | | — | 55965-84-9 | T; R23/24/25<br>C; R34<br>R43<br>N; R50-53 | T; N<br>R: 23/24/25-34-43-50/53<br>S: (2-)26-28-36/37/39-45-60-61 | C ≥ 25 %: T; R23/24/25-34-43<br>3 % ≤ C < 25 %: C; R20/21/22-34-43<br>0,6 % ≤ C < 3 %: C; R34-43<br>0,06 % ≤ C < 0.6 %: Xi; R36/38-43<br>0,0015 % ≤ C < 0.06 %: Xi; R43 | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 613-168-00-0 | 1-vinyl-2-pyrrolidone | D | 201-800-4 | 88-12-0 | Carc. Cat. 3; R40<br>Xn;<br>R20/21/22-48/20<br>Xi; R37-41 | Xn<br>R: 20/21/22-37-40-41-48/20<br>S: 26-36/37/39 | | |
| 613-169-00-6 | 9-vinylcarbazole | | 216-055-0 | 1484-13-5 | Muta. Cat. 3; R68<br>Xn; R21/22<br>Xi; R38<br>R43<br>N; R50-53 | Xn; N<br>R: 21/22-38-43-50/53-68<br>S: 22-23-36/37-60-61 | | |
| 613-170-00-1 | 2,2-ethylmethylthiazolidine | | 404-500-3 | 694-64-4 | Xn; R22<br>Xi; R41<br>R43<br>N; R51-53 | Xn; N<br>R: 22-41-43-51/53<br>S: (2-)24-26-37/39-61 | | |
| 613-171-00-7 | (*RS*)-2-(2,4-dichlorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)hexan-2-ol | | 413-050-7 | 79983-71-4 | Xn; R22<br>R43<br>N; R51-53 | Xn; N<br>R: 22-43-51/53<br>S: (2-)24-37-61 | | |
| 613-172-00-2 | 5-chloro-1,3-dihydro-2*H*-indol-2-one | | 412-200-9 | 17630-75-0 | Repr. Cat. 3; R62<br>Xn; R22<br>R43<br>R52-53 | Xn<br>R: 22-43-62-52/53<br>S: (2-)22-36/37-61 | | |
| 613-173-00-8 | 3-(2,4-dichlorophenyl)-6-fluoro-2-(1*H*-1,2,4-triazol-1-yl)quinazolin-4-(3*H*)-one | | 411-960-9 | 136426-54-5 | T; R23/25-48/25<br>Xn; R21<br>Xi; R38<br>N; R50-53 | T; N<br>R: 21-23/25-38-48/25-50/53<br>S: (1/2-)36/37/39-38-45-60-61 | | |
| 613-174-00-3 | (+/−) 2-(2,4-dichlorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propyl-1,1,2,2-tetrafluoroethylether | | 407-760-7 | 112281-77-3 | Carc. Cat. 3; R40<br>Xn; R20/22<br>N; R51-53 | Xn; N<br>R: 20/22-40-51/53<br>S: (2-)36/37-41-61 | | |
| 613-175-00-9 | (2*RS*,3*RS*)-3-(2-chlorophenyl)-2-(4-fluorophenyl)-[(1*H*-1,2,4-triazol-1-yl)methyl]oxirane | | 406-850-2 | 106325-08-0 | Carc. Cat. 3; R40<br>Repr. Cat. 2; R61<br>Repr. Cat. 3; R62<br>N; R51-53 | T; N<br>R: 61-40-62-51/53<br>S: 53-45-61 | | |
| 613-176-00-4 | 2-methyl-2-azabicyclo[2.2.1]heptane | | 404-810-9 | 4254-95-2 | R10<br>Xn; R21/22-48/20<br>C; R34 | C<br>R: 10-21/22-34-48/20<br>S: (1/2-)16-26-36/37/39-45 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 613-177-00-X | 8-amino-7-methylquinoline | | 412-760-4 | 5470-82-6 | Xn; R21/22<br>R43<br>N; R51/53 | Xn; N<br>R: 21/22-43-51/53<br>S: (2-)36/37-61 | | |
| 613-178-00-5 | 4-ethyl-2-methyl-2-isopentyl-1,3-oxazolidine | | 410-470-2 | 137796-06-6 | C; R34<br>R43 | C<br>R: 34-43<br>S: (1/2-)7/8-26-36/37/39-45 | C ≥ 10 %: C; R34-43<br>5 % ≤ C < 10 %: Xi; R36/37/38-43<br>1 % ≤ C < 5 %: R43 | |
| 613-179-00-0 | lithium 3-oxo-1,2(2*H*)-benzisothiazol-2-ide | | 411-690-1 | 111337-53-2 | Xn; R22<br>C; R34<br>R43<br>N; R51-53 | C; N<br>R: 22-34-43-51/53<br>S: (1/2-)26-36/37/39-45-61 | | |
| 613-180-00-6 | *N*-(1,1-dimethylethyl)bis(2-benzothiazole-sulfen)amide | | 407-430-1 | 3741-80-8 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 615-024-00-2 | 2-phenylethylisocyanate | | 413-080-0 | 1943-82-4 | T; R23<br>Xn; R22<br>C; R35<br>R42/43<br>N; R51-53 | T; C; N<br>R: 22-23-35-42/43-51/53<br>S: (1/2-)23-26-36/37/39-43-45-61 | | |
| 615-025-00-8 | 4,4′-ethylidenediphenyl dicyanate | | 405-740-1 | 47073-92-7 | Xn; R20/22-48/22<br>Xi; R41<br>N; R50-53 | Xn; N<br>R: 20/22-41-48/22-50/53<br>S: (2-)26-36/37/39-60-61 | | |
| 615-026-00-3 | 4,4′-methylenebis(2,6-dimethylphenyl cyanate) | | 405-790-4 | 101657-77-6 | R43<br>R52-53 | Xi<br>R: 43-52/53<br>S: (2-)22-24-37-61 | | |
| 615-028-00-4 | ethyl 2-(isocyanatosulfonyl)benzoate | | 410-220-2 | 77375-79-2 | E; R2<br>R14<br>Xn; R22-48/22<br>Xi; R41<br>R42/43 | E; Xn<br>R: 2-14-22-41-42/43-48/22<br>S: (2-)8-23-26-30-35-36/37/39 | | |
| 615-029-00-X | 2,5-bis-isocyanatomethyl-bi-cyclo[2.2.1]heptane | | 411-280-2 | — | T+; R26<br>Xn; R22<br>C; R34<br>R42/43<br>R52-53 | T+<br>R: 22-26-34-42/43-52/53<br>S: (1/2-)23-26-28-36/37/39-45-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 616-052-00-8 | formamide | | 200-842-0 | 75-12-7 | Repr. Cat. 2; R61 | T<br>R: 61<br>S: 53-45 | | |
| 616-053-00-3 | *N*-methylacetamide | | 201-182-6 | 79-16-3 | Repr. Cat. 2; R61 | T<br>R: 61<br>S: 53-45 | | |
| 616-054-00-9 | iprodione (ISO)<br>3-(3,5-dichlorophenyl)-2,4-dioxo-*N*-isopropylimidazolidine-1-carboxamide | | 253-178-9 | 36734-19-7 | Carc. Cat. 3; R40<br>N; R50-53 | Xn; N<br>R: 40-50/53<br>S: (2-)36/37-60-61 | | |
| 616-055-00-4 | propyzamide (ISO)<br>3,5-dichloro-*N*-(1,1-dimethylprop-2-ynyl)benzamide | | 245-951-4 | 23950-58-5 | Carc. Cat. 3; R40<br>N; R50-53 | Xn; N<br>R: 40-50/53<br>S: (2-)36/37-60-61 | | |
| 616-056-00-X | *N*-methylformamide | E | 204-624-6 | 123-39-7 | Repr. Cat. 2; R61<br>Xn; R21 | T<br>R: 61-21<br>S: 53-45 | | |
| 616-057-00-5 | a mixture of: *N*-[3-hydroxy-2-(2-methylacryloylaminomethoxy)propoxymethyl]-2-methylacrylamide; *N*-[2,3-bis-(2-methylacryloylaminomethoxy)propoxymethyl]-2-methylacrylamide; methacrylamide; 2-methyl-*N*-(2-methylacryloylaminomethoxymethyl)-acrylamide; *N*-(2,3-dihydroxypropoxymethyl)-2-methylacrylamide | | 412-790-8 | — | Carc. Cat. 2; R45<br>Muta. Cat. 3; R68<br>Xn; R48/22 | T<br>R: 45-48/22<br>S: 53-45 | | |
| 616-058-00-0 | 1,3-bis(3-methyl-2,5-dioxo-1*H*-pyrrolinylmethyl)benzene | | 412-570-1 | 119462-56-5 | Xn; R48/22<br>Xi; R41<br>R43<br>N; R50-53 | Xn; N<br>R: 41-43-48/22-50/53<br>S: (2-)26-36/37/39-60-61 | | |
| 616-059-00-6 | 4-((4-(diethylamino)-2-ethoxyphenyl)imino)-1,4-dihydro-1-oxo-*N*-propyl-2-naphthalenecarboxamide | | 412-650-6 | 121487-83-0 | R53 | R: 53<br>S: 61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 616-060-00-1 | condensation product of: 3-(7-carboxyhept-1-yl)-6-hexyl-4-cyclohexene-1,2-dicarboxylic acid with polyamines (primarily aminoethylpiperazine and triethylenetetramine) | | 413-770-1 | — | Xn; R22<br>C; R34<br>R43<br>N; R50-53 | C; N<br>R: 22-34-43-50/53<br>S: (1/2-)26-36/37/39-45-60-61 | | |
| 616-061-00-7 | *N*,*N*′-1,6-hexanediylbis(*N*-(2,2,6,6-tetramethyl-piperidin-4-yl)formamide | | 413-610-0 | 124172-53-8 | Xi; R36<br>R52-53 | Xi<br>R: 36-52/53<br>S: (2-)26-61 | | |
| 616-062-00-2 | *N*-[3-[(2-acetyloxy)ethyl](phenylmethyl)amino]-4-methoxyphenylacetamide | | 411-590-8 | 70693-57-1 | C; R34<br>R52-53 | C<br>R: 34-52/53<br>S: (1/2-)26-36/37/39-45-61 | | |
| 616-063-00-8 | 3-dodecyl-(1-(1,2,2,6,6-pentamethyl-4-piperidin)-yl)-2,5-pyrrolidindione | | 411-920-0 | 106917-30-0 | T; R23<br>Xn; R22-48/22<br>C; R35<br>N; R50-53 | T; C; N<br>R: 22-23-35-48/22-50/53<br>S: (1/2-)26-28-36/37/39-45-60-61 | | |
| 616-064-00-3 | *N*-*tert*-butyl-3-methylpicolinamide | | 406-720-5 | 32998-95-1 | R52-53 | R: 52/53<br>S: 61 | | |
| 616-065-00-9 | 3′-(3-acetyl-4-hydroxyphenyl)-1,1-diethylurea | | 411-970-3 | 79881-89-3 | Xn; R22-48/22 | Xn<br>R: 22-48/22<br>S: (2-)22-36 | | |
| 616-066-00-4 | 5,6,12,13-tetrachloroanthra(2,1,9-*def*:6,5,10-*d*′*e*′*f*′)diisoquinoline-1,3,8,10(2*H*,9*H*)-tetrone | | 405-100-1 | 115662-06-1 | Repr. Cat. 3; R62 | Xn<br>R: 62<br>S: (2-)22-36/37 | | |
| 616-067-00-X | dodecyl 3-(2-(3-benzyl-4-ethoxy-2,5-dioxoimidazolidin-1-yl)-4,4-dimethyl-3-oxovaleramido)-4-chlorobenzoate | | 407-300-4 | 92683-20-0 | R53 | R: 53<br>S: 61 | | |
| 616-068-00-5 | potassium 4-(11-methacrylamidoundecanamido)benzenesulfonate | | 406-500-9 | 174393-75-0 | R43 | Xi<br>R: 43<br>S: (2-)22-24-37 | | |
| 616-069-00-0 | 1-hydroxy-5-(2-methylpropyloxycarbonylamino)-*N*-(3-dodecyloxypropyl)-2-naphthoamide | | 406-210-2 | 110560-22-0 | R53 | R: 53<br>S: 61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 616-070-00-6 | a mixture of: 3,3′-dicyclohexyl-1,1′-methylenebis(4,1-phenylene)diurea; 3-cyclohexyl-1-(4-(4-(3-octadecylureido)benzyl)phenyl)urea;3,3′-dioctadecyl-1,1′-methylenebis(4,1-phenylene)diurea | | 406-530-2 | — | R53 | R: 53<br>S: 22-61 | | |
| 616-071-00-1 | a mixture (1:2:1) of: bis(*N*-cyclohexyl-*N*′-phenyleneureido)methylene; bis(*N*-octadecyl-*N*′-phenyleneureido)methylene; bis(*N*-dicyclohexyl-*N*′-phenyleneureido)methylene | | 406-550-1 | — | R43<br>R53 | Xi<br>R: 43-53<br>S: (2-)22-24-37-61 | | |
| 616-072-00-7 | 1-(2-deoxy-5-O-trityl-ß-D-threopentofuranosyl)thymine | | 407-120-6 | 55612-11-8 | R53 | R: 53<br>S: 61 | | |
| 616-073-00-2 | 4′-ethoxy-2-benzimidazoleanilide | | 407-600-5 | 120187-29-3 | Muta. Cat. 3; R68<br>R53 | Xn<br>R: 68-53<br>S: (2-)22-36/37-61 | | |
| 616-074-00-8 | *N*-butyl-2-(4-morpholinylcarbonyl)benzamide | | 407-730-2 | 104958-67-0 | Xi; R36<br>R43<br>R52-53 | Xi<br>R: 36-43-52/53<br>S: (2-)24-26-37-61 | | |
| 616-075-00-3 | D,L-(*N*,*N*-diethyl-2-hydroxy-2-phenylacetamide) | | 408-120-9 | 65197-96-8 | Xn; R22<br>Xi; R41 | Xn<br>R: 22-41<br>S: (2-)26-39-(46-) | | |
| 616-076-00-9 | *N*-*tert*-butyl-*N*′-(4-ethylbenzoyl)-3,5-dimethylbenzohydrazide | | 412-850-3 | 112410-23-8 | N; R51-53 | N<br>R: 51/53<br>S: 61 | | |
| 616-077-00-4 | a mixture of: 2-(9-methyl-1,3,8,10-tetraoxo-2,3,9,10-tetrahydro-(1*H*,8*H*)-anthra[2,1,9-*def*: 6,5,10-*d*′*e*′*f*′]diisoquinolin-2-ylethansulfonic acid; potassium 2-(9-methyl-1,3,8,10-tetraoxo-2,3,9,10-tetrahydro-(1*H*,8*H*)-anthra[2,1,9-*def*: 6,5,10-*d*′*e*′*f*′]diisoquinolin-2-ylethansulfate | | 411-310-4 | — | Xi; R41 | Xi<br>R: 41<br>S: (2-)26-39 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 616-078-00-X | 2-[2,4-bis(1,1-dimethyl-ethyl)phenoxy]-*N*-(2-hydroxy-5-methyl-phenyl)hexanamide | | 411-330-3 | 104541-33-5 | R53 | R: 53<br>S: 61 | | |
| 616-079-00-5 | 1,6-hexanediyl-bis(2-(2-(1-ethylpentyl)-3-oxazolidinyl)ethyl)carbamate | | 411-700-4 | 140921-24-0 | R43 | Xi<br>R: 43<br>S: (2-)24-37 | | |
| 616-080-00-0 | 4-(2-((3-ethyl-4-methyl-2-oxo-pyrrolin-1-yl)carboxamido)ethyl)benzenesulfonamide) | | 411-850-0 | 119018-29-0 | R52-53 | R: 52/53<br>S: 61 | | |
| 616-081-00-6 | 5-bromo-8-naphtholactam | | 413-480-5 | 24856-00-6 | Xn; R22<br>R43<br>N; R50-53 | Xn; N<br>R: 22-43-50/53<br>S: (2-)22-24-37-60-61 | | |
| 616-082-00-1 | *N*-(5-chloro-3-((4-(diethylamino)-2-methylphenyl)imino-4-methyl-6-oxo-1,4-cyclohexadien-1-yl)benzamide | | 413-200-1 | 129604-78-0 | R43 | Xi<br>R: 43<br>S: (2-)24-37 | | |
| 616-083-00-7 | [2-[(4-nitrophenyl)amino]ethyl]urea | | 410-700-1 | 27080-42-8 | R43<br>R52-53 | Xi<br>R: 43-52/53<br>S: (2-)24-37-61 | | |
| 616-084-00-2 | 2,4-bis[*N*′-(4-methylphenyl)ureido]toluene | | 411-790-5 | — | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 616-085-00-8 | 3-(2,4-dichlorophenyl)-6-fluoroquinazoline-2,4(1*H*,3*H*)-dione | | 412-190-6 | 168900-02-5 | N; R50-53 | N<br>R: 50/53<br>S: 60-61 | | |
| 616-086-00-3 | 2-acetylamino-6-chloro-4-[(4-diethylamino)2-methylphenyl-imino]-5-methyl-1-oxo-2,5-cyclohexadiene | | 412-250-1 | 102387-48-4 | R53 | R: 53<br>S: 61 | | |
| 616-087-00-9 | a mixture of: 7,9,9-trimethyl-3,14-dioxa-4,13-dioxo-5,12-diazahexadecane-1,16-diyl-prop-2-enoate; 7,7,9-trimethyl-3,14-dioxa-4,13-dioxo-5,12-diazahexadecan-1,16-diylprop-2-enoate | | 412-260-6 | 52658-19-2 | Xi; R36<br>R43<br>N; R51-53 | Xi; N<br>R: 36-43-51/53<br>S: (2-)26-36/37-61 | | |

| Index No | Chemical name | Notes related to substances | EC No | CAS No | Classification | Labelling | Concentration limits | Notes related to preparations |
|---|---|---|---|---|---|---|---|---|
| 616-088-00-4 | 2-aminosulfonyl-*N*,*N*-dimethylnicotinamide | | 413-440-7 | 112006-75-4 | R43<br>R52-53 | Xi<br>R: 43-52/53<br>S: (2-)24-37-61 | | |
| 616-089-00-X | 5-(2,4-dioxo-1,2,3,4-tetrahydropyrimidine)-3- fluoro-2-hydroxymethyltetrahydrofuran | | 415-360-8 | 41107-56-6 | Muta. Cat. 3; R68 | Xn<br>R: 68<br>S: (2-)22-36/37 | | |
| 616-090-00-5 | 1-(1,4-benzodioxan-2-ylcarbonyl)piperazine hydrochloride | | 415-660-9 | 70918-74-0 | T; R23/24/25<br>Xn; R48/22<br>N; R51-53 | T; N<br>R: 23/24/25-48/22-51/53<br>S: 53-45-61 | | |
| 616-091-00-0 | 1,3,5-tris-[(2*S* and 2*R*)-2,3-epoxypropyl]-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione | E | 423-400-0 | 59653-74-6 | Muta. Cat. 2; R46<br>T; R23<br>Xn; R22-48/22<br>Xi; R41<br>R43 | T<br>R: 46-22-23-41-43-48/22<br>S: 53-45 | | |
| 617-016-00-4 | 3-hydroxy-1,1-dimethylbutyl 2-ethyl-2-methylheptaneperoxoate | | 413-910-1 | — | O; R7<br>R10<br>Xi; R38<br>N; R50-53 | O; Xi; N<br>R: 7-10-38-50/53<br>S: (2-)7/47-14-36/37/39-60-61 | | |
| 617-017-00-X | a mixture of: 2,2′-bis(*tert*-pentylperoxy)-*p*-diisopropylbenzene; 2,2′-bis(*tert*-pentylperoxy)-*m*-diisopropylbenzene | | 412-140-3 | 32144-25-5 | O; R7<br>R53 | O<br>R: 7-53<br>S: (2-)3/7-14-36/37/39-61 | | |

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| 006-012-00-2 | 603-056-00-X | 612-128-00-X |
| 015-022-00-6 | 604-009-00-6 | 612-147-00-3 |
| 015-048-00-8 | 604-042-00-6 | 612-148-00-9 |
| 015-072-00-9 | 604-055-00-7 | 613-048-00-8 |
| 023-001-00-8 | 605-016-00-7 | 613-049-00-3 |
| 024-012-00-0 | 609-020-00-X | 613-140-00-8 |
| 602-002-00-2 | 612-033-00-3 | 615-023-00-7 |

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*ANNEX 1F*

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| 048-004-00-1 | 602-025-00-8 | |
| 048-005-00-7 | 603-029-00-2 | |

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*ANNEX 1G*

**Index No**

015-015-00-8

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*ANNEX 1H*

**Index No**

603-001-00-X

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*ANNEX 1I*

**Index No**

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|---|---|---|
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| 601-048-00-0 | 609-007-00-9 | 612-035-00-4 |
| 603-063-00-8 | 609-049-00-8 | 612-051-00-1 |

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*ANNEX 1J*

**Index No**

| | | |
|---|---|---|
| 604-005-00-4 | 612-145-00-2 | 612-146-00-8 |

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*ANNEX 2*

ANEXO II — BILAG II — ANHANG II — ΠΑΡΑΡΤΗΜΑ II — ANNEX II — ANNEXE II — ALLEGATO II — BIJLAGE II — ANEXO II — LIITE II — BILAGA II —

**ANEXO II**

**Símbolos e indicaciones de peligro de las sustancias y preparados peligrosos**

**BILAG II**

**Faresymboler og farebetegnelser for farlige stoffer og præparater**

**ANHANG II**

**Gefahrensymbole und -bezeichnungen für gefährliche Stoffe und Zubereitungen**

**ΠΑΡΑΡΤΗΜΑ II**

**Σύμβολα και ενδείξεις κινδύνου για επικίνδυνες ουσίες και παρασκευάσματα**

**ANNEX II**

**Symbols and indications of danger for dangerous substances and preparations**

**ANNEXE II**

**Symboles et indications de danger des substances et préparations dangereuses**

**ALLEGATO II**

**Simboli e indicazioni di pericolo delle sostanze e preparati pericolosi**

**BIJLAGE II**

**Gevaarsymbolen en -aanduidingen van gevaarlijke stoffen en preparaten**

**ANEXO II**

**Símbolos e indicações de perigo das substâncias e preparações perigosas**

**LIITE II**

**Varoitusmerkit ja niiden nimet vaarallisille aineille ja valmisteille**

**BILAGA II**

**Farosymboler och farobeteckningar för farliga ämnen och beredningar**

Nota: Las letras E, O, F, F+, T, T+, C, Xn, Xi y N no forman parte del símbolo.

Bemærkning: Bogstaverne E, O, F, F+, T, T+, C, Xn, Xi og N udgør ikke en del af symbolet.

Anmerkung: Die Buchstaben E, O, F, F+, T, T+, C, Xn, Xi und N sind nicht Bestandteil des Gefahrensymbols.

Σημείωση: Τα γράμματα E, O, F, F+, T, T+, C, Xn, Xi και N δεν αποτελούν μέρος του συμβόλου.

Note: The letters E, O, F, F+, T, T+, C, Xn, Xi and N do not form part of the symbol.

Remarque: Les lettres E, O, F, F+, T, T+, C, Xn, Xi et N ne font pas partie du symbole.

Nota: Le lettere E, O, F, F+, T, T+, C, Xn, Xi e N non fanno parte del simbolo.

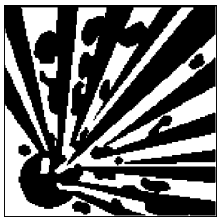
Opmerking: De letters E, O, F, F+, T, T+, C, Xn, Xi en N maken geen deel uit van het gevaarsymbool.

Nota: As letras E, O, F, F+, T, T+, C, Xn, Xi e N não fazem parte do símbolo.

Huomautus: Varoitusmerkkien kirjaintunnukset E, O, F, F+, T, T+, C, Xn, Xi ja N eivät ole osa varoitusmerkkiä.

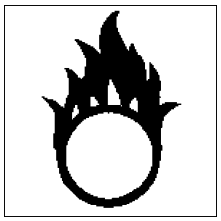
Anmärkning: Bokstäverna E, O, F, F+, T, T+, C, Xn, Xi och N utgör inte en del av symbolen.

**E**



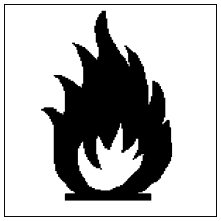
ES: Explosivo
DA: Eksplosiv
DE: Explosionsgefährlich
EL: Εκρηκτικό
EN: Explosive
FR: Explosif
IT: Esplosivo
NL: Ontplofbaar
PT: Explosivo
FI: Räjähtävä
SV: Explosivt

**O**



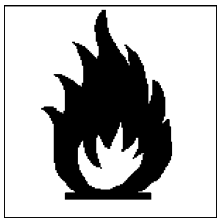
ES: Comburente
DA: Brandnærende
DE: Brandfördernd
EL: Οξειδωτικό
EN: Oxidising
FR: Comburant
IT: Comburente
NL: Oxiderend
PT: Comburente
FI: Hapettava
SV: Oxiderande

**F**



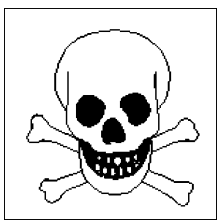
ES: Fácilmente inflamable
DA: Meget brandfarlig
DE: Leichtentzündlich
EL: Πολύ εύφλεκτο
EN: Highly flammable
FR: Facilement inflammable
IT: Facilmente infiammabile
NL: Licht ontvlambaar
PT: Facilmente inflamável
FI: Helposti syttyvä
SV: Mycket brandfarligt

**F+**



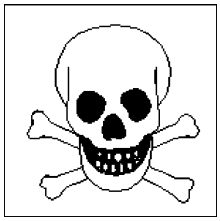
ES: Extremadamente inflamable
DA: Yderst brandfarlig
DE: Hochentzündlich
EL: Εξαιρετικά εύφλεκτο
EN: Extremely flammable
FR: Extrêmement inflammable
IT: Estremamente infiammabile
NL: Zeer licht ontvlambaar
PT: Extremamente inflamável
FI: Erittäin helposti syttyvä
SV: Extremt brandfarligt

**T**



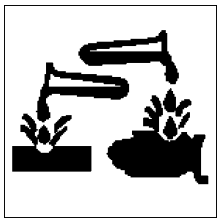
ES: Tóxico
DA: Giftig
DE: Giftig
EL: Τοξικό
EN: Toxic
FR: Toxique
IT: Tossico
NL: Vergiftig
PT: Tóxico
FI: Myrkyllinen
SV: Giftig

**T+**



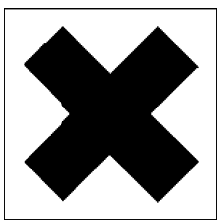
ES: Muy tóxico
DA: Meget giftig
DE: Sehr giftig
EL: Πολύ τοξικό
EN: Very toxic
FR: Très toxique
IT: Molto tossico
NL: Zeer vergiftig
PT: Muito tóxico
FI: Erittäin myrkyllinen
SV: Mycket giftig

**C**



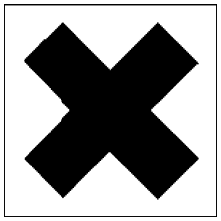
ES: Corrosivo
DA: Ætsende
DE: Ätzend
EL: Διαβρωτικό
EN: Corrosive
FR: Corrosif
IT: Corrosivo
NL: Bijtend
PT: Corrosivo
FI: Syövyttävä
SV: Frätande

**Xn**



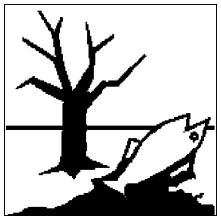
ES: Nocivo
DA: Sundhedsskadelig
DE: Gesundheitsschädlich
EL: Επιβλαβές
EN: Harmful
FR: Nocif
IT: Nocivo
NL: Schadelijk
PT: Nocivo
FI: Haitallinen
SV: Hälsoskadlig

**Xi**



ES: Irritante
DA: Lokalirriterende
DE: Reizend
EL: Ερεθιστικό
EN: Irritant
FR: Irritant
IT: Irritante
NL: Irriterend
PT: Irritante
FI: Ärsyttävä
SV: Irriterande

**N**



ES: Peligroso para el medio ambiente
DA: Miljøfarlig
DE: Umweltgefährlich
EL: Επικίνδυνο για το περιβάλλον
EN: Dangerous for the environment
FR: Dangereux pour l'environnement
IT: Pericoloso per l'ambiente
NL: Milieugevaarlijk
PT: Perigoso para o ambiente
FI: Ympäristölle vaarallinen
SV: Miljöfarlig

*ANNEX 3*

ANEXO III — BILAG III — ANHANG III — ΠΑΡΑΡΤΗΜΑ III — ANNEX III — ANNEXE III — ALLEGATO III — BIJLAGE III — ANEXO III — LIITE III — BILAGA III

**ANEXO III**

**Naturaleza de los riesgos específicos atribuidos a las sustancias y preparados peligrosos**

**BILAG III**

**Arten af de særlige risici, der er forbundet med de farlige stoffer og præparater**

**ANHANG III**

**Bezeichnungen der besonderen Gefahren bei gefährlichen Stoffen und Zubereitungen**

**ΠΑΡΑΡΤΗΜΑ III**

**Φύση των ειδικών κινδύνων που αφορούν επικίνδυνες ουσίες και παρασκευάσματα**

**ANNEX III**

**Nature of special risks attributed to dangerous substances and preparations**

**ANNEXE III**

**Nature des risques particuliers attribués aux substances et préparations dangereuses**

**ALLEGATO III**

**Natura dei rischi specifici attribuiti alle sostanze e preparati pericolosi**

**BIJLAGE III**

**Aard der bijzondere gevaren toegeschreven aan gevaarlijke stoffen en preparaten**

**ANEXO III**

**Natureza dos riscos específicos atribuídos às substâncias e preparações perigosas**

**LIITE III**

**Erityisten vaarojen luonne liittyen vaarallisiin aineisiin ja valmisteisiin**

**BILAGA III**

**Riskfraser som tilldelas farliga ämnen och beredningar**

**R1**

ES: Explosivo en estado seco.

DA: Eksplosiv i tør tilstand.

DE: In trockenem Zustand explosionsgefährlich.

EL: Εκρηκτικό σε ξηρή κατάσταση.

EN: Explosive when dry.

FR: Explosif à l'état sec.

IT: Esplosivo allo stato secco.

NL: In droge toestand ontplofbaar.

PT: Explosivo no estado seco.

FI: Räjähtävää kuivana.

SV: Explosivt i torrt tillstånd.

**R2**

ES: Riesgo de explosión por choque, fricción, fuego u otras fuentes de ignición.

DA: Eksplosionsfarlig ved stød, gnidning, ild eller andre antændelseskilder.

DE: Durch Schlag, Reibung, Feuer oder andere Zündquellen explosionsgefährlich.

EL: Κίνδυνος εκρήξεως από κρούση, τριβή, φωτιά ή άλλες πηγές αναφλέξεως.

EN: Risk of explosion by shock, friction, fire or other sources of ignition.

FR: Risque d'explosion par le choc, la friction, le feu ou d'autres sources d'ignition.

IT: Rischio di esplosione per urto, sfregamento, fuoco o altre sorgenti d'ignizione.

NL: Ontploffingsgevaar door schok, wrijving, vuur of andere ontstekingsoorzaken.

PT: Risco de explosão por choque, fricção, fogo ou outras fontes de ignição.

FI: Räjähtävää iskun, hankauksen, avotulen tai muun sytytyslähteen vaikutuksesta.

SV: Explosivt vid stöt, friktion, eld eller annan antändningsorsak.

**R3**

ES: Alto riesgo de explosión por choque, fricción, fuego u otras fuentes de ignición.

DA: Meget eksplosionsfarlig ved stød, gnidning, ild eller andre antændelseskilder.

DE: Durch Schlag, Reibung, Feuer oder andere Zündquellen besonders explosionsgefährlich.

EL: Πολύ μεγάλος κίνδυνος εκρήξεως από κρούση, τριβή, φωτιά ή άλλες πηγές αναφλέξεως.

EN: Extreme risk of explosion by shock, friction, fire or other sources of ignition.

FR: Grand risque d'explosion par le choc, la friction, le feu ou d'autres sources d'ignition.

IT: Elevato rischio di esplosione per urto, sfregamento, fuoco o altre sorgenti d'ignizione.

NL: Ernstig ontploffingsgevaar door schok, wrijving, vuur of andere ontstekingsoorzaken.

PT: Grande risco de explosão por choque, fricção, fogo ou outras fontes de ignição.

FI: Erittäin helposti räjähtävää iskun, hankauksen, avotulen tai muun sytytyslähteen vaikutuksesta.

SV: Mycket explosivt vid stöt, friktion, eld eller annan antändningsorsak.

**R4**

ES: Forma compuestos metálicos explosivos muy sensibles.

DA: Danner meget følsomme eksplosive metalforbindelser.

DE: Bildet hochempfindliche explosionsgefährliche Metallverbindungen.

EL: Σχηματίζει πολύ ευαίσθητες εκρηκτικές μεταλλικές ενώσεις.

EN: Forms very sensitive explosive metallic compounds.

FR: Forme des composés métalliques explosifs très sensibles.

IT: Forma composti metallici esplosivi molto sensibili.

NL: Vormt met metalen zeer gemakkelijk ontplofbare verbindingen.

PT: Forma compostos metálicos explosivos muito sensíveis.

FI: Muodostaa erittäin herkästi räjähtäviä metalliyhdisteitä.

SV: Bildar mycket känsliga explosiva metallföreningar.

**R5**

ES: Peligro de explosión en caso de calentamiento.

DA: Eksplosionsfarlig ved opvarmning.

DE: Beim Erwärmen explosionsfähig.

EL: Η θέρμανση μπορεί να προκαλέσει έκρηξη.

EN: Heating may cause an explosion.

FR: Danger d'explosion sous l'action de la chaleur.

IT: Pericolo di esplosione per riscaldamento.

NL: Ontploffingsgevaar door verwarming.

PT: Perigo de explosão sob a acção do calor.

FI: Räjähdysvaarallinen kuumennettaessa.

SV: Explosivt vid uppvärmning.

**R6**

ES: Peligro de explosión, en contacto o sin contacto con el aire.

DA: Eksplosiv ved og uden kontakt med luft.

DE: Mit und ohne Luft explosionsfähig.

EL: Εκρηκτικό σε επαφή ή χωρίς επαφή με τον αέρα.

EN: Explosive with or without contact with air.

FR: Danger d'explosion en contact ou sans contact avec l'air.

IT: Esplosivo a contatto o senza contatto con l'aria.

NL: Ontplofbaar met en zonder lucht.

PT: Perigo de explosão com ou sem contacto com o ar.

FI: Räjähtävää sellaisenaan tai ilman kanssa.

SV: Explosivt vid kontakt och utan kontakt med luft.

**R7**

ES: Puede provocar incendios.

DA: Kan forårsage brand.

DE: Kann Brand verursachen.

EL: Μπορεί να προκαλέσει πυρκαγιά.

EN: May cause fire.

FR: Peut provoquer un incendie.

IT: Può provocare un incendio.

NL: Kan brand veroorzaken.

PT: Pode provocar incêndio.

FI: Aiheuttaa tulipalon vaaran.

SV: Kan orsaka brand.

**R8**

ES: Peligro de fuego en contacto con materias combustibles.

DA: Brandfarlig ved kontakt med brandbare stoffer.

DE: Feuergefahr bei Berührung mit brennbaren Stoffen.

EL: Η επαφή με καύσιμο υλικό μπορεί να προκαλέσει πυρκαγιά.

EN: Contact with combustible material may cause fire.

FR: Favorise l'inflammation des matières combustibles.

IT: Può provocare l'accensione di materie combustibili.

NL: Bevordert de ontbranding van brandbare stoffen.

PT: Favorece a inflamação de matérias combustíveis.

FI: Aiheuttaa tulipalon vaaran palavien aineiden kanssa.

SV: Kontakt med brännbart material kan orsaka brand.

**R9**

ES: Peligro de explosión al mezclar con materias combustibles.

DA: Eksplosionsfarlig ved blanding med brandbare stoffer.

DE: Explosionsgefahr bei Mischung mit brennbaren Stoffen.

EL: Εκρηκτικό όταν αναμειχθεί με καύσιμα υλικά.

EN: Explosive when mixed with combustible material.

FR: Peut exploser en mélange avec des matières combustibles.

IT: Esplosivo in miscela con materie combustibili.

NL: Ontploffingsgevaar bij menging met brandbare stoffen.

PT: Pode explodir quando misturado com matérias combustíveis.

FI: Räjähtävää sekoitettaessa palavien aineiden kanssa.

SV: Explosivt vid blandning med brännbart material.

**R10**

ES: Inflamable.

DA: Brandfarlig.

DE: Entzündlich.

EL: Εύφλεκτο.

EN: Flammable.

FR: Inflammable.

IT: Infiammabile.

NL: Ontvlambaar.

PT: Inflamável.

FI: Syttyvää.

SV: Brandfarligt.

**R11**

ES: Fácilmente inflamable.

DA: Meget brandfarlig.

DE: Leichtentzündlich.

EL: Πολύ εύφλεκτο.

EN: Highly flammable.

FR: Facilement inflammable.

IT: Facilmente infiammabile.

NL: Licht ontvlambaar.

PT: Facilmente inflamável.

FI: Helposti syttyvää.

SV: Mycket brandfarligt.

**R12**

ES: Extremadamente inflamable.

DA: Yderst brandfarlig.

DE: Hochentzündlich.

EL: Εξαιρετικά εύφλεκτο.

EN: Extremely flammable.

FR: Extrêmement inflammable.

IT: Estremamente infiammabile.

NL: Zeer licht ontvlambaar.

PT: Extremamente inflamável.

FI: Erittäin helposti syttyvää.

SV: Extremt brandfarligt.

**R14**

ES: Reacciona violentamente con el agua.

DA: Reagerer voldsomt med vand.

DE: Reagiert heftig mit Wasser.

EL: Αντιδρά βίαια με νερό.

EN: Reacts violently with water.

FR: Réagit violemment au contact de l'eau.

IT: Reagisce violentemente con l'acqua.

NL: Reageert heftig met water.

PT: Reage violentamente em contacto com a água.

FI: Reagoi voimakkaasti veden kanssa.

SV: Reagerar häftigt med vatten.

**R15**

ES: Reacciona con el agua liberando gases extremadamente inflamables.

DA: Reagerer med vand under dannelse af yderst brandfarlige gasser.

DE: Reagiert mit Wasser unter Bildung hochentzündlicher Gase.

EL: Σε επαφή με το νερό εκλύει εξαιρετικά εύφλεκτα αέρια.

EN: Contact with water liberates extremely flammable gases.

FR: Au contact de l'eau, dégage des gaz extrêmement inflammables.

IT: A contatto con l'acqua libera gas estremamente infiammabili.

NL: Vormt zeer licht ontvlambaar gas in contact met water.

PT: Em contacto com a água liberta gases extremamente inflamáveis.

FI: Vapauttaa erittäin helposti syttyviä kaasuja veden kanssa.

SV: Vid kontakt med vatten bildas extremt brandfarliga gaser.

**R16**

ES: Puede explosionar en mezcla con substancias comburentes.

DA: Eksplosionsfarlig ved blanding med oxiderende stoffer.

DE: Explosionsgefährlich in Mischung mit brandfördernden Stoffen.

EL: Εκρηκτικό όταν αναμειχθεί με οξειδωτικές ουσίες.

EN: Explosive when mixed with oxidising substances.

FR: Peut exploser en mélange avec des substances comburantes.

IT: Pericolo di esplosione se mescolato con sostanze comburenti.

NL: Ontploffingsgevaar bij menging met oxiderende stoffen.

PT: Explosivo quando misturado com substâncias comburentes.

FI: Räjähtävää hapettavien aineiden kanssa.

SV: Explosivt vid blandning med oxiderande ämnen.

**R17**

ES: Se inflama espontáneamente en contacto con el aire.

DA: Selvantændelig i luft.

DE: Selbstentzündlich an der Luft.

EL: Αυτοαναφλέγεται στον αέρα.

EN: Spontaneously flammable in air.

FR: Spontanément inflammable à l'air.

IT: Spontaneamente infiammabile all'aria.

NL: Spontaan ontvlambaar in lucht.

PT: Espontaneamente inflamável ao ar.

FI: Itsestään syttyvää ilmassa.

SV: Självantänder i luft.

**R18**

ES: Al usarlo pueden formarse mezclas aire-vapor explosivas/inflamables.

DA: Ved brug kan brandbare dampe/eksplosive damp-luftblandinger dannes.

DE: Bei Gebrauch Bildung explosionsfähiger/leichtentzündlicher Dampf/Luft-Gemische möglich.

EL: Κατά τη χρήση μπορεί να σχηματίσει εύφλεκτα/εκρηκτικά μείγματα ατμού-αέρος.

EN: In use, may form flammable/explosive vapour-air mixture.

FR: Lors de l'utilisation, formation possible de mélange vapeur-air inflammable/explosif.

IT: Durante l'uso può formare con aria miscele esplosive/infiammabili.

NL: Kan bij gebruik een ontvlambaar/ontplofbaar damp-luchtmengsel vormen.

PT: Pode formar mistura vapor-ar explosiva/inflamável durante a utilização.

FI: Käytössä voi muodostua syttyvä/räjähtävä höyry-ilmaseos.

SV: Vid användning kan brännbara/explosiva ång-luftblandningar bildas.

**R19**

ES: Puede formar peróxidos explosivos.

DA: Kan danne eksplosive peroxider.

DE: Kann explosionsfähige Peroxide bilden.

EL: Μπορεί να σχηματίσει εκρηκτικά υπεροξείδια.

EN: May form explosive peroxides.

FR: Peut former des peroxydes explosifs.

IT: Può formare perossidi esplosivi.

NL: Kan ontplofbare peroxiden vormen.

PT: Pode formar peróxidos explosivos.

FI: Saattaa muodostaa räjähtäviä peroksideja.

SV: Kan bilda explosiva peroxider.

**R20**

ES: Nocivo por inhalación.

DA: Farlig ved indånding.

DE: Gesundheitsschädlich beim Einatmen.

EL: Επιβλαβές όταν εισπνέεται.

EN: Harmful by inhalation.

FR: Nocif par inhalation.

IT: Nocivo per inalazione.

NL: Schadelijk bij inademing.

PT: Nocivo por inalação.

FI: Terveydelle haitallista hengitettynä.

SV: Farligt vid inandning.

**R21**

ES: Nocivo en contacto con la piel.

DA: Farlig ved hudkontakt.

DE: Gesundheitsschädlich bei Berührung mit der Haut.

EL: Επιβλαβές σε επαφή με το δέρμα.

EN: Harmful in contact with skin.

FR: Nocif par contact avec la peau.

IT: Nocivo a contatto con la pelle.

NL: Schadelijk bij aanraking met de huid.

PT: Nocivo em contacto com a pele.

FI: Terveydelle haitallista joutuessaan iholle.

SV: Farligt vid hudkontakt.

**R22**

ES: Nocivo por ingestión.

DA: Farlig ved indtagelse.

DE: Gesundheitsschädlich beim Verschlucken.

EL: Επιβλαβές σε περίπτωση καταπόσεως.

EN: Harmful if swallowed.

FR: Nocif en cas d'ingestion.

IT: Nocivo per ingestione.

NL: Schadelijk bij opname door de mond.

PT: Nocivo por ingestão.

FI: Terveydelle haitallista nieltynä.

SV: Farligt vid förtäring.

**R23**

ES: Tóxico por inhalación.

DA: Giftig ved indånding.

DE: Giftig beim Einatmen.

EL: Τοξικό όταν εισπνέεται.

EN: Toxic by inhalation.

FR: Toxique par inhalation.

IT: Tossico per inalazione.

NL: Vergiftig bij inademing.

PT: Tóxico por inalação.

FI: Myrkyllistä hengitettynä.

SV: Giftigt vid inandning.

**R24**

ES: Tóxico en contacto con la piel.

DA: Giftig ved hudkontakt.

DE: Giftig bei Berührung mit der Haut.

EL: Τοξικό σε επαφή με το δέρμα.

EN: Toxic in contact with skin.

FR: Toxique par contact avec la peau.

IT: Tossico a contatto con la pelle.

NL: Vergiftig bij aanraking met de huid.

PT: Tóxico em contacto com a pele.

FI: Myrkyllistä joutuessaan iholle.

SV: Giftigt vid hudkontakt.

**R25**

ES: Tóxico por ingestión.

DA: Giftig ved indtagelse.

DE: Giftig beim Verschlucken.

EL: Τοξικό σε περίπτωση καταπόσεως.

EN: Toxic if swallowed.

FR: Toxique en cas d'ingestion.

IT: Tossico per ingestione.

NL: Vergiftig bij opname door de mond.

PT: Tóxico por ingestão.

FI: Myrkyllistä nieltynä.

SV: Giftigt vid förtäring.

**R26**

ES: Muy tóxico por inhalación.

DA: Meget giftig ved indånding.

DE: Sehr giftig beim Einatmen.

EL: Πολύ τοξικό όταν εισπνέεται.

EN: Very toxic by inhalation.

FR: Très toxique par inhalation.

IT: Molto tossico per inalazione.

NL: Zeer vergiftig bij inademing.

PT: Muito tóxico por inalação.

FI: Erittäin myrkyllistä hengitettynä.

SV: Mycket giftigt vid inandning.

**R27**

ES: Muy tóxico en contacto con la piel.

DA: Meget giftig ved hudkontakt.

DE: Sehr giftig bei Berührung mit der Haut.

EL: Πολύ τοξικό σε επαφή με το δέρμα.

EN: Very toxic in contact with skin.

FR: Très toxique par contact avec la peau.

IT: Molto tossico a contatto con la pelle.

NL: Zeer vergiftig bij aanraking met de huid.

PT: Muito tóxico em contacto com a pele.

FI: Erittäin myrkyllistä joutuessaan iholle.

SV: Mycket giftigt vid hudkontakt.

**R28**

ES: Muy tóxico por ingestión.

DA: Meget giftig ved indtagelse.

DE: Sehr giftig beim Verschlucken.

EL: Πολύ τοξικό σε περίπτωση καταπόσεως.

EN: Very toxic if swallowed.

FR: Très toxique en cas d'ingestion.

IT: Molto tossico per ingestione.

NL: Zeer vergiftig bij opname door de mond.

PT: Muito tóxico por ingestão.

FI: Erittäin myrkyllistä nieltynä.

SV: Mycket giftigt vid förtäring.

**R29**

ES: En contacto con agua libera gases tóxicos.

DA: Udvikler giftig gas ved kontakt med vand.

DE: Entwickelt bei Berührung mit Wasser giftige Gase.

EL: Σε επαφή με το νερό ελευθερώνονται τοξικά αέρια.

EN: Contact with water liberates toxic gas.

FR: Au contact de l'eau, dégage des gaz toxiques.

IT: A contatto con l'acqua libera gas tossici.

NL: Vormt vergiftig gas in contact met water.

PT: Em contacto com a água liberta gases tóxicos.

FI: Kehittää myrkyllistä kaasua veden kanssa.

SV: Utvecklar giftig gas vid kontakt med vatten.

**R30**

ES: Puede inflamarse fácilmente al usarlo.

DA: Kan blive meget brandfarlig under brug.

DE: Kann bei Gebrauch leicht entzündlich werden.

EL: Κατά τη χρήση γίνεται πολύ εύφλεκτο.

EN: Can become highly flammable in use.

FR: Peut devenir facilement inflammable pendant l'utilisation.

IT: Può divenire facilmente infiammabile durante l'uso.

NL: Kan bij gebruik licht ontvlambaar worden.

PT: Pode tornar-se facilmente inflamável durante o uso.

FI: Käytettäessä voi muuttua helposti syttyväksi.

SV: Kan bli mycket brandfarligt vid användning.

**R31**

ES: En contacto con ácidos libera gases tóxicos.

DA: Udvikler giftig gas ved kontakt med syre.

DE: Entwickelt bei Berührung mit Säure giftige Gase.

EL: Σε επαφή με οξέα ελευθερώνονται τοξικά αέρια.

EN: Contact with acids liberates toxic gas.

FR: Au contact d'un acide, dégage un gaz toxique.

IT: A contatto con acidi libera gas tossico.

NL: Vormt vergiftige gassen in contact met zuren.

PT: Em contacto com ácidos liberta gases tóxicos.

FI: Kehittää myrkyllistä kaasua hapon kanssa.

SV: Utvecklar giftig gas vid kontakt med syra.

**R32**

ES: En contacto con ácidos libera gases muy tóxicos.

DA: Udvikler meget giftig gas ved kontakt med syre.

DE: Entwickelt bei Berührung mit Säure sehr giftige Gase.

EL: Σε επαφή με οξέα ελευθερώνονται πολύ τοξικά αέρια.

EN: Contact with acids liberates very toxic gas.

FR: Au contact d'un acide, dégage un gaz très toxique.

IT: A contatto con acidi libera gas molto tossico.

NL: Vormt zeer vergiftige gassen in contact met zuren.

PT: Em contacto com ácidos liberta gases muito tóxicos.

FI: Kehittää erittäin myrkyllistä kaasua hapon kanssa.

SV: Utvecklar mycket giftig gas vid kontakt med syra.

**R33**

ES: Peligro de efectos acumulativos.

DA: Kan ophobes i kroppen efter gentagen brug.

DE: Gefahr kumulativer Wirkungen.

EL: Κίνδυνος αθροιστικών επιδράσεων.

EN: Danger of cumulative effects.

FR: Danger d'effets cumulatifs.

IT: Pericolo di effetti cumulativi.

NL: Gevaar voor cumulatieve effecten.

PT: Perigo de efeitos cumulativos.

FI: Terveydellisten haittojen vaara pitkäaikaisessa altistuksessa.

SV: Kan ansamlas i kroppen och ge skador.

**R34**

ES: Provoca quemaduras.

DA: Ætsningsfare.

DE: Verursacht Verätzungen.

EL: Προκαλεί εγκαύματα.

EN: Causes burns.

FR: Provoque des brûlures.

IT: Provoca ustioni.

NL: Veroorzaakt brandwonden.

PT: Provoca queimaduras.

FI: Syövyttävää.

SV: Frätande.

**R35**

ES: Provoca quemaduras graves.

DA: Alvorlig ætsningsfare.

DE: Verursacht schwere Verätzungen.

EL: Προκαλεί σοβαρά εγκαύματα.

EN: Causes severe burns.

FR: Provoque de graves brûlures.

IT: Provoca gravi ustioni.

NL: Veroorzaakt ernstige brandwonden.

PT: Provoca queimaduras graves.

FI: Voimakkaasti syövyttävää.

SV: Starkt frätande.

**R36**

ES: Irrita los ojos.

DA: Irriterer øjnene.

DE: Reizt die Augen.

EL: Ερεθίζει τα μάτια.

EN: Irritating to eyes.

FR: Irritant pour les yeux.

IT: Irritante per gli occhi.

NL: Irriterend voor de ogen.

PT: Irritante para os olhos.

FI: Ärsyttää silmiä.

SV: Irriterar ögonen.

**R37**

ES: Irrita las vías respiratorias.

DA: Irriterer åndedrætsorganerne.

DE: Reizt die Atmungsorgane.

EL: Ερεθίζει το αναπνευστικό σύστημα.

EN: Irritating to respiratory system.

FR: Irritant pour les voies respiratoires.

IT: Irritante per le vie respiratorie.

NL: Irriterend voor de ademhalingswegen.

PT: Irritante para as vias respiratórias.

FI: Ärsyttää hengityselimiä.

SV: Irriterar andningsorganen.

**R38**

ES: Irrita la piel.

DA: Irriterer huden.

DE: Reizt die Haut.

EL: Ερεθίζει το δέρμα.

EN: Irritating to skin.

FR: Irritant pour la peau.

IT: Irritante per la pelle.

NL: Irriterend voor de huid.

PT: Irritante para a pele.

FI: Ärsyttää ihoa.

SV: Irriterar huden.

**R39**

ES: Peligro de efectos irreversibles muy graves.

DA: Fare for varig alvorlig skade på helbred.

DE: Ernste Gefahr irreversiblen Schadens.

EL: Κίνδυνος πολύ σοβαρών μονίμων επιδράσεων.

EN: Danger of very serious irreversible effects.

FR: Danger d'effets irréversibles très graves.

IT: Pericolo di effetti irreversibili molto gravi.

NL: Gevaar voor ernstige onherstelbare effecten.

PT: Perigo de efeitos irreversíveis muito graves.

FI: Erittäin vakavien pysyvien vaurioiden vaara.

SV: Risk för mycket allvarliga bestående hälsoskador.

**R40**

ES: Posibles efectos cancerígenos.

DA: Mulighed for kræftfremkaldende effekt.

DE: Verdacht auf krebserzeugende Wirkung.

EL: Ύποπτο καρκινογένεσης.

EN: Limited evidence of a carcinogenic effect.

FR: Effet cancérogène suspecté — preuves insuffisantes.

IT: Possibilità di effetti cancerogeni — prove insufficienti.

NL: Carcinogene effecten zijn niet uitgesloten.

PT: Possibilidade de efeitos cancerígenos.

FI: Epäillään aiheuttavan syöpäsairauden vaaraa.

SV: Misstänks kunna ge cancer.

**R41**

ES: Riesgo de lesiones oculares graves.

DA: Risiko for alvorlig øjenskade.

DE: Gefahr ernster Augenschäden.

EL: Κίνδυνος σοβαρών οφθαλμικών βλαβών.

EN: Risk of serious damage to eyes.

FR: Risque de lésions oculaires graves.

IT: Rischio di gravi lesioni oculari.

NL: Gevaar voor ernstig oogletsel.

PT: Risco de lesões oculares graves .

FI: Vakavan silmävaurion vaara.

SV: Risk för allvarliga ögonskador.

**R42**

ES: Posibilidad de sensibilización por inhalación.

DA: Kan give overfølsomhed ved indånding.

DE: Sensibilisierung durch Einatmen möglich.

EL: Μπορεί να προκαλέσει ευαισθητοποίηση όταν εισπνέεται.

EN: May cause sensitisation by inhalation.

FR: Peut entraîner une sensibilisation par inhalation.

IT: Può provocare sensibilizzazione per inalazione.

NL: Kan overgevoeligheid veroorzaken bij inademing.

PT: Pode causar sensibilização por inalação.

FI: Altistuminen hengitysteitse voi aiheuttaa herkistymistä.

SV: Kan ge allergi vid inandning

**R43**

ES: Posibilidad de sensibilización en contacto con la piel.

DA: Kan give overfølsomhed ved kontakt med huden.

DE: Sensibilisierung durch Hautkontakt möglich.

EL: Μπορεί να προκαλέσει ευαισθητοποίηση σε επαφή με το δέρμα.

EN: May cause sensitisation by skin contact.

FR: Peut entraîner une sensibilisation par contact avec la peau.

IT: Può provocare sensibilizzazione per contatto con la pelle.

NL: Kan overgevoeligheid veroorzaken bij contact met de huid.

PT: Pode causar sensibilização em contacto com a pele.

FI: Ihokosketus voi aiheuttaa herkistymistä.

SV: Kan ge allergi vid hudkontakt.

**R44**

ES: Riesgo de explosión al calentarlo en ambiente confinado.

DA: Eksplosionsfarlig ved opvarmning under indeslutning.

DE: Explosionsgefahr bei Erhitzen unter Einschluss.

EL: Κίνδυνος εκρήξεως εάν θερμανθεί υπό περιορισμό.

EN: Risk of explosion if heated under confinement.

FR: Risque d'explosion si chauffé en ambiance confinée.

IT: Rischio di esplosione per riscaldamento in ambiente confinato.

NL: Ontploffingsgevaar bij verwarming in afgesloten toestand.

PT: Risco de explosão se aquecido em ambiente fechado.

FI: Räjähdysvaara kuumennettaessa suljetussa astiassa.

SV: Explosionsrisk vid uppvärmning i sluten behållare.

**R45**

ES: Puede causar cáncer.

DA: Kan fremkalde kræft.

DE: Kann Krebs erzeugen.

EL: Μπορεί να προκαλέσει καρκίνο.

EN: May cause cancer.

FR: Peut provoquer le cancer.

IT: Può provocare il cancro.

NL: Kan kanker veroorzaken.

PT: Pode causar cancro.

FI: Aiheuttaa syöpäsairauden vaaraa.

SV: Kan ge cancer.

**R46**

ES: Puede causar alteraciones genéticas hereditarias.

DA: Kan forårsage arvelige genetiske skader.

DE: Kann vererbbare Schäden verursachen.

EL: Μπορεί να προκαλέσει κληρονομικές γενετικές βλάβες.

EN: May cause heritable genetic damage.

FR: Peut provoquer des altérations génétiques héréditaires.

IT: Può provocare alterazioni genetiche ereditarie.

NL: Kan erfelijke genetische schade veroorzaken.

PT: Pode causar alterações genéticas hereditárias.

FI: Saattaa aiheuttaa periytyviä perimävaurioita.

SV: Kan ge ärftliga genetiska skador.

**R48**

ES: Riesgo de efectos graves para la salud en caso de exposición prolongada.

DA: Alvorlig sundhedsfare ved længere tids påvirkning.

DE: Gefahr ernster Gesundheitsschäden bei längerer Exposition.

EL: Κίνδυνος σοβαρής βλάβης της υγείας ύστερα απο παρατεταμένη έκθεση.

EN: Danger of serious damage to health by prolonged exposure.

FR: Risque d'effets graves pour la santé en cas d'exposition prolongée.

IT: Pericolo di gravi danni per la salute in caso di esposizione prolungata.

NL: Gevaar voor ernstige schade aan de gezondheid bij langdurige blootstelling.

PT: Risco de efeitos graves para a saúde em caso de exposição prolongada.

FI: Pitkäaikainen altistus voi aiheuttaa vakavaa haittaa terveydelle.

SV: Risk för allvarliga hälsoskador vid långvarig exponering.

**R49**

ES: Puede causar cáncer por inhalación.

DA: Kan fremkalde kræft ved indånding.

DE: Kann Krebs erzeugen beim Einatmen.

EL: Μπορεί να προκαλέσει καρκίνο όταν εισπνέεται.

EN: May cause cancer by inhalation.

FR: Peut provoquer le cancer par inhalation.

IT: Può provocare il cancro per inalazione.

NL: Kan kanker veroorzaken bij inademing.

PT: Pode causar cancro por inalação.

FI: Aiheuttaa syöpäsairauden vaaraa hengitettynä.

SV: Kan ge cancer vid inandning.

**R50**

ES: Muy tóxico para los organismos acuáticos.

DA: Meget giftig for organismer, der lever i vand.

DE: Sehr giftig für Wasserorganismen.

EL: Πολύ τοξικό για τους υδρόβιους οργανισμούς.

EN: Very toxic to aquatic organisms.

FR: Très toxique pour les organismes aquatiques.

IT: Altamente tossico per gli organismi acquatici.

NL: Zeer vergiftig voor in het water levende organismen.

PT: Muito tóxico para os organismos aquáticos.

FI: Erittäin myrkyllistä vesieliöille.

SV: Mycket giftigt för vattenlevande organismer.

**R51**

ES: Tóxico para los organismos acuáticos.

DA: Giftig for organismer, der lever i vand.

DE: Giftig für Wasserorganismen.

EL: Τοξικό για τους υδρόβιους οργανισμούς.

EN: Toxic to aquatic organisms.

FR: Toxique pour les organismes aquatiques.

IT: Tossico per gli organismi acquatici.

NL: Vergiftig voor in het water levende organismen.

PT: Tóxico para os organismos aquáticos.

FI: Myrkyllistä vesieliöille.

SV: Giftigt för vattenlevande organismer.

**R52**

ES: Nocivo para los organismos acuáticos.

DA: Skadelig for organismer, der lever i vand.

DE: Schädlich für Wasserorganismen.

EL: Επιβλαβές για τους υδρόβιους οργανισμούς.

EN: Harmful to aquatic organisms.

FR: Nocif pour les organismes aquatiques.

IT: Nocivo per gli organismi acquatici.

NL: Schadelijk voor in het water levende organismen.

PT: Nocivo para os organismos aquáticos.

FI: Haitallista vesieliöille.

SV: Skadligt för vattenlevande organismer.

**R53**

ES: Puede provocar a largo plazo efectos negativos en el medio ambiente acuático.

DA: Kan forårsage uønskede langtidsvirkninger i vandmiljøet.

DE: Kann in Gewässern längerfristig schädliche Wirkungen haben.

EL: Μπορεί να προκαλέσει μακροχρόνιες δυσμενείς επιπτώσεις στο υδάτινο περιβάλλον.

EN: May cause long-term adverse effects in the aquatic environment.

FR: Peut entraîner des effets néfastes à long terme pour l'environnement aquatique.

IT: Può provocare a lungo termine effetti negativi per l'ambiente acquatico.

NL: Kan in het aquatisch milieu op lange termijn schadelijke effecten veroorzaken.

PT: Pode causar efeitos nefastos a longo prazo no ambiente aquático.

FI: Voi aiheuttaa pitkäaikaisia haittavaikutuksia vesiympäristössä.

SV: Kan orsaka skadliga långtidseffekter i vattenmiljön.

**R54**

ES: Tóxico para la flora.

DA: Giftig for planter.

DE: Giftig für Pflanzen.

EL: Τοξικό για τη χλωρίδα.

EN: Toxic to flora.

FR: Toxique pour la flore.

IT: Tossico per la flora.

NL: Vergiftig voor planten.

PT: Tóxico para a flora.

FI: Myrkyllistä kasveille.

SV: Giftigt för växter.

**R55**

ES: Tóxico para la fauna.

DA: Giftig for dyr.

DE: Giftig für Tiere.

EL: Τοξικό για την πανίδα.

EN: Toxic to fauna.

FR: Toxique pour la faune.

IT: Tossico per la fauna.

NL: Vergiftig voor dieren.

PT: Tóxico para a fauna.

FI: Myrkyllistä eläimille.

SV: Giftigt för djur.

**R56**

ES: Tóxico para los organismos del suelo.

DA: Giftig for organismer i jordbunden.

DE: Giftig für Bodenorganismen.

EL: Τοξικό για τους οργανισμούς του εδάφους.

EN: Toxic to soil organisms.

FR: Toxique pour les organismes du sol.

IT: Tossico per gli organismi del terreno.

NL: Vergiftig voor bodemorganismen.

PT: Tóxico para os organismos do solo.

FI: Myrkyllistä maaperäeliöille.

SV: Giftigt för marklevande organismer.

**R57**

ES: Tóxico para las abejas.

DA: Giftig for bier.

DE: Giftig für Bienen.

EL: Τοξικό για τις μέλισσες.

EN: Toxic to bees.

FR: Toxique pour les abeilles.

IT: Tossico per le api.

NL: Vergiftig voor bijen.

PT: Tóxico para as abelhas.

FI: Myrkyllistä mehiläisille.

SV: Giftigt för bin.

**R58**

ES: Puede provocar a largo plazo efectos negativos en el medio ambiente.

DA: Kan forårsage uønskede langtidsvirkninger i miljøet.

DE: Kann längerfristig schädliche Wirkungen auf die Umwelt haben.

EL: Μπορεί να προκαλέσει μακροχρόνιες δυσμενείς επιπτώσεις στο περιβάλλον.

EN: May cause long-term adverse effects in the environment.

FR: Peut entraîner des effets néfastes à long terme pour l'environnement.

IT: Può provocare a lungo termine effetti negativi per l'ambiente.

NL: Kan in het milieu op lange termijn schadelijke effecten veroorzaken.

PT: Pode causar efeitos nefastos a longo prazo no ambiente.

FI: Voi aiheuttaa pitkäaikaisia haittavaikutuksia ympäristössä.

SV: Kan orsaka skadliga långtidseffekter i miljön.

**R59**

ES: Peligroso para la capa de ozono.

DA: Farlig for ozonlaget.

DE: Gefährlich für die Ozonschicht.

EL: Επικίνδυνο για τη στιβάδα του όζοντος.

EN: Dangerous for the ozone layer.

FR: Dangereux pour la couche d'ozone.

IT: Pericoloso per lo strato di ozono.

NL: Gevaarlijk voor de ozonlaag.

PT: Perigoso para a camada de ozono .

FI: Vaarallista otsonikerrokselle.

SV: Farligt för ozonskiktet.

**R60**

ES: Puede perjudicar la fertilidad.

DA: Kan skade forplantningsevnen.

DE: Kann die Fortpflanzungsfähigkeit beeinträchtigen.

EL: Μπορεί να εξασθενίσει τη γονιμότητα.

EN: May impair fertility.

FR: Peut altérer la fertilité.

IT: Può ridurre la fertilità.

NL: Kan de vruchtbaarheid schaden.

PT: Pode comprometer a fertilidade.

FI: Voi heikentää hedelmällisyyttä.

SV: Kan ge nedsatt fortplantningsförmåga.

**R61**

ES: Riesgo durante el embarazo de efectos adversos para el feto.

DA: Kan skade barnet under graviditeten.

DE: Kann das Kind im Mutterleib schädigen.

EL: Μπορεί να βλάψει το έμβρυο κατά τη διάρκεια της κύησης.

EN: May cause harm to the unborn child.

FR: Risque pendant la grossesse d'effets néfastes pour l'enfant.

IT: Può danneggiare i bambini non ancora nati.

NL: Kan het ongeboren kind schaden.

PT: Risco durante a gravidez com efeitos adversos na descendência.

FI: Vaarallista sikiölle.

SV: Kan ge fosterskador.

**R62**

ES: Posible riesgo de perjudicar la fertilidad.

DA: Mulighed for skade på forplantningsevnen.

DE: Kann möglicherweise die Fortpflanzungsfähigkeit beeinträchtigen.

EL: Πιθανός κίνδυνος για εξασθένηση της γονιμότητας.

EN: Possible risk of impaired fertility.

FR: Risque possible d'altération de la fertilité.

IT: Possibile rischio di ridotta fertilità.

NL: Mogelijk gevaar voor verminderde vruchtbaarheid.

PT: Possíveis riscos de comprometer a fertilidade.

FI: Voi mahdollisesti heikentää hedelmällisyyttä.

SV: Möjlig risk för nedsatt fortplantningsförmåga.

**R63**

ES: Posible riesgo durante el embarazo de efectos adversos para el feto.

DA: Mulighed for skade på barnet under graviditeten.

DE: Kann das Kind im Mutterleib möglicherweise schädigen.

EL: Πιθανός κίνδυνος δυσμενών επιδράσεων στο έμβρυο κατά τη διάρκεια της κύησης.

EN: Possible risk of harm to the unborn child.

FR: Risque possible pendant la grossesse d'effets néfastes pour l'enfant.

IT: Possibile rischio di danni ai bambini non ancora nati.

NL: Mogelijk gevaar voor beschadiging van het ongeboren kind.

PT: Possíveis riscos durante a gravidez com efeitos adversos na descendência.

FI: Voi olla vaarallista sikiölle.

SV: Möjlig risk för fosterskador.

**R64**

ES: Puede perjudicar a los niños alimentados con leche materna.

DA: Kan skade børn i ammeperioden.

DE: Kann Säuglinge über die Muttermilch schädigen.

EL: Μπορεί να βλάψει τα βρέφη που τρέφονται με μητρικό γάλα.

EN: May cause harm to breastfed babies.

FR: Risque possible pour les bébés nourris au lait maternel.

IT: Possibile rischio per i bambini allattati al seno.

NL: Kan schadelijk zijn via de borstvoeding.

PT: Pode causar danos às crianças alimentadas com leite materno.

FI: Saattaa aiheuttaa haittaa rintaruokinnassa oleville lapsille.

SV: Kan skada spädbarn under amningsperioden.

**R65**

ES: Nocivo: si se ingiere puede causar daño pulmonar.

DA: Farlig: kan give lungeskade ved indtagelse.

DE: Gesundheitsschädlich: kann beim Verschlucken Lungenschäden verursachen.

EL: Επιβλαβές: μπορεί να προκαλέσει βλάβη στους πνεύμονες σε περίπτωση κατάποσης.

EN: Harmful: may cause lung damage if swallowed.

FR: Nocif: peut provoquer une atteinte des poumons en cas d'ingestion.

IT: Nocivo: può causare danni ai polmoni in caso di ingestione.

NL: Schadelijk: kan longschade veroorzaken na verslikken.

PT: Nocivo: pode causar danos nos pulmões se ingerido.

FI: Haitallista: voi aiheuttaa keuhkovaurion nieltäessä.

SV: Farligt: kan ge lungskador vid förtäring.

**R66**

ES: La exposición repetida puede provocar sequedad o formación de grietas en la piel.

DA: Gentagen udsættelse kan give tør eller revnet hud.

DE: Wiederholter Kontakt kann zu spröder oder rissiger Haut führen.

EL: Η παρατεταμένη έκθεση μπορεί να προκαλέσει ξηρότητα δέρματος ή σκάσιμο.

EN: Repeated exposure may cause skin dryness or cracking.

FR: L'exposition répétée peut provoquer dessèchement ou gerçures de la peau.

IT: L'esposizione ripetuta può provocare secchezza e screpolature della pelle.

NL: Herhaalde blootstelling kan een droge of een gebarsten huid veroorzaken.

PT: Pode provocar secura da pele ou fissuras, por exposição repetida.

FI: Toistuva altistus voi aiheuttaa ihon kuivumista tai halkeilua.

SV: Upprepad kontakt kan ge torr hud eller hudsprickor.

**R67**

ES: La inhalación de vapores puede provocar somnolencia y vértigo.

DA: Dampe kan give sløvhed og svimmelhed.

DE: Dämpfe können Schläfrigkeit und Benommenheit verursachen.

EL: Η εισπνοή ατμών μπορεί να προκαλέσει υπνηλία και ζάλη.

EN: Vapours may cause drowsiness and dizziness.

FR: L'inhalation de vapeurs peut provoquer somnolence et vertiges.

IT: L'inalazione dei vapori può provocare sonnolenza e vertigini.

NL: Dampen kunnen slaperigheid en duizeligheid veroorzaken.

PT: Pode provocar sonolência e vertigens, por inalação dos vapores.

FI: Höyryt voivat aiheuttaa uneliaisuutta ja huimausta.

SV: Ångor kan göra att man blir dåsig och omtöcknad.

**R68**

ES: Posibilidad de efectos irreversibles.

DA: Mulighed for varig skade på helbred.

DE: Irreversibler Schaden möglich.

EL: Πιθανοί κίνδυνοι μονίμων επιδράσεων.

EN: Possible risk of irreversible effects.

FR: Possibilité d'effets irréversibles.

IT: Possibilità di effetti irreversibili.

NL: Onherstelbare effecten zijn niet uitgesloten.

PT: Possibilidade de efeitos irreversíveis.

FI: Pysyvien vaurioiden vaara.

SV: Möjlig risk för bestående hälsoskador.

Combinación de frases-R

Kombination af R-sætninger

Kombination der R-Sätze

Συνδυασμός των P-φράσεων

Combination of R-phrases

Combinaison des phrases R

Combinazioni delle frasi R

Combinatie van R-zinnen

Combinação das frases R

Yhdistetyt R-lausekkeet

Sammansatta R-fraser

**R14/15**

ES: Reacciona violentamente con el agua, liberando gases extremadamente inflamables.

DA: Reagerer voldsomt med vand under dannelse af yderst brandfarlige gasser.

DE: Reagiert heftig mit Wasser unter Bildung hochentzündlicher Gase.

EL: Αντιδρά βίαια σε επαφή με νερό εκλύοντας αέρια εξόχως εύφλεκτα.

EN: Reacts violently with water, liberating extremely flammable gases.

FR: Réagit violemment au contact de l'eau en dégageant des gaz extrêmement inflammables.

IT: Reagisce violentemente con l'acqua liberando gas estremamente infiammabili.

NL: Reageert heftig met water en vormt daarbij zeer ontvlambaar gas.

PT: Reage violentamente com a água libertando gases extremamente inflamáveis.

FI: Reagoi voimakkaasti veden kanssa vapauttaen helposti syttyviä kaasuja.

SV: Reagerar häftigt med vatten varvid extremt brandfarliga gaser bildas.

**R15/29**

ES: En contacto con el agua, libera gases tóxicos y extremadamente inflamables.

DA: Reagerer med vand under dannelse af giftige og yderst brandfarlige gasser.

DE: Reagiert mit Wasser unter Bildung giftiger und hochentzündlicher Gase.

EL: Σε επαφή με νερό ελευθερώνονται τοξικά, εξόχως εύφλεκτα αέρια.

EN: Contact with water liberates toxic, extremely flammable gas.

FR: Au contact de l'eau, dégage des gaz toxiques et extrêmement inflammables.

IT: A contatto con acqua libera gas tossici ed estremamente infiammabili.

NL: Vormt vergiftig en zeer ontvlambaar gas in contact met water.

PT: Em contacto com a água liberta gases tóxicos e extremamente inflamáveis.

FI: Vapauttaa myrkyllisiä, helposti syttyviä kaasuja veden kanssa.

SV: Utvecklar giftig och extremt brandfarlig gas vid kontakt med vatten.

**R20/21**

ES: Nocivo por inhalación y en contacto con la piel.

DA: Farlig ved indånding og ved hudkontakt.

DE: Gesundheitsschädlich beim Einatmen und bei Berührung mit der Haut.

EL: Επιβλαβές όταν εισπνέεται και σε επαφή με το δέρμα.

EN: Harmful by inhalation and in contact with skin.

FR: Nocif par inhalation et par contact avec la peau.

IT: Nocivo per inalazione e contatto con la pelle.

NL: Schadelijk bij inademing en bij aanraking met de huid.

PT: Nocivo por inalação e em contacto com a pele.

FI: Terveydelle haitallista hengitettynä ja joutuessaan iholle.

SV: Farligt vid inandning och hudkontakt.

**R20/22**

ES: Nocivo por inhalación y por ingestión.

DA: Farlig ved indånding og ved indtagelse.

DE: Gesundheitsschädlich beim Einatmen und Verschlucken.

EL: Επιβλαβές όταν εισπνέεται και σε περίπτωση καταπόσεως.

EN: Harmful by inhalation and if swallowed.

FR: Nocif par inhalation et par ingestion.

IT: Nocivo per inalazione e ingestione.

NL: Schadelijk bij inademing en opname door de mond.

PT: Nocivo por inalação e ingestão.

FI: Terveydelle haitallista hengitettynä ja nieltynä.

SV: Farligt vid inandning och förtäring.

**R20/21/22**

ES: Nocivo por inhalación, por ingestión y en contacto con la piel.

DA: Farlig ved indånding, ved hudkontakt og ved indtagelse.

DE: Gesundheitsschädlich beim Einatmen, Verschlucken und Berührung mit der Haut.

EL: Επιβλαβές όταν εισπνέεται, σε επαφή με το δέρμα και σε περίπτωση καταπόσεως.

EN: Harmful by inhalation, in contact with skin and if swallowed.

FR: Nocif par inhalation, par contact avec la peau et par ingestion.

IT: Nocivo per inalazione, contatto con la pelle e per ingestione.

NL: Schadelijk bij inademing, opname door de mond en aanraking met de huid.

PT: Nocivo por inalação, em contacto com a pele e por ingestão.

FI: Terveydelle haitallista hengitettynä, joutuessaan iholle ja nieltynä.

SV: Farligt vid inandning, hudkontakt och förtäring.

**R21/22**

ES: Nocivo en contacto con la piel y por ingestión.

DA: Farlig ved hudkontakt og ved indtagelse.

DE: Gesundheitsschädlich bei Berührung mit der Haut und beim Verschlucken.

EL: Επιβλαβές σε επαφή με το δέρμα και σε περίπτωση καταπόσεως.

EN: Harmful in contact with skin and if swallowed.

FR: Nocif par contact avec la peau et par ingestion.

IT: Nocivo a contatto con la pelle e per ingestione.

NL: Schadelijk bij aanraking met de huid en bij opname door de mond.

PT: Nocivo em contacto com a pele e por ingestão.

FI: Terveydelle haitallista joutuessaan iholle ja nieltynä.

SV: Farligt vid hudkontakt och förtäring.

**R23/24**

ES: Tóxico por inhalación y en contacto con la piel.

DA: Giftig ved indånding og ved hudkontakt.

DE: Giftig beim Einatmen und bei Berührung mit der Haut.

EL: Τοξικό όταν εισπνέεται και σε επαφή με το δέρμα.

EN: Toxic by inhalation and in contact with skin.

FR: Toxique par inhalation et par contact avec la peau.

IT: Tossico per inalazione e contatto con la pelle.

NL: Vergiftig bij inademing en bij aanraking met de huid.

PT: Tóxico por inalação e em contacto com a pele.

FI: Myrkyllistä hengitettynä ja joutuessaan iholle.

SV: Giftigt vid inandning och hudkontakt.

**R23/25**

ES: Tóxico por inhalación y por ingestión.

DA: Giftig ved indånding og ved indtagelse.

DE: Giftig beim Einatmen und Verschlucken.

EL: Τοξικό όταν εισπνέεται και σε περίπτωση καταπόσεως.

EN: Toxic by inhalation and if swallowed.

FR: Toxique par inhalation et par ingestion.

IT: Tossico per inalazione e ingestione.

NL: Vergiftig bij inademing en opname door de mond.

PT: Tóxico por inalação e ingestão.

FI: Myrkyllistä hengitettynä ja nieltynä.

SV: Giftigt vid inandning och förtäring.

**R23/24/25**

ES: Tóxico por inhalación, por ingestión y en contacto con la piel.

DA: Giftig ved indånding, ved hudkontakt og ved indtagelse.

DE: Giftig beim Einatmen, Verschlucken und Berührung mit der Haut.

EL: Τοξικό όταν εισπνέεται, σε επαφή με το δέρμα και σε περίπτωση καταπόσεως.

EN: Toxic by inhalation, in contact with skin and if swallowed.

FR: Toxique par inhalation, par contact avec la peau et par ingestion.

IT: Tossico per inalazione, contatto con la pelle e per ingestione.

NL: Vergiftig bij inademing, opname door de mond en aanraking met de huid.

PT: Tóxico por inalação, em contacto com a pele e por ingestão.

FI: Myrkyllistä hengitettynä, joutuessaan iholle ja nieltynä.

SV: Giftigt vid inandning, hudkontakt och förtäring.

**R24/25**

ES: Tóxico en contacto con la piel y por ingestión.

DA: Giftig ved hudkontakt og ved indtagelse.

DE: Giftig bei Berührung mit der Haut und beim Verschlucken.

EL: Τοξικό σε επαφή με το δέρμα και σε περίπτωση καταπόσεως.

EN: Toxic in contact with skin and if swallowed.

FR: Toxique par contact avec la peau et par ingestion.

IT: Tossico a contatto con la pelle e per ingestione.

NL: Vergiftig bij aanraking met de huid en bij opname door de mond.

PT: Tóxico em contacto com a pele e por ingestão.

FI: Myrkyllistä joutuessaan iholle ja nieltynä.

SV: Giftigt vid hudkontakt och förtäring.

**R26/27**

ES: Muy tóxico por inhalación y en contacto con la piel.

DA: Meget giftig ved indånding og ved hudkontakt.

DE: Sehr giftig beim Einatmen und bei Berührung mit der Haut.

EL: Πολύ τοξικό όταν εισπνέεται και σε επαφή με το δέρμα.

EN: Very toxic by inhalation and in contact with skin.

FR: Très toxique par inhalation et par contact avec la peau.

IT: Molto tossico per inalazione e contatto con la pelle.

NL: Zeer vergiftig bij inademing en bij aanraking met de huid.

PT: Muito tóxico por inalação e em contacto com a pele.

FI: Erittäin myrkyllistä hengitettynä ja joutuessaan iholle.

SV: Mycket giftigt vid inandning och hudkontakt.

**R26/28**

ES: Muy tóxico por inhalación y por ingestión.

DA: Meget giftig ved indånding og ved indtagelse.

DE: Sehr giftig beim Einatmen und Verschlucken.

EL: Πολύ τοξικό όταν εισπνέεται και σε περίπτωση καταπόσεως.

EN: Very toxic by inhalation and if swallowed.

FR: Très toxique par inhalation et par ingestion.

IT: Molto tossico per inalazione e per ingestione.

NL: Zeer vergiftig bij inademing en opname door de mond.

PT: Muito tóxico por inalação e ingestão.

FI: Erittäin myrkyllistä hengitettynä ja nieltynä.

SV: Mycket giftigt vid inandning och förtäring.

**R26/27/28**

ES: Muy tóxico por inhalación, por ingestión y en contacto con la piel.

DA: Meget giftig ved indånding, ved hudkontakt og ved indtagelse.

DE: Sehr giftig beim Einatmen, Verschlucken und Berührung mit der Haut.

EL: Πολύ τοξικό όταν εισπνέεται, σε επαφή με το δέρμα και σε περίπτωση καταπόσεως.

EN: Very toxic by inhalation, in contact with skin and if swallowed.

FR: Très toxique par inhalation, par contact avec la peau et par ingestion.

IT: Molto tossico per inalazione, contatto con la pelle e per ingestione.

NL: Zeer vergiftig bij inademing, opname door de mond en aanraking met de huid.

PT: Muito tóxico por inalação, em contacto com a pele e por ingestão.

FI: Erittäin myrkyllistä hengitettynä, joutuessaan iholle ja nieltynä.

SV: Mycket giftigt vid inandning, hudkontakt och förtäring.

**R27/28**

ES: Muy tóxico en contacto con la piel y por ingestión.

DA: Meget giftig ved hudkontakt og ved indtagelse.

DE: Sehr giftig bei Berührung mit der Haut und beim Verschlucken.

EL: Πολύ τοξικό σε επαφή με το δέρμα και σε περίπτωση καταπόσεως.

EN: Very toxic in contact with skin and if swallowed.

FR: Très toxique par contact avec la peau et par ingestion.

IT: Molto tossico a contatto con la pelle e per ingestione.

NL: Zeer vergiftig bij aanraking met de huid en bij opname door de mond.

PT: Muito tóxico em contacto com a pele e por ingestão.

FI: Erittäin myrkyllistä joutuessaan iholle ja nieltynä.

SV: Mycket giftigt vid hudkontakt och förtäring.

**R36/37**

ES: Irrita los ojos y las vías respiratorias.

DA: Irriterer øjnene og åndedrætsorganerne.

DE: Reizt die Augen und die Atmungsorgane.

EL: Ερεθίζει τα μάτια και το αναπνευστικό σύστημα.

EN: Irritating to eyes and respiratory system.

FR: Irritant pour les yeux et les voies respiratoires.

IT: Irritante per gli occhi e le vie respiratorie.

NL: Irriterend voor de ogen en de ademhalingswegen.

PT: Irritante para os olhos e vias respiratórias.

FI: Ärsyttää silmiä ja hengityselimiä.

SV: Irriterar ögonen och andningsorganen.

**R36/38**

ES: Irrita los ojos y la piel.

DA: Irriterer øjnene og huden.

DE: Reizt die Augen und die Haut.

EL: Ερεθίζει τα μάτια και το δέρμα.

EN: Irritating to eyes and skin.

FR: Irritant pour les yeux et la peau.

IT: Irritante per gli occhi e la pelle.

NL: Irriterend voor de ogen en de huid.

PT: Irritante para os olhos e pele.

FI: Ärsyttää silmiä ja ihoa.

SV: Irriterar ögonen och huden.

**R36/37/38**

ES: Irrita los ojos, la piel y las vías respiratorias.

DA: Irriterer øjnene, åndedrætsorganerne og huden.

DE: Reizt die Augen, die Atmungsorgane und die Haut.

EL: Ερεθίζει τα μάτια, το αναπνευστικό σύστημα και το δέρμα.

EN: Irritating to eyes, respiratory system and skin.

FR: Irritant pour les yeux, les voies respiratoires et la peau.

IT: Irritante per gli occhi, le vie respiratorie e la pelle.

NL: Irriterend voor de ogen, de ademhalingswegen en de huid.

PT: Irritante para os olhos, vias respiratórias e pele.

FI: Ärsyttää silmiä, hengityselimiä ja ihoa.

SV: Irriterar ögonen, andningsorganen och huden.

**R37/38**

ES: Irrita las vías respiratorias y la piel.

DA: Irriterer åndedrætsorganerne og huden.

DE: Reizt die Atmungsorgane und die Haut.

EL: Ερεθίζει το αναπνευστικό σύστημα και το δέρμα.

EN: Irritating to respiratory system and skin.

FR: Irritant pour les voies respiratoires et la peau.

IT: Irritante per le vie respiratorie e la pelle.

NL: Irriterend voor de ademhalingswegen en de huid.

PT: Irritante para as vias respiratórias e pele.

FI: Ärsyttää hengityselimiä ja ihoa.

SV: Irriterar andningsorganen och huden.

**R39/23**

ES: Tóxico: peligro de efectos irreversibles muy graves por inhalación.

DA: Giftig: fare for varig alvorlig skade på helbred ved indånding.

DE: Giftig: ernste Gefahr irreversiblen Schadens durch Einatmen.

EL: Τοξικό: κίνδυνος πολύ σοβαρών μόνιμων επιδράσεων όταν εισπνέεται.

EN: Toxic: danger of very serious irreversible effects through inhalation.

FR: Toxique: danger d'effets irréversibles très graves par inhalation.

IT: Tossico: pericolo di effetti irreversibili molto gravi per inalazione.

NL: Vergiftig: gevaar voor ernstige onherstelbare effecten bij inademing.

PT: Tóxico: perigo de efeitos irreversíveis muito graves por inalação.

FI: Myrkyllistä: erittäin vakavien pysyvien vaurioiden vaara hengitettynä.

SV: Giftigt: risk för mycket allvarliga bestående hälsoskador vid inandning.

**R39/24**

ES: Tóxico: peligro de efectos irreversibles muy graves por contacto con la piel.

DA: Giftig: fare for varig alvorlig skade på helbred ved hudkontakt.

DE: Giftig: ernste Gefahr irreversiblen Schadens bei Berührung mit der Haut.

EL: Τοξικό: κίνδυνος πολύ σοβαρών μόνιμων επιδράσεων σε επαφή με το δέρμα.

EN: Toxic: danger of very serious irreversible effects in contact with skin.

FR: Toxique: danger d'effets irréversibles très graves par contact avec la peau.

IT: Tossico: pericolo di effetti irreversibili molto gravi a contatto con la pelle.

NL: Vergiftig: gevaar voor ernstige onherstelbare effecten bij aanraking met de huid.

PT: Tóxico: perigo de efeitos irreversíveis muito graves em contacto com a pele.

FI: Myrkyllistä: erittäin vakavien pysyvien vaurioiden vaara joutuessaan iholle.

SV: Giftigt: risk för mycket allvarliga bestående hälsoskador vid hudkontakt.

**R39/25**

ES: Tóxico: peligro de efectos irreversibles muy graves por ingestión.

DA: Giftig: fare for varig alvorlig skade på helbred ved indtagelse.

DE: Giftig: ernste Gefahr irreversiblen Schadens durch Verschlucken.

EL: Τοξικό: κίνδυνος πολύ σοβαρών μόνιμων επιδράσεων σε περίπτωση καταπόσεως.

EN: Toxic: danger of very serious irreversible effects if swallowed.

FR: Toxique: danger d'effets irréversibles très graves par ingestion.

IT: Tossico: pericolo di effetti irreversibili molto gravi per ingestione.

NL: Vergiftig: gevaar voor ernstige onherstelbare effecten bij opname door de mond.

PT: Tóxico: perigo de efeitos irreversíveis muito graves por ingestão.

FI: Myrkyllistä: erittäin vakavien pysyvien vaurioiden vaara nieltynä.

SV: Giftigt: risk för mycket allvarliga bestående hälsoskador vid förtäring.

**R39/23/24**

ES: Tóxico: peligro de efectos irreversibles muy graves por inhalación y contacto con la piel.

DA: Giftig: fare for varig alvorlig skade på helbred ved indånding og hudkontakt.

DE: Giftig: ernste Gefahr irreversiblen Schadens durch Einatmen und bei Berührung mit der Haut.

EL: Τοξικό: κίνδυνος πολύ σοβαρών μόνιμων επιδράσεων όταν εισπνέεται και σε επαφή με το δέρμα.

EN: Toxic: danger of very serious irreversible effects through inhalation and in contact with skin.

FR: Toxique: danger d'effets irréversibles très graves par inhalation et par contact avec la peau.

IT: Tossico: pericolo di effetti irreversibili molto gravi per inalazione e a contatto con la pelle.

NL: Vergiftig: gevaar voor ernstige onherstelbare effecten bij inademing en aanraking met de huid.

PT: Tóxico: perigo de efeitos irreversíveis muito graves por inalação e em contacto com a pele.

FI: Myrkyllistä: erittäin vakavien pysyvien vaurioiden vaara hengitettynä ja joutuessaan iholle.

SV: Giftigt: risk för mycket allvarliga bestående hälsoskador vid inandning och hudkontakt.

**R39/23/25**

ES: Tóxico: peligro de efectos irreversibles muy graves por inhalación e ingestión.

DA: Giftig: fare for varig alvorlig skade på helbred ved indånding og indtagelse.

DE: Giftig: ernste Gefahr irreversiblen Schadens durch Einatmen und durch Verschlucken.

EL: Τοξικό: κίνδυνος πολύ σοβαρών μόνιμων επιδράσεων όταν εισπνέεται και σε περίπτωση καταπόσεως.

EN: Toxic: danger of very serious irreversible effects through inhalation and if swallowed.

FR: Toxique: danger d'effets irréversibles très graves par inhalation et par ingestion.

IT: Tossico: pericolo di effetti irreversibili molto gravi per inalazione e ingestione.

NL: Vergiftig: gevaar voor ernstige onherstelbare effecten bij inademing en opname door de mond.

PT: Tóxico: perigo de efeitos irreversíveis muito graves por inalação e ingestão.

FI: Myrkyllistä: erittäin vakavien pysyvien vaurioiden vaara hengitettynä ja nieltynä.

SV: Giftigt: risk för mycket allvarliga bestående hälsoskador vid inandning och förtäring.

**R39/24/25**

ES: Tóxico: peligro de efectos irreversibles muy graves por contacto con la piel e ingestión.

DA: Giftig: fare for varig alvorlig skade på helbred ved hudkontakt og indtagelse.

DE: Giftig: ernste Gefahr irreversiblen Schadens bei Berührung mit der Haut und durch Verschlucken.

EL: Τοξικό: κίνδυνος πολύ σοβαρών μόνιμων επιδράσεων σε επαφή με το δέρμα και σε περίπτωση καταπόσεως.

EN: Toxic: danger of very serious irreversible effects in contact with skin and if swallowed.

FR: Toxique: danger d'effets irréversibles très graves par contact avec la peau et par ingestion.

IT: Tossico: pericolo di effetti irreversibili molto gravi a contatto con la pelle e per ingestione.

NL: Vergiftig: gevaar voor ernstige onherstelbare effecten bij aanraking met de huid en opname door de mond.

PT: Tóxico: perigo de efeitos irreversíveis muito graves em contacto com a pele e por ingestão.

FI: Myrkyllistä: erittäin vakavien pysyvien vaurioiden vaara joutuessaan iholle ja nieltynä.

SV: Giftigt: risk för mycket allvarliga bestående hälsoskador vid hudkontakt och förtäring.

**R39/23/24/25**

ES: Tóxico: peligro de efectos irreversibles muy graves por inhalación, contacto con la piel e ingestión.

DA: Giftig: fare for varig alvorlig skade på helbred ved indånding, hudkontakt og indtagelse.

DE: Giftig: ernste Gefahr irreversiblen Schadens durch Einatmen, Berührung mit der Haut und durch Verschlucken.

EL: Τοξικό: κίνδυνος πολύ σοβαρών μόνιμων επιδράσεων όταν εισπνέεται, σε επαφή με το δέρμα και σε περίπτωση καταπόσεως.

EN: Toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed.

FR: Toxique: danger d'effets irréversibles très graves par inhalation, par contact avec la peau et par ingestion.

IT: Tossico: pericolo di effetti irreversibili molto gravi per inalazione, a contatto con la pelle e per ingestione.

NL: Vergiftig: gevaar voor ernstige onherstelbare effecten bij inademing, aanraking met de huid en opname door de mond.

PT: Tóxico: perigo de efeitos irreversíveis muito graves por inalação, em contacto com a pele e por ingestão.

FI: Myrkyllistä: erittäin vakavien pysyvien vaurioiden vaara hengitettynä, joutuessaan iholle ja nieltynä.

SV: Giftigt: risk för mycket allvarliga bestående hälsoskador vid inandning, hudkontakt och förtäring.

**R39/26**

ES: Muy tóxico: peligro de efectos irreversibles muy graves por inhalación.

DA: Meget giftig: fare for varig alvorlig skade på helbred ved indånding.

DE: Sehr giftig: ernste Gefahr irreversiblen Schadens durch Einatmen.

EL: Πολύ τοξικό: κίνδυνος πολύ σοβαρών μόνιμων επιδράσεων όταν εισπνέεται.

EN: Very toxic: danger of very serious irreversible effects through inhalation.

FR: Très toxique: danger d'effets irréversibles très graves par inhalation.

IT: Molto tossico: pericolo di effetti irreversibili molto gravi per inalazione.

NL: Zeer vergiftig: gevaar voor ernstige onherstelbare effecten bij inademing.

PT: Muito tóxico: perigo de efeitos irreversíveis muito graves por inalação.

FI: Erittäin myrkyllistä: erittäin vakavien pysyvien vaurioiden vaara hengitettynä.

SV: Mycket giftigt: risk för mycket allvarliga bestående hälsoskador vid inandning.

**R39/27**

ES: Muy tóxico: peligro de efectos irreversibles muy graves por contacto con la piel.

DA: Meget giftig: fare for varig alvorlig skade på helbred ved hudkontakt.

DE: Sehr giftig: ernste Gefahr irreversiblen Schadens bei Berührung mit der Haut.

EL: Πολύ τοξικό: κίνδυνος πολύ σοβαρών μόνιμων επιδράσεων σε επαφή με το δέρμα.

EN: Very toxic: danger of very serious irreversible effects in contact with skin.

FR: Très toxique: danger d'effets irréversibles très graves par contact avec la peau.

IT: Molto tossico: pericolo di effetti irreversibili molto gravi a contatto con la pelle.

NL: Zeer vergiftig: gevaar voor ernstige onherstelbare effecten bij aanraking met de huid.

PT: Muito tóxico: perigo de efeitos irreversíveis muito graves em contacto com a pele.

FI: Erittäin myrkyllistä: erittäin vakavien pysyvien vaurioiden vaara joutuessaan iholle.

SV: Mycket giftigt: risk för mycket allvarliga bestående hälsoskador vid hudkontakt.

**R39/28**

ES: Muy tóxico: peligro de efectos irreversibles muy graves por ingestión.

DA: Meget giftig: fare for varig alvorlig skade på helbred ved indtagelse.

DE: Sehr giftig: ernste Gefahr irreversiblen Schadens durch Verschlucken.

EL: Πολύ τοξικό: κίνδυνος πολύ σοβαρών μόνιμων επιδράσεων σε περίπτωση καταπόσεως.

EN: Very toxic: danger of very serious irreversible effects if swallowed.

FR: Très toxique: danger d'effets irréversibles très graves par ingestion.

IT: Molto tossico: pericolo di effetti irreversibili molto gravi per ingestione.

NL: Zeer vergiftig: gevaar voor ernstige onherstelbare effecten bij opname door de mond.

PT: Muito tóxico: perigo de efeitos irreversíveis muito graves por ingestão.

FI: Erittäin myrkyllistä: erittäin vakavien pysyvien vaurioiden vaara nieltynä.

SV: Mycket giftigt: risk för mycket allvarliga bestående hälsoskador vid förtäring.

**R39/26/27**

ES: Muy tóxico: peligro de efectos irreversibles muy graves por inhalación y contacto con la piel.

DA: Meget giftig: fare for varig alvorlig skade på helbred ved indånding og hudkontakt.

DE: Sehr giftig: ernste Gefahr irreversiblen Schadens durch Einatmen und bei Berührung mit der Haut.

EL: Πολύ τοξικό: κίνδυνος πολύ σοβαρών μόνιμων επιδράσεων όταν εισπνέεται και σε επαφή με το δέρμα.

EN: Very toxic: danger of very serious irreversible effects through inhalation and in contact with skin.

FR: Très toxique: danger d'effets irréversibles très graves par inhalation et par contact avec la peau.

IT: Molto tossico: pericolo di effetti irreversibili molto gravi per inalazione e a contatto con la pelle.

NL: Zeer vergiftig: gevaar voor ernstige onherstelbare effecten bij inademing en aanraking met de huid.

PT: Muito tóxico: perigo de efeitos irreversíveis muito graves por inalação e em contacto com a pele.

FI: Erittäin myrkyllistä: erittäin vakavien pysyvien vaurioiden vaara hengitettynä ja joutuessaan iholle.

SV: Mycket giftigt: risk för mycket allvarliga bestående hälsoskador vid inandning och hudkontakt.

**R39/26/28**

ES: Muy tóxico: peligro de efectos irreversibles muy graves por inhalación e ingestión.

DA: Meget giftig: fare for varig alvorlig skade på helbred ved indånding og indtagelse.

DE: Sehr giftig: ernste Gefahr irreversiblen Schadens durch Einatmen und durch Verschlucken.

EL: Πολύ τοξικό: κίνδυνος πολύ σοβαρών μόνιμων επιδράσεων όταν εισπνέεται και σε περίπτωση καταπόσεως.

EN: Very toxic: danger of very serious irreversible effects through inhalation and if swallowed.

FR: Très toxique: danger d'effets irréversibles très graves par inhalation et par ingestion.

IT: Molto tossico: pericolo di effetti irreversibili molto gravi per inalazione e ingestione.

NL: Zeer vergiftig: gevaar voor ernstige onherstelbare effecten bij inademing en opname door de mond.

PT: Muito tóxico: perigo de efeitos irreversíveis muito graves por inalação e ingestão.

FI: Erittäin myrkyllistä: erittäin vakavien pysyvien vaurioiden vaara hengitettynä ja nieltynä.

SV: Mycket giftigt: risk för mycket allvarliga bestående hälsoskador vid inandning och förtäring.

**R39/27/28**

ES: Muy tóxico: peligro de efectos irreversibles muy graves por contacto con la piel e ingestión.

DA: Meget giftig: fare for varig alvorlig skade på helbred ved hudkontakt og indtagelse.

DE: Sehr giftig: ernste Gefahr irreversiblen Schadens bei Berührung mit der Haut und durch Verschlucken.

EL: Πολύ τοξικό: κίνδυνος πολύ σοβαρών μόνιμων επιδράσεων σε επαφή με το δέρμα και σε περίπτωση καταπόσεως.

EN: Very toxic: danger of very serious irreversible effects in contact with skin and if swallowed.

FR: Très toxique: danger d'effets irréversibles très graves par contact avec la peau et par ingestion.

IT: Molto tossico: pericolo di effetti irreversibili molto gravi a contatto con la pelle e per ingestione.

NL: Zeer vergiftig: gevaar voor ernstige onherstelbare effecten bij aanraking met de huid en opname door de mond.

PT: Muito tóxico: perigo de efeitos irreversíveis muito graves em contacto com a pele e por ingestão.

FI: Erittäin myrkyllistä: erittäin vakavien pysyvien vaurioiden vaara joutuessaan iholle ja nieltynä.

SV: Mycket giftigt: risk för mycket allvarliga bestående hälsoskador vid hudkontakt och förtäring.

**R39/26/27/28**

ES: Muy tóxico: peligro de efectos irreversibles muy graves por inhalación, contacto con la piel e ingestión.

DA: Meget giftig: fare for varig alvorlig skade på helbred ved indånding, hudkontakt og indtagelse.

DE: Sehr giftig: ernste Gefahr irreversiblen Schadens durch Einatmen, Berührung mit der Haut und durch Verschlucken.

EL: Πολύ τοξικό: κίνδυνος πολύ σοβαρών μόνιμων επιδράσεων όταν εισπνέεται, σε επαφή με το δέρμα και σε περίπτωση καταπόσεως.

EN: Very toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed.

FR: Très toxique: danger d'effets irréversibles très graves par inhalation, par contact avec la peau et par ingestion.

IT: Molto tossico: pericolo di effetti irreversibili molto gravi per inalazione, a contatto con la pelle e per ingestione.

NL: Zeer vergiftig: gevaar voor ernstige onherstelbare effecten bij inademing, aanraking met de huid en opname door de mond.

PT: Muito tóxico: perigo de efeitos irreversíveis muito graves por inalação, em contacto com a pele e por ingestão.

FI: Erittäin myrkyllistä: erittäin vakavien pysyvien vaurioiden vaara hengitettynä, joutuessaan iholle ja nieltynä.

SV: Mycket giftigt: risk för mycket allvarliga bestående hälsoskador vid inandning, hudkontakt och förtäring.

**R42/43**

ES: Posibilidad de sensibilización por inhalación y por contacto con la piel.

DA: Kan give overfølsomhed ved indånding og ved kontakt med huden.

DE: Sensibilisierung durch Einatmen und Hautkontakt möglich.

EL: Μπορεί να προκαλέσει ευαισθητοποίηση όταν εισπνέεται και σε επαφή με το δέρμα.

EN: May cause sensitisation by inhalation and skin contact.

FR: Peut entraîner une sensibilisation par inhalation et par contact avec la peau.

IT: Può provocare sensibilizzazione per inalazione e contatto con la pelle.

NL: Kan overgevoeligheid veroorzaken bij inademing of contact met de huid.

PT: Pode causar sensibilização por inalação e em contacto com a pele.

FI: Altistuminen hengitysteitse ja ihokosketus voi aiheuttaa herkistymistä.

SV: Kan ge allergi vid inandning och hudkontakt.

**R48/20**

ES: Nocivo: riesgo de efectos graves para la salud en caso de exposición prolongada por inhalación.

DA: Farlig: alvorlig sundhedsfare ved længere tids påvirkning ved indånding.

DE: Gesundheitsschädlich: Gefahr ernster Gesundheitsschäden bei längerer Exposition durch Einatmen.

EL: Επιβλαβές: κίνδυνος σοβαρής βλάβης της υγείας ύστερα από παρατεταμένη έκθεση όταν εισπνέεται.

EN: Harmful: danger of serious damage to health by prolonged exposure through inhalation.

FR: Nocif: risque d'effets graves pour la santé en cas d'exposition prolongée par inhalation.

IT: Nocivo: pericolo di gravi danni per la salute in caso di esposizione prolungata per inalazione.

NL: Schadelijk: gevaar voor ernstige schade aan de gezondheid bij langdurige blootstelling bij inademing.

PT: Nocivo: risco de efeitos graves para a saúde em caso de exposição prolongada por inalação.

FI: Terveydelle haitallista: pitkäaikainen altistus voi aiheuttaa vakavaa haittaa terveydelle hengitettynä.

SV: Farligt: risk för allvarliga hälsoskador vid långvarig exponering genom inandning.

**R48/21**

ES: Nocivo: riesgo de efectos graves para la salud en caso de exposición prolongada por contacto con la piel.

DA: Farlig: alvorlig sundhedsfare ved længere tids påvirkning ved hudkontakt.

DE: Gesundheitsschädlich: Gefahr ernster Gesundheitsschäden bei längerer Exposition durch Berührung mit der Haut.

EL: Επιβλαβές: κίνδυνος σοβαρής βλάβης της υγείας ύστερα από παρατεταμένη έκθεση σε επαφή με το δέρμα.

EN: Harmful: danger of serious damage to health by prolonged exposure in contact with skin.

FR: Nocif: risque d'effets graves pour la santé en cas d'exposition prolongée par contact avec la peau.

IT: Nocivo: pericolo di gravi danni alla salute in caso di esposizione prolungata a contatto con la pelle.

NL: Schadelijk: gevaar voor ernstige schade aan de gezondheid bij langdurige blootstelling bij aanraking met de huid.

PT: Nocivo: risco de efeitos graves para a saúde em caso de exposição prolongada em contacto com a pele.

FI: Terveydelle haitallista: pitkäaikainen altistus voi aiheuttaa vakavaa haittaa terveydelle joutuessaan iholle.

SV: Farligt: risk för allvarliga hälsoskador vid långvarig exponering genom hudkontakt.

**R48/22**

ES: Nocivo: riesgo de efectos graves para la salud en caso de exposición prolongada por ingestión.

DA: Farlig: alvorlig sundhedsfare ved længere tids påvirkning ved indtagelse.

DE: Gesundheitsschädlich: Gefahr ernster Gesundheitsschäden bei längerer Exposition durch Verschlucken.

EL: Επιβλαβές: κίνδυνος σοβαρής βλάβης της υγείας ύστερα από παρατεταμένη έκθεση σε περίπτωση καταπόσεως.

EN: Harmful: danger of serious damage to health by prolonged exposure if swallowed.

FR: Nocif: risque d'effets graves pour la santé en cas d'exposition prolongée par ingestion.

IT: Nocivo: pericolo di gravi danni alla salute in caso di esposizione prolungata per ingestione.

NL: Schadelijk: gevaar voor ernstige schade aan de gezondheid bij langdurige blootstelling bij opname door de mond.

PT: Nocivo: risco de efeitos graves para a saúde em caso de exposição prolongada por ingestão.

FI: Terveydelle haitallista: pitkäaikainen altistus voi aiheuttaa vakavaa haittaa terveydelle nieltynä.

SV: Farligt: risk för allvarliga hälsoskador vid långvarig exponering genom förtäring.

**R48/20/21**

ES: Nocivo: riesgo de efectos graves para la salud en caso de exposición prolongada por inhalación y contacto con la piel.

DA: Farlig: alvorlig sundhedsfare ved længere tids påvirkning ved indånding og hudkontakt.

DE: Gesundheitsschädlich: Gefahr ernster Gesundheitsschäden bei längerer Exposition durch Einatmen und durch Berührung mit der Haut.

EL: Επιβλαβές: κίνδυνος σοβαρής βλάβης της υγείας ύστερα από παρατεταμένη έκθεση όταν εισπνέεται και σε επαφή με το δέρμα.

EN: Harmful: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin.

FR: Nocif: risque d'effets graves pour la santé en cas d'exposition prolongée par inhalation et par contact avec la peau.

IT: Nocivo: pericolo di gravi danni alla salute in caso di esposizione prolungata per inalazione e a contatto con la pelle.

NL: Schadelijk: gevaar voor ernstige schade aan de gezondheid bij langdurige blootstelling bij inademing en aanraking met de huid.

PT: Nocivo: risco de efeitos graves para a saúde em caso de exposição prolongada por inalação e em contacto com a pele.

FI: Terveydelle haitallista: pitkäaikainen altistus voi aiheuttaa vakavaa haittaa terveydelle hengitettynä ja joutuessaan iholle.

SV: Farligt: risk för allvarliga hälsoskador vid långvarig exponering genom inandning och hudkontakt.

**R48/20/22**

ES: Nocivo: riesgo de efectos graves para la salud en caso de exposición prolongada por inhalación e ingestión.

DA: Farlig: alvorlig sundhedsfare ved længere tids påvirkning ved indånding og indtagelse.

DE: Gesundheitsschädlich: Gefahr ernster Gesundheitsschäden bei längerer Exposition durch Einatmen und durch Verschlucken.

EL: Επιβλαβές: κίνδυνος σοβαρής βλάβης της υγείας ύστερα από παρατεταμένη έκθεση όταν εισπνέεται και σε περίπτωση καταπόσεως.

EN: Harmful: danger of serious damage to health by prolonged exposure through inhalation and if swallowed.

FR: Nocif: risque d'effets graves pour la santé en cas d'exposition prolongée par inhalation et par ingestion.

IT: Nocivo: pericolo di gravi danni alla salute in caso di esposizione prolungata per inalazione e ingestione.

NL: Schadelijk: gevaar voor ernstige schade aan de gezondheid bij langdurige blootstelling bij inademing en opname door de mond.

PT: Nocivo: risco de efeitos graves para a saúde em caso de exposição prolongada por inalação e ingestão.

FI: Terveydelle haitallista: pitkäaikainen altistus voi aiheuttaa vakavaa haittaa terveydelle hengitettynä ja nieltynä.

SV: Farligt: risk för allvarliga hälsoskador vid långvarig exponering genom inandning och förtäring.

**R48/21/22**

ES: Nocivo: riesgo de efectos graves para la salud en caso de exposición prolongada por contacto con la piel e ingestión.

DA: Farlig: alvorlig sundhedsfare ved længere tids påvirkning ved hudkontakt og indtagelse.

DE: Gesundheitsschädlich: Gefahr ernster Gesundheitsschäden bei längerer Exposition durch Berührung mit der Haut und durch Verschlucken.

EL: Επιβλαβές: κίνδυνος σοβαρής βλάβης της υγείας ύστερα από παρατεταμένη έκθεση σε επαφή με το δέρμα και σε περίπτωση καταπόσεως.

EN: Harmful: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed.

FR: Nocif: risque d'effets graves pour la santé en cas d'exposition prolongée par contact avec la peau et par ingestion.

IT: Nocivo: pericolo di gravi danni alla salute in caso di esposizione prolungata a contatto con la pelle e per ingestione.

NL: Schadelijk: gevaar voor ernstige schade aan de gezondheid bij langdurige blootstelling bij aanraking met de huid en opname door de mond.

PT: Nocivo: risco de efeitos graves para a saúde em caso de exposição prolongada em contacto com a pele e por ingestão.

FI: Terveydelle haitallista: pitkäaikainen altistus voi aiheuttaa vakavaa haittaa terveydelle joutuessaan iholle ja nieltynä.

SV: Farligt: risk för allvarliga hälsoskador vid långvarig exponering genom hudkontakt och förtäring.

**R48/20/21/22**

ES: Nocivo: riesgo de efectos graves para la salud en caso de exposición prolongada por inhalación, contacto con la piel e ingestión.

DA: Farlig: alvorlig sundhedsfare ved længere tids påvirkning ved indånding, hudkontakt og indtagelse.

DE: Gesundheitsschädlich: Gefahr ernster Gesundheitsschäden bei längerer Exposition durch Einatmen, Berührung mit der Haut und durch Verschlucken.

EL: Επιβλαβές: κίνδυνος σοβαρής βλάβης της υγείας ύστερα από παρατεταμένη έκθεση όταν εισπνέεται, σε επαφή με το δέρμα και σε περίπτωση καταπόσεως.

EN: Harmful: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed.

FR: Nocif: risque d'effets graves pour la santé en cas d'exposition prolongée par inhalation, par contact avec la peau et par ingestion.

IT: Nocivo: pericolo di gravi danni alla salute in caso di esposizione prolungata per inalazione, a contatto con la pelle e per ingestione.

NL: Schadelijk: gevaar voor ernstige schade aan de gezondheid bij langdurige blootstelling bij inademing, aanraking met de huid en opname door de mond.

PT: Nocivo: risco de efeitos graves para a saúde em caso de exposição prolongada por inalação, em contacto com a pele e por ingestão.

FI: Terveydelle haitallista: pitkäaikainen altistus voi aiheuttaa vakavaa haittaa terveydelle hengitettynä, joutuessaan iholle ja nieltynä.

SV: Farligt: risk för allvarliga hälsoskador vid långvarig exponering genom inandning, hudkontakt och förtäring.

**R48/23**

ES: Tóxico: riesgo de efectos graves para la salud en caso de exposición prolongada por inhalación.

DA: Giftig: alvorlig sundhedsfare ved længere tids påvirkning ved indånding.

DE: Giftig: Gefahr ernster Gesundheitsschäden bei längerer Exposition durch Einatmen.

EL: Τοξικό: κίνδυνος σοβαρής βλάβης της υγείας ύστερα από παρατεταμένη έκθεση όταν εισπνέεται.

EN: Toxic: danger of serious damage to health by prolonged exposure through inhalation.

FR: Toxique: risque d'effets graves pour la santé en cas d'exposition prolongée par inhalation.

IT: Tossico: pericolo di gravi danni alla salute in caso di esposizione prolungata per inalazione.

NL: Vergiftig: gevaar voor ernstige schade aan de gezondheid bij langdurige blootstelling bij inademing.

PT: Tóxico: risco de efeitos graves para a saúde em caso de exposição prolongada por inalação.

FI: Myrkyllistä: pitkäaikainen altistus voi aiheuttaa vakavaa haittaa terveydelle hengitettynä.

SV: Giftigt: risk för allvarliga hälsoskador vid långvarig exponering genom inandning.

**R48/24**

ES: Tóxico: riesgo de efectos graves para la salud en caso de exposición prolongada por contacto con la piel.

DA: Giftig: alvorlig sundhedsfare ved længere tids påvirkning ved hudkontakt.

DE: Giftig: Gefahr ernster Gesundheitsschäden bei längerer Exposition durch Berührung mit der Haut.

EL: Τοξικό: κίνδυνος σοβαρής βλάβης της υγείας ύστερα από παρατεταμένη έκθεση σε επαφή με το δέρμα.

EN: Toxic: danger of serious damage to health by prolonged exposure in contact with skin.

FR: Toxique: risque d'effets graves pour la santé en cas d'exposition prolongée par contact avec la peau.

IT: Tossico: pericolo di gravi danni alla salute in caso di esposizione prolungata a contatto con la pelle.

NL: Vergiftig: gevaar voor ernstige schade aan de gezondheid bij langdurige blootstelling bij aanraking met de huid.

PT: Tóxico: risco de efeitos graves para a saúde em caso de exposição prolongada em contacto com a pele.

FI: Myrkyllistä: pitkäaikainen altistus voi aiheuttaa vakavaa haittaa terveydelle joutuessaan iholle.

SV: Giftigt: risk för allvarliga hälsoskador vid långvarig exponering genom hudkontakt.

**R48/25**

ES: Tóxico: riesgo de efectos graves para la salud en caso de exposición prolongada por ingestión.

DA: Giftig: alvorlig sundhedsfare ved længere tids påvirkning ved indtagelse.

DE: Giftig: Gefahr ernster Gesundheitsschäden bei längerer Exposition durch Verschlucken.

EL: Τοξικό: κίνδυνος σοβαρής βλάβης της υγείας ύστερα από παρατεταμένη έκθεση σε περίπτωση καταπόσεως.

EN: Toxic: danger of serious damage to health by prolonged exposure if swallowed.

FR: Toxique: risque d'effets graves pour la santé en cas d'exposition prolongée par ingestion.

IT: Tossico: pericolo di gravi danni alla salute in caso di esposizione prolungata per ingestione.

NL: Vergiftig: gevaar voor ernstige schade aan de gezondheid bij langdurige blootstelling bij opname door de mond.

PT: Tóxico: risco de efeitos graves para a saúde em caso de exposição prolongada por ingestão.

FI: Myrkyllistä: pitkäaikainen altistus voi aiheuttaa vakavaa haittaa terveydelle nieltynä.

SV: Giftigt: risk för allvarliga hälsoskador vid långvarig exponering genom förtäring.

**R48/23/24**

ES: Tóxico: riesgo de efectos graves para la salud en caso de exposición prolongada por inhalación y contacto con la piel.

DA: Giftig: alvorlig sundhedsfare ved længere tids påvirkning ved indånding og hudkontakt.

DE: Giftig: Gefahr ernster Gesundheitsschäden bei längerer Exposition durch Einatmen und durch Berührung mit der Haut.

EL: Τοξικό: κίνδυνος σοβαρής βλάβης της υγείας ύστερα από παρατεταμένη έκθεση όταν εισπνέεται και σε επαφή με το δέρμα.

EN: Toxic: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin.

FR: Toxique: risque d'effets graves pour la santé en cas d'exposition prolongée par inhalation et par contact avec la peau.

IT: Tossico: pericolo di gravi danni alla salute in caso di esposizione prolungata per inalazione e a contatto con la pelle.

NL: Vergiftig: gevaar voor ernstige schade aan de gezondheid bij langdurige blootstelling bij inademing en aanraking met de huid.

PT: Tóxico: risco de efeitos graves para a saúde em caso de exposição prolongada por inalação e em contacto com a pele.

FI: Myrkyllistä: pitkäaikainen altistus voi aiheuttaa vakavaa haittaa terveydelle hengitettynä ja joutuessaan iholle.

SV: Giftigt: risk för allvarliga hälsoskador vid långvarig exponering genom inandning och hudkontakt.

**R48/23/25**

ES: Tóxico: riesgo de efectos graves para la salud en caso de exposición prolongada por inhalación e ingestión.

DA: Giftig: alvorlig sundhedsfare ved længere tids påvirkning ved indånding og indtagelse.

DE: Giftig: Gefahr ernster Gesundheitsschäden bei längerer Exposition durch Einatmen und durch Verschlucken.

EL: Τοξικό: κίνδυνος σοβαρής βλάβης της υγείας ύστερα από παρατεταμένη έκθεση όταν εισπνέεται και σε περίπτωση καταπόσεως.

EN: Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed.

FR: Toxique: risque d'effets graves pour la santé en cas d'exposition prolongée par inhalation et par ingestion.

IT: Tossico: pericolo di gravi danni alla salute in caso di esposizione prolungata per inalazione ed ingestione.

NL: Vergiftig: gevaar voor ernstige schade aan de gezondheid bij langdurige blootstelling bij inademing en opname door de mond.

PT: Tóxico: risco de efeitos graves para a saúde em caso de exposição prolongada por inalação e ingestão.

FI: Myrkyllistä: pitkäaikainen altistus voi aiheuttaa vakavaa haittaa terveydelle hengitettynä ja nieltynä.

SV: Giftigt: risk för allvarliga hälsoskador vid långvarig exponering genom inandning och förtäring.

**R48/24/25**

ES: Tóxico: riesgo de efectos graves para la salud en caso de exposición prolongada por contacto con la piel e ingestión.

DA: Giftig: alvorlig sundhedsfare ved længere tids påvirkning ved hudkontakt og indtagelse.

DE: Giftig: Gefahr ernster Gesundheitsschäden bei längerer Exposition durch Berührung mit der Haut und durch Verschlucken.

EL: Τοξικό: κίνδυνος σοβαρής βλάβης της υγείας ύστερα από παρατεταμένη έκθεση σε επαφή με το δέρμα και σε περίπτωση καταπόσεως.

EN: Toxic: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed.

FR: Toxique: risque d'effets graves pour la santé en cas d'exposition prolongée par contact avec la peau et par ingestion.

IT: Tossico: pericolo di gravi danni alla salute in caso di esposizione prolungata a contatto con la pelle e per ingestione.

NL: Vergiftig: gevaar voor ernstige schade aan de gezondheid bij langdurige blootstelling bij aanraking met de huid en opname door de mond.

PT: Tóxico: risco de efeitos graves para a saúde em caso de exposição prolongada em contacto com a pele e por ingestão.

FI: Myrkyllistä: pitkäaikainen altistus voi aiheuttaa vakavaa haittaa terveydelle joutuessaan iholle ja nieltynä.

SV: Giftigt: risk för allvarliga hälsoskador vid långvarig exponering genom hudkontakt och förtäring.

**R48/23/24/25**

ES: Tóxico: riesgo de efectos graves para la salud en caso de exposición prolongada por inhalación, contacto con la piel e ingestión.

DA: Giftig: alvorlig sundhedsfare ved længere tids påvirkning ved indånding, hudkontakt og indtagelse.

DE: Giftig: Gefahr ernster Gesundheitsschäden bei längerer Exposition durch Einatmen, Berührung mit der Haut und durch Verschlucken.

EL: Τοξικό: κίνδυνος σοβαρής βλάβης της υγείας ύστερα από παρατεταμένη έκθεση όταν εισπνέεται, σε επαφή με το δέρμα και σε περίπτωση καταπόσεως.

EN: Toxic: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed.

FR: Toxique: risque d'effets graves pour la santé en cas d'exposition prolongée par inhalation, par contact avec la peau et par ingestion.

IT: Tossico: pericolo di gravi danni alla salute in caso di esposizione prolungata per inalazione, a contatto con la pelle e per ingestione.

NL: Vergiftig: gevaar voor ernstige schade aan de gezondheid bij langdurige blootstelling bij inademing, aanraking met de huid en opname door de mond.

PT: Tóxico: risco de efeitos graves para a saúde em caso de exposição prolongada por inalação, em contacto com a pele e por ingestão.

FI: Myrkyllistä: pitkäaikainen altistus voi aiheuttaa vakavaa haittaa terveydelle hengitettynä, joutuessaan iholle ja nieltynä.

SV: Giftigt: risk för allvarliga hälsoskador vid långvarig exponering genom inandning, hudkontakt och förtäring.

**R50/53**

ES: Muy tóxico para los organismos acuáticos, puede provocar a largo plazo efectos negativos en el medio ambiente acuático.

DA: Meget giftig for organismer, der lever i vand; kan forårsage uønskede langtidsvirkninger i vandmiljøet.

DE: Sehr giftig für Wasserorganismen, kann in Gewässern längerfristig schädliche Wirkungen haben.

EL: Πολύ τοξικό για τους υδρόβιους οργανισμούς, μπορεί να προκαλέσει μακροχρόνιες δυσμενείς επιπτώσεις στο υδάτινο περιβάλλον.

EN: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

FR: Très toxique pour les organismes aquatiques, peut entraîner des effets néfastes à long terme pour l'environnement aquatique.

IT: Altamente tossico per gli organismi acquatici, può provocare a lungo termine effetti negativi per l'ambiente acquatico.

NL: Zeer vergiftig voor in het water levende organismen; kan in het aquatisch milieu op lange termijn schadelijke effecten veroorzaken.

PT: Muito tóxico para os organismos aquáticos, podendo causar efeitos nefastos a longo prazo no ambiente aquático.

FI: Erittäin myrkyllistä vesieliöille, voi aiheuttaa pitkäaikaisia haittavaikutuksia vesiympäristössä.

SV: Mycket giftigt för vattenlevande organismer, kan orsaka skadliga långtidseffekter i vattenmiljön.

**R51/53**

ES: Tóxico para los organismos acuáticos, puede provocar a largo plazo efectos negativos en el medio ambiente acuático.

DA: Giftig for organismer, der lever i vand; kan forårsage uønskede langtidsvirkninger i vandmiljøet.

DE: Giftig für Wasserorganismen, kann in Gewässern längerfristig schädliche Wirkungen haben.

EL: Τοξικό για τους υδρόβιους οργανισμούς, μπορεί να προκαλέσει μακροχρόνιες δυσμενείς επιπτώσεις στο υδάτινο περιβάλλον.

EN: Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

FR: Toxique pour les organismes aquatiques, peut entraîner des effets néfastes à long terme pour l'environnement aquatique.

IT: Tossico per gli organismi acquatici, può provocare a lungo termine effetti negativi per l'ambiente acquatico.

NL: Vergiftig voor in het water levende organismen; kan in het aquatisch milieu op lange termijn schadelijke effecten veroorzaken.

PT: Tóxico para os organismos aquáticos, podendo causar efeitos nefastos a longo prazo no ambiente aquático.

FI: Myrkyllistä vesieliöille, voi aiheuttaa pitkäaikaisia haittavaikutuksia vesiympäristössä.

SV: Giftigt för vattenlevande organismer, kan orsaka skadliga långtidseffekter i vattenmiljön.

**R52/53**

ES: Nocivo para los organismos acuáticos, puede provocar a largo plazo efectos negativos en el medio ambiente acuático.

DA: Skadelig for organismer, der lever i vand; kan forårsage uønskede langtidsvirkninger i vandmiljøet.

DE: Schädlich für Wasserorganismen, kann in Gewässern längerfristig schädliche Wirkungen haben.

EL: Επιβλαβές για τους υδρόβιους οργανισμούς, μπορεί να προκαλέσει μακροχρόνιες δυσμενείς επιπτώσεις στο υδάτινο περιβάλλον.

EN: Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

FR: Nocif pour les organismes aquatiques, peut entraîner des effets néfastes à long terme pour l'environnement aquatique.

IT: Nocivo per gli organismi acquatici, può provocare a lungo termine effetti negativi per l'ambiente acquatico.

NL: Schadelijk voor in het water levende organismen; kan in het aquatisch milieu op lange termijn schadelijke effecten veroorzaken.

PT: Nocivo para os organismos aquáticos, podendo causar efeitos nefastos a longo prazo no ambiente aquático.

FI: Haitallista vesieliöille, voi aiheuttaa pitkäaikaisia haittavaikutuksia vesiympäristössä.

SV: Skadligt för vattenlevande organismer, kan orsaka skadliga långtidseffekter i vattenmiljön.

**R68/20**

ES: Nocivo: posibilidad de efectos irreversibles por inhalación.

DA: Farlig: mulighed for varig skade på helbred ved indånding.

DE: Gesundheitsschädlich: Möglichkeit irreversiblen Schadens durch Einatmen.

EL: Επιβλαβές: πιθανοί κίνδυνοι μονίμων επιδράσεων όταν εισπνέεται.

EN: Harmful: possible risk of irreversible effects through inhalation.

FR: Nocif: possibilité d'effets irréversibles par inhalation.

IT: Nocivo: possibilità di effetti irreversibili per inalazione.

NL: Schadelijk: bij inademing zijn onherstelbare effecten niet uitgesloten.

PT: Nocivo: possibilidade de efeitos irreversíveis por inalação.

FI: Terveydelle haitallista: pysyvien vaurioiden vaara hengitettynä.

SV: Farligt: möjlig risk för bestående hälsoskador vid inandning.

**R68/21**

ES: Nocivo: posibilidad de efectos irreversibles por contacto con la piel

DA: Farlig: mulighed for varig skade på helbred ved hudkontakt.

DE: Gesundheitsschädlich: Möglichkeit irreversiblen Schadens bei Berührung mit der Haut.

EL: Επιβλαβές: πιθανοί κίνδυνοι μονίμων επιδράσεων σε επαφή με το δέρμα.

EN: Harmful: possible risk of irreversible effects in contact with skin.

FR: Nocif: possibilité d'effets irréversibles par contact avec la peau.

IT: Nocivo: possibilità di effetti irreversibili a contatto con la pelle.

NL: Schadelijk: bij aanraking met de huid zijn onherstelbare effecten niet uitgesloten.

PT: Nocivo: possibilidade de efeitos irreversíveis em contacto com a pele.

FI: Terveydelle haitallista: pysyvien vaurioiden vaara joutuessaan iholle.

SV: Farligt: möjlig risk för bestående hälsoskador vid hudkontakt.

**R68/22**

ES: Nocivo: posibilidad de efectos irreversibles por ingestión.

DA: Farlig: mulighed for varig skade på helbred ved indtagelse.

DE: Gesundheitsschädlich: Möglichkeit irreversiblen Schadens durch Verschlucken.

EL: Επιβλαβές: πιθανοί κίνδυνοι μονίμων επιδράσεων σε περίπτωση καταπόσεως.

EN: Harmful: possible risk of irreversible effects if swallowed.

FR: Nocif: possibilité d'effets irréversibles par ingestion.

IT: Nocivo: possibilità di effetti irreversibili per ingestione.

NL: Schadelijk: bij opname door de mond zijn onherstelbare effecten niet uitgesloten.

PT: Nocivo: possibilidade de efeitos irreversíveis por ingestão.

FI: Terveydelle haitallista: pysyvien vaurioiden vaara nieltynä.

SV: Farligt: möjlig risk för bestående hälsoskador vid förtäring.

**R68/20/21**

ES: Nocivo: posibilidad de efectos irreversibles por inhalación y contacto con la piel.

DA: Farlig: mulighed for varig skade på helbred ved indånding og hudkontakt.

DE: Gesundheitsschädlich: Möglichkeit irreversiblen Schadens durch Einatmen und bei Berührung mit der Haut.

EL: Επιβλαβές: πιθανοί κίνδυνοι μονίμων επιδράσεων όταν εισπνέεται και σε επαφή με το δέρμα.

EN: Harmful: possible risk of irreversible effects through inhalation and in contact with skin.

FR: Nocif: possibilité d'effets irréversibles par inhalation et par contact avec la peau.

IT: Nocivo: possibilità di effetti irreversibili per inalazione e a contatto con la pelle.

NL: Schadelijk: bij inademing en aanraking met de huid zijn onherstelbare effecten niet uitgesloten.

PT: Nocivo: possibilidade de efeitos irreversíveis por inalação e em contacto com a pele.

FI: Terveydelle haitallista: pysyvien vaurioiden vaara hengitettynä ja joutuessaan iholle.

SV: Farligt: möjlig risk för bestående hälsoskador vid inandning och hudkontakt.

**R68/20/22**

ES: Nocivo: posibilidad de efectos irreversibles por inhalación e ingestión.

DA: Farlig: mulighed for varig skade på helbred ved indånding og indtagelse.

DE: Gesundheitsschädlich: Möglichkeit irreversiblen Schadens durch Einatmen und durch Verschlucken.

EL: Επιβλαβές: πιθανοί κίνδυνοι μονίμων επιδράσεων όταν εισπνέεται και σε περίπτωση καταπόσεως.

EN: Harmful: possible risk of irreversible effects through inhalation and if swallowed.

FR: Nocif: possibilité d'effets irréversibles par inhalation et par ingestion.

IT: Nocivo: possibilità di effetti irreversibili per inalazione e ingestione.

NL: Schadelijk: bij inademing en opname door de mond zijn onherstelbare effecten niet uitgesloten.

PT: Nocivo: possibilidade de efeitos irreversíveis por inalação e ingestão.

FI: Terveydelle haitallista: pysyvien vaurioiden vaara hengitettynä ja nieltynä.

SV: Farligt: möjlig risk för bestående hälsoskador vid inandning och förtäring.

**R68/21/22**

ES: Nocivo: posibilidad de efectos irreversibles por contacto con la piel e ingestión.

DA: Farlig: mulighed for varig skade på helbred ved hudkontakt og indtagelse.

DE: Gesundheitsschädlich: Möglichkeit irreversiblen Schadens bei Berührung mit der Haut und durch Verschlucken.

EL: Επιβλαβές: πιθανοί κίνδυνοι μονίμων επιδράσεων σε επαφή με το δέρμα και σε περίπτωση καταπόσεως.

EN: Harmful: possible risk of irreversible effects in contact with skin and if swallowed.

FR: Nocif: possibilité d'effets irréversibles par contact avec la peau et par ingestion.

IT: Nocivo: possibilità di effetti irreversibili a contatto con la pelle e per ingestione.

NL: Schadelijk: bij aanraking met de huid en opname door de mond zijn onherstelbare effecten niet uitgesloten.

PT: Nocivo: possibilidade de efeitos irreversíveis em contacto com a pele e por ingestão.

FI: Terveydelle haitallista: pysyvien vaurioiden vaara joutuessaan iholle ja nieltynä.

SV: Farligt: möjlig risk för bestående hälsoskador vid hudkontakt och förtäring.

**R68/20/21/22**

ES: Nocivo: posibilidad de efectos irreversibles por inhalación, contacto con la piel e ingestión.

DA: Farlig: mulighed for varig skade på helbred ved indånding, hudkontakt og indtagelse.

DE: Gesundheitsschädlich: Möglichkeit irreversiblen Schadens durch Einatmen, Berührung mit der Haut und durch Verschlucken.

EL: Επιβλαβές: πιθανοί κίνδυνοι μονίμων επιδράσεων όταν εισπνέεται, σε επαφή με το δέρμα και σε περίπτωση καταπόσεως.

EN: Harmful: possible risk of irreversible effects through inhalation, in contact with skin and if swallowed.

FR: Nocif: possibilité d'effets irréversibles par inhalation, par contact avec la peau et par ingestion.

IT: Nocivo: possibilità di effetti irreversibili per inalazione, a contatto con la pelle e per ingestione.

NL: Schadelijk: bij inademing, aanraking met de huid en opname door de mond zijn onherstelbare effecten niet uitgesloten.

PT: Nocivo: possibilidade de efeitos irreversíveis por inalação, em contacto com a pele e por ingestão.

FI: Terveydelle haitallista: pysyvien vaurioiden vaara hengitettynä, joutuessaan iholle ja nieltynä.

SV: Farligt: möjlig risk för bestående hälsoskador vid inandning, hudkontakt och förtäring.

*ANNEX 4*

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**ANEXO IV**

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**ANEXO IV**

**Conselhos de prudência relativos a substâncias e preparações perigosas**

**LIITE IV**

**Vaarallisten aineiden ja valmisteiden turvallisuusohjeet**

**BILAGA IV**

**Skyddsfraser för farliga ämnen och beredningar**

**S1**

ES: Consérvese bajo llave.

DA: Opbevares under lås.

DE: Unter Verschluss aufbewahren.

EL: Να φυλάσσεται κλειδωμένο.

EN: Keep locked up.

FR: Conserver sous clé.

IT: Conservare sotto chiave.

NL: Achter slot bewaren.

PT: Guardar fechado à chave.

FI: Säilytettävä lukitussa tilassa.

SV: Förvaras i låst utrymme.

**S2**

ES: Manténgase fuera del alcance de los niños.

DA: Opbevares utilgængeligt for børn.

DE: Darf nicht in die Hände von Kindern gelangen.

EL: Μακρυά από παιδιά.

EN: Keep out of the reach of children.

FR: Conserver hors de portée des enfants.

IT: Conservare fuori della portata dei bambini.

NL: Buiten bereik van kinderen bewaren.

PT: Manter fora do alcance das crianças.

FI: Säilytettävä lasten ulottumattomissa.

SV: Förvaras oåtkomligt för barn.

**S3**

ES: Consérvese en lugar fresco.

DA: Opbevares køligt.

DE: Kühl aufbewahren.

EL: Να φυλάσσεται σε δροσερό μέρος.

EN: Keep in a cool place.

FR: Conserver dans un endroit frais.

IT: Conservare in luogo fresco.

NL: Op een koele plaats bewaren.

PT: Guardar em lugar fresco.

FI: Säilytettävä viileässä.

SV: Förvaras svalt.

**S4**

ES: Manténgase lejos de locales habitados.

DA: Må ikke opbevares i nærheden af beboelse.

DE: Von Wohnplätzen fernhalten.

EL: Μακρυά από κατοικημένους χώρους.

EN: Keep away from living quarters.

FR: Conserver à l'écart de tout local d'habitation.

IT: Conservare lontano da locali di abitazione.

NL: Verwijderd van woonruimten opbergen.

PT: Manter fora de qualquer zona de habitação.

FI: Ei saa säilyttää asuintiloissa.

SV: Förvaras avskilt från bostadsutrymmen.

**S5**

ES: Consérvese en … (*líquido apropiado a especificar por el fabricante*).

DA: Opbevares under … (*en egnet væske, som angives af fabrikanten*).

DE: Unter … aufbewahren (*geeignete Flüssigkeit vom Hersteller anzugeben*).

EL: Να διατηρείται το περιεχόμενο μέσα σε … (*το είδος του κατάλληλου υγρού καθορίζεται από τον παραγωγό*).

EN: Keep contents under … (*appropriate liquid to be specified by the manufacturer*).

FR: Conserver sous … (*liquide approprié à spécifier par le fabricant*).

IT: Conservare sotto … (*liquido appropriato da indicarsi da parte del fabbricante*).

NL: Onder … houden (*geschikte vloeistof aan te geven door fabrikant*).

PT: Manter sob … (*líquido apropriado a especificar pelo produtor*).

FI: Sisältö säilytettävä … (*tarkoitukseen soveltuvan nesteen ilmoittaa valmistaja/maahantuoja*).

SV: Förvara innehållet i … (*lämplig vätska anges av tillverkaren*).

**S6**

ES: Consérvese en … (*gas inerte a especificar por el fabricante*).

DA: Opbevares under … (*en inaktiv gas, som angives af fabrikanten*).

DE: Unter … aufbewahren (*inertes Gas vom Hersteller anzugeben*).

EL: Να διατηρείται σε ατμόσφαιρα … (*το είδος του αδρανούς αερίου καθορίζεται από τον παραγωγό*).

EN: Keep under … (*inert gas to be specified by the manufacturer*).

FR: Conserver sous … (*gaz inerte à spécifier par le fabricant*).

IT: Conservare sotto … (*gas inerte da indicarsi da parte del fabbricante*).

NL: Onder … houden (*inert gas aan te geven door fabrikant*).

PT: Manter sob … (*gás inerte a especificar pelo produtor*).

FI: Säilytettävä … (*inertin kaasun ilmoittaa valmistaja/maahantuoja*).

SV: Förvaras i … (*inert gas anges av tillverkaren*).

**S7**

ES: Manténgase el recipiente bien cerrado.

DA: Emballagen skal holdes tæt lukket.

DE: Behälter dicht geschlossen halten.

EL: Το δοχείο να διατηρείται ερμητικά κλεισμένο.

EN: Keep container tightly closed.

FR: Conserver le récipient bien fermé.

IT: Conservare il recipiente ben chiuso.

NL: In goed gesloten verpakking bewaren.

PT: Manter o recipiente bem fechado.

FI: Säilytettävä tiiviisti suljettuna.

SV: Förpackningen förvaras väl tillsluten.

**S8**

ES: Manténgase el recipiente en lugar seco.

DA: Emballagen skal opbevares tørt.

DE: Behälter trocken halten.

EL: Το δοχείο να προστατεύεται από την υγρασία.

EN: Keep container dry.

FR: Conserver le récipient à l'abri de l'humidité.

IT: Conservare al riparo dall'umidità.

NL: Verpakking droog houden.

PT: Manter o recipiente ao abrigo da humidade.

FI: Säilytettävä kuivana.

SV: Förpackningen förvaras torrt.

**S9**

ES: Consérvese el recipiente en lugar bien ventilado.

DA: Emballagen skal opbevares på et godt ventileret sted.

DE: Behälter an einem gut gelüfteten Ort aufbewahren.

EL: Το δοχείο να διατηρείται σε καλά αεριζόμενο μέρος.

EN: Keep container in a well-ventilated place.

FR: Conserver le récipient dans un endroit bien ventilé.

IT: Conservare il recipiente in luogo ben ventilato.

NL: Op een goed geventileerde plaats bewaren.

PT: Manter o recipiente num local bem ventilado.

FI: Säilytettävä paikassa, jossa on hyvä ilmanvaihto.

SV: Förpackningen förvaras på väl ventilerad plats.

**S12**

ES: No cerrar el recipiente herméticamente.

DA: Emballagen må ikke lukkes tæt.

DE: Behälter nicht gasdicht verschließen.

EL: Μη διατηρείτε το δοχείο ερμητικά κλεισμένο.

EN: Do not keep the container sealed.

FR: Ne pas fermer hermétiquement le récipient.

IT: Non chiudere ermeticamente il recipiente.

NL: De verpakking niet hermetisch sluiten.

PT: Não fechar o recipiente hermeticamente.

FI: Pakkausta ei saa sulkea ilmatiiviisti.

SV: Förpackningen får inte tillslutas lufttätt.

**S13**

ES: Manténgase lejos de alimentos, bebidas y piensos.

DA: Må ikke opbevares sammen med fødevarer, drikkevarer og foderstoffer.

DE: Von Nahrungsmitteln, Getränken und Futtermitteln fernhalten.

EL: Μακρυά από τρόφιμα, ποτά και ζωοτροφές.

EN: Keep away from food, drink and animal feedingstuffs.

FR: Conserver à l'écart des aliments et boissons, y compris ceux pour animaux.

IT: Conservare lontano da alimenti o mangimi e da bevande.

NL: Verwijderd houden van eet- en drinkwaren en van diervoeder.

PT: Manter afastado de alimentos e bebidas, incluindo os dos animais.

FI: Ei saa säilyttää yhdessä elintarvikkeiden eikä eläinravinnon kanssa.

SV: Förvaras åtskilt från livsmedel och djurfoder.

**S14**

ES: Consérvese lejos de … (*materiales incompatibles a especificar por el fabricante*).

DA: Opbevares adskilt fra … (*uforligelige stoffer, som angives af fabrikanten*).

DE: Von … fernhalten (*inkompatible Substanzen sind vom Hersteller anzugeben*).

EL: Μακρυά από … (*ασύμβατες ουσίες καθορίζονται από τον παραγωγό*).

EN: Keep away from … (*incompatible materials to be indicated by the manufacturer*).

FR: Conserver à l'écart des … (*matières incompatibles à indiquer par le fabricant*).

IT: Conservare lontano da … (*sostanze incompatibili da precisare da parte del produttore*).

NL: Verwijderd houden van … (*stoffen waarmee contact vermeden dient te worden aan te geven door de fabrikant*).

PT: Manter afastado de … (*matérias incompatíveis a indicar pelo produtor*).

FI: Säilytettävä erillään … (*yhteensopimattomat aineet ilmoittaa valmistaja/maahantuoja*).

SV: Förvaras åtskilt från … (*oförenliga ämnen anges av tillverkaren*).

**S15**

ES: Conservar alejado del calor.

DA: Må ikke udsættes for varme.

DE: Vor Hitze schützen.

EL: Μακρυά από θερμότητα.

EN: Keep away from heat.

FR: Conserver à l'écart de la chaleur.

IT: Conservare lontano dal calore.

NL: Verwijderd houden van warmte.

PT: Manter afastado do calor.

FI: Suojattava lämmöltä.

SV: Får inte utsättas för värme.

**S16**

ES: Conservar alejado de toda llama o fuente de chispas — No fumar.

DA: Holdes væk fra antændelseskilder — Rygning forbudt.

DE: Von Zündquellen fernhalten — Nicht rauchen.

EL: Μακρυά από πηγές ανάφλεξης — Απαγορεύεται το κάπνισμα.

EN: Keep away from sources of ignition — No smoking.

FR: Conserver à l'écart de toute flamme ou source d'étincelles — Ne pas fumer.

IT: Conservare lontano da fiamme e scintille — Non fumare.

NL: Verwijderd houden van ontstekingsbronnen — Niet roken.

PT: Manter afastado de qualquer chama ou fonte de ignição — Não fumar.

FI: Eristettävä sytytyslähteistä — Tupakointi kielletty.

SV: Förvaras åtskilt från antändningskällor – Rökning förbjuden.

**S17**

ES: Manténgase lejos de materias combustibles.

DA: Holdes væk fra brandbare stoffer.

DE: Von brennbaren Stoffen fernhalten.

EL: Μακρυά από καύσιμα υλικά.

EN: Keep away from combustible material.

FR: Tenir à l'écart des matières combustibles.

IT: Tenere lontano da sostanze combustibili.

NL: Verwijderd houden van brandbare stoffen.

PT: Manter afastado de matérias combustíveis.

FI: Säilytettävä erillään syttyvistä kemikaaleista.

SV: Förvaras åtskilt från brandfarliga ämnen.

**S18**

ES: Manipúlese y ábrase el recipiente con prudencia.

DA: Emballagen skal behandles og åbnes med forsigtighed.

DE: Behälter mit Vorsicht öffnen und handhaben.

EL: Χειριστείτε και ανοίξτε το δοχείο προσεκτικά.

EN: Handle and open container with care.

FR: Manipuler et ouvrir le récipient avec prudence.

IT: Manipolare ed aprire il recipiente con cautela.

NL: Verpakking voorzichtig behandelen en openen.

PT: Manipular e abrir o recipiente com prudência.

FI: Pakkauksen käsittelyssä ja avaamisessa on noudatettava varovaisuutta.

SV: Förpackningen hanteras och öppnas försiktigt.

**S20**

ES: No comer ni beber durante su utilización.

DA: Der må ikke spises eller drikkes under brugen.

DE: Bei der Arbeit nicht essen und trinken.

EL: Μην τρώτε ή πίνετε όταν το χρησιμοποιείτε.

EN: When using do not eat or drink.

FR: Ne pas manger et ne pas boire pendant l'utilisation.

IT: Non mangiare né bere durante l'impiego.

NL: Niet eten of drinken tijdens gebruik.

PT: Não comer nem beber durante a utilização.

FI: Syöminen ja juominen kielletty kemikaalia käsiteltäessä.

SV: Ät inte eller drick inte under hanteringen

**S21**

ES: No fumar durante su utilización.

DA: Der må ikke ryges under brugen.

DE: Bei der Arbeit nicht rauchen.

EL: Μην καπνίζετε όταν το χρησιμοποιείτε.

EN: When using do not smoke.

FR: Ne pas fumer pendant l'utilisation.

IT: Non fumare durante l'impiego.

NL: Niet roken tijdens gebruik.

PT: Não fumar durante a utilização.

FI: Tupakointi kielletty kemikaalia käytettäessä.

SV: Rök inte under hanteringen.

**S22**

ES: No respirar el polvo.

DA: Undgå indånding af støv.

DE: Staub nicht einatmen.

EL: Μην αναπνέετε την σκόνη.

EN: Do not breathe dust.

FR: Ne pas respirer les poussières.

IT: Non respirare le polveri.

NL: Stof niet inademen.

PT: Não respirar as poeiras.

FI: Vältettävä pölyn hengittämistä.

SV: Undvik inandning av damm.

**S23**

ES: No respirar los gases/humos/vapores/aerosoles [*denominación(es) adecuada(s) a especificar por el fabricante*].

DA: Undgå indånding af gas/røg/dampe/aerosol-tåger (*den eller de pågældende betegnelser angives af fabrikanten*).

DE: Gas/Rauch/Dampf/Aerosol nicht einatmen (*geeignete Bezeichnung(en) vom Hersteller anzugeben*).

EL: Μην αναπνέετε αέρια/αναθυμιάσεις/ατμούς/εκνεφώματα (*η κατάλληλη διατύπωση καθορίζεται από τον παραγωγό*).

EN: Do not breathe gas/fumes/vapour/spray (*appropriate wording to be specified by the manufacturer*).

FR: Ne pas respirer les gaz/fumées/vapeurs/aérosols [*terme(s) approprié(s) à indiquer par le fabricant*].

IT: Non respirare i gas/fumi/vapori/aerosoli [*termine(i) appropriato(i) da precisare da parte del produttore*].

NL: Gas/rook/damp/spuitnevel niet inademen (*toepasselijke term(en) aan te geven door de fabrikant*).

PT: Não respirar os gases/vapores/fumos/aerossóis [*termo(s) apropriado(s) a indicar pelo produtor*].

FI: Vältettävä kaasun/huurun/höyryn/sumun hengittämistä (*oikean sanamuodon valitsee valmistaja/maahantuoja*).

SV: Undvik inandning av gas/rök/ånga/dimma (*lämplig formulering anges av tillverkaren*).

**S24**

ES: Evítese el contacto con la piel.

DA: Undgå kontakt med huden.

DE: Berührung mit der Haut vermeiden.

EL: Αποφεύγετε την επαφή με το δέρμα.

EN: Avoid contact with skin.

FR: Éviter le contact avec la peau.

IT: Evitare il contatto con la pelle.

NL: Aanraking met de huid vermijden.

PT: Evitar o contacto com a pele.

FI: Varottava kemikaalin joutumista iholle.

SV: Undvik kontakt med huden.

**S25**

ES: Evítese el contacto con los ojos.

DA: Undgå kontakt med øjnene.

DE: Berührung mit den Augen vermeiden.

EL: Αποφεύγετε την επαφή με τα μάτια.

EN: Avoid contact with eyes.

FR: Éviter le contact avec les yeux.

IT: Evitare il contatto con gli occhi.

NL: Aanraking met de ogen vermijden.

PT: Evitar o contacto com os olhos.

FI: Varottava kemikaalin joutumista silmiin.

SV: Undvik kontakt med ögonen.

**S26**

ES: En caso de contacto con los ojos, lávense inmediata y abundantemente con agua y acúdase a un médico.

DA: Kommer stoffet i øjnene, skylles straks grundigt med vand og læge kontaktes.

DE: Bei Berührung mit den Augen sofort gründlich mit Wasser abspülen und Arzt konsultieren.

EL: Σε περίπτωση επαφής με τα μάτια πλύνετέ τα αμέσως με άφθονο νερό και ζητήστε ιατρική συμβουλή.

EN: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.

FR: En cas de contact avec les yeux, laver immédiatement et abondamment avec de l'eau et consulter un spécialiste.

IT: In caso di contatto con gli occhi, lavare immediatamente e abbondantemente con acqua e consultare un medico.

NL: Bij aanraking met de ogen onmiddellijk met overvloedig water afspoelen en deskundig medisch advies inwinnen.

PT: Em caso de contacto com os olhos, lavar imediata e abundantemente com água e consultar um especialista.

FI: Roiskeet silmistä huuhdeltava välittömästi runsaalla vedellä ja mentävä lääkäriin.

SV: Vid kontakt med ögonen, spola genast med mycket vatten och kontakta läkare.

**S27**

ES: Quítese inmediatamente la ropa manchada o salpicada.

DA: Tilsmudset tøj tages straks af.

DE: Beschmutzte, getränkte Kleidung sofort ausziehen.

EL: Αφαιρέστε αμέσως όλα τα ενδύματα που έχουν μολυνθεί.

EN: Take off immediately all contaminated clothing.

FR: Enlever immédiatement tout vêtement souillé ou éclaboussé.

IT: Togliersi di dosso immediatamente gli indumenti contaminati.

NL: Verontreinigde kleding onmiddellijk uittrekken.

PT: Retirar imediatamente todo o vestuário contaminado.

FI: Riisuttava välittömästi saastunut vaatetus.

SV: Tag genast av alla nedstänkta kläder.

**S28**

ES: En caso de contacto con la piel, lávese inmediata y abundantemente con … (*productos a especificar por el fabricante*).

DA: Kommer stof på huden vaskes straks med store mængder … (*angives af fabrikanten*).

DE: Bei Berührung mit der Haut sofort abwaschen mit viel … (*vom Hersteller anzugeben*).

EL: Σε περίπτωση επαφής με το δέρμα, πλυθείτε αμέσως με άφθονο … (*το είδος του υγρού καθορίζεται από τον παραγωγό*).

EN: After contact with skin, wash immediately with plenty of … (*to be specified by the manufacturer*).

FR: Après contact avec la peau, se laver immédiatement et abondamment avec … (*produits appropriés à indiquer par le fabricant*).

IT: In caso di contatto con la pelle lavarsi immediatamente ed abbondantemente con … (*prodotti idonei da indicarsi da parte del fabbricante*).

NL: Na aanraking met de huid onmiddellijk wassen met veel … (*aan te geven door de fabrikant*).

PT: Após contacto com a pele, lavar imediata e abundantemente com … (*produtos adequados a indicar pelo produtor*).

FI: Roiskeet iholta huuhdeltava välittömästi runsaalla määrällä … (*aineen ilmoittaa valmistaja/maahantuoja*).

SV: Vid kontakt med huden tvätta genast med mycket … (*anges av tillverkaren*).

**S29**

ES: No tirar los residuos por el desagüe.

DA: Må ikke tømmes i kloakafløb.

DE: Nicht in die Kanalisation gelangen lassen.

EL: Μην αδειάζετε το υπόλοιπο του περιεχομένου στην αποχέτευση.

EN: Do not empty into drains.

FR: Ne pas jeter les résidus à l'égout.

IT: Non gettare i residui nelle fognature.

NL: Afval niet in de gootsteen werpen.

PT: Não deitar os resíduos no esgoto.

FI: Ei saa tyhjentää viemäriin.

SV: Töm ej i avloppet.

**S30**

ES: No echar jamás agua a este producto.

DA: Hæld aldrig vand på eller i produktet.

DE: Niemals Wasser hinzugießen.

EL: Ποτέ μην προσθέτετε νερό στο προϊόν αυτό.

EN: Never add water to this product.

FR: Ne jamais verser de l'eau dans ce produit.

IT: Non versare acqua sul prodotto.

NL: Nooit water op deze stof gieten.

PT: Nunca adicionar água a este produto.

FI: Tuotteeseen ei saa lisätä vettä.

SV: Häll aldrig vatten på eller i produkten.

**S33**

ES: Evítese la acumulación de cargas electroestáticas.

DA: Træf foranstaltninger mod statisk elektricitet.

DE: Maßnahmen gegen elektrostatische Aufladungen treffen.

EL: Λάβετε προστατευτικά μέτρα έναντι ηλεκτροστατικών εκκενώσεων.

EN: Take precautionary measures against static discharges.

FR: Éviter l'accumulation de charges électrostatiques.

IT: Evitare l'accumulo di cariche elettrostatiche.

NL: Maatregelen treffen tegen ontladingen van statische elektriciteit.

PT: Evitar acumulação de cargas electrostáticas.

FI: Estettävä staattisen sähkön aiheuttama kipinöinti.

SV: Vidtag åtgärder mot statisk elektricitet.

**S35**

ES: Elimínense los residuos del producto y sus recipientes con todas las precauciones posibles.

DA: Materialet og dets beholder skal bortskaffes på en sikker måde.

DE: Abfälle und Behälter müssen in gesicherter Weise beseitigt werden.

EL: Το υλικό και ο περιέκτης του πρέπει να διατεθεί με ασφαλή τρόπο.

EN: This material and its container must be disposed of in a safe way.

FR: Ne se débarrasser de ce produit et de son récipient qu'en prenant toutes les précautions d'usage.

IT: Non disfarsi del prodotto e del recipiente se non con le dovute precauzioni.

NL: Deze stof en de verpakking op veilige wijze afvoeren.

PT: Não se desfazer deste produto e do seu recipiente sem tomar as precauções de segurança devidas.

FI: Tämä aine ja sen pakkaus on hävitettävä turvallisesti.

SV: Produkt och förpackning skall oskadliggöras på säkert sätt.

**S36**

ES: Úsese indumentaria protectora adecuada.

DA: Brug særligt arbejdstøj.

DE: Bei der Arbeit geeignete Schutzkleidung tragen.

EL: Να φοράτε κατάλληλη προστατευτική ενδυμασία.

EN: Wear suitable protective clothing.

FR: Porter un vêtement de protection approprié.

IT: Usare indumenti protettivi adatti.

NL: Draag geschikte beschermende kleding.

PT: Usar vestuário de protecção adequado.

FI: Käytettävä sopivaa suojavaatetusta.

SV: Använd lämpliga skyddskläder.

**S37**

ES: Úsense guantes adecuados.

DA: Brug egnede beskyttelseshandsker under arbejdet.

DE: Geeignete Schutzhandschuhe tragen.

EL: Να φοράτε κατάλληλα γάντια.

EN: Wear suitable gloves.

FR: Porter des gants appropriés.

IT: Usare guanti adatti.

NL: Draag geschikte handschoenen.

PT: Usar luvas adequadas.

FI: Käytettävä sopivia suojakäsineitä.

SV: Använd lämpliga skyddshandskar.

**S38**

ES: En caso de ventilación insuficiente, úsese equipo respiratorio adecuado.

DA: Brug egnet åndedrætsværn, hvis effektiv ventilation ikke er mulig.

DE: Bei unzureichender Belüftung Atemschutzgerät anlegen.

EL: Σε περίπτωση ανεπαρκούς αερισμού, χρησιμοποιείτε κατάλληλη αναπνευστική συσκευή.

EN: In case of insufficient ventilation, wear suitable respiratory equipment.

FR: En cas de ventilation insuffisante, porter un appareil respiratoire approprié.

IT: In caso di ventilazione insufficiente, usare un apparecchio respiratorio adatto.

NL: Bij ontoereikende ventilatie een geschikte adembescherming dragen.

PT: Em caso de ventilação insuficiente, usar equipamento respiratório adequado.

FI: Kemikaalin käyttö edellyttää tehokasta ilmanvaihtoa tai sopivaa hengityksensuojainta.

SV: Använd lämpligt andningsskydd vid otillräcklig ventilation.

**S39**

ES: Úsese protección para los ojos/la cara.

DA: Brug beskyttelsesbriller/ansigtsskærm under arbejdet.

DE: Schutzbrille/Gesichtsschutz tragen.

EL: Χρησιμοποιείτε συσκευή προστασίας ματιών/προσώπου.

EN: Wear eye/face protection.

FR: Porter un appareil de protection des yeux/du visage.

IT: Proteggersi gli occhi/la faccia.

NL: Een bescherming voor de ogen/voor het gezicht dragen.

PT: Usar um equipamento protector para os olhos/face.

FI: Käytettävä silmien- tai kasvonsuojainta.

SV: Använd skyddsglasögon eller ansiktsskydd.

**S40**

ES: Para limpiar el suelo y los objetos contaminados por este producto, úsese … (*a especificar por el fabricante*).

DA: Gulvet og tilsmudsede genstande renses med … (*midlerne angives af fabrikanten*).

DE: Fußboden und verunreinigte Gegenstände mit … reinigen (*Material vom Hersteller anzugeben*).

EL: Για τον καθαρισμό του δαπέδου και όλων των αντικειμένων που έχουν μολυνθεί από το υλικό αυτό χρησιμοποιείτε … (*το είδος καθορίζεται από τον παραγωγό*).

EN: To clean the floor and all objects contaminated by this material, use … (*to be specified by the manufacturer*).

FR: Pour nettoyer le sol ou les objets souillés par ce produit, utiliser … (*à préciser par le fabricant*).

IT: Per pulire il pavimento e gli oggetti contaminati da questo prodotto, usare … (*da precisare da parte del produttore*).

NL: Voor de reiniging van de vloer en alle voorwerpen verontreinigd met dit materiaal, … gebruiken (*aan te geven door de fabrikant*).

PT: Para limpeza do chão e objectos contaminados por este produto, utilizar … (*a especificar pelo produtor*).

FI: Kemikaali puhdistettava pinnoilta käyttäen … (*kemikaalin ilmoittaa valmistaja/maahantuoja*).

SV: Golv och förorenade föremål tvättas med … (*anges av tillverkaren*).

**S41**

ES: En caso de incendio y/o de explosión no respire los humos.

DA: Undgå at indånde røgen ved brand eller eksplosion.

DE: Explosions- und Brandgase nicht einatmen.

EL: Σε περίπτωση πυρκαγιάς ή/και εκρήξεως μην αναπνέετε τους καπνούς.

EN: In case of fire and/or explosion do not breathe fumes.

FR: En cas d'incendie et/ou d'explosion, ne pas respirer les fumées.

IT: In caso di incendio e/o esplosione non respirare i fumi.

NL: In geval van brand en/of explosie inademen van rook vermijden.

PT: Em caso de incêndio e/ou explosão não respirar os fumos.

FI: Vältettävä palamisessa tai räjähdyksessä muodostuvan savun hengittämistä.

SV: Undvik inandning av rök vid brand eller explosion.

**S42**

ES: Durante las fumigaciones/pulverizaciones, úsese equipo respiratorio adecuado [*denominación(es) adecuada(s) a especificar por el fabricante*].

DA: Brug egnet åndedrætsværn ved rygning/sprøjtning (*den eller de pågældende betegnelser angives af fabrikanten*).

DE: Beim Räuchern/Versprühen geeignetes Atemschutzgerät anlegen (*geeignete Bezeichnung(en) vom Hersteller anzugeben*).

EL: Κατά τη διάρκεια υποκαπνισμού/ψεκάσματος χρησιμοποιείτε κατάλληλη αναπνευστική συσκευή (*η κατάλληλη διατύπωση καθορίζεται από τον παραγωγό*).

EN: During fumigation/spraying wear suitable respiratory equipment (*appropriate wording to be specified by the manufacturer*).

FR: Pendant les fumigations/pulvérisations, porter un appareil respiratoire approprié [*terme(s) approprié(s) à indiquer par le fabricant*].

IT: Durante le fumigazioni/polimerizzazioni usare un apparecchio respiratorio adatto [*termine(i) appropriato(i) da precisare da parte del produttore*].

NL: Tijdens de ontsmetting/bespuiting een geschikte adembescherming dragen (*geschikte term(en) door de fabrikant aan te geven*).

PT: Durante as fumigações/pulverizações usar equipamento respiratório adequado [*termo(s) adequado(s) a indicar pelo produtor*].

FI: Kaasutuksen/ruiskutuksen aikana käytettävä sopivaa hengityksensuojainta (*oikean sanamuodon valitsee valmistaja/maahantuoja*).

SV: Använd lämpligt andningsskydd vid gasning/sprutning (*specificeras av tillverkaren*).

**S43**

ES: En caso de incendio, utilizar … (*los medios de extinción los debe especificar el fabricante*). (*Si el agua aumenta el riesgo, se deberá añadir: «No usar nunca agua»*).

DA: Brug … ved brandslukning (*den nøjagtige type brandslukningsudstyr angives af fabrikanten. Såfremt vand ikke må bruges tilføjes: »Brug ikke vand«*).

DE: Zum Löschen … (*vom Hersteller anzugeben*) verwenden. (*Wenn Wasser die Gefahr erhöht, anfügen: „Kein Wasser verwenden“.*).

EL: Σε περίπτωση πυρκαγιάς χρησιμοποιείτε … (*Αναφέρεται το ακριβές είδος μέσων πυρόσβεσης. Εάν το νερό αυξάνει τον κίνδυνο, προστίθεται: «Μη χρησιμοποιείτε ποτέ νερό»*).

EN: In case of fire, use … (*indicate in the space the precise type of fire-fighting equipment. If water increases risk, add 'Never use water'*).

FR: En cas d'incendie, utiliser … (*moyens d'extinction à préciser par le fabricant. Si l'eau augmente les risques, ajouter: «Ne jamais utiliser d'eau»*).

IT: In caso di incendio usare … (*mezzi estinguenti idonei da indicarsi da parte del fabbricante. Se l'acqua aumenta il rischio precisare «Non usare acqua»*).

NL: In geval van brand … gebruiken (*blusmiddelen aan te duiden door de fabrikant. Indien water het risico vergroot toevoegen: „Nooit water gebruiken.”*).

PT: Em caso de incêndio, utilizar … (*meios de extinção a especificar pelo produtor. Se a água aumentar os riscos, acrescentar «Nunca utilizar água»*).

FI: Sammutukseen käytettävä … (*ilmoitettava sopiva sammutusmenetelmä. Jos vesi lisää vaaraa, lisättävä sanat: Sammutukseen ei saa käyttää vettä*).

SV: Vid brandsläckning använd … (*ange lämplig metod. Om vatten ökar riskerna, lägg till: ”Använd aldrig vatten”*).

**S45**

ES: En caso de accidente o malestar, acúdase inmediatamente al médico (si es posible, muéstresele la etiqueta).

DA: Ved ulykkestilfælde eller ved ildebefindende er omgående lægebehandling nødvendig; vis etiketten, hvis det er muligt.

DE: Bei Unfall oder Unwohlsein sofort Arzt zuziehen (wenn möglich, dieses Etikett vorzeigen).

EL: Σε περίπτωση ατυχήματος ή αν αισθανθείτε αδιαθεσία ζητήστε αμέσως ιατρική συμβουλή (δείξτε την ετικέττα αν είναι δυνατό).

EN: In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

FR: En cas d'accident ou de malaise, consulter immédiatement un médecin (si possible, lui montrer l'étiquette).

IT: In caso di incidente o di malessere consultare immediatamente il medico (se possibile, mostrargli l'etichetta).

NL: Bij een ongeval of indien men zich onwel voelt, onmiddellijk een arts raadplegen (indien mogelijk hem dit etiket tonen).

PT: Em caso de acidente ou de indisposição, consultar imediatamente o médico (se possível mostrar-lhe o rótulo).

FI: Onnettomuuden sattuessa tai tunnettaessa pahoinvointia hakeuduttava heti lääkärin hoitoon (näytettävä tätä etikettiä, mikäli mahdollista).

SV: Vid olycksfall, illamående eller annan påverkan, kontakta omedelbart läkare. Visa om möjligt etiketten.

**S46**

ES: En caso de ingestión, acúdase inmediatamente al médico y muéstresele la etiqueta o el envase.

DA: Ved indtagelse, kontakt omgående læge og vis denne beholder eller etiket.

DE: Bei Verschlucken sofort ärztlichen Rat einholen und Verpackung oder Etikett vorzeigen.

EL: Σε περίπτωση κατάποσης ζητήστε αμέσως ιατρική συμβουλή και δείξτε αυτό το δοχείο ή την ετικέττα.

EN: If swallowed, seek medical advice immediately and show this container or label.

FR: En cas d'ingestion, consulter immédiatement un médecin et lui montrer l'emballage ou l'étiquette.

IT: In caso d'ingestione consultare immediatamente il medico e mostrargli il contenitore o l'etichetta.

NL: In geval van inslikken onmiddellijk een arts raadplegen en verpakking of etiket tonen.

PT: Em caso de ingestão, consultar imediatamente o médico e mostrar-lhe a embalagem ou o rótulo.

FI: Jos ainetta on nielty, hakeuduttava heti lääkärin hoitoon ja näytettävä tämä pakkaus tai etiketti.

SV: Vid förtäring kontakta genast läkare och visa denna förpackning eller etiketten.

**S47**

ES: Consérvese a una temperatura no superior a … °C (*a especificar por el fabricante*).

DA: Må ikke opbevares ved temperaturer på over … °C (*angives af fabrikanten*).

DE: Nicht bei Temperaturen über … °C aufbewahren (*vom Hersteller anzugeben*).

EL: Να διατηρείται σε θερμοκρασία που δεν υπερβαίνει τους … °C (*καθορίζεται από τον παραγωγό*).

EN: Keep at temperature not exceeding … °C (*to be specified by the manufacturer*).

FR: Conserver à une température ne dépassant pas … °C (*à préciser par le fabricant*).

IT: Conservare a temperatura non superiore a … °C (*da precisare da parte del fabbricante*).

NL: Bewaren bij een temperatuur beneden … °C (*aan te geven door de fabrikant*).

PT: Conservar a uma temperatura que não exceda … °C (*a especificar pelo produtor*).

FI: Säilytettävä alle … °C:n lämpötilassa (*valmistaja/maahantuoja ilmoittaa lämpötilan*).

SV: Förvaras vid en temperatur som inte överstiger … °C (*anges av tillverkaren*).

**S48**

ES: Consérvese húmedo con … (*medio apropiado a especificar por el fabricante*).

DA: Holdes befugtet med … (*passende middel angives af fabrikanten*).

DE: Feucht halten mit … (*geeignetes Mittel vom Hersteller anzugeben*).

EL: Να διατηρείται υγρό με … (*το κατάλληλο υλικό καθορίζεται από τον παραγωγό*).

EN: Keep wet with … (*appropriate material to be specified by the manufacturer*).

FR: Maintenir humide avec … (*moyen approprié à préciser par le fabricant*).

IT: Mantenere umido con … (*mezzo appropriato da precisare da parte del fabbricante*).

NL: Inhoud vochtig houden met … (*middel aan te geven door de fabrikant*).

PT: Manter húmido com … (*material adequado a especificar pelo produtor*).

FI: Säilytettävä kosteana … (*valmistaja/maahantuoja ilmoittaa sopivan aineen*).

SV: Innehållet skall hållas fuktigt med … (*lämpligt material anges av tillverkaren*).

**S49**

ES: Consérvese únicamente en el recipiente de origen.

DA: Må kun opbevares i den originale emballage.

DE: Nur im Originalbehälter aufbewahren.

EL: Διατηρείται μόνο μέσα στο αρχικό δοχείο.

EN: Keep only in the original container.

FR: Conserver uniquement dans le récipient d'origine.

IT: Conservare soltanto nel recipiente originale.

NL: Uitsluitend in de oorspronkelijke verpakking bewaren.

PT: Conservar unicamente no recipiente de origem.

FI: Säilytettävä vain alkuperäispakkauksessa.

SV: Förvaras endast i originalförpackningen.

**S50**

ES: No mezclar con … (*a especificar por el fabricante*).

DA: Må ikke blandes med … (*angives af fabrikanten*).

DE: Nicht mischen mit … (*vom Hersteller anzugeben*).

EL: Να μην αναμειχθεί με … (*καθορίζεται από τον παραγωγό*).

EN: Do not mix with … (*to be specified by the manufacturer*).

FR: Ne pas mélanger avec … (*à spécifier par le fabricant*).

IT: Non mescolare con … (*da specificare da parte del fabbricante*).

NL: Niet vermengen met … (*aan te geven door de fabrikant*).

PT: Não misturar com … (*a especificar pelo produtor*).

FI: Ei saa sekoittaa … (*valmistaja/maahantuoja ilmoittaa aineen) kanssa*.

SV: Blanda inte med … (*anges av tillverkaren*).

**S51**

ES: Úsese únicamente en lugares bien ventilados.

DA: Må kun bruges på steder med god ventilation.

DE: Nur in gut gelüfteten Bereichen verwenden.

EL: Να χρησιμοποιείται μόνο σε καλά αεριζόμενο χώρο.

EN: Use only in well-ventilated areas.

FR: Utiliser seulement dans des zones bien ventilées.

IT: Usare soltanto in luogo ben ventilato.

NL: Uitsluitend op goed geventileerde plaatsen gebruiken.

PT: Utilizar somente em locais bem ventilados.

FI: Huolehdittava hyvästä ilmanvaihdosta.

SV: Sörj för god ventilation.

**S52**

ES: No usar sobre grandes superficies en locales habitados.

DA: Bør ikke anvendes til større flader i beboelses- eller opholdsrum.

DE: Nicht großflächig für Wohn- und Aufenthaltsräume zu verwenden.

EL: Δεν συνιστάται η χρήση σε ευρείες επιφάνειες σε εσωτερικούς χώρους.

EN: Not recommended for interior use on large surface areas.

FR: Ne pas utiliser sur de grandes surfaces dans les locaux habités.

IT: Non utilizzare su grandi superfici in locali abitati.

NL: Niet voor gebruik op grote oppervlakken in woon- en verblijfruimten.

PT: Não utilizar em grandes superfícies nos locais habitados.

FI: Ei suositella sisäkäyttöön laajoilla pinnoilla.

SV: Olämpligt för användning inomhus vid behandling av stora ytor.

**S53**

ES: Evítese la exposición — recábense instrucciones especiales antes del uso.

DA: Undgå enhver kontakt — indhent særlige anvisninger før brug.

DE: Exposition vermeiden — vor Gebrauch besondere Anweisungen einholen.

EL: Αποφεύγετε την έκθεση — εφοδιαστείτε με τις ειδικές οδηγίες πριν από τη χρήση.

EN: Avoid exposure — obtain special instructions before use.

FR: Éviter l'exposition — se procurer des instructions spéciales avant l'utilisation.

IT: Evitare l'esposizione — procurarsi speciali istruzioni prima dell'uso.

NL: Blootstelling vermijden — vóór gebruik speciale aanwijzingen raadplegen.

PT: Evitar a exposição — obter instruções específicas antes da utilização.

FI: Vältettävä altistumista — ohjeet luettava ennen käyttöä.

SV: Undvik exponering – Begär specialinstruktioner före användning.

**S56**

ES: Elimínense esta sustancia y su recipiente en un punto de recogida pública de residuos especiales o peligrosos.

DA: Aflever dette materiale og dets beholder til et indsamlingssted for farligt affald og problemaffald.

DE: Dieses Produkt und seinen Behälter der Problemabfallentsorgung zuführen.

EL: Το υλικό αυτό και ο περιέκτης του να εναποτεθούν σε χώρο συλλογής επικινδύνων ή ειδικών αποβλήτων.

EN: Dispose of this material and its container to hazardous or special waste collection point.

FR: Éliminer ce produit et son récipient dans un centre de collecte des déchets dangereux ou spéciaux.

IT: Smaltire questo materiale e i relativi contenitori in un punto di raccolta rifiuti pericolosi o speciali.

NL: Deze stof en de verpakking naar inzamelpunt voor gevaarlijk of bijzonder afval brengen.

PT: Eliminar este produto e o seu recipiente, enviando-os para local autorizado para a recolha de resíduos perigosos ou especiais.

FI: Tämä aine ja sen pakkaus on toimitettava ongelmajätteen vastaanottopaikkaan.

SV: Lämna detta material och dess behållare till insamlingsställe för farligt avfall.

**S57**

ES: Utilícese un envase de seguridad adecuado para evitar la contaminación del medio ambiente.

DA: Skal indesluttes forsvarligt for at undgå miljøforurening.

DE: Zur Vermeidung einer Kontamination der Umwelt geeigneten Behälter verwenden.

EL: Να χρησιμοποιηθεί ο κατάλληλος περιέκτης για να αποφευχθεί μόλυνση του περιβάλλοντος.

EN: Use appropriate container to avoid environmental contamination.

FR: Utiliser un récipient approprié pour éviter toute contamination du milieu ambiant.

IT: Usare contenitori adeguati per evitare l'inquinamento ambientale.

NL: Neem passende maatregelen om verspreiding in het milieu te voorkomen.

PT: Utilizar um recipiente adequado para evitar a contaminação do ambiente.

FI: Käytettävä sopivaa säilytystapaa ympäristön likaantumisen ehkäisemiseksi.

SV: Förvaras på lämpligt sätt för att undvika miljöförorening.

**S59**

ES: Remitirse al fabricante o proveedor para obtener información sobre su recuperación/reciclado.

DA: Indhent oplysninger om genvinding/genanvendelse hos producenten/leverandøren.

DE: Informationen zur Wiederverwendung/Wiederverwertung beim Hersteller/Lieferanten erfragen.

EL: Ζητήστε πληροφορίες από τον παραγωγό/προμηθευτή για ανάκτηση/ανακύκλωση.

EN: Refer to manufacturer/supplier for information on recovery/recycling.

FR: Consulter le fabricant/fournisseur pour des informations relatives à la récupération/au recyclage.

IT: Richiedere informazioni al produttore/fornitore per il recupero/riciclaggio.

NL: Raadpleeg fabrikant/leverancier voor informatie over terugwinning/recycling.

PT: Solicitar ao produtor/fornecedor informações relativas à sua recuperação/reciclagem.

FI: Hanki valmistajalta/luovuttajalta tietoja uudelleenkäytöstä/kierrätyksestä.

SV: Rådfråga tillverkare/leverantör om återvinning/återanvändning.

**S60**

ES: Elimínense el producto y su recipiente como residuos peligrosos.

DA: Dette materiale og dets beholder skal bortskaffes som farligt affald.

DE: Dieses Produkt und sein Behälter sind als gefährlicher Abfall zu entsorgen.

EL: Το υλικό και ο περιέκτης του να θεωρηθούν κατά τη διάθεση τους επικίνδυνα απόβλητα.

EN: This material and its container must be disposed of as hazardous waste.

FR: Éliminer le produit et son récipient comme un déchet dangereux.

IT: Questo materiale e il suo contenitore devono essere smaltiti come rifiuti pericolosi.

NL: Deze stof en de verpakking als gevaarlijk afval afvoeren.

PT: Este produto e o seu recipiente devem ser eliminados como resíduos perigosos.

FI: Tämä aine ja sen pakkaus on käsiteltävä ongelmajätteenä.

SV: Detta material och dess behållare skall tas om hand som farligt avfall.

**S61**

ES: Evítese su liberación al medio ambiente. Recábense instrucciones específicas de la ficha de datos de seguridad.

DA: Undgå udledning til miljøet. Se særlig vejledning/leverandørbrugsanvisning.

DE: Freisetzung in die Umwelt vermeiden. Besondere Anweisungen einholen/Sicherheitsdatenblatt zu Rate ziehen.

EL: Αποφύγετε την ελευθέρωσή του στο περιβάλλον. Αναφερθείτε σε ειδικές οδηγίες/δελτίο δεδομένων ασφαλείας.

EN: Avoid release to the environment. Refer to special instructions/safety data sheets.

FR: Éviter le rejet dans l'environnement. Consulter les instructions spéciales/la fiche de données de sécurité.

IT: Non disperdere nell'ambiente. Riferirsi alle istruzioni speciali/ schede informative in materia di sicurezza.

NL: Voorkom lozing in het milieu. Vraag om speciale instructies/veiligheidskaart.

PT: Evitar a libertação para o ambiente. Obter instruções específicas/fichas de segurança.

FI: Vältettävä päästämistä ympäristöön. Lue erityisohjeet/käyttöturvallisuustiedote.

SV: Undvik utsläpp till miljön. Läs särskilda instruktioner/varuinformationsblad.

**S62**

ES: En caso de ingestión no provocar el vómito: acúdase inmediatamente al médico y muéstresele la etiqueta o el envase.

DA: Ved indtagelse, undgå at fremprovokere opkastning: kontakt omgående læge og vis denne beholder eller etiket.

DE: Bei Verschlucken kein Erbrechen herbeiführen. Sofort ärztlichen Rat einholen und Verpackung oder dieses Etikett vorzeigen.

EL: Σε περίπτωση κατάποσης να μην προκληθεί εμετός: ζητήστε αμέσως ιατρική συμβουλή και δείξτε αυτό το δοχείο ή την ετικέττα του.

EN: If swallowed, do not induce vomiting: seek medical advice immediately and show this container or label.

FR: En cas d'ingestion, ne pas faire vomir. Consulter immédiatement un médecin et lui montrer l'emballage ou l'étiquette.

IT: In caso di ingestione non provocare il vomito: consultare immediatamente il medico e mostrargli il contenitore o l'etichetta.

NL: Bij inslikken niet het braken opwekken; direct een arts raadplegen en de verpakking of het etiket tonen.

PT: Em caso de ingestão, não provocar o vómito. Consultar imediatamente um médico e mostrar-lhe a embalagem ou o rótulo.

FI: Jos kemikaalia on nielty, ei saa oksennuttaa: hakeuduttava välittömästi lääkärin hoitoon ja näytettävä tämä pakkaus tai etiketti.

SV: Vid förtäring, framkalla ej kräkning. Kontakta genast läkare och visa denna förpackning eller etiketten.

**S63**

ES: En caso de accidente por inhalación, alejar a la víctima de la zona contaminada y mantenerla en reposo.

DA: Ved ulykkestilfælde ved indånding bringes tilskadekomne ud i frisk luft og holdes i ro.

DE: Bei Unfall durch Einatmen: Verunfallten an die frische Luft bringen und ruhigstellen.

EL: Σε περίπτωση ατυχήματος λόγω εισπονής: απομακρύνετε το θύμα από το μολυσμένο χώρο και αφήστε το να ηρεμήσει.

EN: In case of accident by inhalation: remove casualty to fresh air and keep at rest.

FR: En cas d'accident par inhalation, transporter la victime hors de la zone contaminée et la garder au repos.

IT: In caso di incidente per inalazione, allontanare l'infortunato dalla zona contaminata e mantenerlo a riposo.

NL: Bij een ongeval door inademing: slachtoffer in de frisse lucht brengen en laten rusten.

PT: Em caso de inalação acidental, remover a vítima da zona contaminada e mantê-la em repouso.

FI: Jos ainetta on onnettomuuden sattuessa hengitetty: siirrä henkilö raittiiseen ilmaan ja pidä hänet levossa.

SV: Vid olycksfall via inandning, flytta den drabbade till frisk luft och låt vila.

**S64**

ES: En caso de ingestión, enjuáguese la boca con agua (solamente si la persona está consciente).

DA: Ved indtagelse, skyl munden med vand (kun hvis personen er ved bevidsthed).

DE: Bei Verschlucken Mund mit Wasser ausspülen (nur wenn Verunfallter bei Bewusstsein ist).

EL: Σε περίπτωση κατάποσης, ξεπλύνετε το στόμα με νερό (μόνο εφόσον το θύμα διατηρεί τις αισθήσεις του).

EN: If swallowed, rinse mouth with water (only if the person is conscious).

FR: En cas d'ingestion, rincer la bouche avec de l'eau (seulement si la personne est consciente).

IT: In caso di ingestione, sciacquare la bocca con acqua (solamente se l'infortunato è cosciente).

NL: Bij inslikken, mond met water spoelen (alleen als de persoon bij bewustzijn is).

PT: Em caso de ingestão, lavar repetidamente a boca com água (apenas se a vítima estiver consciente).

FI: Jos ainetta on nielty, huuhtele suu vedellä (vain jos henkilö on tajuissaan).

SV: Vid förtäring, skölj munnen med vatten (endast om personen är vid medvetande)

Combinación de frases-S

Kombination af S-sætninger

Kombination der S-Sätze

Συνδυασμός των S-φράσεων

Combination of S-phrases

Combinaison des phrases S

Combinazioni delle frasi S

Combinatie van S-zinnen

Combinação das frases S

Yhdistetyt S-lausekkeet

Sammansatta S-fraser

**S1/2**

ES: Consérvese bajo llave y manténgase fuera del alcance de los niños.

DA: Opbevares under lås og utilgængeligt for børn.

DE: Unter Verschluss und für Kinder unzugänglich aufbewahren.

EL: Φυλάξτε το κλειδωμένο και μακρυά από παιδιά.

EN: Keep locked up and out of the reach of children.

FR: Conserver sous clef et hors de portée des enfants.

IT: Conservare sotto chiave e fuori della portata dei bambini.

NL: Achter slot en buiten bereik van kinderen bewaren.

PT: Guardar fechado à chave e fora do alcance das crianças.

FI: Säilytettävä lukitussa tilassa ja lasten ulottumattomissa.

SV: Förvaras i låst utrymme och oåtkomligt för barn.

**S3/7**

ES: Consérvese el recipiente bien cerrado y en lugar fresco.

DA: Emballagen opbevares tæt lukket på et køligt sted.

DE: Behälter dicht geschlossen halten und an einem kühlen Ort aufbewahren.

EL: Διατηρείστε το δοχείο ερμητικά κλεισμένο σε δροσερό μέρος.

EN: Keep container tightly closed in a cool place.

FR: Conserver le récipient bien fermé dans un endroit frais.

IT: Tenere il recipiente ben chiuso in luogo fresco.

NL: Gesloten verpakking op een koele plaats bewaren.

PT: Conservar em recipiente bem fechado em lugar fresco.

FI: Säilytettävä tiiviisti suljettuna viileässä paikassa.

SV: Förpackningen förvaras väl tillsluten och svalt.

**S3/9/14**

ES: Consérvese en lugar fresco y bien ventilado y lejos de … (*materiales incompatibles, a especificar por el fabricante*).

DA: Opbevares køligt, godt ventileret og adskilt fra … (*uforligelige stoffer angives af fabrikanten*).

DE: An einem kühlen, gut gelüfteten Ort, entfernt von … aufbewahren (*die Stoffe, mit denen Kontakt vermieden werden muss, sind vom Hersteller anzugeben*).

EL: Διατηρείται σε δροσερό και καλά αεριζόμενο μέρος μακρυά από … (*ασύμβατα υλικά που υποδεικνύονται από τον παραγωγό*).

EN: Keep in a cool, well-ventilated place away from … (*incompatible materials to be indicated by the manufacturer*).

FR: Conserver dans un endroit frais et bien ventilé à l'écart des … (*matières incompatibles à indiquer par le fabricant*).

IT: Conservare in luogo fresco e ben ventilato lontano da … (*materiali incompatibili da precisare da parte del fabbricante*).

NL: Bewaren op een koele, goed geventileerde plaats verwijderd van … (*stoffen waarmee contact vermeden dient te worden, aan te geven door de fabrikant*).

PT: Conservar em lugar fresco e bem ventilado ao abrigo de … (*matérias incompatíveis a indicar pelo produtor*).

FI: Säilytettävä erillään … (*yhteensopimattomat aineet ilmoittaa valmistaja/maahantuoja) viileässä paikassa, jossa on hyvä ilmanvaihto*.

SV: Förvaras svalt, på väl ventilerad plats åtskilt från … (*oförenliga ämnen anges av tillverkaren*).

**S3/9/14/49**

ES: Consérvese únicamente en el recipiente de origen, en lugar fresco y bien ventilado y lejos de … (*materiales incompatibles, a especificar por el fabricante*).

DA: Må kun opbevares i originalemballagen på et køligt, godt ventileret sted og adskilt fra … (*uforligelige stoffer angives af fabrikanten*).

DE: Nur im Originalbehälter an einem kühlen, gut gelüfteten Ort, entfernt von … aufbewahren (*die Stoffe, mit denen Kontakt vermieden werden muss, sind vom Hersteller anzugeben*).

EL: Διατηρείται μόνο μέσα στο αρχικό δοχείο σε δροσερό και καλά αεριζόμενο μέρος μακρυά από … (*ασύμβατα υλικά που υποδεικνύονται από τον παραγωγό*).

EN: Keep only in the original container in a cool, well-ventilated place away from … (*incompatible materials to be indicated by the manufacturer*).

FR: Conserver uniquement dans le récipient d'origine dans un endroit frais et bien ventilé à l'écart de … (*matières incompatibles à indiquer par le fabricant*).

IT: Conservare soltanto nel contenitore originale in luogo fresco e ben ventilato lontano da … (*materiali incompatibili da precisare da parte del fabbricante*).

NL: Uitsluitend in de oorspronkelijke verpakking bewaren op een koele, goed geventileerde plaats verwijderd van … (*stoffen waarmee contact vermeden dient te worden, aan te geven door de fabrikant*).

PT: Conservar unicamente no recipiente de origem, em lugar fresco e bem ventilado ao abrigo de … (*matérias incompatíveis a indicar pelo produtor*).

FI: Säilytettävä alkuperäispakkauksessa viileässä paikassa, jossa on hyvä ilmanvaihto erillään … (*yhteensopimattomat aineet ilmoittaa valmistaja/maahantuoja*).

SV: Förvaras endast i originalförpackningen på sval, väl ventilerad plats åtskilt från … (*oförenliga ämnen anges av tillverkaren*).

**S3/9/49**

ES: Consérvese únicamente en el recipiente de origen, en lugar fresco y bien ventilado.

DA: Må kun opbevares i originalemballagen på et køligt, godt ventileret sted.

DE: Nur im Originalbehälter an einem kühlen, gut gelüfteten Ort aufbewahren.

EL: Διατηρείται μόνο μέσα στο αρχικό δοχείο σε δροσερό και καλά αεριζόμενο μέρος.

EN: Keep only in the original container in a cool, well-ventilated place.

FR: Conserver uniquement dans le récipient d'origine dans un endroit frais et bien ventilé.

IT: Conservare soltanto nel contenitore originale in luogo fresco e ben ventilato.

NL: Uitsluitend in de oorspronkelijke verpakking bewaren op een koele, goed geventileerde plaats.

PT: Conservar unicamente no recipiente de origem, em lugar fresco e bem ventilado.

FI: Säilytettävä alkuperäispakkauksessa viileässä paikassa, jossa on hyvä ilmanvaihto.

SV: Förvaras endast i originalförpackningen på sval, väl ventilerad plats.

**S3/14**

ES: Consérvese en lugar fresco y lejos de … (*materiales incompatibles, a especificar por el fabricante*).

DA: Opbevares køligt og adskilt fra … (*uforligelige stoffer angives af fabrikanten*).

DE: An einem kühlen, von … entfernten Ort aufbewahren (*die Stoffe, mit denen Kontakt vermieden werden muss, sind vom Hersteller anzugeben*).

EL: Διατηρείται σε δροσερό μέρος μακρυά από … (*ασύμβατα υλικά που υποδεικνύονται από τον παραγωγό*).

EN: Keep in a cool place away from … (*incompatible materials to be indicated by the manufacturer*).

FR: Conserver dans un endroit frais à l'écart des … (*matières incompatibles à indiquer par le fabricant*).

IT: Conservare in luogo fresco lontano da … (*materiali incompatibili da precisare da parte del fabbricante*).

NL: Bewaren op een koele plaats verwijderd van … (*stoffen waarmee contact vermeden dient te worden, aan te geven door de fabrikant*).

PT: Conservar em lugar fresco ao abrigo de … (*matérias incompatíveis a indicar pelo produtor*).

FI: Säilytettävä viileässä erillään … (*yhteensopimattomat aineet ilmoittaa valmistaja/maahantuoja*).

SV: Förvaras svalt och åtskilt från … (*oförenliga ämnen anges av tillverkaren*).

**S7/8**

ES: Manténgase el recipiente bien cerrado y en lugar seco.

DA: Emballagen skal holdes tæt lukket og opbevares tørt.

DE: Behälter trocken und dicht geschlossen halten.

EL: Το δοχείο να διατηρείται ερμητικά κλεισμένο και να προστατεύεται από την υγρασία.

EN: Keep container tightly closed and dry.

FR: Conserver le récipient bien fermé et à l'abri de l'humidité.

IT: Conservare il recipiente ben chiuso e al riparo dall'umidità.

NL: Droog houden en in een goed gesloten verpakking bewaren.

PT: Conservar o recipiente bem fechado e ao abrigo da humidade.

FI: Säilytettävä kuivana ja tiiviisti suljettuna.

SV: Förpackningen förvaras väl tillsluten och torrt.

**S7/9**

ES: Manténgase el recipiente bien cerrado y en lugar bien ventilado.

DA: Emballagen skal holdes tæt lukket og opbevares på et godt ventileret sted.

DE: Behälter dicht geschlossen an einem gut gelüfteten Ort aufbewahren.

EL: Το δοχείο να διατηρείται ερμητικά κλεισμένο και σε καλά αεριζόμενο μέρος.

EN: Keep container tightly closed and in a well-ventilated place.

FR: Conserver le récipient bien fermé et dans un endroit bien ventilé.

IT: Tenere il recipiente ben chiuso e in luogo ben ventilato.

NL: Gesloten verpakking op een goed geventileerde plaats bewaren.

PT: Manter o recipiente bem fechado em local bem ventilado.

FI: Säilytettävä tiiviisti suljettuna paikassa, jossa on hyvä ilmanvaihto.

SV: Förpackningen förvaras väl tillsluten på väl ventilerad plats.

**S7/47**

ES: Manténgase el recipiente bien cerrado y consérvese a una temperatura no superior a … °C (*a especificar por el fabricante*).

DA: Emballagen skal holdes tæt lukket og opbevares ved temperaturer på ikke over … °C (*angives af fabrikanten*).

DE: Behälter dicht geschlossen und nicht bei Temperaturen über … °C aufbewahren (*vom Hersteller anzugeben*).

EL: Διατηρείστε το δοχείο καλά κλεισμένο σε θερμοκρασία που δεν υπερβαίνει τους … °C (*να καθοριστεί από τον παραγωγό*).

EN: Keep container tightly closed and at a temperature not exceeding … °C (*to be specified by the manufacturer*).

FR: Conserver le récipient bien fermé et à une température ne dépassant pas … °C (*à préciser par le fabricant*).

IT: Tenere il recipiente ben chiuso e a temperatura non superiore a … °C (*da precisare da parte del fabbricante*).

NL: Gesloten verpakking bewaren bij een temperatuur beneden … °C (*aan te geven door de fabrikant*).

PT: Manter o recipiente bem fechado e conservar a uma temperatura que não exceda … °C (*a especificar pelo produtor*).

FI: Säilytettävä tiiviisti suljettuna ja alle … °C:n lämpötilassa (*valmistaja/maahantuoja ilmoittaa lämpötilan*).

SV: Förpackningen förvaras väl tillsluten vid en temperatur som inte överstiger … °C (*anges av tillverkaren*).

**S20/21**

ES: No comer, ni beber, ni fumar durante su utilización.

DA: Der må ikke spises, drikkes eller ryges under brugen.

DE: Bei der Arbeit nicht essen, trinken oder rauchen.

EL: Όταν το χρησιμοποιείτε μην τρώτε, μην πίνετε, μην καπνίζετε.

EN: When using do not eat, drink or smoke.

FR: Ne pas manger, ne pas boire et ne pas fumer pendant l'utilisation.

IT: Non mangiare, né bere, né fumare durante l'impiego.

NL: Niet eten, drinken of roken tijdens gebruik.

PT: Não comer, beber ou fumar durante a utilização.

FI: Syöminen, juominen ja tupakointi kielletty kemikaalia käytettäessä.

SV: Ät inte, drick inte eller rök inte under hanteringen.

**S24/25**

ES: Evítese el contacto con los ojos y la piel.

DA: Undgå kontakt med huden og øjnene.

DE: Berührung mit den Augen und der Haut vermeiden.

EL: Αποφεύγετε επαφή με το δέρμα και τα μάτια.

EN: Avoid contact with skin and eyes.

FR: Éviter le contact avec la peau et les yeux.

IT: Evitare il contatto con gli occhi e con la pelle.

NL: Aanraking met de ogen en de huid vermijden.

PT: Evitar o contacto com a pele e os olhos.

FI: Varottava kemikaalin joutumista iholle ja silmiin.

SV: Undvik kontakt med huden och ögonen.

**S27/28**

ES: Después del contacto con la piel, quítese inmediatamente toda la ropa manchada o salpicada y lávese inmediata y abundantemente con … (*productos a especificar por el fabricante*).

DA: Kommer stof på huden, tages tilsmudset tøj straks af og der vaskes med store mængder … (*angives af fabrikanten*).

DE: Bei Berührung mit der Haut beschmutzte, getränkte Kleidung sofort ausziehen und Haut sofort abwaschen mit viel … (*vom Hersteller anzugeben*).

EL: Σε περίπτωση επαφής με το δέρμα, αφαιρέστε αμέσως όλα τα μολυσμένα ρούχα και πλύνετε αμέσως με άφθονο … (*το είδος του υγρού καθορίζεται από τον παραγωγό*).

EN: After contact with skin, take off immediately all contaminated clothing, and wash immediately with plenty of … (*to be specified by the manufacturer*).

FR: Après contact avec la peau, enlever immédiatement tout vêtement souillé ou éclaboussé et se laver immédiatement et abondamment avec … (*produits appropriés à indiquer par le fabricant*).

IT: In caso di contatto con la pelle, togliersi di dosso immediatamente gli indumenti contaminati e lavarsi immediatamente e abbondantemente con … (*prodotti idonei da indicarsi da parte del fabbricante*).

NL: Na contact met de huid, alle besmette kleding onmiddellijk uittrekken en de huid onmiddellijk wassen met veel … (*aan te geven door de fabrikant*).

PT: Em caso de contacto com a pele, retirar imediatamente toda a roupa contaminada e lavar imediata e abundantemente com … (*produto adequado a indicar pelo produtor*).

FI: Ihokosketuksen jälkeen, saastunut vaatetus on riisuttava välittömästi ja roiskeet huuhdeltava välittömästi runsaalla määrällä … (*aineen ilmoittaa valmistaja/maahantuoja*).

SV: Vid kontakt med huden, tag genast av alla nedstänkta kläder och tvätta genast med mycket … (*anges av tillverkaren*).

**S29/35**

ES: No tirar los residuos por el desagüe; elimínense los residuos del producto y sus recipientes con todas las precauciones posibles.

DA: Må ikke tømmes i kloakafløb; materialet og dets beholder skal bortskaffes på en sikker måde.

DE: Nicht in die Kanalisation gelangen lassen; Abfälle und Behälter müssen in gesicherter Weise beseitigt werden.

EL: Μην αδειάζετε το υπόλοιπο τουπεριεχομένου στην αποχέτευση, διαθέστε αυτό το υλικό και τον περιέκτη του κατά ασφαλή τρόπο.

EN: Do not empty into drains; dispose of this material and its container in a safe way.

FR: Ne pas jeter les résidus à l'égout; ne se débarrasser de ce produit et de son récipient qu'en prenant toutes les précautions d'usage.

IT: Non gettare i residui nelle fognature; non disfarsi del prodotto e del recipiente se non con le dovute precauzioni.

NL: Afval niet in de gootsteen werpen; stof en verpakking op veilige wijze afvoeren.

PT: Não deitar os resíduos no esgoto; não eliminar o produto e o seu recipiente sem tomar as precauções de segurança devidas.

FI: Ei saa tyhjentää viemäriin; tämä aine ja sen pakkaus on hävitettävä turvallisesti.

SV: Töm ej i avloppet, oskadliggör produkt och förpackning på säkert sätt.

**S29/56**

ES: No tirar los residuos por el desagüe; elimínese esta sustancia y su recipiente en un punto de recogida pública de residuos especiales o peligrosos.

DA: Må ikke tømmes i kloakafløb, aflever dette materiale og dets beholder til et indsamlingssted for farligt affald og problemaffald.

DE: Nicht in die Kanalisation gelangen lassen; dieses Produkt und seinen Behälter der Problemabfallentsorgung zuführen.

EL: Μην αδειάζετε το υπόλοιπο του περιεχομένου στην αποχέτευση. Το υλικό αυτό και ο περιέκτης του να εναποτεθούν σε δημόσιο χώρο συλλογής επικινδύνων ή ειδικών αποβλήτων.

EN: Do not empty into drains, dispose of this material and its container at hazardous or special waste collection point.

FR: Ne pas jeter les résidus à l'égout, éliminer ce produit et son récipient dans un centre de collecte des déchets dangereux ou spéciaux.

IT: Non gettare i residui nelle fognature; smaltire questo materiale e i relativi contenitori in un punto di raccolta rifiuti pericolosi o speciali.

NL: Afval niet in de gootsteen werpen; deze stof en de verpakking naar een inzamelpunt voor gevaarlijk of bijzonder afval brengen.

PT: Não deitar os resíduos no esgoto; eliminar este produto e o seu recipiente enviando-os para local autorizado para a recolha de resíduos perigosos ou especiais.

FI: Ei saa tyhjentää viemäriin; tämä aine ja sen pakkaus on toimitettava ongelmajätteen vastaanottopaikkaan.

SV: Töm ej i avloppet, lämna detta material och dess behållare till insamlingsställe för farligt avfall.

**S36/37**

ES: Úsense indumentaria y guantes de protección adecuados.

DA: Brug særligt arbejdstøj og egnede beskyttelseshandsker.

DE: Bei der Arbeit geeignete Schutzhandschuhe und Schutzkleidung tragen.

EL: Φοράτε κατάλληλη προστατευτική ενδυμασία και γάντια.

EN: Wear suitable protective clothing and gloves.

FR: Porter un vêtement de protection et des gants appropriés.

IT: Usare indumenti protettivi e guanti adatti.

NL: Draag geschikte handschoenen en beschermende kleding.

PT: Usar vestuário de protecção e luvas adequadas.

FI: Käytettävä sopivaa suojavaatetusta ja suojakäsineitä.

SV: Använd lämpliga skyddskläder och skyddshandskar.

**S36/37/39**

ES: Úsense indumentaria y guantes adecuados y protección para los ojos/la cara.

DA: Brug særligt arbejdstøj, egnede beskyttelseshandsker og -briller/ansigtsskærm.

DE: Bei der Arbeit geeignete Schutzkleidung, Schutzhandschuhe und Schutzbrille/Gesichtsschutz tragen.

EL: Φοράτε κατάλληλη προστατευτική ενδυμασία, γάντια και συσκευή προστασίας ματιών/προσώπου.

EN: Wear suitable protective clothing, gloves and eye/face protection.

FR: Porter un vêtement de protection approprié, des gants et un appareil de protection des yeux/du visage.

IT: Usare indumenti protettivi e guanti adatti e proteggersi gli occhi/la faccia.

NL: Draag geschikte beschermende kleding, handschoenen en een beschermingsmiddel voor de ogen/het gezicht.

PT: Usar vestuário de protecção, luvas e equipamento protector para os olhos/face adequados.

FI: Käytettävä sopivaa suojavaatetusta, suojakäsineitä ja silmien- tai kasvonsuojainta.

SV: Använd lämpliga skyddskläder, skyddshandskar samt skyddsglasögon eller ansiktsskydd.

**S36/39**

ES: Úsense indumentaria adecuada y protección para los ojos/la cara.

DA: Brug særligt arbejdstøj og egnede beskyttelsesbriller/ansigtsskærm.

DE: Bei der Arbeit geeignete Schutzkleidung und Schutzbrille/Gesichtsschutz tragen.

EL: Φοράτε κατάλληλη προστατευτική ενδυμασία και συσκευή προστασίας ματιών/προσώπου.

EN: Wear suitable protective clothing and eye/face protection.

FR: Porter un vêtement de protection approprié et un appareil de protection des yeux/du visage.

IT: Usare indumenti protettivi adatti e proteggersi gli occhi/la faccia.

NL: Draag geschikte beschermende kleding en een beschermingsmiddel voor de ogen/het gezicht.

PT: Usar vestuário de protecção e equipamento protector para os olhos/face adequados.

FI: Käytettävä sopivaa suojavaatetusta ja silmien- tai kasvonsuojainta.

SV: Använd lämpliga skyddskläder samt skyddsglasögon eller ansiktsskydd.

**S37/39**

ES: Úsense guantes adecuados y protección para los ojos/la cara.

DA: Brug egnede beskyttelseshandsker og -briller/ansigtsskærm under arbejdet.

DE: Bei der Arbeit geeignete Schutzhandschuhe und Schutzbrille/Gesichtsschutz tragen.

EL: Φοράτε κατάλληλα γάντια και συσκευή προστασίας ματιών/προσώπου.

EN: Wear suitable gloves and eye/face protection.

FR: Porter des gants appropriés et un appareil de protection des yeux/du visage.

IT: Usare guanti adatti e proteggersi gli occhi/la faccia.

NL: Draag geschikte handschoenen en een beschermingsmiddel voor de ogen/het gezicht.

PT: Usar luvas e equipamento protector para os olhos/face adequados.

FI: Käytettävä sopivia suojakäsineitä ja silmien- tai kasvonsuojainta.

SV: Använd lämpliga skyddshandskar samt skyddsglasögon eller ansiktsskydd.

**S47/49**

ES: Consérvese únicamente en el recipiente de origen y a temperatura no superior a … °C (*a especificar por el fabricante*).

DA: Må kun opbevares i originalemballagen ved en temperatur på ikke over … °C (*angives af fabrikanten*).

DE: Nur im Originalbehälter bei einer Temperatur von nicht über … °C (*vom Hersteller anzugeben) aufbewahren.*

EL: Διατηρείται μόνο μέσα στο αρχικό δοχείο σε θερμοκρασία που δέν υπερβαίνει τους … °C (*καθορίζεται από τον παραγωγό*).

EN: Keep only in the original container at a temperature not exceeding … °C (*to be specified by the manufacturer*).

FR: Conserver uniquement dans le récipient d'origine à une température ne dépassant pas … °C (*à préciser par le fabricant*).

IT: Conservare soltanto nel contenitore originale a temperatura non superiore a … °C (*da precisare da parte del fabbricante*).

NL: Uitsluitend in de oorspronkelijke verpakking bewaren bij een temperatuur beneden … °C (*aan te geven door de fabrikant*).

PT: Conservar unicamente no recipiente de origem a temperatura que não exceda … °C (*a especificar pelo produtor*).

FI: Säilytettävä alkuperäispakkauksessa alle … °C:n lämpötilassa (*valmistaja/maahantuoja ilmoittaa lämpötilan*).

SV: Förvaras endast i originalförpackningen vid en temperatur som inte överstiger … °C (*anges av tillverkaren*).

*ANNEX 5A*

EN: B.13/14. Mutagenicity — reverse mutation test using bacteria.

(Does not concern the ES version)

(Does not concern the DA version)

(Does not concern the DE version)

(Does not concern the EL version)

(Does not concern the FR version)

(Does not concern the IT version)

(Does not concern the NL version)

(Does not concern the PT version)

(Does not concern the FI version)

(Does not concern the SV version)

*ANNEX 5B*

FR: L'administration du témoin positif par une voie différente de celle utilisée pour la substance d'essai est acceptable.

(Does not concern the ES version)

(Does not concern the DA version)

(Does not concern the DE version)

(Does not concern the EL version)

(Does not concern the EN version)

(Does not concern the IT version)

(Does not concern the NL version)

(Does not concern the PT version)

(Does not concern the FI version)

(Does not concern the SV version)

*ANNEX 5C*

$$\text{EN: } t(\text{min}) = \frac{\text{Irradiation dose } (J/cm^2 \times 1\,000)}{\text{Irradiance } (mW/cm^2 \times 60)} \quad (1\ J = 1\ W\ sec)$$

(Does not concern the ES version)

(Does not concern the DA version)

(Does not concern the DE version)

(Does not concern the EL version)

(Does not concern the FR version)

(Does not concern the IT version)

(Does not concern the NL version)

(Does not concern the PT version)

(Does not concern the FI version)

(Does not concern the SV version)

*ANNEX 5D*

## B.26. SUBCHRONIC ORAL TOXICITY TEST

## REPEATED DOSE 90-DAY ORAL TOXICITY STUDY IN RODENTS

### 1. METHOD

This subchronic oral toxicity test method is a replicate of the OECD TG 408 (1998).

### 1.1. INTRODUCTION

In the assessment and evaluation of the toxic characteristics of a chemical, the determination of subchronic oral toxicity using repeated doses may be carried out after initial information on toxicity has been obtained from acute or repeated dose 28-day toxicity tests. The 90-day study provides information on the possible health hazards likely to arise from repeated exposure over a prolonged period of time covering post-weaning maturation and growth well into adulthood. The study will provide information on the major toxic effects, indicate target organs and the possibility of accumulation, and can provide an estimate of a no observed adverse effect level of exposure which can be used in selecting dose levels for chronic studies and for establishing safety criteria for human exposure.

The method places additional emphasis on neurological endpoints and gives an indication of immunological and reproductive effects. The need for careful clinical observations of the animals, so as to obtain as much information as possible, is also stressed. This study should allow for the identification of chemicals with the potential to cause neurotoxic, immunological or reproductive organ effects, which may warrant further in-depth investigation.

See also General Introduction Part B.

### 1.2. DEFINITIONS

**Dose**: is the amount of test substance administered. Dose is expressed as weight (g, mg) or as weight of test substance per unit weight of test animal (e.g. mg/kg), or as constant dietary concentrations (ppm).

**Dosage**: is a general term comprising of dose, its frequency and the duration of dosing.

**NOAEL**: is the abbreviation for no observed adverse effect level and is the highest dose level where no adverse treatment-related findings are observed.

### 1.3. PRINCIPLE OF THE TEST METHOD

The test substance is orally administered daily in graduated doses to several groups of experimental animals, one dose level per group for a period of 90 days. During the period of administration the animals are observed closely for signs of toxicity. Animals which die or are killed during the test are necropsied and, at the conclusion of the test, surviving animals are also killed and necropsied.

### 1.4. DESCRIPTION OF THE TEST METHOD

#### 1.4.1. **Preparations of animals**

Healthy animals, which have been acclimated to laboratory conditions for at least five days and have not been subjected to previous experimental procedures, should be used. The test animals should be characterised as to species, strain, source, sex, weight and/or age. Animals should be randomly assigned to the control and treatment groups. Cages should be arranged in such a way that possible effects due to cage placement are minimised. Each animal should be assigned a unique identification number.

1.4.2. **Preparations of doses**

The test substance is administered by gavage or via the diet or drinking water. The method of oral administration is dependent on the purpose of the study, and the physical/chemical properties of the test material.

Where necessary, the test substance is dissolved or suspended in a suitable vehicle. It is recommended that, wherever possible, the use of an aqueous solution/suspension be considered first, followed by consideration of a solution/emulsion in oil (e.g. corn oil) and then by possible solution in other vehicles. For vehicles other than water the toxic characteristics of the vehicle must be known. The stability of the test substance under the conditions of administration should be determined.

1.4.3. **Test conditions**

1.4.3.1. *Experimental animals*

The preferred species is the rat, although other rodent species, e.g. the mouse, may be used. Commonly used laboratory strains of young healthy adult animals should be employed. The females should be nulliparous and non-pregnant. Dosing should begin as soon as possible after weaning and, in any case, before the animals are nine weeks old. At the commencement of the study the weight variation of animals used should be minimal and not exceed ± 20 % of the mean weight of each sex. Where the study is conducted as a preliminary to a long-term chronic toxicity study, animals from the same strain and source should be used in both studies.

1.4.3.2. *Number and sex*

At least 20 animals (10 female and 10 male) should be used at each dose level. If interim kills are planned, the number should be increased by the number of animals scheduled to be killed before the completion of the study. Based on previous knowledge of the chemical or a close analogue, consideration should be given to including an additional satellite group of 10 animals (five per sex) in the control and in the top dose group for observation, after the treatment period, of reversibility or persistence of any toxic effects. The duration of this post-treatment period should be fixed appropriately with regard to the effects observed.

1.4.3.3. *Dose levels*

At least three dose levels and a concurrent control shall be used, except where a limit test is conducted (see 1.4.3.4). Dose levels may be based on the results of repeated dose or range finding studies and should take into account any existing toxicological and toxicokinetic data available for the test substance or related materials. Unless limited by the physical-chemical nature or biological effects of the test substance, the highest dose level should be chosen with the aim to induce toxicity but not death or severe suffering. A descending sequence of dose levels should be selected with a view to demonstrating any dosage related response and a no observed adverse effect level (NOAEL) at the lowest dose level. Two to four fold intervals are frequently optimal for setting the descending dose levels and addition of a fourth test group is often preferable to using very large intervals (e.g. more than a factor of about 6-10) between dosages.

The control group shall be an untreated group or a vehicle-control group if a vehicle is used in administering the test substance. Except for treatment with the test substance, animals in the control group should be handled in an identical manner to those in the test groups. If a vehicle is used, the control group shall receive the vehicle in the highest volume used. If a test substance is administered in the diet, and causes reduced dietary intake, then a pair-fed control group may be useful in distinguishing between reductions due to palatability or toxicological alterations in the test model.

Consideration should be given to the following characteristics of the vehicle and other additives, as appropriate: effects on the absorption, distribution, metabolism, or retention of the test substance; effects on the chemical properties of the test substance which may alter its toxic characteristics; and effects on the food or water consumption or the nutritional status of the animals.

1.4.3.4. *Limit test*

If a test at one dose level, equivalent to at least 1 000 mg/kg body weight/day, using the procedures described for this study, produces no observed adverse effects and if toxicity would not be expected based upon data from structurally related substances, then a full study using three dose levels may not be considered necessary. The limit test applies except when human exposure indicates the need for a higher dose level to be used.

1.5. PROCEDURE

1.5.1. **Administration of doses**

The animals are dosed with the test substance daily seven days each week for a period of 90 days. Any other dosing regime, e.g. five days per week, needs to be justified. When the test substance is administered by gavage, this should be done in a single dose to the animals using a stomach tube or a suitable intubation cannula. The maximum volume of liquid that can be administered at one time depends on the size of the test animal. The volume should not exceed 1 ml/100 g body weight, except in the case of aqueous solutions where 2 ml/100 g body weight may be used. Except for irritating or corrosive substances which will normally reveal exacerbated effects with higher concentrations, variability in test volume should be minimised by adjusting the concentration to ensure a constant volume at all dose levels.

For substances administered via the diet or drinking water it is important to ensure that the quantities of the test substance involved do not interfere with normal nutrition or water balance. When the test substance is administered in the diet either a constant dietary concentration (ppm) or a constant dose level in terms of the animal's body weight may be used; the alternative used must be specified. For a substance administered by gavage, the dose should be given at similar times each day, and adjusted as necessary to maintain a constant dose level in terms of animal body weight. Where a 90-day study is used as a preliminary to a long-term chronic toxicity study, a similar diet should be used in both studies.

1.5.2. **Observations**

The observation period should be at least 90 days. Animals in a satellite group scheduled for follow-up observations should be kept for an appropriate period without treatment to detect persistence of, or recovery from toxic effects.

General clinical observations should be made at least once a day, preferably at the same time(s) each day, taking into consideration the peak period of anticipated effects after dosing. The clinical condition of the animals should be recorded. At least twice daily, usually at the beginning and end of each day, all animals are inspected for signs of morbidity and mortality.

At least once prior to the first exposure (to allow for within-subject comparisons), and once a week thereafter, detailed clinical observations should be made in all animals. These observations should be made outside the home cage, preferably in a standard arena and at similar times on each occasion. They should be carefully recorded, preferably using scoring systems, explicitly defined by the testing laboratory. Effort should be made to ensure that variations in the observation conditions are minimal. Signs noted should include, but not be limited to, changes in skin, fur, eyes, mucous membranes, occurrence of secretions and excretions and autonomic activity (e.g. lacrimation, pilo-erection, pupil size, unusual respiratory pattern). Changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypes (e.g. excessive grooming, repetitive circling) or bizarre behaviour (e.g. self-mutilation, walking backwards) should also be recorded (1).

Ophthalmological examination, using an ophthalmoscope or equivalent suitable equipment, should be made prior to the administration of the test substance and at the termination of the study, preferably in all animals but at least in the high dose and control groups. If changes in the eyes are detected all animals should be examined.

Towards the end of the exposure period and in any case not earlier than in week 11, sensory reactivity to stimuli of different types (1) (e.g. auditory, visual and proprioceptive stimuli) (2), (3), (4), assessment of grip strength (5) and motor activity assessment (6) should be conducted. Further details of the procedures that could be followed are given in the respective references. However, alternative procedures than those referenced could also be used.

Functional observations conducted towards the end of the study may be omitted when data on functional observations are available from other studies and the daily clinical observations did not reveal any functional deficits.

Exceptionally, functional observations may also be omitted for groups that otherwise reveal signs of toxicity to an extent that would significantly interfere with the functional test performance.

1.5.2.1. *Body weight and food/water consumption*

All animals should be weighed at least once a week. Measurements of food consumption should be made at least weekly. If the test substance is administered via the drinking water, water consumption should also be measured at least weekly. Water consumption may also be considered for dietary or gavage studies during which drinking activity may be altered.

1.5.2.2. *Haematology and clinical biochemistry*

Blood samples should be taken from a named site and stored, if applicable, under appropriate conditions. At the end of the test period, samples are collected just prior to or as part of the procedure for killing the animals.

The following haematological examinations should be made at the end of the test period and when any interim blood samples may have been collected: haematocrit, haemoglobin concentration, erythrocyte count, total and differential leukocyte count, platelet count and a measure of blood clotting time/potential.

Clinical biochemistry determinations to investigate major toxic effects in tissues and, specifically, effects on kidney and liver, should be performed on blood samples obtained from each animal just prior to or as part of the procedure for killing the animals (apart from those found moribund and/or intercurrently killed). In a similar manner to haematological investigations, interim sampling for clinical biochemical tests may be performed. Overnight fasting of the animals prior to blood sampling is recommended ([1]). Determinations in plasma or serum should include sodium, potassium, glucose, total cholesterol, urea, blood urea nitrogen, creatinine, total protein and albumin, and more than two enzymes indicative of hepatocellular effects (such as alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transpeptidase, and sorbitol dehydrogenase). Measurements of additional enzymes (of hepatic or other origin) and bile acids, which may provide useful information under certain circumstances, may also be included.

Optionally, the following urinalysis determinations could be performed during the last week of the study using timed urine volume collection: appearance, volume, osmolality or specific gravity, pH, protein, glucose and blood/blood cells.

In addition, studies to investigate serum markers of general tissue damage should be considered. Other determinations that should be carried out if the known properties of the test substance may, or are suspected to, affect related metabolic profiles include calcium, phosphorus, fasting triglycerides, specific hormones, methaemoglobin and cholinesterase. These need to be identified for chemicals in certain classes or on a case-by-case basis.

Overall, there is a need for a flexible approach, depending on the species and the observed and/or expected effect from a given substance.

If historical baseline data are inadequate, consideration should be given as to whether haematological and clinical biochemistry variables need to be determined before dosing commences; it is generally not recommended that this data be generated before treatment (7).

1.5.2.3. *Gross necropsy*

All animals in the study shall be subjected to a full, detailed gross necropsy which includes careful examination of the external surface of the body, all orifices, and the cranial, thoracic and abdominal cavities and their contents. The liver, kidneys, adrenals, testes, epididymides, uterus, ovaries, thymus, spleen, brain and heart of all animals (apart from those found moribund and/or intercurrently killed) should be trimmed of any adherent tissue, as appropriate, and their wet weight taken as soon as possible after dissection to avoid drying.

([1]) For a number of measurements in serum and plasma, most notably for glucose, overnight fasting would be preferable. The major reason for this preference is that the increased variability which would inevitably result from non-fasting, would tend to mask more subtle effects and make interpretation difficult. On the other hand, however, overnight fasting may interfere with the general metabolism of the animals and, particularly in feeding studies, may disturb the daily exposure to the test substance. If overnight fasting is adopted, clinical biochemical determinations should be performed after the conduct of functional observations of the study.

The following tissues should be preserved in the most appropriate fixation medium for both the type of tissue and the intended subsequent histopathological examination: all gross lesions, brain (representative regions including cerebrum, cerebellum and medulla/pons), spinal cord (at three levels: cervical, mid-thoracic and lumbar), pituitary, thyroid, parathyroid, thymus, oesophagus, salivary glands, stomach, small and large intestines (including Peyer's patches), liver, pancreas, kidneys, adrenals, spleen, heart, trachea and lungs (preserved by inflation with fixative and then immersion), aorta, gonads, uterus, accessory sex organs, female mammary gland, prostate, urinary bladder, gall bladder (mouse), lymph nodes (preferably one lymph node covering the route of administration and another one distant from the route of administration to cover systemic effects), peripheral nerve (sciatic or tibial) preferably in close proximity to the muscle, a section of bone marrow (and/or a fresh bone marrow aspirate), skin and eyes (if changes were observed during ophthalmological examinations). The clinical and other findings may suggest the need to examine additional tissues. Also any organs considered likely to be target organs based on the known properties of the test substance should be preserved.

1.5.2.4. *Histopathology*

Full histopathology should be carried out on the preserved organs and tissues of all animals in the control and high dose groups. These examinations should be extended to animals of all other dosage groups, if treatment-related changes are observed in the high dose group.

All gross lesions should be examined.

When a satellite group is used, histopathology should be performed on tissues and organs identified as showing effects in the treated groups.

## 2. DATA AND REPORTING

### 2.1. DATA

Individual data should be provided. Additionally, all data should be summarised in tabular form showing for each test group the number of animals at the start of the test, the number of animals found dead during the test or killed for humane reasons and the time of any death or humane kill, the number showing signs of toxicity, a description of the signs of toxicity observed, including time of onset, duration, and severity of any toxic effects, the number of animals showing lesions, the type of lesions and the percentage of animals displaying each type of lesion.

When applicable, numerical results should be evaluated by an appropriate and generally acceptable statistical method. The statistical methods and the data to be analysed should be selected during the design of the study.

### 2.2. TEST REPORT

The test report must include the following information:

2.2.1. **Test substance:**

— physical nature, purity and physico-chemical properties,

— identification data,

— vehicle (if appropriate): justification for choice of vehicle, if other than water.

2.2.2. **Test species:**

— species and strain used,

— number, age and sex of animals,

— source, housing conditions, diet etc.,

— individual weights of animals at the start of the test.

2.2.3. **Test conditions:**

— rationale for dose level selection,

— details of test substance formulation/diet preparation, achieved concentration, stability and homogeneity of the preparation,

— details of the administration of the test substance,

— actual doses (mg/kg body weight/day), and conversion factor from diet/drinking water test substance concentration (ppm) to the actual dose, if applicable,

— details of food and water quality.

2.2.4. **Results:**

— body weight and body weight changes,

— food consumption, and water consumption, if applicable,

— toxic response data by sex and dose level, including signs of toxicity,

— nature, severity and duration of clinical observations (whether reversible or not),

— results of ophthalmological examination,

— sensory activity, grip strength and motor activity assessments (when available),

— haematological tests with relevant base-line values,

— clinical biochemistry tests with relevant base-line values,

— terminal body weight, organ weights and organ/body weight ratios,

— necropsy findings,

— a detailed description of all histopathological findings,

— absorption data if available,

— statistical treatment of results, where appropriate;

Discussion of results.

Conclusions.

3. **REFERENCES**

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*ANNEX 5E*

## B.27. SUBCHRONIC ORAL TOXICITY TEST

## REPEATED DOSE 90-DAY ORAL TOXICITY STUDY IN NON-RODENTS

### 1. METHOD

This subchronic oral toxicity test method is a replicate of the OECD TG 409 (1998).

### 1.1. INTRODUCTION

In the assessment and evaluation of the toxic characteristics of a chemical, the determination of subchronic oral toxicity using repeated doses may be carried out after initial information on toxicity has been obtained from acute or repeated dose 28-day toxicity tests. The 90-day study provides information on the possible health hazards likely to arise from repeated exposure over a period of rapid growth and into young adulthood. The study will provide information on the major toxic effects, indicate target organs and the possibility of accumulation, and can provide an estimate of a no observed adverse effect level of exposure which can be used in selecting dose levels for chronic studies and for establishing safety criteria for human exposure.

The test method allows for the identification in non-rodent species of adverse effects of chemical exposure and should only be used:

— where effects observed in other studies indicate a need for clarification/characterisation in a second, non-rodent species, or

— where toxicokinetic studies indicate that the use of a specific non-rodent species is the most relevant choice of laboratory animal, or

— where other specific reasons justify the use of a non-rodent species.

See also General Introduction Part B.

### 1.2. DEFINITIONS

**Dose**: is the amount of test substance administered. Dose is expressed as weight (g, mg) or as weight of test substance per unit weight of test animal (e.g., mg/kg), or as constant dietary concentrations (ppm).

**Dosage**: is a general term comprising of dose, its frequency and the duration of dosing.

**NOAEL**: is the abbreviation for no observed adverse effect level and is the highest dose level where no adverse treatment-related findings are observed.

### 1.3. PRINCIPLE OF THE TEST METHOD

The test substance is orally administered daily in graduated doses to several groups of experimental animals, one dose level per group for a period of 90 days. During the period of administration the animals are observed closely for signs of toxicity. Animals which die or are killed during the test are necropsied and at the conclusion of the test surviving animals are also killed and necropsied.

### 1.4. DESCRIPTION OF THE TEST METHOD

#### 1.4.1. Selection of animal species

The commonly used non-rodent species is the dog, which should be of a defined breed; the beagle is frequently used. Other species, e.g. swine, mini-pigs, may also be used. Primates are not recommended and their use should be justified. Young, healthy animals should be employed, and in the case of the dog, dosing should begin preferably at 4-6 months and not later than nine months of age. Where the study is

conducted as a preliminary to a long-term chronic toxicity study, the same species/breed should be used in both studies.

1.4.2. **Preparation of animals**

Healthy young animals, which have been acclimated to laboratory conditions and have not been subjected to previous experimental procedures, should be used. The duration of acclimatisation will depend upon the selected test species and their source. At least five days for dogs or purpose bred swine from a resident colony and at least two weeks for these animals if from external sources are recommended. The test animals should be characterised as to species, strain, source, sex, weight and/or age. Animals should be randomly assigned to the control and treatment groups. Cages should be arranged in such a way that possible effects due to cage placement are minimised. Each animal should be assigned a unique identification number.

1.4.3. **Preparations of doses**

The test substance may be administered in the diet or in the drinking water, by gavage or in capsules. The method of oral administration is dependent on the purpose of the study, and the physical-chemical properties of the test material.

Where necessary, the test substance is dissolved or suspended in a suitable vehicle. It is recommended that, wherever possible, the use of an aqueous solution/suspension be considered first, followed by consideration of a solution/emulsion in oil (e.g. corn oil) and then by possible solution in other vehicles. For vehicles other than water the toxic characteristics of the vehicle must be known. The stability of the test substance under the conditions of administration should be determined.

1.5. PROCEDURE

1.5.1. **Number and sex of animals**

At least eight animals (four female and four male) should be used at each dose level. If interim kills are planned, the number should be increased by the number of animals scheduled to be killed before the completion of the study. The number of animals at the termination of the study must be adequate for a meaningful evaluation of toxic effects. Based on previous knowledge of the substance or a close analogue, consideration should be given to including an additional satellite group of eight animals (four per sex) in control and in top dose group for observation after the treatment period of reversibility or persistence of any toxic effects. The duration of this post-treatment period should be fixed appropriately with regard to the effects observed.

1.5.2. **Dosage**

At least three dose levels and a concurrent control shall be used, except where a limit test is conducted (see 1.5.3). Dose levels may be based on the results of repeated dose or range finding studies and should take into account any existing toxicological and toxicokinetic data available for the test compound or related materials. Unless limited by the physical-chemical nature or biological effects of the test substance, the highest dose level should be chosen with the aim to induce toxicity but not death or severe suffering. A descending sequence of dose levels should be selected with a view to demonstrating any dosage related response and a no observed adverse effect level (NOAEL) at the lowest dose level. Two- to fourfold intervals are frequently optimal for setting the descending dose levels and addition of a fourth test group is often preferable to using very large intervals (e.g., more than a factor of about 6-10) between dosages.

The control group shall be an untreated group or a vehicle-control group if a vehicle is used in administering the test substance. Except for treatment with the test substance, animals in the control group should be handled in an identical manner to those in the test groups. If a vehicle is used, the control group shall receive the vehicle in the highest volume used. If a test substance is administered in the diet, and causes reduced dietary intake, then a pair-fed control group may be useful in distinguishing between reductions due to palatability or toxicological alterations in the test model.

Consideration should be given to the following characteristics of the vehicle and other additives, as appropriate: effects on the absorption, distribution, metabolism, or retention of the test substance; effects on the chemical properties of the test substance which may alter its toxic characteristics; and effects on the food or water consumption or the nutritional status of the animals.

1.5.3. **Limit test**

If a test at one dose level, equivalent to at least 1 000 mg/kg body weight/day, using the procedures described for this study, produces no observed adverse effects and if toxicity would not be expected based upon data from structurally related substances, then a full study using three dose levels may not be considered necessary. The limit test applies except when human exposure indicates the need for a higher dose level to be used.

1.5.4. **Administration of doses**

The animals are dosed with the test substance daily seven days each week for a period of 90 days. Any other dosing regime, e.g. five days per week, needs to be justified. When the test substance is administered by gavage, this should be done in a single dose to the animals using a stomach tube or a suitable intubation cannula. The maximum volume of liquid that can be administered at one time depends on the size of the test animal. Normally the volume should be kept as low as possible. Except for irritating or corrosive substances which will normally reveal exacerbated effects with higher concentrations, variability in test volume should be minimised by adjusting the concentration to ensure a constant volume at all dose levels.

For substances administered via the diet or drinking water it is important to ensure that the quantities of the test substance involved do not interfere with normal nutrition or water balance. When the test substance is administered in the diet either a constant dietary concentration (ppm) or a constant dose level in terms of the animal's body weight may be used; any alternative used must be specified. For a substance administered by gavage or by capsule, the dose should be given at similar times each day, and adjusted as necessary to maintain a constant dose level in terms of animal body weight. Where the 90-day study is used as a preliminary to a long term chronic toxicity study, a similar diet should be used in both studies.

1.5.5. **Observations**

The observation period should be at least 90 days. Animals in a satellite group scheduled for follow-up observations should be kept for an appropriate period without treatment to detect persistence of, or recovery from toxic effects.

General clinical observations should be made at least once a day, preferably at the same time(s) each day, taking into consideration the peak period of anticipated effects after dosing. The clinical condition of the animals should be recorded. At least twice daily, usually at the beginning and end of each day, all animals should be inspected for signs of morbidity and mortality.

At least once prior to the first exposure (to allow for within-subject comparisons), and once a week thereafter, detailed clinical observations should be made in all animals. These observations should be made, where practical outside the home cage in a standard arena and preferably at similar times on each occasion. Effort should be made to ensure that variations in the observation conditions are minimal. Signs of toxicity should be carefully recorded, including time of onset, degree and duration. Observations should include, but not be limited to, changes in skin, fur, eyes, mucous membranes, occurrence of secretions and excretions and autonomic activity (e.g. lacrimation, pilo-erection, pupil size, unusual respiratory pattern). Changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypes (e.g. excessive grooming, repetitive circling) or any bizarre behaviour should also be recorded.

Ophthalmological examination, using an ophthalmoscope or equivalent suitable equipment, should be made prior to the administration of the test substance and at the termination of the study, preferably in all animals but at least in the high dose and control groups. If treatment related changes in the eyes are detected all animals should be examined.

1.5.5.1. *Body weight and food/water consumption*

All animals should be weighed at least once a week. Measurements of food consumption should be made at least weekly. If the test substance is administered via the drinking water, water consumption should also be measured at least weekly. Water consumption may also be considered for dietary or gavage studies during which drinking activity may be altered.

1.5.5.2. *Haematology and clinical biochemistry*

Blood samples should be taken from a named site and stored, if applicable, under appropriate conditions. At the end of the test period, samples are collected just prior to or as part of the procedure for killing the animals.

Haematology, including haematocrit, haemoglobin concentration, erythrocyte count, total and differential leukocyte count, platelet count and a measure of clotting potential such as clotting time, prothrombin time, or thromboplastin time should be investigated at the start of the study, then either at monthly intervals or midway through the test period and finally at the end of the test period.

Clinical biochemistry determinations to investigate major toxic effects in tissues and, specifically, effects on kidney and liver, should be performed on blood samples obtained from all animals at the start, then either at monthly intervals or midway through the test and finally at the end of the test period. Test areas which should be considered are electrolyte balance, carbohydrate metabolism, and liver and kidney function. The selection of specific tests will be influenced by observations on the mode of action of the test substance. Animals should be fasted for a period appropriate to the species prior to blood sampling. Suggested determinations include calcium, phosphorus, chloride, sodium, potassium, fasting glucose, alanine aminotransferase, aspartate aminotransferase, ornithine decarboxylase, gamma glutamyl transpeptidase, urea nitrogen, albumin, blood creatinine, total bilirubin and total serum protein measurements.

Urinalysis determinations should be performed at least at the start, then midway and finally at the end of the study using timed urine volume collection. Urinalysis determinations include appearance, volume, osmolality or specific gravity, pH, protein, glucose and blood/blood cells. Additional parameters may be employed where necessary to extend the investigation of observed effect(s).

In addition, studies to investigate markers of general tissue damage should be considered. Other determinations which may be necessary for an adequate toxicological evaluation include analyses of lipids, hormones, acid/base balance, methaemoglobin, and cholinesterase inhibition. Additional clinical biochemistry may be employed where necessary to extend the investigation of observed effects. These need to be identified for chemicals in certain classes or on a case-by-case basis.

Overall, there is a need for a flexible approach, depending on the species and the observed and/or expected effect from a given substance.

1.5.5.3. *Gross necropsy*

All animals in the study shall be subjected to a full, detailed gross necropsy which includes careful examination of the external surface of the body, all orifices, and the cranial, thoracic and abdominal cavities and their contents. The liver with gall bladder, kidneys, adrenals, testes, epididymides, ovaries, uterus, thyroid (with parathyroids), thymus, spleen, brain and heart of all animals (apart from those found moribund and/or inter-currently killed) should be trimmed of any adherent tissue, as appropriate, and their wet weight taken as soon as possible after dissection to avoid drying.

The following tissues should be preserved in the most appropriate fixation medium for both the type of tissue and the intended subsequent histopathological examination: all gross lesions, brain (representative regions including cerebrum, cerebellum and medulla/pons), spinal cord (at three levels: cervical, mid-thoracic and lumbar), pituitary, eyes, thyroid, parathyroid, thymus, oesophagus, salivary glands, stomach, small and large intestines (including Peyer's patches), liver, gall bladder, pancreas, kidneys, adrenals, spleen, heart, trachea and lungs, aorta, gonads, uterus, accessory sex organs, female mammary gland, prostate, urinary bladder, lymph nodes (preferably one lymph node covering the route of administration and another one distant from the route of administration to cover systemic effects), peripheral nerve (sciatic or tibial) preferably in close proximity to the muscle, a section of bone marrow

(and/or a fresh bone marrow aspirate) and skin. The clinical and other findings may suggest the need to examine additional tissues. Also any organs considered likely to be target organs based on the known properties of the test substance should be preserved.

1.5.5.4. *Histopathology*

Full histopathology should be carried out on the preserved organs and tissues in at least all animals in control and high dose group. The examination should be extended to animals of all other dosage groups, if treatment-related changes are observed in the high dose group.

All gross lesions should be examined.

When a satellite group is used, histopathology should be performed on tissues and organs identified as showing effects in the treated groups.

## 2. DATA AND REPORTING

### 2.1. DATA

Individual data should be provided. Additionally, all data should be summarised in tabular form showing for each test group the number of animals at the start of the test, the number of animals found dead during the test or killed for humane reasons and the time of any death or humane kill, the number showing signs of toxicity, a description of the signs of toxicity observed, including time of onset, duration, and severity of any toxic effects, the number of animals showing lesions, the type of lesions and the percentage of animals displaying each type of lesion.

When applicable, numerical results should be evaluated by an appropriate and generally acceptable statistical method. The statistical methods and the data to be analysed should be selected during the design of the study.

### 2.2. TEST REPORT

The test report must include the following information:

2.2.1. **Test substance:**

— physical nature, purity and physico-chemical properties,

— identification data.

— vehicle (if appropriate): justification for choice of vehicle, if other than water.

2.2.2. **Test species:**

— species and strain used,

— number, age and sex of animals,

— source, housing conditions, diet etc.,

— individual weights of animals at the start of the test.

2.2.3. **Test conditions:**

— rationale for dose level selection,

— details of test substance formulation/diet preparation, achieved concentration, stability and homogeneity of the preparation,

— details of the administration of the test substance,

— actual doses (mg/kg body weight/day), and conversion factor from diet/drinking water test substance concentration (ppm) to the actual dose, if applicable,

— details of food and water quality.

2.2.4. **Results**

— body weight/body weight changes,

— food consumption, and water consumption, if applicable,

— toxic response data by sex and dose level, including signs of toxicity,

— nature, severity and duration of clinical observations (whether reversible or not),

— ophthalmological examination,

— haematological tests with relevant base-line values,

— clinical biochemistry tests with relevant base-line values,

— terminal body weight, organ weights and organ/body weight ratios,

— necropsy findings,

— a detailed description of all histopathological findings,

— statistical treatment of results, where appropriate.

Discussion of results.

Conclusions.

*ANNEX 5F*

## C.14. FISH JUVENILE GROWTH TEST

### 1. METHOD

This growth toxicity test method is a replicate of the OECD TG 215 (2000).

### 1.1. INTRODUCTION

This test is designed to assess the effects of prolonged exposure to chemicals on the growth of juvenile fish. It is based on a method, developed and ring-tested (1) (3) within the European Union, for assessing the effects of chemicals on the growth of juvenile rainbow trout (*Oncorynchus mykiss*) under flow-through conditions. Other well documented species may be used. For example, experience has been gained from growth tests with zebrafish (*Danio rerio*) (2) (4) (5) and ricefish (medaka, *Oryzias latipes*) (6) (7) (8).

See also General Introduction Part C.

### 1.2. DEFINITIONS

**Lowest observed effect concentration (LOEC)**: is the lowest tested concentration of a test substance at which the substance is observed to have a significant effect (at $p < 0,05$) when compared with the control. However, all test concentrations above the LOEC must have a harmful effect equal to or greater than those observed at the LOEC.

**No observed effect concentration (NOEC)**: is the test concentration immediately below the LOEC.

**$EC_x$**: in this test method is the concentration of the test substance which causes a x % variation in growth rate of the fish when compared with controls.

**Loading rate**: is the wet weight of fish per volume of water.

**Stocking density**: is the number of fish per volume of water.

**Individual fish specific growth rate**: expresses the growth rate of one individual based on its initial weight.

**Tank-average specific growth rate**: expresses the mean growth rate of a tank population at one concentration.

**Pseudo specific growth rate**: expresses the individual growth rate compared to the mean initial weight of the tank population.

### 1.3. PRINCIPLE OF THE TEST METHOD

Juvenile fish in exponential growth phase are placed, after being weighted, in test chambers and are exposed to a range of sublethal concentrations of the test substance dissolved in water preferably under flow-through, or, if not possible, under appropriate semi-static (static-renewal) conditions. The test duration is 28 days. Fish are fed daily. The food ration is based on initial fish weights and may be recalculated after 14 days. At the end of the test, the fish are weighed again. Effects on growth rates are analysed using a regression model in order to estimate the concentration that would cause a x % variation in growth rate, i.e. $EC_x$ (e.g. $EC_{10}$, $EC_{20}$, or $EC_{30}$). Alternatively, the data may be compared with control values in order to determine the lowest observed effect concentration (LOEC) and hence the no observed effect concentration (NOEC).

### 1.4. INFORMATION ON THE TEST SUBSTANCE

Results of an acute toxicity test (see test method C.1) preferably performed with the species chosen for this test, should be available. This implies that the water solubility and the vapour pressure of the test substance are known and a reliable analytical method is available for the quantification of the substance in the test solutions with known and reported accuracy and limit of detection is available.

Useful information includes the structural formula, purity of the substance, stability in water and light, $pK_a$, $P_{ow}$ and results of a test for ready biodegradability (see test method C.4).

1.5. VALIDITY OF THE TEST

For the test to be valid the following conditions apply:

— the mortality in the control(s) must not exceed 10 % at the end of the test,

— the mean weight of fish in the control(s) must have increased enough to permit the detection of the minimum variation of growth rate considered as significant. A ring-test (3) has shown that for rainbow trout the mean weight of fish in the controls must have increased by at least the half (i.e. 50 %) of their mean initial weight over 28 days; e.g. initial weight: 1 g/fish (= 100 %), final weight after 28 days: ≥ 1,5 g/fish (≥ 150 %),

— the dissolved oxygen concentration must have been at least 60 % of the air saturation value (ASV) throughout the test,

— the water temperature must not differ by more than ± 1 °C between test chambers at any one time during the test and should be maintained within a range of 2 °C within the temperature ranges specified for the test species (Appendix 1).

1.6. DESCRIPTION OF THE TEST METHOD

1.6.1. **Apparatus**

Normal laboratory equipment and especially the following:

(a) oxygen and pH meters;

(b) equipment for determination of water hardness and alkalinity;

(c) adequate apparatus for temperature control and preferably continuous monitoring;

(d) tanks made of chemically inert material and of suitable capacity in relation to the recommended loading and stocking density (see section 1.8.5 and Appendix 1);

(e) suitably accurate balance (i.e. accurate to ± 0,5 %).

1.6.2. **Water**

Any water in which the test species shows suitable long-term survival and growth may be used as a test water. It should be of constant quality during the period of the test. The pH of the water should be within the range 6,5 to 8,5, but during a given test it should be within a range of ± 0,5 pH units. Hardness above 140 mg/l (as $CaCO_3$) is recommended. In order to ensure that the dilution water will not unduly influence the test result (for example by complexion of test substance), samples should be taken at intervals for analysis. Measurements of heavy metals (e.g. Cu, Pb, Zn, Hg, Cd and Ni), major anions and cations (e.g. Ca, Mg, Na, K, Cl and $SO_4$), pesticides (e.g. total organophosphorus and total organochlorine pesticides), total organic carbon and suspended solids should be made, for example, every three months where a dilution water is known to be relatively constant in quality. If water quality has been demonstrated to be constant over at least one year, determinations can be less frequent and intervals extended (e.g. every six months). Some chemical characteristics of an acceptable dilution water are listed in Appendix 2.

1.6.3. **Test solutions**

Test solutions of the chosen concentrations are prepared by dilution of a stock solution.

The stock solution should preferably be prepared by simply mixing or agitating the test substance in the diluition water by using mechanical means (e.g. stirring or ultrasonication). Saturation columns (solubility columns) can be used for achieving a suitable concentrated stock solution.

The use of solvents or dispersants (solubilising agents) may be required in some cases in order to produce a suitably concentrated stock solution. Examples of suitable solvents are acetone, ethanol, methanol, dimethylsulfoxide, dimethylformamide and triethyleneglycol. Examples of suitable dispersants are Cremophor

RH40, Tween 80, Methylcellulose 0,01 % and HCO-40. Care should be taken when using readily biodegradable agents (e.g. acetone) and/or highly volatile compounds as these can cause problems with bacterial built-up in flow-through tests. When a solubilising agent is used it must have no significant effects on the fish growth nor visible adverse effects on the juvenile as revealed by a solvent-only control.

For flow-through tests, a system which continually dispenses and dilutes a stock solution of the test substance (e.g. metering pump, proportional diluter, saturator system) is required to deliver a series of concentrations to the test chambers. The flow rates of stock solutions and dilution water should be checked at intervals, preferably daily, during the test and should not vary by more than 10 % throughout the test. A ring-test (3) has shown that, for rainbow trout, a frequency of water removal during the test of 6 litres/g of fish/day is acceptable (see section 1.8.2.2).

For semi-static (renewal) tests, the frequency of medium renewal will depend on the stability of the test substance, but a daily water renewal is recommended. If, from preliminary stability tests (see section 1.4), the test substance concentration is not stable (i.e. outside the range 80-120 % of nominal or falling below 80 % of the measured initial concentration) over the renewal period, consideration should be given to the use of a flow-through test.

1.6.4. **Selection of species**

Rainbow trout (*Oncorhynchus mykiss*) is the recommended species for this test since most experience has been gained from ring-test with this species (1) (3). However, other well documented species can be used but the test procedure may have to be adapted to provide suitable test conditions. For example, experience is also available with zebrafish (*Danio rerio*) (4) (5) and ricefish (medaka, *Oryzias latipes*) (6) (7) (8). The rationale for the selection of the species and the experimental method should be reported in this case.

1.6.5. **Holding of fish**

The test fish shall be selected from a population of a single stock, preferably from the same spawning, which has been held for at least two weeks prior to the test under conditions of water quality and illumination similar to those used in the test. They should be fed a minimum ration of 2 % body weight per day and preferably 4 % body weight per day throughout the holding period and during the test.

Following a 48-hour setting-in period, mortalities are recorded and the following criteria applied:

— mortalities of greater than 10 % of the population in seven days: reject the entire batch,

— mortalities of between 5 % and 10 % of the population: acclimation for seven additional days; if more than 5 % mortality during the second seven days, reject the entire batch,

— mortalities of less than 5 % of the population in seven days: accept the batch.

Fish should not receive treatment for disease in the two weeks preceding the test, or during the test.

1.7. TEST DESIGN

The 'test design' relates to the selection of the number and spacing of the test concentrations, the number of tanks at each concentration level and the number of fish per tank. Ideally, the test design should be chosen with regard to:

(a) the objective of the study;

(b) the method of statistical analysis that will be used;

(c) the availability and cost of experimental resources.

The statement of the objective should, if possible, specify the statistical power at which a given size of difference (e.g. in growth rate) is required to be detected or, alternatively, the precision with which the $EC_x$ (e.g. with x = 10, 20, or 30, and preferably not less than 10) is required to be estimated. Without this, a firm prescription of the size of the study cannot be given.

It is important to recognise that a design which is optimal (makes best use of resources) for use with one method of statistical analysis is not necessarily optimal for another. The recommended design for the estimation of a LOEC/NOEC would not therefore be the same as that recommended for analysis by regression.

In most of cases, regression analysis is preferable to the analysis of variance, for reasons discussed by Stephan and Rogers (9). However, when no suitable regression model is found ($r^2 < 0,9$) NOEC/LOEC should be used.

1.7.1. **Design for analysis by regression**

The important considerations in the design of a test to be analysed by regression are:

(a) the effect concentration (e.g. $EC_{10,20,30}$) and the concentration range over which the effect of the test substance is of interest, should necessarily be spanned by the concentrations included in the test. The precision with which estimates of effect concentrations can be made, will be best when the effect concentration is in the middle of the range of concentrations tested. A preliminary range-finding test may be helpful in selecting appropriate test concentrations;

(b) to enable satisfactory statistical modelling, the test should include at least one control tank and five additional tanks at different concentrations. Where appropriate, when a solubilising agent is used, one control containing the solubilising agent at the highest tested concentration should be run in addition to the test series (see sections 1.8.3 and 1.8.4);

(c) an appropriate geometric series or logarithmic series (10) (see Appendix 3) may be used. Logarithmic spacing of test concentration is to be preferred;

(d) if more than six tanks are available, the additional tanks should either be used to provide replication or distributed across the range of concentrations in order to enable closer spacing of the levels. Either of these measures are equally desirable.

1.7.2. **Design for estimation of a NOEC/LOEC using analysis of variance (ANOVA)**

There should preferably be replicate tanks at each concentration, and statistical analysis should be at the tank level (11). Without replicate tanks, no allowance can be made for variability between tanks beyond that due to individual fish. However, experience has shown (12) that between-tank variability was very small compared with within-tank (i.e. between-fish) variability in the case examined. Therefore a relatively acceptable alternative is to perform statistical analysis at the level of individual fish.

Conventionally, at least five test concentrations in a geometric series with a factor preferably not exceeding 3,2 are used.

Generally, when tests are performed with replicate tanks, the number of replicate control tanks and therefore the number of fish should be the double of the number in each of the test concentrations, which should be of equal size (13) (14) (15). On the opposite, in absence of replicate tanks, the number of fish in the control group should be the same as the number in each test concentration.

If the ANOVA is to be based on tanks rather than individual fish (which would entail either individual marking of the fish or the use of 'pseudo' specific growth rates (see section 2.1.2)), there is a need for enough replication of tanks to enable the standard deviation of 'tanks within concentrations' to be determined. This means that the degrees of freedom for error in the analysis of variance should be at least 5 (11). If only the controls are replicated, there is a danger that the error variability will be biased because it may increase with the mean value of the growth rate in question. Since growth rate is likely to decrease with increasing concentration, this will tend to lead to an overestimate of the variability.

1.8. PROCEDURE

1.8.1. **Selection and weighing of test fish**

It is important to minimise variation in weight of the fish at the beginning of the test. Suitable size ranges for the different species recommended for use in this test are given in Appendix 1. For the whole batch of fish used in the test, the range in individual weights at the start of the test should ideally be kept to within ± 10 %

of the arithmetic mean weight and, in any case, should not exceed 25 %. It is recommended to weight a subsample of fish before the test in order to estimate the mean weigh.

Food should be withheld from the stock population for 24 hours prior to the start of the test. Fish should then be chosen at random. Using a general anaesthetic (e.g. an aqueous solution of 100 mg/l tricaine methane sulphonate (MS 222) neutralised by the addition of two parts of sodium bicarbonate per part of MS 222), fish should be weighted individually as wet weights (blotted dry) to the precision given in Appendix 1. Those fish with weights within the intended range should be retained and then should be randomly distributed between the test vessels. The total wet weight of fish in each test vessel should be recorded. The use of anaesthetics likewise handling of fish (including blotting and weighing) may cause stress and injuries to the juvenile fish, in particular for those species of small size. Therefore handling of juvenile fish must be done with the utmost care to avoid stressing and injuring test animals.

The fish are weighed again on day 28 of the test (see section 1.8.6). However, if it is deemed necessary to recalculate the food ration, fish can be weighed again on day 14 of the test (see section 1.8.2.3). Another method such as the photographic method could be used to determine changes in fish size on the basis of which food rations could be adjusted.

1.8.2. **Conditions of exposure**

1.8.2.1. *Duration*

The test duration is ≥ 28 days.

1.8.2.2. *Loading rates and stocking densities*

It is important that the loading rate and stocking density is appropriate for the test species used (see Appendix 1). If the stocking density is too high, then overcrowding stress will occur leading to reduced growth rates and possibly to disease. If it is too low, territorial behaviour may be induced which could also affect growth. In any case, the loading rate should be low enough in order that a dissolved oxygen concentration of at least 60 % ASV can be maintained without aeration. A ring-test (3) has shown that, for rainbow trout, a loading rate of 16 trouts of 3-5 g in a 40-litre volume is acceptable. Recommended frequency of water removal during the test is 6 litres/g of fish/day.

1.8.2.3. *Feeding*

The fish should be fed with an appropriate food (Appendix 1) at a sufficient rate to induce acceptable growth rate. Care should be taken to avoid microbial growth and water turbidity. For rainbow trout, a rate of 4 % of their body weight per day is likely to satisfy these conditions (3) (16) (17) (18). The daily ration may be divided into two equal portions and given to the fish in two feeds per day, separated by at least five hours. The ration is based on the initial total fish weight for each test vessel. If the fish are weighted again on day 14, the ration is then recalculated. Food should be withheld from the fish 24 hours prior to weighing.

Uneaten food and fecal material should be removed from the test vessels each day by carefully cleaning the bottom of each tank using a suction.

1.8.2.4. *Light and temperature*

The photoperiod and water temperature should be appropriate for the test species (Appendix 1).

1.8.3. **Test concentrations**

Normally five concentrations of the test substance are required, regardless of the test design (see section 1.7.2). Prior knowledge of the toxicity of the test substance (e.g. from an acute test and/or from range-finding studies) should help in selecting appropriate test concentrations. Justification should be given if fewer than five concentrations are used. The highest tested concentration should not exceed the substance solubility limit in water.

Where a solubilising agent is used to assist in stock solution preparation, its final concentration should not be greater than 0,1 ml/l and should preferably be the same in all test vessels (see section 1.6.3). However, every effort should be made to avoid use of such materials.

1.8.4. **Controls**

The number of dilution-water controls depends on the test design (see sections 1.7-1.7.2). If a solubilising agent is used, then the same number of solubilising-agent controls as dilution-water controls should also be included.

1.8.5. **Frequency of analytical determinations and measurements**

During the test, the concentrations of test substance are determined at regular intervals (see below).

In flow-through tests, the flow rates of diluent and toxicant stock solution should be checked at intervals, preferably daily, and should not vary by more than 10 % throughout the test. Where the test substance concentrations are expected to be within ± 20 % of the nominal values (i.e. within the range 80-120 %; see sections 1.6.2 and 1.6.3), it is recommended that, as a minimum, the highest and lowest test concentrations be analysed at the start of the test and at weekly intervals thereafter. For the test where the concentration of the test substance is not expected to remain within ± 20 % of nominal (on the basis of stability data of the test substance), it is necessary to analyse all test concentrations, but following the same regime.

In semi-static (renewal) tests where the concentration of the test substance is expected to remain within ± 20 % of the nominal values, it is recommended that, as a minimum, the highest and lowest test concentrations be analysed when freshly prepared and immediately prior to renewal at the start of the study and weekly thereafter. For tests where the concentration of the test substance is not expected to remain within ± 20 % of nominal, all test concentrations must be analysed following the same regime as for more stable substances.

It is recommended that results be based on measured concentrations. However, if evidence is available to demonstrate that the concentration of the test substance in solution has been satisfactorily maintained within ± 20 % of the nominal or measured initial concentration throughout the test, then the results can be based on nominal or measured values.

Samples may need to be filtered (e.g. using a 0,45 μm pore size) or centrifuged. Centrifugation is the recommended procedure. However, if the test material does not adsorb to filters, filtration may also be acceptable.

During the test, dissolved oxygen, pH and temperature should be measured in all test vessels. Total hardness, alkalinity and salinity (if relevant) should be measured in the controls and one vessel at the highest concentration. As a minimum, dissolved oxygen and salinity (if relevant) should be measured three times (at the beginning, middle and end of the test). In semi-static tests, it is recommended that dissolved oxygen be measured more frequently, preferably before and after each water renewal or at least once a week. The pH should be measured at the beginning and end of each water renewal in static renewal test and at least weekly in flow-through tests. Hardness and alkalinity should be measured once each test. Temperature should preferably be monitored continuously in at least one test vessel.

1.8.6. **Observations**

Weight: at the end of the test all surviving fish must be weighed as wet weights (blotted dry) either in groups by test vessel or individually. Weighing of animals by test vessel is preferred to individual weights which require that fish be individually marked. In the case of the measurement of individual weights for determination of individual fish specific growth rate, the marking technique selected should avoid stressing the animals (alternatives to freeze marking may be appropriate, e.g. the use of coloured fine fishing line).

The fish should be examined daily during the test period and any external abnormalities (such as haemorrhage, discoloration) and abnormal behaviour noted. Any mortalities should be recorded and the dead fish removed as soon as possible. Dead fish are not replaced, the loading rate and stocking density being sufficient to avoid effects on growth through changes in number of fish per tank. However, the feeding rate will need to be adjusted.

## 2. DATA AND REPORTING

### 2.1. TREATMENT OF RESULTS

It is recommended that a statistician be involved in both the design and analysis of the test since this test method allows for considerable variation in experimental design as for example, in the number of test chambers, number of test concentrations, number of fish, etc. In view of the options available in test design, specific guidance on statistical procedure is not given here.

Growth rates should not be calculated for test vessels where the mortality exceeds 10 %. However, mortality rate should be indicated for all test concentrations.

Whichever method is used to analyse the data, the central concept is the specific growth rate r between time $t_1$ and time $t_2$. This can be defined in several ways depending on whether fish are individually marked or not or whether a tank average is required.

$$r_1 = \frac{\log_e w_2 - \log_e w_1}{t_2 - t_1} \times 100$$

$$r_2 = \frac{\overline{\log_e w_2} - \overline{\log_e w_1}}{t_2 - t_1} \times 100$$

$$r_3 = \frac{\log_e w_2 - \overline{\log_e w_1}}{t_2 - t_1} \times 100$$

where,

$r_1$ = individual fish specific growth rate

$r_2$ = tank-average specific growth rate

$r_3$ = 'pseudo' specific growth rate

$w_1$, $w_2$ = weights of a particular fish at times $t_1$ and $t_2$, respectively

$\log_e w_1$ = logarithm of the weight of an individual fish at the start of the study period

$\log_e w_2$ = logarithm of the weight of an individual fish at the end of the study period

$\overline{\log_e w_1}$ = average of the logarithms of the values $w_1$ for the fish in the tank at the start of the study period

$\overline{\log_e w_2}$ = average of the logarithms of the values $w_2$ for the fish in the tank at the end of the study period

$t_1$, $t_2$ = time (days) at start and end of study period

$r_1$, $r_2$, $r_3$ can be calculated for the 0-28 days period and, where appropriate (i.e. when measurement at day 14 has been done) for the 0-14 and 14-28 days periods.

#### 2.1.1. Analysis of results by regression (concentration-response modelling)

This method of analysis fits a suitable mathematical relationship between the specific growth rate and concentration, and hence enables the estimation of the '$EC_x$' i.e. any required EC value. Using this method the calculation of r for individual fish ($r_1$) is not necessary and instead, the analysis can be based on the tank-average value of r ($r_2$). This last method is preferred. It is also more appropriate in case of the use of smallest species.

The tank-average specific growth rates ($r_2$) should be plotted graphically against concentration, in order to inspect the concentration response relationship.

For expressing the relationship between $r_2$ and concentration, an appropriate model should be chosen and its choice must be supported by appropriate reasoning.

If the numbers of fish surviving in each tank are unequal, then the process of model fitting, whether simple or non-linear, should be weighted to allow for unequal sizes of groups.

The method of fitting the model must enable an estimate of, for example, the $EC_{20}$ and of its dispersion (either standard error or confidence interval) to be derived. The graph of the fitted model should be shown in relation to the data so that the adequacy of the fit of the model can be seen (9) (19) (20) (21).

2.1.2. **Analysis of results for the estimation of the LOEC**

If the test has included replication of tanks at all concentration levels, the estimation of the LOEC could be based on an analysis of variance (ANOVA) of the tank-average specific growth rate (see section 2.1), followed by a suitable method (e.g. Dunnett's or Williams' test (13) (14) (15) (22)) of comparing the average r for each concentration with the average r for the controls to identify the lowest concentration for which this difference is significant at a 0,05 probability level. If the required assumptions for parametric methods are not met — non-normal distribution (e.g. Shapiro-Wilk's test) or heterogeneous variance (Bartlett's test), consideration should be given to transforming the data to homogenise variances prior to performing the ANOVA, or to carrying out a weighted ANOVA.

If the test has not included replication of tanks at each concentration, an ANOVA based on tanks will be insensitive or impossible. In this situation, an acceptable compromise is to base the ANOVA on the 'pseudo' specific growth rate $r_3$ for individual fish.

The average $r_3$ for each test concentration may then be compared with the average $r_3$ for the controls. The LOEC can then be identified as before. It must be recognised that this method provides no allowance for, nor protection against, variability between tanks, beyond that which is accounted for by the variability between individual fish. However, experience has shown (9) that between-tank variability was very small compared with within-tank (i.e. between-fish) variability. If individual fish are not included in the analysis, the method of outlier identification and justification for its use must be provided.

2.2. INTERPRETATION OF RESULTS

The results should be interpreted with caution where measured toxicant concentrations in test solutions occur at levels near the detection limit of the analytical method or, in semi static tests, when the concentration of the test substance decreases between freshly prepared solution and before renewal.

2.3. TEST REPORT

The test report must include the following information:

2.3.1. **Test substance:**

— physical nature and relevant physical-chemical properties,

— chemical identification data including purity and analytical method for quantification of the test substance where appropriate.

2.3.2. **Test species**

— scientific name, possibly,

— strain, size, supplier, any pre-treatment, etc.

2.3.3. **Test conditions:**

— test procedure used (e.g. semi-static/renewal, flow-through, loading, stocking density, etc.),

— test design (e.g. number of test vessels, test concentrations and replicates, number of fish per vessel),

— method of preparation of stock solutions and frequency of renewal (the solubilising agent and its concentration must be given, when used),

— the nominal test concentrations, the means of the measured values and their standard deviations in the test vessels and the method by which these were attained and evidence that the measurements refer to the concentrations of the test substance in true solution,

— dilution water characteristics: pH, hardness, alkalinity, temperature, dissolved oxygen concentration, residual chlorine levels (if measured), total organic carbon, suspended solids, salinity of the test medium (if measured) and any other measurements made,

— water quality within test vessels: pH, hardness, temperature and dissolved oxygen concentration,

— detailed information on feeding, (e.g. type of food(s), source, amount given and frequency).

2.3.4. **Results:**

— evidence that controls met the validity criterion for survival, and data on mortalities occurring in any of the test concentrations,

— statistical analytical techniques used, statistics based on replicates or fish, treatment of data and justification of techniques used,

— tabulated data on individual and mean fish weights on days 0, 14 (if measured) and 28 values of tank-average or pseudo specific growth rates (as appropriate) for the periods 0-28 days or possibly 0-14 and 14-28,

— results of the statistical analysis (i.e. regression analysis or ANOVA) preferably in tabular and graphical form and the LOEC ($p = 0,05$) and the NOEC or $EC_x$ with, when possible, standard errors, as appropriate,

— incidence of any unusual reactions by the fish and any visible effects produced by the test substance.

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*APPENDIX 1*

**FISH SPECIES RECOMMENDED FOR TESTING AND SUITABLE TEST CONDITIONS**

| Species | Recommended test temperature range (°C) | Photoperiod (hours) | Recommended range for initial fish weight (g) | Required measurement precision | Loading rate (g/l) | Stocking density (per litre) | Food | Test duration (days) |
|---|---|---|---|---|---|---|---|---|
| **Recommended species:** | | | | | | | | |
| *Oncorhynchus mykiss*<br>Rainbow trout | 12,5-16,0 | 12-16 | 1-5 | To nearest 100 mg | 1,2-2,0 | 4 | Dry propietary salmonid fry food | ≥ 28 |
| **Other well documented species:** | | | | | | | | |
| *Danio rerio*<br>Zebrafish | 21-25 | 12-16 | 0,050-0,100 | To nearest 1 mg | 0,2-1,0 | 5-10 | Live food<br>(*Brachionus Artemia*) | ≥ 28 |
| *Oryzias latipes*<br>Ricefish (Medaka) | 21-25 | 12-16 | 0,050-0,100 | To nearest 1 mg | 0,2-1,0 | 5-20 | Live food<br>(*Brachionus Artemia*) | ≥ 28 |

*APPENDIX 2*

**SOME CHEMICAL CHARACTERISTICS OF AN ACCEPTABLE DILUTION WATER**

| Substance | Concentrations |
|---|---|
| Particulate matter | < 20 mg/l |
| Total organic carbon | < 2 mg/l |
| Unionised ammonia | < 1 µg/l |
| Residual chlorine | < 10 µg/l |
| Total organophosphorus pesticides | < 50 ng/l |
| Total organochlorine pesticides plus polychlorinated biphenyls | < 50 ng/l |
| Total organic chlorine | < 25 ng/l |

*APPENDIX 3*

**LOGARITHMIC SERIES OF CONCENTRATIONS SUITABLE FOR TOXICITY TEST** (9)

| Column (number of concentrations between 100 and 10, or between 10 and 1) ([1]) | | | | | | |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 32 | 46 | 56 | 63 | 68 | 72 | 75 |
| 10 | 22 | 32 | 40 | 46 | 52 | 56 |
| 3,2 | 10 | 18 | 25 | 32 | 37 | 42 |
| 1,0 | 4,6 | 10 | 16 | 22 | 27 | 32 |
| | 2,2 | 5,6 | 10 | 15 | 19 | 24 |
| | 1,0 | 3,2 | 6,3 | 10 | 14 | 18 |
| | | 1,8 | 4,0 | 6,8 | 10 | 13 |
| | | 1,0 | 2,5 | 4,6 | 7,2 | 10 |
| | | | 1,6 | 3,2 | 5,2 | 7,5 |
| | | | 1,0 | 2,2 | 3,7 | 5,6 |
| | | | | 1,5 | 2,7 | 4,2 |
| | | | | 1,0 | 1,9 | 3,2 |
| | | | | | 1,4 | 2,4 |
| | | | | | 1,0 | 1,8 |
| | | | | | | 1,3 |
| | | | | | | 1,0 |

([1]) A series of five (or more) successive concentrations may be chosen from a column. Mid-points between concentrations in column (x) are found in column (2x + 1). The values listed can represent concentrations expressed as percentage per volume or weight (mg/l or µg/l). Values can be multiplied or divided by any power of 10 as appropriate. Column 1 might be used if there was considerable uncertainty on the toxicity level.

## C.15. FISH, SHORT-TERM TOXICITY TEST ON EMBRYO AND SAC-FRY STAGES

### 1. METHOD

This short-term toxicity test method is a replicate of the OECD TG 212 (1998).

#### 1.1. INTRODUCTION

This short-term toxicity test on fish embryo and sac-fry stages is a short-term test in which the life stages from the newly fertilised egg to the end of the sac-fry stage are exposed. No feeding is provided in the embryo and sac-fry test, and the test should thus be terminated while the sac-fry are still nourished from the yolk sac.

The test is intended to define lethal, and to a limited extent, sublethal effects of chemicals on the specific stages and species tested. This test would provide useful information in that it could (a) form a bridge between lethal and sublethal tests, (b) be used as a screening test for either a full early life stage test or for chronic toxicity tests and (c) be used for testing species where husbandry techniques are not sufficiently advanced to cover the period of change from endogenous to exogenous feeding.

It should be borne in mind that only tests incorporating all stages of the life-cycle of fish are generally liable to give an accurate estimate of the chronic toxicity of chemicals to fish, and that any reduced exposure with respect to life stages may reduce the sensitivity and thus underestimate the chronic toxicity. It is therefore expected that the embryo and sac-fry test would be less sensitive than a full early life stage test, particularly with respect to chemicals with high lipophilicity (log $P_{ow}$ > 4) and chemicals with a specific mode of toxic action. However smaller differences in sensitivity between the two tests would be expected for chemicals with a non-specific, narcotic mode of action (1).

Prior to the publication of this test, most experience with this embryo and sac-fry test has been with the freshwater fish *Danio rerio* Hamilton-Buchanan (Teleostei, Cyprinidae — common name zebrafish). More detailed guidance on test performance for this species is therefore given in Appendix 1. This does not preclude the use of other species for which experience is also available (Tables IA and IB).

#### 1.2. DEFINITIONS

**Lowest observed effect concentration (LOEC)**: is the lowest tested concentration of a test substance at which the substance is observed to have a significant effect (at $p < 0,05$) when compared with the control. However, all test concentrations above the LOEC must have a harmful effect equal to or greater than those observed at the LOEC.

**No observed effect concentration (NOEC)**: is the test concentration immediately below the LOEC.

#### 1.3. PRINCIPLE OF THE TEST

The embryo and sac-fry stages of fish are exposed to a range of concentrations of the test substance dissolved in water. Within the protocol a choice is possible between a semi-static and a flow-through procedure. The choice depends on the nature of the test substance. The test is begun by placing fertilised eggs in the test chambers and is terminated just before the yolk sac of any larvae in any of the test chambers has been completely absorbed or before mortalities by starvation start in controls. Lethal and sub-lethal effects are assessed and compared with control values to determine the lowest observed effect concentration and hence the no observed effect concentration. Alternatively, they may be analysed using a regression model in order to estimate the concentration that would cause a given percentage effect (i.e. $LC/EC_x$, where x is a defined % effect).

#### 1.4. INFORMATION ON THE TEST SUBSTANCE

Results of an acute toxicity test (see method C.1) preferably performed with the species chosen for this test, should be available. The results may be useful in selecting an appropiate range of test concentrations in the early life stages test. Water solubility (including solubility in the test water) and the vapour pressure of the test substance should be known. A reliable analytical method for the quantification of the substance in the test solutions with known and reported accuracy and limit of detection should be available.

Information on the test substance which is useful in establishing the test conditions includes the structural formula, purity of the substance, stability in light, stability under the conditions of the test, pKa, $P_{ow}$ and results of a test for ready biodegradability (see method C.4).

1.5. VALIDITY OF THE TEST

For a test to be valid, the following conditions apply:

— overall survival of fertilised eggs in the controls and where relevant, in the solvent-only vessels must be greater than or equal to the limits defined in Appendices 2 and 3,

— the dissolved oxygen concentration must be between 60 and 100 % of the air saturation value (ASV) throughout the test,

— the water temperature must not differ by more than ± 1,5 °C between test chambers or between successive days at any time during the test and should be within the temperature ranges specified for the test species (Appendices 2 and 3).

1.6. DESCRIPTION OF THE TEST METHOD

1.6.1. **Test chambers**

Any glass or other chemically inert vessels can be used. The dimensions of the vessels should be large enough to allow compliance with the loading rate (see section 1.7.1.2). It is recommended that test chambers be randomly positioned in the test area. A randomised block design with each treatment being present in each block is preferable to a completely randomised design when there are systematic effects in the laboratory that can be controlled using blocking. Blocking, if used, should be taken account of in the subsequent data analysis. The test chambers should be shielded from unwanted disturbance.

1.6.2. **Selection of fish species**

Recommended fish species are given in Table 1A. This does not preclude the use of other species (examples are given in Table 1B), but the test procedure may have to be adapted to provide suitable test conditions. The rationale for the selection of the species and the experimental method should be reported in this case.

1.6.3. **Holding of the brood fish**

Details on holding the brood stock under satisfactory conditions may be found in OECD TG 210 ([1]) and in references (2) (3) (4) (5) (6).

1.6.4. **Handling of embryos and larvae**

Embryos and larvae may be exposed, within the main vessel, in smaller vessels fitted with mesh sides or ends to permit a flow of test solution through the vessel. Non-turbulent flow through these small vessels may be induced by suspending them from an arm arranged to move the vessel up and down but always keeping the organisms submerged; a siphon-flush system can also be used. Fertilised eggs of salmonid fishes can be supported on racks or meshes with apertures sufficiently large to allow larvae to drop through after hatching. The use of pasteur pipettes is appropriate to remove the embryos and larvaes in the semi-static tests with complete daily renewal (see paragraph 1.6.6).

Where egg containers, grids or meshes have been used to hold eggs within the main test vessel, these restraints should be removed after the larvae hatch ([1]), except that meshes should be retained to prevent the escape of the fish. If there is a need to transfer the larvae, they should not be exposed to the air and nets should not be used to release fish from egg containers (such a caution may not be necessary for some less fragile species, e.g. the carp). The timing of this transfer varies with the species and transfer may not always be necessary. For the semi-static technique, beakers or shallow containers may be used, and, if necessary, equipped with a mesh screen slightly elevated above the bottom of the beaker. If the volume of these containers is sufficient to comply with loading requirements, (see 1.7.1.2) no transfer of embryo or larvae may be necessary.

([1]) OECD, Paris, 1992, Test Guideline 210, Fish, Early-life Stage Toxicity Test.

1.6.5. **Water**

Any water which conforms to the chemical characteristics of an acceptable dilution water as listed in Appendix 4 and in which the test species shows control survival at least as good as that described in Appendices 2 and 3 is suitable as a test water. It should be of constant quality during the period of the test. The pH should remain within a range of ± 0,5 pH units. In order to ensure that the dilution water will not unduly influence the test result (for example by complexation of test substance), or adversely affect the performance of the brood stock, samples should be taken at intervals for analysis. Measurements of heavy metals (e.g. Cu, Pb, Zn, Hg, Cd and Ni), major anions and cations (e.g. Ca, Mg, Na, K, Cl and $SO_4$), pesticides (e.g. total organophosphorus and total organochlorine pesticides), total organic carbon and suspended solids should be made, for example, every three months, where a dilution water is known to be relatively constant in quality. If water quality has been demonstrated to be constant over at least one year, determinations can be less frequent and intervals extended (e.g. every six months).

1.6.6. **Test solutions**

Test solutions of the chosen concentrations are prepared by dilution of a stock solution.

The stock solution should preferably be prepared by simply mixing or agitating the test substance in the dilution water by using mechanical means (e.g. stirring and ultrasonication). Saturation colums (solubility columns) can be used for achieving a suitable concentrated stock solution. As far as possible, the use of solvents or dispersants (solubilising agents) should be avoided; however, such coupounds may be required in some cases in order to produced a suitably concentrated stock solution. Examples of suitable solvents are acetone, ethanol, methanol, dimethylformamide and triethyleneglycol. Examples of suitable dispersants are Cremophor RH40, Tween 80, methylcellulose 0,01 % and HCO-40. Care should be taken when using readily biodegradable agents (e.g. acetone) and/or highly volatile as these can cause problems with bacterial built-up in flow-through tests. When a solubilising agent is used it must have no significant effect on survival nor visible adverse effect on the early-life stages as revealed by a solvent-only control. However, every effort should be made to avoid the use of such materials.

For the semi-static technique, two different renewal procedures may be followed; either (i) new test solutions are prepared in clean vessels and surviving eggs and larvae gently transferred into the new vessels in a small volume of old solution, avoiding exposure to air, or (ii) the test organisms are retained in the vessels whilst a proportion (at least three quarters) of the test water is changed. The frequency of medium renewal will depend on the stability of the test substance, but a daily water renewal is recommended. If, from preliminary stability tests (see section 1.4), the test substance concentration is not stable (i.e.outside the range 80-120 % of nominal or falling below 80 % of the measured initial concentration) over the renewal period, consideration should be given to the use of a flow-through test. In any case, care should be taken to avoid stressing the larvae during the water renewal operation.

For flow-through tests, a system which continually dispenses and dilutes a stock solution of the test substance (e.g. metering pump, proportional diluter, saturator system) is required to deliver a series of concentrations to the test chambers. The flow rates of stock solutions and dilution water should be checked at intervals, preferably daily, and should not vary by more than 10 % throughout the test. A flow rate equivalent to at least five test chamber volumes per 24 hours has been found suitable (2).

1.7. PROCEDURE

Useful information on the performance of fish embryo and sac-fry toxicity tests is available in the literature, some examples of which are included in the literature section of this text (7) (8) (9).

1.7.1. **Conditions of exposure**

1.7.1.1. *Duration*

The test should start preferably within 30 minutes after the eggs have been fertilised. The embryos are immersed in the test solution before, or as soon as possible after, commencement of the blastodisc cleavage stage and in any case before the onset of the gastrula stage. For eggs obtained from commercial supplier, it may not be possible to start the test immediately after fertilisation. As the sensitivity of the test may be seriously influenced by delaying the start of the test, the test should be initiated within eight hours after fertilisation. As larvae are not fed during the exposure period, the test should be terminated just before the

yolk sac of any larvae in any of the test chambers has been completely absorbed or before mortalities by starvation start in controls. The duration will depend upon the species used. Some recommended durations are given in Appendices 2 and 3.

1.7.1.2. *Loading*

The number of fertilised eggs at the start of the test should be sufficient to meet statistical requirements. They should be randomly distributed among treatments, and at least 30 fertilised eggs, divided equally (or as equally as possible since it can be difficult to obtain equal batches when using some species) between at least three replicate test chambers, should be used per concentration. The loading rate (biomass per volume of test solution) should be low enough in order that a dissolved oxygen concentration of at least 60 % ASV can be maintained without aeration. For flow-through tests, a loading rate not exceeding 0,5 g/l per 24 hours and not exceeding 5 g/l of solution at any time has bean recommended (2).

1.7.1.3. *Light and temperature*

The photoperiod and test water temperature should be appropriate for the test species (Appendices 2 and 3). For the purpose of temperature monitoring, it may be appropriate to use an additional test vessel.

1.7.2. **Test concentrations**

Normally, five concentrations of the test substance spaced by a constant factor not exceeding 3,2 are required. The curve relating $LC_{50}$ to period of exposure in the acute study should be considered when selecting the range of test concentrations. The use of fewer than five concentrations, for example in limit tests, and a narrower concentration interval may be appropriate in some circumstances. Justification should be provided if fewer than five concentrations are used. Concentrations of the substance higher than the 96 hour $LC_{50}$ or 100 mg/l, whichever is the lower, need not be tested. Substances should not be tested above their solubility limit in in the test water.

When a solubilising agent is used to aid preparation of test solutions (see section 1.6.6), its final concentration in the test vessels should not be greater than 0,1 ml/l and should be the same in all test vessels.

1.7.3. **Controls**

One dilution-water control (replicated as appropriate) and also, if relevant, one control containing the solubilising-agent (replicated as appropriate) should be run in addition to the test series.

1.7.4. **Frequency of analytical determinations and measurements**

During the test, the concentrations of the test substance are determined at regular intervals.

In semi-static tests where the concentration of the test substance is expected to remain within ± 20 % of the nominal (i.e. within the range 80-120 %; see section 1.4 and 1.6.6), it is recommended that, as a minimum, the highest and lowest test concentrations be analysed when freshly prepared and immediately prior to renewal on at least three occasions spaced evenly over the test (i.e. analyses should be made on a sample from the same solution — when freshly prepared and at renewal).

For tests where the concentration of the test substance is not expected to remain within ± 20 % of nominal (on the basis of stability data of the substance), it is necessary to analyse all test concentrations, when freshly prepared and at renewal, but following the same regime (i.e. on at least three occasions spaced evenly over the test). Determination of test substance concentrations prior to renewal need only be performed on one replicate vessel at each test concentration. Determinations should be made no more than seven days apart. It is recommended that results be based on measured concentrations. However, if evidence is available to demonstrate that the concentration of the test substance in solution has been satisfactorily maintained within ± 20 % of the nominal or measured initial concentration throughout the test, then results can be based on nominal or measured initial values.

For flow-through tests, a similar sampling regime to that described for semi-static tests is appropriate (but measurement of 'old' solutions is not applicable in this case). However, if the test duration is more than seven days, it may be advisable to increase the number of sampling occasions during the first week (e.g. three sets of measurements) to ensure that the test concentrations are remaining stable.

Samples may need to be centrifuged or filtered (e.g. using a 0,45 μm pore size). However, since neither centrifuging nor filtration appears always to separate the non-bioavailable fraction of the test substance from that which is bioavailable, samples may not be subjected to those treatments.

During the test, dissolved oxygen, pH and temperature should be measured in all test vessels. Total hardness and salinity (if relevant) should be measured in the controls and one vessel at the highest concentration. As a minimum, dissolved oxygen and salinity (if relevant) should be measured three times (at the beginning, middle and end of the test). In semi-static tests, it is recommended that dissolved oxygen be measured more frequently, preferably before and after each water renewal or at least once at week. The pH should be measured at the beginning and end of each water renewal in semi-static test and at least weekly in flow-through tests. Hardness should be measured once each test. Temperature should be measured daily and it should preferably be monitored continuously in at least one test vessel.

1.7.5. **Observations**

1.7.5.1. *Stage of embryonic development*

The embryonic stage (i.e. gastrula stage) at the beginning of exposure to the test substance should be verified as precisely as possible. This can be done using a representative sample of eggs suitably preserved and cleared. The literature may also be consulted for the description and illustration of embryonic stages (2) (5) (10) (11).

1.7.5.2. *Hatching and survival*

Observations on hatching and survival should be made at least once daily and numbers recorded. It may be desirable to make more frequent observations at the beginning of the test (e.g. each 30 minutes during the first three hours), since in some cases, survival times can be more relevant than only the number of deaths (e.g. when there are acute toxic effects). Dead embryos and larvae should be removed as soon as observed since they can decompose rapidly. Extreme care should be taken when removing dead individuals not to knock or physically damage adjacent eggs/larvae, these being extremely delicate and sensitive. Criteria for death vary according to life stage:

— **for eggs**: particularly in the early stages, a marked loss of translucency and change in colouration, caused by coagulation and/or precipitation of protein, leading to a white opaque appearance,

— **for embryos**: absence of body movement and/or absence of heartbeat and/or opaque discoloration in species whose embryos are normally translucent,

— **for larvae**: immobility and/or absence of respiratory movement and/or absence of heartbeat and/or white opaque colouration of central nervous system and/or lack of reaction mechanical stimulus.

1.7.5.3. *Abnormal appearance*

The number of larvae showing abnormality of body form and/or pigmentation, and the stage of yolk-sac absorption, should be recorded at adequate intervals depending on the duration of the test and the nature of the abnormality described. It should be noted that abnormal embryos and larvae occur naturally and can be of the order of several per cent in the control(s) in some species. Abnormal animals should only be removed from the test vessels on death.

1.7.5.4. *Abnormal behaviour*

Abnormalities, e.g. hyperventilation, uncoordinated swimming, and atypical quiescence should be recorded at adequate intervals depending on the duration of the test. These effects, although difficult to quantify, can, when observed, aid in the interpretation of mortality data i.e. provide information on the mode of toxic action of the substance.

1.7.5.5. *Length*

At the end of the test, measurement of individual lengths is recommended; standard, fork or total length may be used. If however, caudal fin rot or fin erosion occurs, standard lengths should be used. Generally, in a well-run test, the coefficient of variation for length among replicates in the controls should be ≤ 20 %.

1.7.5.6. *Weight*

At the end of the test, individual weights can be measured; dry weights (24 hours at 60 °C) are preferable to wet weights (blotted dry). Generally, in a well-run test, the coefficient of variation for weight among replicates in the controls should be ≤ 20 %.

These observations will result in some or all of the following data being available for statistical analysis:

— cumulative mortality,

— numbers of healthy larvae at end of test,

— time to start of hatching and end of hatching (i.e. 90 % hatching in each replicate),

— numbers of larvae hatching each day,

— length (and weight) of surviving animals at end of the test,

— numbers of larvae that are deformed or of abnormal appearance,

— numbers of larvae exhibiting abnormal behaviour.

## 2. DATA AND REPORTING

### 2.1. TREATMENT OF RESULTS

It is recommended that a statistician be involved in both the design and analysis of the test since the method allows for considerable variation in experimental design as, for example, in the number of test chambers, number of test concentrations, starting number of fertilised eggs and in the parameters measured. In view of the options available in test design, specific guidance on statistical procedures is not given here.

If LOEC/NOECs are to be estimated, it will be necessary for variations to be analysed within each set of replicates using analysis of variance (ANOVA) or contingency table procedures. In order to make a multiple comparison between the results at the individual concentrations and those for the controls, Dunnett's method may be found useful (12) (13). Other useful examples are also available (14) (15). The size of the effect detectable using ANOVA or other procedures (i.e. the power of the test) should be calculated and reported. It should be noted that not all the observations listed in section 1.7.5.6 are suitable for statistical analysis using ANOVA. For example, cumulative mortality and numbers of healthy larvae at the end of the test could be analysed using probit methods.

If $LC/EC_x$s are to be estimated, (a) suitable curve(s), such as the logistic curve, should be fitted to the data of interest using a statistical method such as least squares or non-linear least squares. The curve(s) should be parameterised so that the $LC/EC_x$ of interest and its standard error can be estimated directly. This will greatly ease the calculation of the confidence limits around the $LC/EC_x$. Unless there are good reasons to prefer different confidence levels, two-sided 95 % confidence should be quoted. The fitting procedure should preferably provide a means for assessing the significance of the lack of fit. Graphical methods for fitting curves can be used. Regression analysis is suitable for all observations listed in section 1.7.5.6.

### 2.2. INTERPRETATION OF RESULTS

The results should be interpreted with caution where measured toxicant concentrations in test solutions occur at levels near the detection limit of the analytical method. The interpretation of results for concentrations above the water solubility of the substance should also be made with care.

### 2.3. TEST REPORT

The test report must include the following information:

2.3.1. **Test substance:**

— physical nature and relevant physical-chemical properties,

— chemical identification data, including purity and analytical method for quantification of the tests substance where appropriate.

2.3.2. **Test species:**

— scientific name, strain, numbers of parental fish (i.e. how many females were used for providing the required numbers of eggs in the test), source and method of collection of the fertilised eggs and subsequent handling.

2.3.3. **Test conditions:**

— test procedure used (e.g. semi-static or flow-through, time period from fertilisation to start the test, loading, etc),

— photoperiod(s),

— test design (e.g. number of test chambers and replicates, number of embryos per replicate),

— method of preparation of stock solutions and frequency of renewal (the solubilising agent and its concentration must be given, when used),

— the nominal test concentrations, the measured values, their means and their standard deviations in the test vessels and the method by which these were attained and, if the test substance is soluble in water at concentrations below those tested, evidence should be provided that the measurements refer to the concentrations of the test substance in solution,

— dilution water characteristics: pH, hardness, temperature, dissolved oxygen concentration, residual chlorine levels (if measured), total organic carbon, suspended solids, salinity of the test medium (if measured) and any other measurements made,

— water quality within test vessels: pH, hardness, temperature and dissolved oxygen concentration.

2.3.4. **Results:**

— results from any preliminary studies on the stability of the test substance,

— evidence that controls met the overall survival acceptability standard of the test species (Appendices 2 and 3),

— data on mortality/survival at embryo and larval stages and overall mortality/survival,

— days to hatch and numbers hatched,

— data for length (and weight),

— incidence and description of morphological abnormalities, if any,

— incidence and description of behavioural effects, if any,

— statistical analysis and treatment of data,

— for tests analysed using ANOVA, the lowest observed effect concentration (LOEC) at $p = 0,05$ and the no observed effect concentration (NOEC) for each response assessed, including a description of the statistical procedures used and an indication of what size of effect could be detected,

— for tests analysed using regression techniques, the $LC/EC_x$ and confidence intervals and a graph of the fitted model used for its calculation,

— explanation for any deviation from this testing method.

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TABLE 1A: Fish species recommended for testing

| Freshwater |
|---|
| *Oncorhynchus mykiss*<br>Rainbow trout (9) (16) |
| *Danio rerio*<br>Zebrafish (7) (17) (18) |
| *Cyprinus caprio*<br>Common carp (8) (19) |
| *Oryzias latipes*<br>Japanese ricefish/Medaka (20) (21) |
| *Pimephales promelas*<br>Fathead minnow (8) (22) |

TABLE 1B: Examples of other well-documented species which have also been used

| Freshwater | Saltwater |
|---|---|
| *Carassius auratus*<br>Goldfish (8) | *Menidia peninsulae*<br>Tidewater silverside (23) (24) (25) |
| *Lepomis macrochirus*<br>Bluegill (8) | *Clupea harengus*<br>Herring (24) (25) |
| | *Gadus morhua*<br>Cod (24) (25) |
| | *Cyprinodon variegatus*<br>Sheepshead minnow (23) (24) (25) |

*APPENDIX 1*

## GUIDANCE ON PERFORMANCE OF A TOXICITY TEST ON EMBRYOS AND SAC-FRY OF ZEBRAFISH *(BRACHYDANIO RERIO)*

### INTRODUCTION

The zebrafish originates from the Coromandel coast of India where it inhabits fast-flowing streams. It is a common aquarium fish of the carp family, and information about procedures for its care and culture can be found in standard reference books on tropical fish. Its biology and use in fishery research have been reviewed by Laale (1).

The fish rarely exceeds 45 mm in length. The body is cylindrical with 7-9 dark-blue horizontal silvery stripes. These stripes run into the caudal and anal fins. The back is olive-green. Males are slimmer than females. Females are more silvery and the abdomen is distended, particularly prior to spawning.

Adult fishes are able to tolerate large fluctuations in temperature, pH and hardness. However, in order to get healthy fish which produce eggs of good quality, optimal conditions should be provided.

During spawning the male pursues and butts the female, and as the eggs are expelled they are fertilised. The eggs, which are transparent and non-adhesive, fall to the bottom where they may be eaten by the parents. Spawning is influenced by light. If the morning light is adequate, the fish usually spawns in the early hours following daybreak.

A female can produce batches of several hundreds of eggs at weekly intervals.

### CONDITIONS OF PARENTAL FISH, REPRODUCTION AND EARLY-LIFE STAGES

Select a suitable number of healthy fish and keep these in a suitable water (e.g. Appendix 4) for at least two weeks prior to the intended spawning. The group of fish should be allowed to breed at least once before producing the batch of eggs used in the test. The density of fish during this period should not exceed 1 gram of fish per litre. Regular changes of water or the use of purification systems will enable the density to be higher. The temperature in the holding tanks should be maintained at 25 ± 2 °C. The fish should be provided with a varied diet, which may consist of, for example, appropriate commercial dry food, live newly hatched Arthemia, chironomids, Daphnia, white worms (Enchytraeids).

Two procedures are outlined below, which in practice have led to a sufficient batch of healthy, fertilised eggs for a test to be run:

(i) Eight females and 16 males are placed in a tank containing 50 litres of dilution water, shielded from direct light and left as undisturbed as possible for at least 48 hours. A spawning tray is placed at the bottom of the aquarium in the afternoon the day before start of the test. The spawning tray consists of a frame (plexi-glass or other suitable material), 5-7 cm high with a 2-5 mm coarse net attached at the top and a 10-30 μm fine net at the bottom. A number of 'spawning-trees', consisting of untwisted nylon rope, are attached to the coarse net of the frame. After the fish have been left in dark for 12 hours, a faint light is turned on which will initiate the spawning. Two to four hours after spawning, the spawning tray is removed and the eggs collected. The spawning tray will prevent the fish from eating the eggs and at the same time permit an easy collection of the eggs. The group of fish should have spawned at least once before the spawning from which eggs are used for testing.

(ii) Five to 10 male and female fish are housed individually at least two weeks prior to the intended spawning. After 5-10 days, the abdomens of the females will be distended and their genital papillae visible. Male fish lack papillae. Spawning is performed in spawning tanks equipped with a false mesh bottom (as above). The tank is filled with dilution water, so that the depth of water above the mesh is 5-10 cm. One female and two males are placed in the tank the day before the intended spawning. The water temperature is gradually increased one degree higher than the acclimatisation temperature. The light is turned off and the tank is left as undisturbed as possible. In the morning a faint light is turned on which will initiate spawning. After 2-4 hours, the fish are removed and the eggs collected. If larger batches of eggs are needed than can be obtained from one female, a sufficient number of spawning tanks may be set-up in parallel. By recording the reproduction success of the individual females prior to the test (size of batch and quality), those females with highest reproduction success may be selected for breeding.

The eggs should be transferred to the test vessels by means of glass tubes (inner diameter not less than 4 mm) provided with a flexible suction bulb. The amount of water accompanying the eggs on their transfer should be as small as possible. The eggs are heavier than water and sink out of the tube. Care should be taken to prevent eggs (and larvae) coming into contact with the air. Microscopic examination of sample(s) of the batch(es) should be carried out to ensure that there are no irregularities in the first developmental stages. Disinfection of the eggs is not allowed.

The mortality rate of the eggs is highest within the first 24 hours after fertilisation. A mortality of 5-40 % is often seen during this period. Eggs degenerate as a result of unsuccessful fertilisation or development failures. The quality of the batch of eggs seems to depend on the female fish, as some females consistently produce good quality eggs, others never will. Also the development rate and the rate of hatching vary from one batch to another. The successfully fertilised eggs and the yolk sac larvae survive well, normally above 90 %. At 25 °C the eggs will hatch 3-5 days after fertilization and the yolk sac will be absorbed approximately 13 days after fertilisation.

The embryonic development has been well defined by Hisaoka and Battle (2). Due to the transparency of the eggs and post-hatch larvae, the development of the fish may be followed and the presence of malformations may be observed. Approximately four hours after spawning, the non-fertilised eggs may be distinguished from the fertilised (3). For this examination, eggs and larvae are placed in test vessels of small volume and studied under a microscope.

The test conditions, which apply to the early life stages, are listed in Appendix 2. Optimal values for pH values and hardness of the dilution water are 7,8 and 250 mg $CaCO_3$/l respectively.

## CALCULATIONS AND STATISTICS

A two-stage approach is proposed. First, the data on mortality, abnormal development and hatching-time are analysed statistically. Then, for those concentrations at which no adverse effects on any of these parameters have been detected, the body length is statistically evaluated. This approach is advisable since the toxicant may selectively kill smaller fish, delay hatching-time and induce gross malformations, thus leading to biased length measurements. Furthermore, there will be roughly the same number of fish to be measured per treatment, ensuring the validity of the test statistics.

## $LC_{50}$ AND $EC_{50}$ DETERMINATIONS

The percentage of surviving eggs and larvae is calculated and corrected for mortality in the controls in accordance with Abbott's formula (4):

$$P = 100 - \left( \frac{C - P'}{C} \times 100 \right)$$

where,

P = corrected % survival

P′ = % survival observed in the test concentration

C = survival in the control

If possible, the $LC_{50}$ is determined by a suitable method at the end of the test.

If the inclusion of morphological abnormalities in the $EC_{50}$ statistic is desired, guidance can be found in Stephan (5).

## ESTIMATION OF LOEC AND NOEC

An objective of the egg and sac-fry test is to compare the non-zero concentrations with the control, i.e. to determine the LOEC. Therefore multiple comparison procedures should be utilised (6) (7) (8) (9) (10).

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*APPENDIX 2*

**TEST CONDITIONS, DURATION AND SURVIVAL CRITERIA FOR RECOMMENDED SPECIES**

| Species | Temperature (°C) | Salinity (0/00) | Photoperiod (hours) | Duration of stages (days) | | Typical duration of test | Survival of control (minimum %) | |
|---|---|---|---|---|---|---|---|---|
| | | | | Embryo | Sac-fry | | Hatching success | Post-hatch |
| FRESHWATER | | | | | | | | |
| *Brachydanio rerio*<br>Zebrafish | 25 ± 1 | — | 12-16 | 3-5 | 8-10 | As soon as possible after fertilisation (early gastrula stage) to 5 days post-hatch (8-10 days) | 80 | 90 |
| *Oncorhynchus mykiss*<br>Rainbow trout | 10 ± 1 (1)<br>12 ± 1 (2) | — | 0 (3) | 30-35 | 25-30 | As soon as possible after fertilisation (early gastrula stage) to 20 days post-hatch (50-55 days) | 66 | 70 |
| *Cyprinus carpio*<br>Common carp | 21-25 | — | 12-16 | 5 | > 4 | As soon as possible after fertilisation (early gastrula stage) to 4 days post-hatch (8-9 days) | 80 | 75 |
| *Oryzias latipes*<br>Japanese ricefish/Medaka | 24 ± 1 (1)<br>23 ± 1 (2) | — | 12-16 | 8-11 | 4-8 | As soon as possible after fertilisation (early gastrula stage) to 5 days post-hatch (13-16 days) | 80 | 80 |
| *Pimephales promelas*<br>Fathead minnow | 25 ± 2 | — | 16 | 4-5 | 5 | As soon as possible after fertilisation (early gastrula stage) to 4 days post-hatch (8-9 days) | 60 | 70 |

(1) For embryos.
(2) For larvae.
(3) Darkness for embryo and larvae until one week after hatching except when they are being inspected. Then subdued lighting throughout the test.

*APPENDIX 3*

**TEST CONDITIONS, DURATION AND SURVIVAL CRITERIA FOR OTHER WELL-DOCUMENTED SPECIES**

| Species | Temperature (°C) | Salinity (0/00) | Photoperiod (hours) | Duration of stages (days) | | Typical duration of embryo and sac-fry test | Survival of control (minimum %) | |
|---|---|---|---|---|---|---|---|---|
| | | | | Embryo | Sac-fry test | | Hatching success | Post-hatch |
| FRESHWATER | | | | | | | | |
| *Carassius auratus*<br>Goldfish | 24 ± 1 | — | — | 3-4 | > 4 | As soon as possible after fertilisation (early gastrula stage) to 4 days post-hatch (7 days) | — | 80 |
| *Leopomis macrochirus*<br>Blugill sunfish | 21 ± 1 | — | 16 | 3 | > 4 | As soon as possible after fertilisation (early gastrula stage) to 4 days post-hatch (7 days) | — | 75 |
| SALTWATER | | | | | | | | |
| *Menidia peninsulae*<br>Tidewater silverside | 22-25 | 15-22 | 12 | 1,5 | 10 | As soon as possible after fertilisation (early gastrula stage) to 5 days post-hatch (6-7 days) | 80 | 60 |
| *Clupea harengus*<br>Herring | 10 ± 1 | 8-15 | 12 | 20-25 | 3-5 | As soon as possible after fertilisation (early gastrula stage) to 3 days post-hatch (23-27 days) | 60 | 80 |
| *Gadus morhua*<br>Cod | 5 ± 1 | 5-30 | 12 | 14-16 | 3-5 | As soon as possible after fertilisation (early gastrula stage) to 3 days post-hatch (18 days) | 60 | 80 |
| *Cyprinodon variegatus*<br>Sheepshead minnow | 25 ± 1 | 15-30 | 12 | — | — | As soon as possible after fertilisation (early gastrula stage) to 4/7 days post-hatch (28 days) | > 75 | 80 |

*APPENDIX 4*

**SOME CHEMICAL CHARACTERISTICS OF AN ACCEPTABLE DILUTION WATER**

| Substance | Concentrations |
|---|---|
| Particulate matter | < 20 mg/l |
| Total organic carbon | < 2 mg/l |
| Unionised ammonia | < 1 µg/l |
| Residual chlorine | < 10 µg/l |
| Total organophosphorus pesticides | < 50 ng/l |
| Total organochlorine pesticides plus polychlorinated biphenyls | < 50 ng/l |
| Total organic chlorine | < 25 ng/l |

## C.16. HONEYBEES — ACUTE ORAL TOXICITY TEST

### 1. METHOD

This acute toxicity test method is a replicate of the OECD TG 213 (1998).

#### 1.1. INTRODUCTION

This toxicity test is a laboratory method, designed to assess the oral acute toxicity of plant protection products and other chemicals, to adult worker honeybees.

In the assessment and evaluation of toxic characteristics of substances, determination of acute oral toxicity in honeybees may be required, e.g. when exposure of bees to a given chemical is likely. The acute oral toxicity test is carried out to determine the inherent toxicity of pesticides and other chemicals to bees. The results of this test should be used to define the need for further evaluation. In particular, this method can be used in step-wise programmes for evaluating the hazards of pesticides to bees, based on sequential progression from laboratory toxicity tests to semi-field and field experiments (1). Pesticides can be tested as active substances (a.s.) or as formulated products.

A toxic standard should be used to verify the sensitivity of the bees and the precision of the test procedure.

#### 1.2. DEFINITIONS

**Acute oral toxicity**: is the adverse effects occurring within a maximum period of 96 hours (h) of an oral administration of a single dose of test substance.

**Dose**: is the amount of test substance consumed. Dose is expressed as mass (μg) of test substance per test animal (μg/bee). The real dose for each bee can not be calculated as the bees are fed collectively, but an average dose can be estimated (totally consumed test substance/number of test bees in one cage).

**$LD_{50}$ (median lethal dose) oral**: is a statistically derived single dose of a substance that can cause death in 50 % of animals when administered by the oral route. The $LD_{50}$ value is expressed in (μg) of test substance per bee. For pesticides, the test substance may be either an active substance (a.s.) or a formulated product containing one or more than one active substance.

**Mortality**: an animal is recorded as dead when it is completely immobile.

#### 1.3. PRINCIPLE OF THE TEST METHOD

Adult worker honeybees (*Apis mellifera*) are exposed to a range of doses of the test substance dispersed in sucrose solution. The bees are then fed the same diet, free of the test substance. Mortality is recorded daily during at least 48 h and compared with control values. If the mortality rate is increasing between 24 h and 48 h whilst control mortality remains at an accepted level, i.e. ≤ 10 %, it is appropriate to extend the duration of the test to a maximum of 96 h. The results are analysed in order to calculate the $LD_{50}$ at 24 h and 48 h and, in case the study is prolonged, at 72 h and 96 h.

#### 1.4. VALIDITY OF THE TEST

For a test to be valid, the following conditions apply:

— the average mortality for the total number of controls must not exceed 10 % at the end of the test,

— the $LD_{50}$ of the toxic standard meets the specified range.

#### 1.5. DESCRIPTION OF THE TEST METHOD

##### 1.5.1. Collection of bees

Young adult worker bees of the same race should be used, i.e. bees of the same age, feeding status, etc. Bees should be obtained from adequately fed, healthy, as far as possible disease-free and queen-right colonies with known history and physiological status. They could be collected in the morning of use or in the evening

before test and kept under test conditions to the next day. Bees collected from frames without brood are suitable. Collection in early spring or late autumn should be avoided as the bees have a changed physiology during this time. If tests must be conduced in early spring or late autumn, bees can be emerged in an incubator and reared for one week with 'bee bread' (pollen collected from the comb) and sucrose solution. Bees treated with chemical substances, such as antibiotics, anti-varroa products, etc., should not be used for toxicity test for four weeks from the time of the end of the last treatment.

1.5.2. **Housing and feeding conditions**

Easy to clean and well-ventilated cages are used. Any appropriate material can be used, e.g. stainless steel, wire mesh, plastic or disposable wooden cages, etc. Groups of 10 bees per cage are preferred. The size of test cages should be appropriate to the number of bees, i.e. providing adequate space.

The bees should be held in the dark in an experimental room at a temperature of 25 ± 2 °C. The relative humidity, normally around 50—70 %, should be recorded throughout the test. Handling procedures, including treatment and observations may be conducted under (day) light. Sucrose solution in water with a final concentration of 500 g/l (50 % w/v) is used as food. After given test doses, food should be provided *ad libitum*. The feeding system should allow recording food intake for each cage (see section 1.6.3.1). A glass tube (approximately 50 mm long and 10 mm wide with the open end narrowed to about 2 mm diameter) can be used.

1.5.3. **Preparation of bees**

The collected bees are randomly allocated to test cages, which are randomly placed in the experimental room.

The bees may be starved for up to 2 h before the initiation of the test. It is recommended that the bees are deprived of food prior to treatment so that all bees are equal in terms of their gut contents at the start of the test. Moribund bees should be rejected and replaced by healthy bees before starting the test.

1.5.4. **Preparation of doses**

Where the test substance is a water miscible compound this may be dispersed directly in 50 % sucrose solution. For technical products and substances of low water solubility, vehicles such as organic solvent, emulsifiers or dispersants of low toxicity to bees may be used (e.g. acetone, dimethylformamide, dimethylsulfoxide). The concentration of the vehicle depends on the solubility of the test substance and it should be the same for all concentrations tested. However, a concentration of the vehicle of 1 % is generally appropriate and should not be exceeded.

Appropriate control solutions should be prepared, i.e. where a solvent or a dispersant is used to solubilise the test substance, two separate control groups should be used: a solution in water, and a sucrose solution with the solvent/carrier at the concentration used in dosing solutions.

1.6. PROCEDURE

1.6.1. **Test and control groups**

The number of doses and replicates tested should meet the statistical requirements for determination of $LD_{50}$ with 95 % confidence limits. Normally, five doses in a geometric series, with a factor not exceeding 2,2, and covering the range for $LD_{50}$, are required for the test. However, the dilution factor and the number of concentrations for dosage have to be determined in relation to the slope of the toxicity curve (dose versus mortality) and with consideration taken to the statistical method which is chosen for analysis of the results. A range-finding test enables the choice of the appropriate concentrations for dosage.

A minimum of three replicate test groups, each of 10 bees, should be dosed with each test concentration. A minimum of three control batches, each of 10 bees, should be run in addition to the test series. Control batches should also be included for the solvents/carriers used (see section 1.5.4).

1.6.2. **Toxic standard**

A toxic standard should be included in the test series. At least three doses should be selected to cover the expected $LD_{50}$ value. A minimum of three replicate cages, each containing ten bees, should be used with each test dose. The preferred toxic standard is dimethoate, for which the reported oral $LD_{50}$-24 h is in the range 0,10-0,35 µg a.s./bee (2). However, other toxic standards would be acceptable where sufficient data can be provided to verify the expected dose response (e.g. parathion).

1.6.3. **Exposure**

1.6.3.1. *Administration of doses*

Each test group of bees must be provided with 100-200 µl of 50 % sucrose solution in water, containing the test substance at the appropriate concentration. A larger volume is required for products of low solubility, low toxicity or low concentration in the formulation, as higher proportions in the sucrose solution have to be used. The amount of treated diet consumed per group should be monitored. Once consumed (usually within 3-4 h), the feeder should be removed from the cage and replaced with one containing sucrose solution alone. The sucrose solutions are then provided *ad libitum*. For some compounds, at higher concentrations rejection of test dose may result in little or no food being consumed. After a maximum of 6 h, unconsumed treated diet should be replaced with the sucrose solution alone. The amount of treated diet consumed should be assessed (e.g. measurement of volume/weight of treated diet remaining).

1.6.3.2. *Duration*

The duration of the test is preferably 48 h after the test solution has been replaced with sucrose solution alone. If mortality continues to rise by more than 10 % after the first 24 h, the test duration should be extended to a maximum of 96 h provided that control mortality does not exceed 10 %.

1.6.4. **Observations**

Mortality is recorded at 4 h after starting the test and thereafter at 24 h and 48 h (i.e. after giving dose). If a prolonged observation period is required, further assessments should be made at 24-h intervals, up to a maximum of 96 h, provided that the control mortality does not exceed 10 %.

The amount of diet consumed per group should be estimated. Comparison of the rates of consumption of treated and untreated diet within the given 6 h can provide information about palatability of the treated diet.

All abnormal behavioural effects observed during the testing period should be recorded.

1.6.5. **Limit test**

In some cases (e.g. when a test substance is expected to be of low toxicity) a limit test may be performed, using 100 µg a.s./bee in order to demonstrate that the $LD_{50}$ is greater than this value. The same procedure should be used, including three replicate test groups for the test dose, the relevant controls, the assessment of the amount of treated diet comsumed, and the use of the toxic standard. If mortalities occur, a full study should be conducted. If sublethal effects are observed (see section 1.6.4), these should be recorded.

2. **DATA AND REPORTING**

2.1. DATA

Data should be summarised in tabular form, showing for each treatment group, as well as control and toxic standard groups, the number of bees used, mortality at each observation time and number of bees with adverse behaviour. Analyse the mortality data by appropriate statistical methods (e.g. probit analysis, moving average, binomial probability) (3) (4). Plot dose-response curves at each recommended observation time and calculate the slopes of the curves and the median lethal doses ($LD_{50}$) with 95 % confidence limits. Corrections for control mortality could be made using Abbott's correction (4) (5). Where treated diet is not completely consumed, the dose of test substance consumed per group should be determined. $LD_{50}$ should be expressed in µg of test substance per bee.

2.2. TEST REPORT

The test report must include the following information:

2.2.1. **Test substance:**

— physical nature and relevant physical-chemical properties (e.g. stability in water, vapour pressure),

— chemical identification data, including structural formula, purity (i.e. for pesticides, the identity and concentration of active substance(s)).

2.2.2. **Test species:**

— scientific name, race, approximate age (in weeks), collection method, date of collection,

— information on colonies used for collection of test bees including health, any adult disease, any pre-treatment, etc.

2.2.3. **Test conditions:**

— temperature and relative humidity of experimental room,

— housing conditions including type, size and material of cages,

— methods of preparation of stock and test solutions (the solvent and its concentration must be given, when used),

— method of preparation of stock solutions and frequency of renewal (the solubilising agent and its concentration must be given, when used),

— test design, e.g. number and test concentrations used, number of controls; for each test concentration and control, number of replicate cages and number of bees per cage,

— date of test.

2.2.4. **Results:**

— results of preliminary range-finding study if performed,

— raw data: mortality at each dose tested at each observation time,

— graph of the dose-response curves at the end of the test,

— $LD_{50}$ values with 95 % confidence limits, at each of the recommended observation times, for test substance and toxic standard,

— statistical procedures used for determining the $LD_{50}$,

— mortality in controls,

— other biological effects observed or measured e.g. abnormal behaviour of the bees (including rejection of the test dose), rate of consumption of diet in treated and untreated groups,

— any deviation from the test procedures described here and any other relevant information.

3. **REFERENCES**

(1) EPPO/Council of Europe (1993). Decision-Making Scheme for the Environmental Risk Assessment of Plant Protection Products — Honeybees. EPPO Bulletin, Vol. 23, N.1, pp. 151-165. March 1993.

(2) Gough, H. J., McIndoe, E.C., Lewis, G.B. (1994). The use of dimethoate as a reference compound in laboratory acute toxicity tests on honeybees (*Apis mellifera* L.) 1981-1992. Journal of Apicultural Research, 22, pp. 119-125.

(3) Litchfield, J.T. and Wilcoxon, F. (1949). A simplified method of evaluating dose-effect experiments. Jour. Pharmacol. and Exper. Ther., 96, pp. 99-113.

(4) Finney, D. J. (1971). Probit Analysis. 3rd ed., Cambridge, London and New York.

(5) Abbott, W. S. (1925). A method for computing the effectiveness of an insecticide. Jour. Econ. Entomol., 18, pp. 265-267.

## C.17. HONEYBEES — ACUTE CONTACT TOXICITY TEST

### 1. METHOD

This acute toxicity test method is a replicate of the OECD TG 214 (1998).

#### 1.1. INTRODUCTION

This toxicity test is a laboratory method, designed to assess the acute contact toxicity of plant protection products and other chemicals to adult worker honeybees.

In the assessment and evaluation of toxic characteristics of substances, determination of acute contact toxicity in honeybees may be required, e.g. when exposure of bees to a given chemical is likely. The acute contact toxicity test is carried out to determine the inherent toxicity of pesticides and other chemicals to bees. The results of this test should be used to define the need for further evaluation. In particular, this method can be used in step-wise programmes for evaluating the hazards of pesticides to bees, based on sequential progression from laboratory toxicity tests to semi-field and field experiments (1). Pesticides can be tested as active substances (a.s.) or as formulated products.

A toxic standard should be used to verify the sensitivity of the bees and the precision of the test procedure.

#### 1.2. DEFINITIONS

**Acute oral toxicity**: is the adverse effects occurring within a maximum period of 96 hours of a topical application of a single dose of a substance.

**Dose**: is the amount of test substance applied. Dose is expressed as mass (μg) of test substance per test animal (μg/bee).

**$LD_{50}$ (median lethal dose) contact**: is a statistically derived single dose of a substance that can cause death in 50 % of animals when administered by the contact. The $LD_{50}$ value is given in μg of test substance per bee. For pesticides, the test substance may be either an active substance (a.s.) or a formulated product containing one or more than one active substance.

**Mortality**: an animal is recorded as dead when it is completely immobile.

#### 1.3. PRINCIPLE OF THE TEST METHOD

Adult worker honeybees (*Apis mellifera*) are exposed to a range of doses of the test substance dissolved in appropriate carrier, by direct application to the thorax (droplets). The test duration is 48 h. If the mortality rate is increasing between 24 h and 48 h whilst control mortality remains at an accepted level, i.e. ≤ 10 %, it is appropriate to extend the duration of the test to a maximum of 96 h. Mortality is recorded daily and compared with control values. The results are analysed in order to calculate the $LD_{50}$ at 24 h and 48 h, and in case the study is prolonged at 72 h and 96 h.

#### 1.4. VALIDITY OF THE TEST

For a test to be valid, the following conditions apply:

— the average mortality for the total numbers of controls must not exceed 10 % at the end of the test,

— the $LD_{50}$ of the toxic standard meets the specified range.

#### 1.5. DESCRIPTION OF THE TEST METHOD

##### 1.5.1. **Collection of bees**

Young adult worker bees should be used, i.e. bees of the same age, feeding status, race etc. Bees should be obtained from adequately fed, healthy, as far as possible disease-free and queen-right colonies with known history and physiological status. They could be collected in the morning of use or in the evening before test

and kept under test conditions to the next day. Bees collected from frames without brood are suitable. Collection in early spring or late autumn should be avoided, as the bees have a changed physiology during the time. If tests have to be conduced in early spring or late autumn, bees can be emerged in an incubator and reared for one week with 'bee bread' (pollen collected from the comb) and sucrose solution. Bees treated with chemical substances, such as antibiotics, anti-varroa products, etc., should not be used for toxicity test for four weeks from the time of the end of the last treatment.

1.5.2. **Housing and feeding conditions**

Easy to clean and well-ventilated cages are used. Any appropriate material can be used, e.g. stainless steel, wire mesh, plastic, disposable wooden cages, etc. The size of test cages should be appropriate to the number of bees, i.e. providing adequate space. Groups of ten bees per cage are preferred.

The bees should be held in the dark in an experimental room at a temperature of 25 ± 2 °C. The relative humidity, normally around 50-70 %, should be recorded throughout the test. Handling procedures, including treatment and observations may be conducted under (day) light. Sucrose solution in water with a final concentration of 500 g/l (50 % w/v) should be used as food and provided *ad libitum* during the test time, using a bee feeder. This can be a glass tube (approximately 50 mm long and 10 mm wide with the open end narrowed to about 2 mm diameter).

1.5.3. **Preparation of bees**

The collected bees may be anaesthetised with carbon dioxide or nitrogen for application of the test substance. The amount of anaesthetic used and time of exposure should be minimised. Moribund bees should be rejected and replaced by healthy bees before starting the test.

1.5.4. **Preparation of doses**

The test substance is to be applied as solution in a carrier, i.e. an organic solvent or a water solution with a wetting agent. As organic solvent, acetone is preferred but other organic solvents of low toxicity to bees may be used (e.g. dimethylformamide, dimethylsulfoxide). For water dispersed formulated products and highly polar organic substances not soluble in organic carrier solvents, solutions may be easier to apply if prepared in a weak solution of a commercial wetting agent (e.g. Agral, Cittowett, Lubrol, Triton, Tween).

Appropriate control solutions should be prepared, i.e. where a solvent or a dispersant is used to solubilise the test substance, two separate control groups should be used, one treated with water, and one treated with the solvent/dispersant.

1.6. PROCEDURE

1.6.1. **Test and control groups**

The number of doses and replicates tested should meet the statistical requirements for determination $LD_{50}$ with 95 % confidence limits. Normally five doses in a geometric series, with a factor not exceeding 2,2, and covering the range for $LD_{50}$, are required for the test. However, the number of doses have to be determined in relation to the slope of the toxicity curve (dose versus mortality) and with consideration taken to the statistical method which is chosen for analysis of the results. A range-finding test enables the choice of the appropriate doses.

A minimum of three replicate test groups, each of 10 bees, should be dosed with each test concentration.

A minimum of three control batches, each of 10 bees, should be run in addition to the test series. If an organic solvent or a wetting agent is used three additional control batches of each 10 bees for the solvent or the wetting agent have to be included.

1.6.2. **Toxic standard**

A toxic standard must be included in the test series. At least three doses should be selected to cover the expected $LD_{50}$ value. A minimum of three replicate cages, each containing 10 bees, should be used with each test dose. The preferred toxic standard is dimethoate, for which the reported contact $LD_{50}$-24 h is in the range 0,10-0,30 µg a.s./bee (2). However, other toxic standards would be acceptable where sufficient data can be provided to verify the expected dose response (e.g. parathion).

1.6.3. **Exposure**

1.6.3.1. *Administration of doses*

Anaesthetised bees are individually treated by topical application.The bees are randomly assigned to the different test doses and controls. A volume of 1 µl of solution containing the test substance at the suitable concentration should be applied with a microapplicator to the dorsal side of the thorax of each bee. Other volumes may be used, if justified. After application, the bees are allocated to test cages and supplied with sucrose solutions.

1.6.3.2. *Duration*

The duration of the test is preferably 48 h. If mortality increases by more than 10 % between 24 h and 48 h, the test duration should be extended up to a maximum of 96 h provided that control mortality does not exceed 10 %.

1.6.4. **Observations**

Mortality is recorded at 4 h after dosing and thereafter at 24–h and 48 h. If a prolonged observation period is required, further assessments should be made, at 24-h intervals, to a maximum of 96 h, provided that the control mortality does not exceeding 10 %.

All abnormal behavioural effects observed during the testing period should be recorded.

1.6.5. **Limit test**

In some cases (e.g. when a test substance is expected to be of low toxicity) limit test may be performed, using 100 µg a.s./bee in order to demonstrate that the $LD_{50}$ is greater than this value. The same procedure should be used, including three replicate test groups for the test dose, the relevant controls, and the use of the toxic standard. If mortalities occur, a full study should be conducted. If sublethal effects are observed (see section 1.6.4) these should be recorded.

2. **DATA AND REPORTING**

2.1. DATA

Data should be summarised in tabular form, showing for each treatment group, as well as, control and toxic standard groups, the number of bees used, mortality at each observation time and number of bees with adverse behaviour. Analyse the mortality data by appropriate statistical methods (e.g. probit analysis, moving average, binomial probability) (3) (4). Plot dose-response curves at each recommended observation time (i.e. 24 h, 48 h and, if relevant, 72 h, 96 h) and calculate the slopes of the curves and the median lethal doses ($LD_{50}$) with 95 % confidence limits. Corrections for control mortality could be made using Abbott's correction (4) (5). $LD_{50}$ should be expressed in µg of test substance per bee.

2.2. TEST REPORT

The test report must include the following information:

2.2.1. **Test substance:**

— physical nature and physical-chemical properties (e.g. stability in water, vapour pressure),

— chemical identification data, including structural formula, purity (i.e. for pesticides, the identity and concentration of active substance(s)).

2.2.2. **Test species:**

— scientific name, race, approximate age (in weeks), collection method, date of collection,

— information on colonies used for collection of test bees including health, any adult disease, any pre-treatment, etc.

2.2.3. **Test conditions:**

— temperature and relative humidity of experimental room,

— housing conditions including type, size and material of cages,

— methods of administration of test substance, e.g. carrier solvent used, volume of test solution applied anaesthetics used,

— test design, e.g. number and test doses used, number of controls; for each test dose and control, number of replicate cages and number of bees per cage,

— date of test.

2.2.4. **Results:**

— results of preliminary range-finding study if performed,

— raw data: mortality at each concentration tested at each observation time,

— graph of the dose-response curves at the end of the test,

— $LD_{50}$ values, with 95 % confidence limits, at each of the recommended observation times, for test substance and toxic standard,

— statistical procedures used for determining the $LD_{50}$,

— mortality in controls,

— other biological effects observed or measured and any abnormal responses of the bees,

— any deviation from the test method procedures described here and any other relevant information.

3. **REFERENCES**

(1) EPPO/Council of Europe (1993). Decision-Making Scheme for the Environmental Risk Assessment of Plant Protection Products — Honeybees. EPPO bulletin, Vol. 23, N.1, pp. 151-165. March 1993.

(2) Gough, H. J., McIndoe, E. C., Lewis, G. B. (1994). The use of dimethoate as a reference compound in laboratory acute toxicity tests on honeybees (*Apis mellifera* L.), 1981-1992. Journal of Apicultural Research 22, pp. 119-125.

(3) Litchfield, J. T. and Wilcoxon, F. (1949). A simplified method of evaluating dose-effect experiments. Jour. Pharmacol. and Exper. Ther., 96, pp. 99-113.

(4) Finney, D. J. (1971). Probit Analysis. 3rd ed., Cambridge, London and New York.

(5) Abbott, W. S. (1925). A method for computing the effectiveness of an insecticide. Jour. Econ. Entomol. 18, pp. 265-267.

## C.18. ADSORPTION/DESORPTION USING A BATCH EQUILIBRIUM METHOD

### 1. METHOD

This method is a replicate of the OECD TG 106, for the Determination of Soil Adsorption/Desorption, using a Batch Equilibrium Method (2000).

#### 1.1. INTRODUCTION

The method takes into account a ring test and a workshop for soil selection for the development of an adsorption test (1) (2) (3) (4) and also existing guidelines at national level (5) (6) (7) (8) (9) (10) (11).

Adsorption/desorption studies are useful for generating essential information on the mobility of chemicals and their distribution in the soil, water and air compartments of the biosphere (12) (13) (14) (15) (16) (17) (18) (19) (20) (21). The information can be used in the prediction or estimation, for example, of the availability of a chemical for degradation (22) (23), transformation and uptake by organisms (24); leaching through the soil profile (16) (18) (19) (21) (25) (26) (27) (28); volatility from soil (21) (29) (30); run-off from land surfaces into natural waters (18) (31) (32). Adsorption data can be used for comparative and modelling purposes (19) (33) (34) (35).

The distribution of a chemical between soil and aqueous phases is a complex process depending on a number of different factors: the chemical nature of the substance (12) (36) (37) (38) (39) (40), the characteristics of the soil (4) (12) (13) (14) (41) (42) (43) (44) (45) (46) (47) (48) (49), and climatic factors such as rainfall, temperature, sunlight and wind. Thus, the numerous phenomena and mechanisms involved in the process of adsorption of a chemical by soil cannot be completely defined by a simplified laboratory model such as the present method. However, even if this attempt cannot cover all the environmentally possible cases, it provides valuable information on the environmental relevance of the adsorption of a chemical.

See also General Introduction.

#### 1.2. SCOPE

The method is aimed at estimating the adsorption/desorption behaviour of a substance on soils. The goal is to obtain a sorption value which can be used to predict partitioning under a variety of environmental conditions; to this end, equilibrium adsorption coefficients for a chemical on various soils are determined as a function of soil characteristics (e.g. organic carbon content, clay content and soil texture and pH). Different soil types have to be used in order to cover as widely as possible the interactions of a given substance with naturally occurring soils.

In this method, adsorption represents the process of the binding of a chemical to surfaces of soils; it does not distinguish between different adsorption processes (physical and chemical adsorption) and such processes as surface catalysed degradation, bulk adsorption or chemical reaction. Adsorption that will occur on colloids particles (diameter < 0,2 μm) generated by the soils is not taken into account.

The soil parameters that are believed most important for adsorption are: organic carbon content (3) (4) (12) (13) (14) (41) (43) (44) (45) (46) (47) (48); clay content and soil texture (3) (4) (41) (42) (43) (44) (45) (46) (47) (48) and pH for ionisable compounds (3) (4) (42). Other soil parameters which may have an impact on the adsorption/desorption of a particular substance are the effective cation exchange capacity (ECEC), the content of amorphous iron and aluminium oxides, particularly for volcanic and tropical soils (4), as well as the specific surface (49).

The test is designed to evaluate the adsorption of a chemical on different soil types with a varying range of organic carbon content, clay content and soil texture, and pH. It comprises three tiers:

**Tier 1**: Preliminary study in order to determine:

- the soil/solution ratio,
- the equilibrium time for adsorption and the amount of test substance adsorbed at equilibrium,
- the adsorption of the test substance on the surfaces of the test vessels and the stability of the test substance during the test period.

**Tier 2**: Screening test: the adsorption is studied in five different soil types by means of adsorption kinetics at a single concentration and determination of distribution coefficient $K_d$ and $K_{oc}$.

**Tier 3**: Determination of Freundlich adsorption isotherms to determine the influence of concentration on the extent of adsorption on soils.

Study of desorption by means of desorption kinetics/Freundlich desorption isotherms (Appendix 1).

1.3. DEFINITIONS AND UNITS

| Symbol | Definition | Units |
|---|---|---|
| $A_{t_i}$ | adsorption percentage at the time $t_i$ | % |
| $A_{eq}$ | adsorption percentage at adsorption equilibrium | % |
| $m_s^{ads}(t_i)$ | mass of the test substance adsorbed on the soil at the time $t_i$ | µg |
| $m_s^{ads}(\Delta t_i)$ | mass of the test substance adsorbed on the soil during the time interval $\Delta t_i$ | µg |
| $m_s^{ads}(eq)$ | mass of the test substance adsorbed on the soil at adsorption equilibrium | µg |
| $m_0$ | mass of the test substance in the test tube, at the beginning of the adsorption test | µg |
| $m_m^{ads}(t_i)$ | mass of the test substance measured in an aliquot ($v_a^A$) at the time point $t_i$ | µg |
| $m_{aq}^{ads}(eq)$ | mass of the substance in the solution at adsorption equilibrium | µg |
| $m_{soil}$ | quantity of the soil phase, expressed in dry mass of soil | g |
| $C_{st}$ | mass concentration of the stock solution of the substance | µg $cm^{-3}$ |
| $C_0$ | initial mass concentration of the test solution in contact with the soil | µg $cm^{-3}$ |
| $C_{aq}^{ads}(t_i)$ | mass concentration of the substance in the aqueous phase at the time $t_i$ that the analysis is performed | µg $cm^{-3}$ |
| $C_s^{ads}(eq)$ | content of the substance adsorbed on soil at adsorption equilibrium | µg $g^{-1}$ |
| $C_{aq}^{ads}(eq)$ | mass concentration of the substance in the aqueous phase at adsorption equilibrium | µg $cm^{-3}$ |
| $V_0$ | initial volume of the aqueous phase in contact with the soil during the adsorption test | $cm^3$ |
| $v_a^A$ | volume of the aliquot in which the test substance is measured | $cm^3$ |
| $K_d$ | distribution coefficient for adsorption | $cm^3$ $g^{-1}$ |
| $K_{oc}$ | organic carbon normalised adsorption coefficient | $cm^3$ $g^{-1}$ |
| $K_{om}$ | organic matter normalised distribution coefficient | $cm^3$ $g^{-1}$ |
| $K_F^{ads}$ | Freundlich adsorption coefficient | µg $^{1-1/n}$ $(cm^3)$ $^{1/n}$ $g^{-1}$ |
| 1/n | Freundlich exponent | |
| $D_{t_i}$ | desorption percentage at a point time $t_i$ | % |
| $D_{\Delta t_i}$ | desorption percentage corresponding to a time interval $\Delta t_i$ | % |
| $K_{des}$ | apparent desorption coefficient | $cm^3$ $g^{-1}$ |
| $K_F^{des}$ | Freundlich desorption coefficient | µg $^{1-1/n}$ $(cm^3)$ $^{1/n}$ $g^{-1}$ |
| $m_{aq}^{des}(t_i)$ | mass of the test substance desorbed from soil at the time $t_i$ | µg |

| Symbol | Definition | Units |
|---|---|---|
| $m_{aq}^{des}$ ($\Delta t_i$) | mass of the test substance desorbed from soil during the time $\Delta t_i$ | µg |
| $m_m^{des}$(eq) | mass of the substance determined analytically in the aqueous phase at desorption equilibrium | µg |
| $m_{aq}^{des}$(eq) | total mass of the test substance desorbed at desorption equilibrium | µg |
| $m_s^{des}(\Delta t_i)$ | mass of the substance remaining adsorbed on the soil after the time interval $\Delta t_i$ | µg |
| $m_{aq}^{A}$ | mass of the substance left over from the adsorption equilibrium due to incomplete volume replacement | µg |
| $C_s^{des}$(eq) | content of the test substance remaining adsorbed on the soil at desorption equilibrium | µg $g^{-1}$ |
| $C_{aq}^{des}$(eq) | mass concentration of the test substance in the aqueous phase at desorption equilibrium | µg $cm^{-3}$ |
| $V_T$ | total volume of the aqueous phase in contact with the soil during the desorption kinetics experiment performed with the serial method | $cm^3$ |
| $V_R$ | volume of the supernatant removed from the tube after the attainment of adsorption equilibrium and replaced by the same volume of a 0,01 M $CaCl_2$ solution | $cm^3$ |
| $v_a^D$ | volume of the aliquot sampled for analytical purpose from the time (i), during the desorption kinetics experiment performed with the serial method | $cm^3$ |
| $V_r^i$ | volume of the solution taken from the tube (i) for the measurement of the test substance, in desorption kinetics experiment (parallel method) | $cm^3$ |
| $V_r^F$ | volume of the solution taken from the tube for the measurement of the test substance, at desorption equilibrium | $cm^3$ |
| MB | mass balance | % |
| $m_E$ | total mass of the test substance extracted from soil and walls of the test vessel in two steps | µg |
| $V_{rec}$ | volume of the supernatant recovered after the adsorption equilibrium | $cm^3$ |
| $P_{ow}$ | octanol/water partition coefficient | |
| pKa | dissociation constant | |
| $S_w$ | water solubility | g $l^{-1}$ |

1.4. PRINCIPLE OF THE TEST METHOD

Known volumes of solutions of the test substance, non-labelled or radiolabelled, at known concentrations in 0,01 M $CaCl_2$ are added to soil samples of known dry weight which have been pre-equilibrated in 0,01 M $CaCl_2$. The mixture is agitated for an appropriate time. The soil suspensions are then separated by centrifugation and, if so wished, filtration and the aqueous phase is analysed. The amount of test substance adsorbed on the soil sample is calculated as the difference between the amount of test substance initially present in solution and the amount remaining at the end of the experiment (indirect method).

As an option, the amount of the test substance adsorbed can also be directly determined by analysis of soil (direct method). This procedure which involves step-wise soil extraction with appropriate solvent, is recommended in cases where the difference in the solution concentration of the substance cannot be accurately determined. Examples of such cases are: adsorption of the test substance on surface of the test vessels, instability of the test substance in the time scale of the experiment, weak adsorption giving only small concentration change in the solution; and strong adsorption yielding low concentration which cannot be

accurately determined. If radiolabelled substance is used, the soil extraction may be avoided by analysis of the soil phase by combustion and liquid scintillation counting. However, liquid scintillation counting is an unspecific technique which cannot differentiate between parental and transformation products; therefore it should be used only if the test chemical is stable for the duration of the study.

1.5. INFORMATION ON THE TEST SUBSTANCE

Chemical reagents should be of analytical grade. The use of non-labelled test substances with known composition and preferably at least 95 % purity or of radiolabelled test substances with known composition and radio-purity, is recommended. In the case of short half-life tracers, decay corrections should be applied.

Before carrying out a test for adsorption-desorption, the following information about the test substance should be available:

(a) water solubility (A.6);

(b) vapour pressure (A.4) and/or Henry's Law Constant;

(c) abiotic degradation: hydrolysis as a function of pH (C.7);

(d) partition coefficient (A.8);

(e) ready biodegradability (C.4) or aerobic and anaerobic transformation in soil;

(f) pKa of ionisable substances;

(g) direct photolysis in water (i.e. UV-Vis absorption spectrum in water, quantum yield) and photodegradation on soil.

1.6. APPLICABILITY OF THE TEST

The test is applicable to chemical substances for which an analytical method with sufficient accuracy is available. An important parameter that can influence the reliability of the results, especially when the indirect method is followed, is the stability of the test substance in the time scale of the test. Thus, it is a prerequisite to check the stability in a preliminary study; if a transformation in the time scale of the test is observed, it is recommended that the main study be performed by analysing both soil and aqueous phases.

Difficulties may arise in conducting this test for test substances with low water solubility ($S_w < 10^{-4}$ g $l^{-1}$), as well as for highly charged substances, due to the fact that the concentration in the aqueous phase cannot be measured analytically with sufficient accuracy. In these cases, additional steps have to be taken. Guidance on how to deal with these problems is given in the relevant sections of this method.

When testing volatile substances, care should be taken to avoid losses during the study.

1.7. DESCRIPTION OF THE METHOD

1.7.1. **Apparatus and chemical reagents**

Standard laboratory equipment, especially the following:

(a) Tubes or vessels to conduct the experiments. It is important that these tubes or vessels:

— fit directly in the centrifuge apparatus in order to minimise handling and transfer errors,

— be made of an inert material, which minimises adsorption of the test substance on its surface.

(b) Agitation device: overhead shaker or equivalent equipment; the agitation device should keep the soil in suspension during shaking.

(c) Centrifuge: preferably high-speed, e.g. centrifugation forces > 3 000 g, temperature controlled, capable of removing particles with a diameter greater than 0,2 µm from aqueous solution. The containers should be capped during agitation and centrifugation to avoid volatility and water losses; to minimise adsorption on them, deactivated caps such as teflon lined screw caps should be used.

(d) Optional: filtration device; filters of 0,2 µm porosity, sterile, single use. Special care should be taken in the choice of the filter material, to avoid any losses of the test substance on it; for poorly soluble test substances, organic filter material is not recommended.

(e) Analytical instrumentation, suitable for measuring the concentration of the test chemical.

(f) Laboratory oven, capable of maintaining a temperature of 103 °C to 110 °C.

1.7.2. **Characterisation and selection of soils**

The soils should be characterised by three parameters considered to be largely responsible for the adsorptive capacity: organic carbon, clay content and soil texture, and pH. As already mentioned (see Scope) other physico-chemical properties of the soil may have an impact on the adsorption/desorption of a particular substance and should be considered in such cases.

The methods used for soil characterisation are very important and can have a significant influence on the results. Therefore, it is recommended that soil pH should be measured in a solution of 0,01 M $CaCl_2$ (that is the solution used in adsorption/desorption testing) according to the corresponding ISO method (ISO-10390-1). It is also recommended that the other relevant soil properties be determined according to standard methods (for example ISO 'Handbook of Soil Analysis'); this permits the analysis of sorption data to be based on globally standardised soil parameters. Some guidance for existing standard methods of soil analysis and characterisation is given in references (50-52). For calibration of soil test methods, the use of reference soils is recommended.

Guidance for selection of soils for adsorption/desorption experiments is given in Table 1. The seven selected soils cover soil types encountered in temperate geographical zones. For ionisable test substances, the selected soils should cover a wide range of pH, in order to be able to evaluate the adsorption of the substance in its ionised and unionised forms. Guidance on how many different soils to use at the various stages of the test is given under 1.9. Performance of the test.

If other soil types are preferred, they should be characterised by the same parameters and should have similar variation in properties to those described in Table 1, even if they do not match the criteria exactly.

Table 1: **Guidance for selection of soil samples for adsorption-desorption**

| Soil type | pH range (in 0,01 M $CaCl_2$) | Organic carbon content (%) | Clay content (%) | Soil texture [1] |
|---|---|---|---|---|
| 1 | 4,5-5,5 | 1,0-2,0 | 65-80 | clay |
| 2 | > 7,5 | 3,5-5,0 | 20-40 | clay loam |
| 3 | 5,5-7,0 | 1,5-3,0 | 15-25 | silt loam |
| 4 | 4,0-5,5 | 3,0-4,0 | 15-30 | loam |
| 5 | < 4,0-6,0 [2] | < 0,5-1,5 [2] [3] | < 10-15 [2] | loamy sand |
| 6 | > 7,0 | < 0,5-1,0 [2] [3] | 40-65 | clay loam/clay |
| 7 | < 4,5 | > 10 | < 10 | sand/loamy sand |

[1] According to FAO and the US system (85).
[2] The respective variables should preferably show values within the range given. If, however, difficulties in finding appropriate soil material occur, values below the indicated minimum are accepted.
[3] Soils with less than 0,3 % organic carbon may disturb correlation between organic content and adsorption. Thus, it is recommended the use of soils with a minimum organic carbon content of 0,3 %.

1.7.3. **Collection and storage of soil samples**

1.7.3.1. *Collection*

No specific sampling techniques or tools are recommended; the sampling technique depends on the purpose of the study (53) (54) (55) (56) (57) (58).

The following should be considered:

(a) detailed information on the history of the field site is necessary; this includes location, vegetation cover, treatments with pesticides and/or fertilisers, biological additions or accidental contamination. Recommendations of the ISO standard on soil sampling (ISO 10381-6) should be followed with respect to the description of the sampling site;

(b) the sampling site has to be defined by UTM (Universal Transversal Mercator-Projection/European Horizontal Datum) or geographical coordinates; this could allow recollection of a particular soil in the future or could help in defining soil under various classification systems used in different countries. Also, only A horizon up to a maximum depth of 20 cm should be collected. Especially for the soil type n. 7 if a $O_h$ horizon is present as part of the soil, it should be included in the sampling.

The soil samples should be transported using containers and under temperature conditions which guarantee that the initial soil properties are not significantly altered.

1.7.3.2. *Storage*

The use of soils freshly taken from the field is preferred. Only if this is not possible soil can be stored at ambient temperature and should be kept air-dried. No limit on the storage time is recommended, but soils stored for more than three years should be re-analysed prior to the use with respect to their organic carbon content, pH and CEC.

1.7.3.3. *Handling and preparation of soil samples for the test*

The soils are air-dried at ambient temperature (preferably between 20-25 °C). Disaggregation should be performed with minimal force, so that the original texture of the soil will be changed as little as possible. The soils are sieved to a particle size ≤ 2 mm; recommendations of the ISO standard on soil sampling (ISO 10381-6) should be followed with respect to the sieving process. Careful homogenisation is recommended, as this enhances the reproducibility of the results. The moisture content of each soil is determined on three aliquots with heating at 105 °C until there is no significant change in weight (approximately 12 h). For all calculations the mass of soil refers to oven dry mass, i.e. the weight of soil corrected for moisture content.

1.7.4. **Preparation of the test substance for application to soil**

The test substance is dissolved in a solution of 0,01 M $CaCl_2$ in distilled or deionised water; the $CaCl_2$ solution is used as the aqueous solvent phase to improve centrifugation and minimise cation exchange. The concentration of the stock solution should preferably be three orders of magnitude higher than the detection limit of the analytical method used. This threshold safeguards accurate measurements with respect to the methodology followed in this method; additionally, the stock solution concentration should be below water solubility of the test substance.

The stock solution should preferably be prepared just before application to soil samples and should be kept closed in the dark at 4 °C. The storage time depends on the stability of the test substance and its concentration in the solution.

Only for poorly soluble substances ($S_w < 10^{-4}$ g $l^{-1}$), an appropriate solubilising agent may be needed when it is difficult to dissolve the test substance. This solubilising agent: (a) should be miscible with water such as methanol or acetonitrile; (b) its concentration should not exceed 1 % of the total volume of the stock solution and should constitute less than that in the solution of the test substance which will come in contact with the soil (preferably less than 0,1 %); and (c) should not be a surfactant or undergo solvolytic reactions with the test chemical. The use of a solubilising agent should be stipulated and justified in the reporting of the data.

Another alternative for poorly soluble substances is to add the test substance to the test system by spiking: the test substance is dissolved in an organic solvent, an aliquot of which is added to the system of soil and 0,01 M solution of $CaCl_2$ in distilled or deionised water. The content of organic solvent in the aqueous phase should be kept as low as possible, normally not exceeding 0,1 %. Spiking from an organic solution may suffer from volume unreproducibility. Thus, an additional error may be introduced as the test substance and co-solvent concentration would not be the same in all tests.

1.8. PREREQUISITES FOR PERFORMING THE ADSORPTION/DESORPTION TEST

1.8.1. **Analytical method**

The key parameters that can influence the accuracy of sorption measurements include the accuracy of the analytical method in analysis of both the solution and adsorbed phases, the stability and purity of the test substance, the attainment of sorption equilibrium, the magnitude of the solution concentration change, the soil/solution ratio and changes in the soil structure during the equilibration process (35) (59-62). Some examples bearing upon the accuracy issues are given in Appendix 2.

The reliability of the analytical method used must be checked at the concentration range which is likely to occur during the test. The experimenter should feel free to develop an appropriate method with appropriate accuracy, precision, reproducibility, detection limits and recovery. Guidance on how to perform such a test is given by the experiment below.

An appropriate volume of 0,01 M $CaCl_2$, e.g. 100 $cm^3$, is agitated during 4 h with a weight of soil, e.g. 20 g, of high adsorbability, i.e. with high organic carbon and clay content; these weights and volumes may vary depending on analytical needs, but a soil/solution ratio of 1:5 is a convenient starting point. The mixture is centrifuged and the aqueous phase may be filtrated. A certain volume of the test substance stock solution is added to the latter to reach a nominal concentration within the concentration range which is likely to occur during the test. This volume should not exceed 10 % of the final volume of the aqueous phase, in order to change as little as possible the nature of the pre-equilibration solution. The solution is analysed.

One blank run consisting of the system soil + $CaCl_2$ solution (without test substance) must be included, in order to check for artefacts in the analytical method and for matrix effects caused by the soil.

The analytical methods which can be used for sorption measurements include gas-liquid chromatography (GLC), high-performance liquid chromatography (HPLC), spectrometry (e.g. GC/mass spectrometry, HPLC/mass spectrometry) and liquid scintillation counting (for radiolabelled substances). Independent of the analytical method used, it is considered suitable if the recoveries are between 90 % and 110 % of the nominal value. In order to allow for detection and evaluation after partitioning has taken place, the detection limits of the analytical method should be at least two orders of magnitude below the nominal concentration.

The characteristics and detection limits of the analytical method available for carrying out adsorption studies play an important role in defining the test conditions and the whole experimental performance of the test. This method follows a general experimental path and provides recommendations and guidance for alternative solutions where the analytical method and laboratory facilities may impose limitations.

1.8.2. **Selection of optimal soil/solution ratios**

Selection of appropriate soil to solution ratios for sorption studies depends on the distribution coefficient $K_d$ and the relative degree of adsorption desired. The change of the substance concentration in the solution determines the statistical accuracy of the measurement based on the form of adsorption equation and the limit of the analytical methodology, in detecting the concentration of the chemical in solution. Therefore, in general practice it is useful to settle on a few fixed ratios, for which the percentage adsorbed is above 20 %, and preferably > 50 % (62), while care should be taken to keep the test substance concentration in the aqueous phase high enough to be measured accurately. This is particularly important in the case of high adsorption percentages.

A convenient approach to selecting the appropriate soil/water ratios, is based on an estimate of the $K_d$ value either by preliminary studies or by established estimation techniques (Appendix 3). Selection of an appropriate ratio can then be made based on a plot of soil/solution ratio versus $K_d$ for fixed percentages of adsorption (Fig. 1). In this plot it is assumed that the adsorption equation is linear ([1]). The applicable relationship is obtained by rearranging equation (4) of the $K_d$ in the form of equation (1):

$$\frac{V_0}{m_{soil}} = \left( \frac{m_0}{m_s^{ads}(eq)} - 1 \right) K_d \qquad (1)$$

([1]) $C_s^{ads}(eq) = K_d \cdot C_{aq}^{ads}(eq)$

or in its logarithmic form assuming that $R = m_{soil}/V_0$ and $A_{eq}\%/100 = \frac{m_s^{ads}(eq)}{m_0}$:

$$\log R = -\log K_d + \log\left[\frac{(A_{eq}\%/100)}{(1 - A_{eq}\%/100)}\right] \quad (2)$$

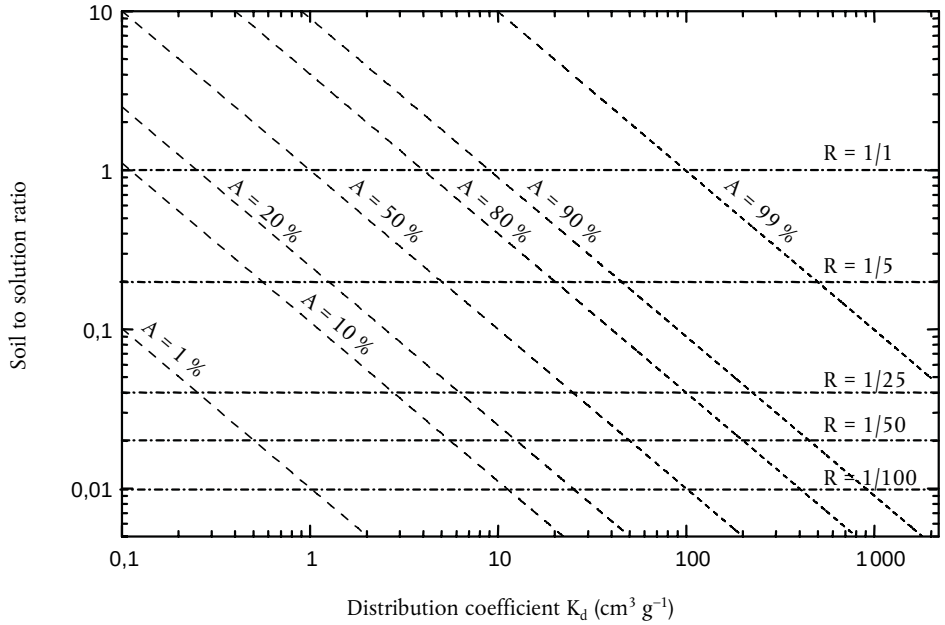


**Fig. 1.** Relationship between soil to solution ratios and $K_d$ at various percentages of adsorbed test substance

Fig. 1 shows soil/solution ratios required as a function of $K_d$ for different levels of adsorption. For example, with a soil/solution ratio of 1:5 and a $K_d$ of 20, approximately 80 % adsorption would occur. To obtain 50 % adsorption for the same $K_d$, a 1:25 ratio must be used. This approach to selecting the appropriate soil/solution ratios gives the investigator the flexibility to meet experimental needs.

Areas which are more difficult to deal with are those where the chemical is highly or very slightly adsorbed. Where low adsorption occurs, a 1:1 soil/solution ratio is recommended, although for some very organic soil types smaller ratios may be necessary to obtain a slurry. Care must be taken with the analytical methodology to measure small changes in solution concentration; otherwise the adsorption measurement will be inaccurate. On the other hand, at very high distribution coefficients $K_d$, one can go up to a 1:100 soil/solution ratio in order to leave a significant amount of chemical in solution. However, care must be taken to ensure good mixing, and adequate time must be allowed for the system to equilibrate. An alternative approach to deal with these extreme cases when adequate analytical methodology is missing, is to predict the $K_d$ value applying estimation techniques based, for example, on $P_{ow}$ values (Appendix 3). This could be useful especially for low adsorbed/polar chemicals with $P_{ow} < 20$ and for lipophilic/highly sorptive chemicals with $P_{ow} > 10^4$.

1.9. PERFORMANCE OF THE TEST

1.9.1. **Test conditions**

All experiments are done at ambient temperature and, if possible, at a constant temperature between 20 °C and 25 °C.

Centrifugation conditions should allow the removal of particles larger than 0,2 μm from the solution. This value triggers the smallest sized particle that is considered as a solid particle, and is the limit between solid and colloid particles. Guidance on how to determine the centrifugation conditions is given in Appendix 4.

If the centrifugation facilities cannot guarantee the removal of particles larger than 0,2 μm, a combination of centrifugation and filtration with 0,2 μm filters could be used. These filters should be made of a suitable inert material to avoid any losses of the test substance on them. In any case, it should be proven that no losses of the test substance occur during filtration.

1.9.2. **Tier 1 — Preliminary study**

The purpose of conducting a preliminary study has already been given in section Scope. Guidance for setting up such a test is given with the experiment suggested below.

1.9.2.1. *Selection of optimal soil/solution ratios*

Two soil types and three soil/solution ratios (six experiments) are used. One soil type has high organic carbon and low clay content, and the other low organic carbon and high clay content. The following soil to solution ratios are suggested:

— 50 g soil and 50 $cm^3$ aqueous solution of the test substance (ratio 1/1),

— 10 g soil and 50 $cm^3$ aqueous solution of the test substance (ratio 1/5),

— 2 g soil and 50 $cm^3$ aqueous solution of the test substance (ratio 1/25).

The minimum amount of soil on which the experiment can be carried out depends on the laboratory facilities and the performance of analytical methods used. However, it is recommended to use at least 1 g, and preferably 2 g, in order to obtain reliable results from the test.

One control sample with only the test substance in 0,01 M $CaCl_2$ solution (no soil) is subjected to precisely the same steps as the test systems, in order to check the stability of the test substance in $CaCl_2$ solution and its possible adsorption on the surfaces of the test vessels.

A blank run per soil with the same amount of soil and total volume of 50 $cm^3$ 0,01 M $CaCl_2$ solution (without test substance) is subjected to the same test procedure. This serves as a background control during the analysis to detect interfering substances or contaminated soils.

All the experiments, included controls and blanks, should be performed at least in duplicate. The total number of the samples which should be prepared for the study can be calculated with respect to the methodology which will be followed.

Methods for the preliminary study and the main study are generally the same, exceptions are mentioned where relevant.

The air-dried soil samples are equilibrated by shaking with a minimum volume of 45 $cm^3$ of 0,01 M $CaCl_2$ overnight (12 h) before the day of the experiment. Afterwards, a certain volume of the stock solution of the test substance is added in order to adjust the final volume to 50 $cm^3$. This volume of the stock solution added: (a) should not exceed 10 % of the final 50 $cm^3$ volume of the aqueous phase in order to change as little as possible the nature of the pre-equilibration solution; and (b) should preferably result in an initial concentration of the test substance being in contact with the soil ($C_0$) at least two orders of magnitude higher than the detection limit of the analytical method; this threshold safeguards the ability to perform accurate measurements even when strong adsorption occurs (> 90 %) and to determine later the adsorption isotherms. It is also recommended, if possible, that the initial substance concentration ($C_0$) not exceed half of its solubility limit.

An example of how to calculate the concentration of the stock solution ($C_{st}$) is given below. A detection limit of 0,01 μg $cm^{-3}$ and 90 % adsorption are assumed; thus, the initial concentration of the test substance in contact with the soil should preferably be 1μg $cm^{-3}$ (two orders of magnitude higher than the detection limit). Supposing that the maximum recommended volume of the stock solution is added, i.e. 5 to 45 $cm^3$ 0,01 M $CaCl_2$ equilibration solution (= 10 % of the stock solution to 50 $cm^3$ total volume of aqueous phase), the concentration of the stock solution should be 10 μg $cm^{-3}$; this is three orders of magnitude higher than the detection limit of the analytical method.

The pH of the aqueous phase should be measured before and after contact with the soil since it plays an important role in the whole adsorption process, especially for ionisable substances.

The mixture is shaken until adsorption equilibrium is reached. The equilibrium time in soils is highly variable, depending on the chemical and the soil; a period of 24 h is generally sufficient (77). In the preliminary study, samples may be collected sequentially over a 48 h period of mixing (for example at 4, 8, 24, 48 h). However, times of analysis should be considered with flexibility with respect to the work schedule of the laboratory.

There are two options for the analysis of the test substance in the aqueous solution: (a) the parallel method and (b) the serial method. It should be stressed that, although the parallel method is experimentally more tedious, the mathematical treatment of the results is simpler (Appendix 5). However, the choice of the methodology to be followed, is left to the experimenter who will need to consider the available laboratory facilities and resources.

(a) Parallel method: samples with the same soil/solution ratio are prepared, as many as the time intervals at which it is desired to study the adsorption kinetics. After centrifugation and if so wished filtration, the aqueous phase of the first tube is recovered as completely as possible and is measured after, for example, 4 h, that of the second tube after 8 h, that of the third after 24, etc.

(b) Serial method: only a duplicate sample is prepared for each soil/solution ratio. At defined time intervals the mixture is centrifuged to separate the phases. A small aliquot of the aqueous phase is immediately analysed for the test substance; then the experiment continues with the original mixture. If filtration is applied after centrifugation, the laboratory should have facilities to handle filtration of small aqueous aliquots. It is recommended that the total volume of the aliquots taken not exceed 1 % of the total volume of the solution, in order not to change significantly the soil/solution ratio and to decrease the mass of solute available for adsorption during the test.

The percentage adsorption $A_{t_i}$ is calculated at each time point ($t_i$) on the basis of the nominal initial concentration and the measured concentration at the sampling time ($t_i$), corrected for the value of the blank. Plots of the $A_{t_i}$ versus time (Fig. 1 Appendix 5) are generated in order to estimate the achievement of equilibrium plateau ([1]). The $K_d$ value at equilibrium is also calculated. Based on this $K_d$ value, appropriate soil/solution ratios are selected from Fig.1, so that the percentage adsorption reaches above 20 % and preferably > 50 % (61). All the applicable equations and principles of plotting are given in the section on Data and reporting and in Appendix 5.

1.9.2.2. *Determination of adsorption equilibration time and of the amount of test substance adsorbed at equilibrium*

As already mentioned, plots of $A_{t_i}$ or $C_{aq}^{ads}$ versus time permit estimation of the achievement of the adsorption equilibrium and the amount of test substance adsorbed at equilibrium. Figs. 1 and 2 in the Appendix 5 show examples of such plots. Equilibration time is the system needs to reach a plateau.

If, with a particular soil, no plateau but a steady increase is found, this may be due to complicating factors such as biodegradation or slow diffusion. Biodegradation can be shown by repeating the experiment with a sterilised sample of the soil. If no plateau is achieved even in this case, the experimenter should search for other phenomena that could be involved in his specific studies; this could be done with appropriate modifications of the experiment conditions (temperature, shaking times, soil/solution ratios). It is left to the experimenter to decide whether to continue the test procedure in spite of a possible failure to achieve an equilibrium.

1.9.2.3. *Adsorption on the surface of the test vessel and stability of the test substance*

Some information on the adsorption of the test substance on the surface of test vessels, as well as its stability, can be derived by analysing the control samples. If a depletion more than the standard error of the analytical method is observed, abiotic degradation and/or adsorption on the surface of the test vessel could be involved. Distinction between these two phenomena could be achieved by thoroughly washing the walls of the vessel with a known volume of an appropriate solvent and subjecting the wash solution to analysis for the test substance. If no adsorption on the surface of the test vessels is observed, the depletion demonstrates abiotic unstability of the test substance. If adsorption is found, changing the material of the test vessels is necessary. However, data on the adsorption on the surface of the test vessels gained from this experiment cannot be directly extrapolated to soil/solution experiment. The presence of soil will affect this adsorption.

Additional information on the stability of the test substance can be derived by determination of the parental mass balance over time. This means that the aqueous phase, extracts of soil and test vessel walls are analysed for the test substance. The difference between the mass of the test chemical added and the sum of the test chemical masses in the aqueous phase, extracts of the soil and test vessel walls is equal to the mass degraded and/or volatilised and/or not extracted. In order to perform a mass balance determination, the adsorbion equilibrium should have been reached within the period of the experiment.

The mass balance is performed on both soils and for one soil/solution ratio per soil that gives a depletion above 20 % and preferably > 50 % at equilibrium. When the ratio-finding experiment is completed with the

([1]) Plots of the concentration of the test substance in the aqueous phase ($C_{aq}^{ads}$) versus time could also be used to estimate the achievement of the equilibrium plateau (see Fig. 2 in Appendix 5).

analysis of the last sample of the aqueous phase after 48 h, the phases are separated by centrifugation and, if so wished, filtration. The aqueous phase is recovered as much as possible, and a suitable extraction solvent (extraction coefficient of at least 95 %) is added to the soil to extract the test substance. At least two successive extractions are recommended. The amount of test substance in the soil and test vessel extracts is determined and the mass balance is calculated (equation 10, Data and reporting). If it is less than 90 %, the test substance is considered to be unstable in the time scale of the test. However, studies could still be continued, taking into account the unstability of the test substance; in this case it is recommended to analyse both phases in the main study.

1.9.3. **Tier 2 — Adsorption kinetics at one concentration of the test substance**

Five soils are used, selected from Table 1. There is an advantage to including some or all of the soils used in the preliminary study, if appropriate, among these five soils. In this case, Tier 2 has not to be repeated for the soils used in preliminary study.

The equilibration time, the soil/solution ratio, the weight of the soil sample, the volume of the aqueous phase in contact with the soil and concentration of the test substance in the solution are chosen based on the preliminary study results. Analysis should preferably be done approximately after 2, 4, 6, 8 (possibly also 10) and 24 h contact time; the agitation time may be extended to a maximum of 48 h in case a chemical requires longer equilibration time with respect to ratio-finding results. However, times of analysis could be considered with flexibility.

Each experiment (one soil and one solution) is done at least in duplicate to allow estimation of the variance of the results. In every experiment one blank is run. It consists of the soil and 0,01 M $CaCl_2$ solution, without test substance, and of weight and volume, respectively, identical to those of the experiment. A control sample with only the test substance in 0,01 M $CaCl_2$ solution (without soil) is subjected to the same test procedure, serving to safeguard against the unexpected.

The percentage adsorption is calculated at each time point $A_{t_i}$ and/or time interval $A_{\Delta t_i}$ (according to the need) and is plotted versus time. The distribution coefficient $K_d$ at equilibrium, as well as the organic carbon normalised adsorption coefficient $K_{oc}$ (for non-polar organic chemicals), are also calculated.

Results of the adsorption kinetics test

The linear $K_d$ value is generally accurate to describe sorptive behaviour in soil (35) (78) and represents an expression of inherent mobility of chemicals in soil. For example, in general chemicals with $K_d \leq 1$ $cm^3$ $g^{-1}$ are considered to be qualitatively mobile. Similarly, a mobility classification scheme based on $K_{oc}$ values has been developed by MacCall et al. (16). Additionally, leaching classification schemes exist based on a relationship between $K_{oc}$ and DT-50 ([1]) (32) (79).

Also, according to error analysis studies (61), $K_d$ values below 0,3 $cm^3$ $g^{-1}$ cannot be estimated accurately from a decrease in concentration in the aqueous phase, even when the most favourable (from point of view of accuracy) soil/solution ratio is applied, i.e. 1:1. In this case analysis of both phases, soil and solution, is recommended.

With respect to the above remarks, it is recommended that the study of the adsorptive behaviour of a chemical in soil and its potential mobility be continued by determining Freundlich adsorption isotherms for these systems, for which an accurate determination of $K_d$ is possible with the experimental protocol followed in this test method. Accurate determination is possible if the value which results by multiplying the $K_d$ with the soil/solution ratio is > 0,3, when measurements are based on concentration decrease in the aqueous phase (indirect method), or > 0,1, when both phases are analysed (direct method) (61).

1.9.4. **Tier 3 — Adsorption isotherms and desorption kinetics/desorption isotherms**

1.9.4.1. *Adsorption isotherms*

Five test substance concentrations are used, covering preferably two orders of magnitude; in the choice of these concentrations the water solubility and the resulting aqueous equilibrium concentrations should be taken into account. The same soil/solution ratio per soil should be kept along the study. The adsorption test is performed as described above, with the only difference that the aqueous phase is analysed only once at the time necessary to reach equilibrium as determined before in Tier 2. The equilibrium concentrations in the

([1]) DT-50: degradation time for 50 % of the test substance.

solution are determined and the amount adsorbed is calculated from the depletion of the test substance in the solution or with the direct method. The adsorbed mass per unit mass of soil is plotted as a function of the equilibrium concentration of the test substance (see Data and reporting).

Results from the adsorption isotherms experiment

Among the mathematical adsorption models proposed so far, the Freundlich isotherm is the one most frequently used to describe adsorption processes. More detailed information on the interpretation and importance of adsorption models is provided in the references (41) (45) (80) (81) (82).

**Note**: It should be mentioned that a comparison of $K_F$ (Freundlich adsorption coefficient) values for different substances is only possible if these $K_F$ values are expressed in the same units (83).

1.9.4.2. *Desorption kinetics*

The purpose of this experiment is to investigate whether a chemical is reversibly or irreversibly adsorbed on a soil. This information is important, since the desorption process also plays an important role in the behaviour of a chemical in field soil. Moreover, desorption data are useful inputs in the computer modelling of leaching and dissolved run-off simulation. If a desorption study is desired, it is recommended that the study described below be carried out on each system for which an accurate determination of $K_d$ in the preceding adsorption kinetics experiment was possible.

Likewise with the adsorption kinetics study, there are two options to proceed with the desorption kinetics experiment: (a) the parallel method and (b) the serial method. The choice of methodology to be followed is left to the experimenter who will need to consider the available laboratory facilities and resources.

(a) Parallel method: for each soil which is chosen to proceed with the desorption study, samples with the same soil/solution ratio are prepared, as many as the time intervals at which it is desired to study the desorption kinetics. Preferably, the same time intervals as in the adsorption kinetics experiment should be used; however, the total time may be extended as appropriate in order the system to reach desorption equilibrium. In every experiment (one soil, one solution) one blank is run. It consists of the soil and 0,01 M $CaCl_2$ solution, without test substance, and of weight and volume, respectively, identical to those of the experiment. As a control sample the test substance in 0,01 M $CaCl_2$ solution (without soil) is subjected to the same test procedure. All the mixtures of the soil with the solution is agitating until to reach adsorption equilibrium (as determined before in Tier 2). Then, the phases are separated by centrifugation and the aqueous phases are removed as much as possible. The volume of solution removed is replaced by an equal volume of 0,01 M $CaCl_2$ without test substance and the new mixtures are agitated again. The aqueous phase of the first tube is recovered as completely as possible and is measured after, for example, 2 h, that of the second tube after 4 h, that of the third after 6 h, etc. until the desorption equilibrium is reached.

(b) Serial method: after the adsorption kinetics experiment, the mixture is centrifuged and the aqueous phase is removed as much as possible. The volume of solution removed is replaced by an equal volume of 0,01 M $CaCl_2$ without test substance. The new mixture is agitated until the desorption equilibrium is reached. During this time period, at defined time intervals, the mixture is centrifuged to separate the phases. A small aliquot of the aqueous phase is immediately analysed for the test substance; then, the experiment continues with the original mixture. The volume of each individual aliquot should be less than 1 % of the total volume. The same quantity of fresh 0,01 M $CaCl_2$ solution is added to the mixture to maintain the soil to solution ratio, and the agitation continues until the next time interval.

The percentage desorption is calculated at each time point ($D_{t_i}$) and/or time interval ($D_{\Delta t_i}$) (according to the needs of the study) and is plotted versus time. The desorption coefficient of $K_{des}$ at equilibrium is also calculated. All applicable equations are given in Data and reporting and Appendix 5.

Results from desorption kinetics experiment

Common plots of the percentage desorption $D_{t_i}$ and adsorption $A_{t_i}$ versus time, allow estimation of the reversibility of the adsorption process. If the desorption equilibrium is attained even within twice the time of the adsorption equilibrium, and the total desorption is more than 75 % of the amount adsorbed, the adsorption is considered to be reversible.

1.9.4.3. *Desorption isotherms*

Freundlich desorption isotherms are determined on the soils used in the adsorption isotherms experiment. The desorption test is performed as described in the section Desorption kinetics, with the only difference that the aqueous phase is analysed only once, at desorption equilibrium. The amount of the test substance desorbed is calculated. The content of test substance remaining adsorbed on soil at desorption equilibrium is plotted as a function of the equilibrium concentration of the test substance in solution (see Data and reporting and Appendix 5).

## 2. DATA AND REPORTING

The analytical data are presented in tabular form (see Appendix 6). Individual measurements and averages calculated are given. Graphical representations of adsorption isotherms are provided. The calculations are made as described below.

For the purpose of the test, it is considered that the weight of 1 $cm^3$ of aqueous solution is 1 g. The soil/solution ratio may be expressed in units of w/w or w/vol with the same figure.

### 2.1. ADSORPTION

The adsorption ($A_{t_i}$) is defined as the percentage of substance adsorbed on the soil related to the quantity present at the beginning of the test, under the test conditions. If the test substance is stable and does not adsorb significantly to the container wall, $A_{t_i}$ is calculated at each time point $t_i$, according to the equation:

$$A_{t_i} = \frac{m_s^{ads}(t_i) \cdot 100}{m_0} (\%) \quad (3)$$

where:

$A_{t_i}$ = adsorption percentage at the time point $t_i$ (%);

$m_s^{ads}(t_i)$ = mass of the test substance adsorbed on the soil at the time $t_i$ (μg);

$m_0$ = mass of the test substance in the test tube, at the beginning of the test (μg).

Detailed information on how to calculate the percentage of adsorption $A_{t_i}$ for the parallel and serial methods is given in Appendix 5.

The distribution coefficient $K_d$ is the ratio between the content of the substance in the soil phase and the mass concentration of the substance in the aqueous solution, under the test conditions, when adsorption equilibrium is reached.

$$K_d = \frac{C_s^{ads}(eq)}{C_{aq}^{ads}(eq)} = \frac{m_s^{ads}(eq)}{m_{aq}^{ads}(eq)} \frac{V_0}{m_{soil}} (cm^3\ g^{-1}) \quad (4)$$

where:

$C_s^{ads}(eq)$ = content of the substance adsorbed on the soil at adsorption equilibrium (μg $g^{-1}$)

$C_{aq}^{ads}(eq)$ = mass concentration of the substance in the aqueous phase at adsorption equilibrium (μg $cm^{-3}$). This concentration is analytically determined taking into account the values given by the blanks

$m_s^{ads}(eq)$ = mass of the substance adsorbed on the soil at adsorption equilibrium (μg)

$m_{aq}^{ads}(eq)$ = mass of the substance in the solution at adsorption equilibrium (μg)

$m_{soil}$ = quantity of the soil phase, expressed in dry mass of soil (g)

$v_0$ = initial volume of the aqueous phase in contact with the soil ($cm^3$).

The relation between $A_{eq}$ and $K_d$ is given by:

$$K_d = \frac{A_{eq}}{100 - A_{eq}} \frac{V_0}{m_{soil}} (cm^3\ g^{-1}) \quad (5)$$

where:

$A_{eq}$ = percentage of adsorption at adsorption equilibrium, %.

The organic carbon normalised adsorption coefficient $K_{oc}$ relates the distribution coefficient $K_d$ to the content of organic carbon of the soil sample:

$$K_{oc} = K_d \cdot \frac{100}{\%oc} (cm^3\ g^{-1}) \quad (6)$$

where:

% oc = percentage of organic carbon in the soil sample (g $g^{-1}$).

$K_{oc}$ coefficient represents a single value which characterises the partitioning mainly of non-polar organic chemicals between organic carbon in the soil or sediment and water. The adsorption of these chemicals is correlated with the organic content of the sorbing solid (7); thus, $K_{oc}$ values depend on the specific characteristics of the humic fractions which differ considerably in sorption capacity, due to differences in origin, genesis, etc.

2.1.1. **Adsorption isotherms**

The Freundlich adsorption isotherms equation relates the amount of the test substance adsorbed to the concentration of the test substance in solution at equilibrium (equation 8).

The data are treated as under 'Adsorption' and, for each test tube, the content of the test substance adsorbed on the soil after the adsorption test ($C_s^{ads}(eq)$, elsewhere denoted as x/m) is calculated. It is assumed that equilibrium has been attained and that $C_s^{ads}(eq)$ represents the equilibrium value:

$$C_s^{ads}(eq) = \frac{m_s^{ads}(eq)}{m_{soil}} = \frac{\left[C_0 - C_{aq}^{ads}(eq)\right] \cdot V_0}{m_{soil}} (\mu g\ g^{-1}) \quad (7)$$

The Freundlich adsorption equation is shown in (8):

$$C_s^{ads}(eq) = K_F^{ads} \cdot C_{aq}^{ads}(eq)^{1/n}\ (\mu g\ g^{-1}) \quad (8)$$

or in the linear form:

$$\log C_s^{ads}(eq) = \log K_F^{ads} + 1/n \cdot \log C_{aq}^{ads}(eq) \quad (9)$$

where:

$K_F^{ads}$ = Freundlich adsorption coefficient; its dimension is $cm^3\ g^{-1}$ only if 1/n = 1; in all other cases, the slope 1/n is introduced in the dimension of $K_F^{ads}$ $(\mu g^{1-1/n} (cm^3)^{1/n}\ g^{-1})$

n = regression constant; 1/n generally ranges between 0,7-1,0, indicating that sorption data is frequently slightly non-linear.

Equations (8) and (9) are plotted and the values of $K_F^{ads}$ and 1/n are calculated by regression analysis using equation 9. The correlation coefficient $r^2$ of the log equation is also calculated. An example of such plots is given in Fig. 2.

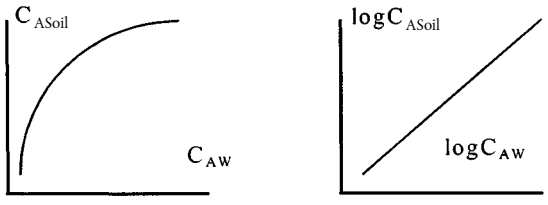


**Fig. 2.** Freundlich adsorption plot, normal and linearised

2.1.2. **Mass balance**

The mass balance (MB) is defined as the percentage of substance which can be analytically recovered after an adsorption test versus the nominal amount of substance at the beginning of the test.

The treatment of data will differ if the solvent is completely miscible with water. In the case of water-miscible solvent, the treatment of data described under 'Desorption' may be applied to determine the amount of substance recovered by solvent extraction. If the solvent is less miscible with water, the determination of the amount recovered has to be made.

The mass balance MB for the adsorption is calculated as follows; it is assumed that the term ($m_E$) corresponds to the sum of the test chemical masses extracted from the soil and surface of the test vessel with an organic solvent:

$$MB = \frac{\left(V_{rec} \cdot C_{aq}^{ads}(eq) + m_E\right) \cdot 100}{V_0 \cdot C_0} \ (\%) \qquad (10)$$

where:

MB = mass balance (%)

$m_E$ = total mass of test substance extracted from the soil and walls of the test vessel in two steps (μg)

$C_0$ = initial mass concentration of the test solution in contact with the soil (μg $cm^{-3}$)

$V_{rec}$ = volume of the supernatant recovered after the adsorption equilibrium ($cm^{-3}$).

2.2. DESORPTION

The desorption (D) is defined as the percentage of the test substance which is desorbed, related to the quantity of substance previously adsorbed, under the test conditions:

$$D_{t_i} = \frac{m_{aq}^{des}(t_i)}{m_s^{ads}(eq)} \cdot 100 \ (\%) \qquad (11)$$

where:

$D_{t_i}$ = desorption percentage at a time point $t_i$ (%)

$m_{aq}^{des}(t_i)$ = mass of the test substance desorbed from soil at a time point $t_i$ (μg)

$m_s^{des}(eq)$ = mass of the test substance adsorbed on soil at adsorption equilibrium (μg).

Detailed information on how to calculate the percentage of desorption $D_{t_i}$ for the parallel and serial methods is given in Appendix 5.

The apparent desorption coefficient ($K_{des}$) is, under the test conditions, the ratio between the content of the substance remaining in the soil phase and the mass concentration of the desorbed substance in the aqueous solution, when desorption equilibrium is reached:

$$K_{des} = \frac{m_s^{ads}(eq) - m_{aq}^{des}(eq)}{m_{aq}^{des}(eq)} \frac{V_T}{m_{soil}} (cm^3\ g^{-1}) \qquad (12)$$

where:

$K_{des}$ = desorption coefficient ($cm^3\ g^{-1}$)

$m_{aq}^{des}(eq)$ = total mass of the test substance desorbed from soil at desorption equilibrium (μg)

$V_T$ = total volume of the aqueous phase in contact with the soil during the desorption kinetics test ($cm^3$).

Guidance for calculating the $m_{aq}^{des}(eq)$ is given in Appendix 5 under the heading 'Desorption'.

Remark:

If the adsorption test which was preceded, was performed with the parallel method the volume $V_T$ in equation 12 is considered to be equal to $V_0$.

2.2.1. **Desorption isotherms**

The Freundlich desorption isotherms equation relates the content of the test substance remaining adsorbed on the soil to the concentration of the test substance in solution at desorption equilibrium (equation 16).

For each test tube, the content of the substance remaining adsorbed on soil at desorption equilibrium is calculated as follows:

$$C_s^{des}(eq) = \frac{m_s^{ads}(eq) - m_{aq}^{des}(eq)}{m_{soil}} (\mu g\ g^{-1}) \quad (13)$$

$m_{aq}^{des}(eq)$ is defined as:

$$m_{aq}^{des}(eq) = m_m^{des}(eq) \cdot \frac{V_0}{V_r^F} - m_{aq}^A(\mu g) \quad (14)$$

where:

$C_s^{des}(eq)$ = content of the test substance remaining adsorbed on the soil at desorption equilibrium (µg $g^{-1}$)

$m_m^{des}(eq)$ = mass of substance determined analytically in the aqueous phase at desorption equilibrium (µg)

$m_{aq}^A$ = mass of the test substance left over from the adsorption equilibrium due to incomplete volume replacement (µg)

$m_{aq}^{des}(eq)$ = mass of the substance in the solution at adsorption equilibrium (µg)

$$m_{aq}^A = m_{aq}^{ads}(eq) \cdot \left(\frac{V_0 - V_R}{V_0}\right) \quad (15)$$

$V_r^F$ = volume of the solution taken from the tube for the measurement of the test substance, at desorption equilibrium ($cm^3$)

$V_R$ = volume of the supernatant removed from the tube after the attainment of adsorption equilibrium and replaced by the same volume of a 0,01 M $CaCl_2$ solution ($cm^3$).

The Freundlich desorption equation is shown in (16):

$$C_s^{des}(eq) = K_F^{des} \cdot C_{aq}^{des}(eq)^{1/n} (\mu g\ g^{-1}) \quad (16)$$

or in the linear form:

$$\log C_s^{des}(eq) = \log K_F^{des} + 1/n \cdot \log C_{aq}^{des}(eq) \quad (17)$$

where:

$K_F^{des}$ = Freundlich desorption coefficient

n = regression constant

$C_{aq}^{des}(eq)$ = mass concentration of the substance in the aqueous phase at desorption equilibrium (µg $cm^{-3}$).

The equations 16 and 17 can be plotted and the value of $K_F^{des}$ and 1/n are calculated by regression analysis using the equation 17.

Remark:

If the Freundlich adsorption or desorption exponent 1/n is equal to 1, the Freundlich adsorption or desorption binding constant ($K_F^{ads}$ and $K_F^{des}$) will be equal to the adsorption or desorption equilibrium constants ($K_d$ and $K_{des}$) respectively, and plots of $C_s$ vs $C_{aq}$ will be linear. If the exponents are not equal to 1, plots of $C_s$ vs $C_{aq}$ will be non-linear and the adsorption and desorption constants will vary along the isotherms.

2.2.2. **Testreport**

The test report should include the following information:

— Complete identification of the soil samples used including:

  — geographical reference of the site (latitude, longitude),

  — date of sampling,

  — use pattern (e.g. agricultural soil, forest, etc.),

  — depth of sampling,

  — sand/silt/clay content,

  — pH values (in 0,01 M $CaCl_2$),

  — organic carbon content,

  — organic matter content,

  — nitrogen content,

  — C/N ratio,

  — cation exchange capacity (mmol/kg),

  — all information relating to the collection and storage of soil samples,

  — where appropriate, all relevant information for the interpretation of the adsorption/desorption of the test substance,

  — reference of the methods used for the determination of each parameter,

— information on the test substance as appropriate,

— temperature of the experiments,

— centrifugation conditions,

— analytical procedure used to analyse the test substance,

— justification for any use of solubilising agent for the preparation of the stock solution of the test substance,

— explanations of corrections made in the calculations, if relevant,

— data according to the form sheet (Appendix 6) and graphical presentations,

— all information and observations helpful for the interpretation of the test results.

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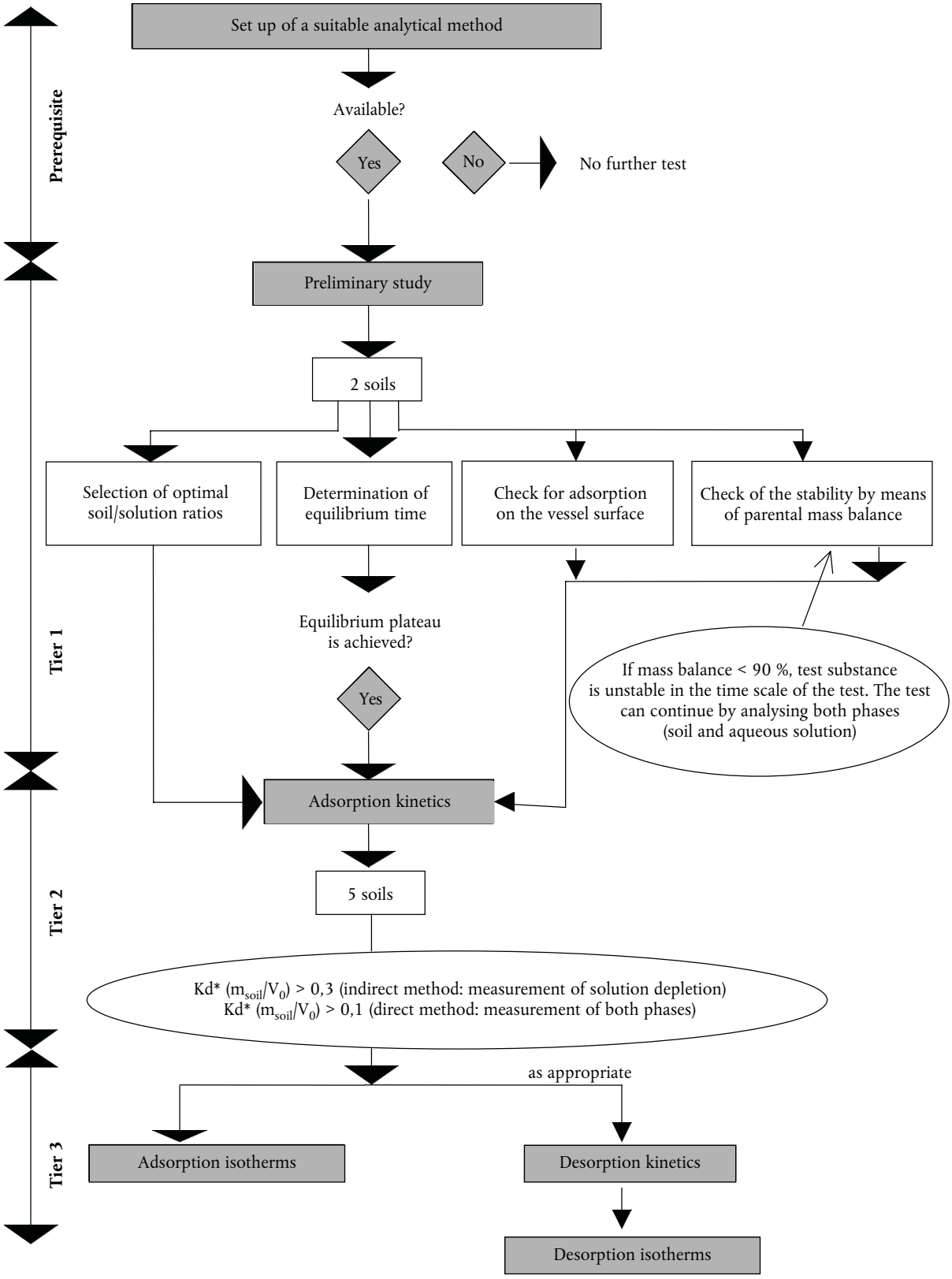
*APPENDIX 1*

**TESTING SCHEME**



*APPENDIX 2*

**INFLUENCE OF ACCURACY OF ANALYTICAL METHOD AND CONCENTRATION CHANGE ON ACCURACY OF ADSORPTION RESULTS**

From the following table (84) it becomes obvious that when the difference between the initial mass ($m_0$ = 110 µg) and equilibrium mass ($m_{aq}^{ads}$ (eq) = 100 µg) of the test substance in the solution is very small, an error of 5 % in the measurement of equilibrium concentration results in an error of 50 % in the calculation of the mass of the substance adsorbed in soil ($m_s^{ads}$ (eq)) and of 52,4 % in the calculation of the $K_d$.

Amount of soil $m_{soil}$ = 10 g
Volume of solution $V_0$ = 100 $cm^3$

| | $m_{aq}^{ads}$ (eq) (µg) | $C_{aq}^{ads}$ (eq) (µg $cm^{-3}$) | R | ($m_s^{ads}$ (eq)* (µg) | $C_s^{ads}$ (eq)* (µg $g^{-1}$) | R‡ | $K_d$* | R‡ |
|---|---|---|---|---|---|---|---|---|
| | **FOR A = 9 %** | | | | | | | |
| $m_0$ = 110 µg or $C_0$ = 1,100 µg/$cm^3$ | 100 | 1,000 | true value | 10 | 1,00 | true value | 1 | |
| | 101 | 1,010 | 1 % | 9 | 0,90 | 10 % | 0,891 | 10,9 % |
| | 105 | 1,050 | 5 % | 5 | 0,50 | 50 % | 0,476 | 52,4 % |
| | 109 | 1,090 | 9 % | 1 | 0,10 | 90 % | 0,092 | 90,8 % |
| | **FOR A = 55 %** | | | | | | | |
| $m_0$ = 110 µg or $C_0$ = 1,100 µg/$cm^3$ | 50,0 | 0,500 | true value | 60,0 | 6,00 | true value | 12,00 | |
| | 50,5 | 0,505 | 1 % | 59,5 | 5,95 | 0,8 % | 11,78 | 1,8 % |
| | 52,5 | 0,525 | 5 % | 57,5 | 5,75 | 4,0 % | 10,95 | 8,8 % |
| | 55,0 | 0,550 | 10 % | 55,0 | 5,50 | 8,3 % | 10,00 | 16,7 % |
| | **FOR A = 99 %** | | | | | | | |
| $m_0$ = 110 µg or $C_0$ = 1,100 µg/$cm^3$ | 1,100 | 0,011 | true value | 108,9 | 10,89 | true value | 990 | |
| | 1,111 | 0,01111 | 1 % | 108,889 | 10,8889 | 0,01 % | 980 | 1,0 % |
| | 1,155 | 0,01155 | 5 % | 108,845 | 10,8845 | 0,05 % | 942 | 4,8 % |
| | 1,21 | 0,0121 | 10 % | 108,790 | 10,8790 | 0,10 % | 899 | 9,2 % |

Where:

$$*m_s^{ads}(eq) = m_0 - m_{aq}^{ads}(eq),\ C_s^{ads}(eq) = \frac{\left[C_0 - C_{aq}^{ads}(eq)\right] V_0}{m_{bodem}},\ K_d = \frac{m_s^{ads}(eq)}{m_{aq}^{ads}(eq)} \frac{V_0}{m_{bodem}}$$

$m_s^{ads}$ (eq) = mass of the test substance in the soil phase at equilibrium, µg

$m_{aq}^{ads}$ (eq) = mass of the test substance in the aqueous phase at equilibrium, µg

$C_s^{ads}$ (eq) = content of the test substance in the soil phase at equilibrium, µg $g^{-1}$

$C_{aq}^{ads}$ (eq) = mass concentration of the test substance in the aqueous phase at equilibrium, µg $cm^{-3}$

R = analytical error in the determination of the $m_{aq}^{ads}$ (eq)

R‡ = calculated error due to the analytical error R.

*APPENDIX 3*

## ESTIMATION TECHNIQUES FOR $K_d$

1. Estimation techniques permit prediction of $K_d$ based on correlations with, for example, $P_{ow}$ values (12) (39) (63-68), water solubility data (12) (19) (21) (39) (68-73), or polarity data derived by application of HPLC on reversed phase (74-76). As shown in Tables 1 and 2, is the $K_{oc}$ or $K_{om}$ that are calculated from these equations and then, indirectly, the $K_d$ from the equations:

$$K_{oc} = K_d \cdot \frac{100}{\%oc} \, (cm^3 \, g^{-1}) \qquad K_{om} = \frac{K_d}{1,724} \cdot \frac{100}{\%oc} \, (cm^3 \, g^{-1})$$

2. The concept of these correlations is based on two assumptions: (1) it is the organic matter of the soil that mainly influences the adsorption of a substance; and (2) the interactions involved are mainly non-polar. As a result, these correlations: (1) are not, or are only to some extent, applicable to polar substances, and (2) are not applicable in cases where the organic matter content of the soil is very small (12). In addition, although satisfactory correlations have been found between $P_{ow}$ and adsorption (19), the same cannot be said for the relationship between water solubility and extent of adsorption (19) (21); so far the studies are very contradictory.

3. Some examples of correlations between the adsorption coefficient and the octanol-water partition coefficient, as well as water solubility are given in Tables 1 and 2, respectively.

**Table 1.** Examples of correlations between the adsorption distribution coefficient and the octanol-water partition coefficient; for further examples (12) (68)

| Substances | Correlations | Authors |
|---|---|---|
| Substituted ureas | $\log K_{om} = 0,69 + 0,52 \log P_{ow}$ | Briggs (1981) (39) |
| Aromatic chlorinated | $\log K_{oc} = -0,779 + 0,904 \log P_{ow}$ | Chiou et al. (1983) (65) |
| Various pesticides | $\log K_{om} = 4,4 + 0,72 \log P_{ow}$ | Gerstl and Mingelgrin (1984) (66) |
| Aromatic hydrocarbons | $\log K_{oc} = -2,53 + 1,15 \log P_{ow}$ | Vowles and Mantoura (1987) (67) |

**Table 2.** Examples of correlations between the adsorption distribution coefficient and water solubility; for further examples see (68) (69)

| Compounds | Correlations | Authors |
|---|---|---|
| Various pesticides | $\log K_{om} = 3,8 - 0,561 \log S_w$ | Gerstl and Mingelgrin (1984) (66) |
| Aliphatic, aromatic chlorinated substances | $\log K_{om} = (4,040 +/- 0,038) - (0,557 +/- 0,012) \log S_w$ | Chiou et al. (1979) (70) |
| α-naphtol | $\log K_{oc} = 4,273 - 0,686 \log S_w$ | Hasset et al. (1981) (71) |
| Cyclic, aliphatic aromatic substances | $\log K_{oc} = -1,405 - 0,921 \log S_w - 0,00953$ (mp-25) | Karickhoff (1981) (72) |
| Various compounds | $\log K_{om} = 2,75 - 0,45 \log S_w$ | Moreale van Blade (1982) (73) |

*APPENDIX 4*

**CALCULATIONS FOR DEFINING THE CENTRIFUGATION CONDITIONS**

1. The centrifugation time is given by the following formula, assuming spherical particles:

$$t = \frac{9}{2}\left[\frac{\eta}{\omega^2 r p^2(\rho_s - \rho_{aq})}\right] \ln(R_b/R_t) \quad (1)$$

For simplification purposes, all parameters are described in non-SI units (g, cm).

where:

$\omega$ = rotational speed (=2 π rpm/60), rad $s^{-1}$

rpm = revolutions per minute

$\eta$ = viscosity of solution, g $s^{-1}$ $cm^{-1}$

$r_p$ = particle radius, cm

$\rho_s$ = soil density, g $cm^{-3}$

$\rho_{aq}$ = solution density, g $cm^{-3}$

$R_t$ = distance from the centre of centrifuge rotor to top of solution in centrifuge tube, cm

$R_b$ = distance from the centre of centrifuge rotor to bottom in centrifuge tube, cm

$R_b$-$R_t$ = length of the soil/solution mixture in the centrifuge tube, cm.

In general practice, double the calculated times is used to ensure complete separation.

2. The equation (1) can be simplified further if we consider the viscosity ($\eta$) and the density ($\rho_{aq}$) of the solution as equal to the viscosity and density of water at 25 °C; thus, $\eta = 8{,}95 \times 10^{-3}$ g $s^{-1}$ $cm^{-1}$ and $\rho_{aq} = 1{,}0$ g, $cm^{-3}$.

Then, the centrifugation time is given by the equation (2):

$$t = \frac{3,7}{(rpm)^2 \cdot r_p^2(\rho s - 1)} \ln \frac{Rb}{Rt} \quad (2)$$

3. From the equation 2 it becomes apparent that two parameters are important in defining the centrifugation condition, i.e. time (t) and speed (rpm), in order to achieve separation of particles with a specific size (in our case 0,1 μm radius): (1) the density of the soil and (2) the length of the mixture in the centrifuge tube ($R_b$-$R_t$), i.e. the distance which a soil particle covers from the top of the solution to the bottom of the tube; obviously, for a fixed volume the length of the mixture in the tube will depend on the square of the radius of the tube.

4. Fig. 1 presents variations in the centrifugation time (t) versus centrifugation speed (rpm) for different soil densities ($\rho_s$) (Fig. 1a) and different lengths of the mixture in the centrifuge tubes (Fig. 1b). From Fig. 1a the influence of the soil density appears obvious; for example, for a classical centrifugation of 3 000 rpm the centrifugation time is approximately 240 min. for 1,2 g $cm^3$ soil density, while it is only 50 min. for 2,0 g $cm^3$. Similarly, from Fig. 1b, for a classical centrifugation of 3 000 rpm the centrifugation time is approximately 50 min. for a length of the mixture of 10 cm and only 7 min. for a length of 1 cm. However, it is important to find an optimal relation between centrifugation which requires the less length possible and easy handling for the experimenter in separating the phases after centrifugation.

5. Moreover, when defining the experimental conditions for the separation of soil/solution phases, it is important to consider the possible existence of a third 'pseudo-phase', the colloids. These particles, with a size less than 0,2 µm, can have an important impact on the whole adsorption mechanism of a substance in a soil suspension. When centrifugation is performed as described above, colloids remain in the aqueous phase and are subjected to analysis together with the aqueous phase. Thus, the information about their impact is lost.

   If the conducting laboratory has ultracentrifugation or ultrafiltration facilities, the adsorption/desorption of a substance in soil could be studied more in depth, including information on the adsorption of the substance on the colloids. In this case, an ultracentrifugation at 60 000 rpm/min. or an ultrafiltration with filter porosity of 100 000 Daltons should be applied in order to separate the three phases soil, colloids, solution. The test protocol should also be modified accordingly, in order all three phases to be subjected to substance analysis.

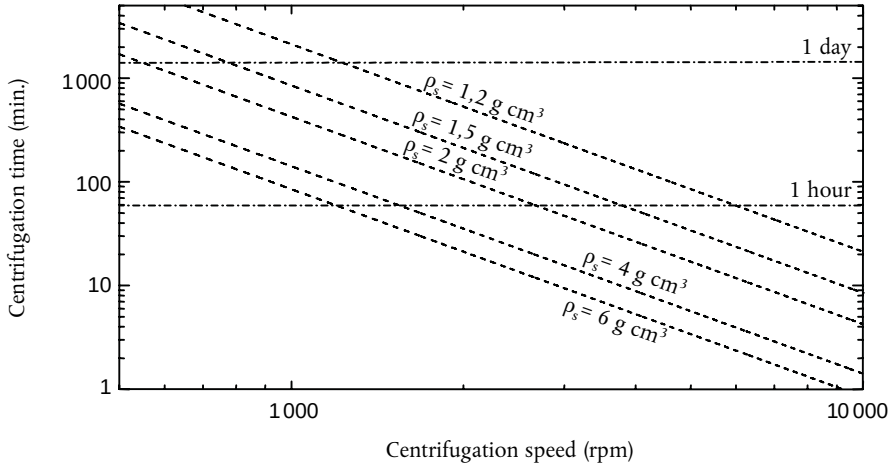



**Fig. 1a.** Variations of centrifugation time (t) versus centrifugation speed (rpm) for different soil densities ($\rho_s$). $R_t$ = 10 cm, $R_b$-$R_t$ = 10 cm, $\eta$ = 8,95 × $10^{-3}$ g $s^{-1}$ $cm^{-1}$ and $\rho_{aq}$ = 1,0 g $cm^{-3}$ at 25 °C.

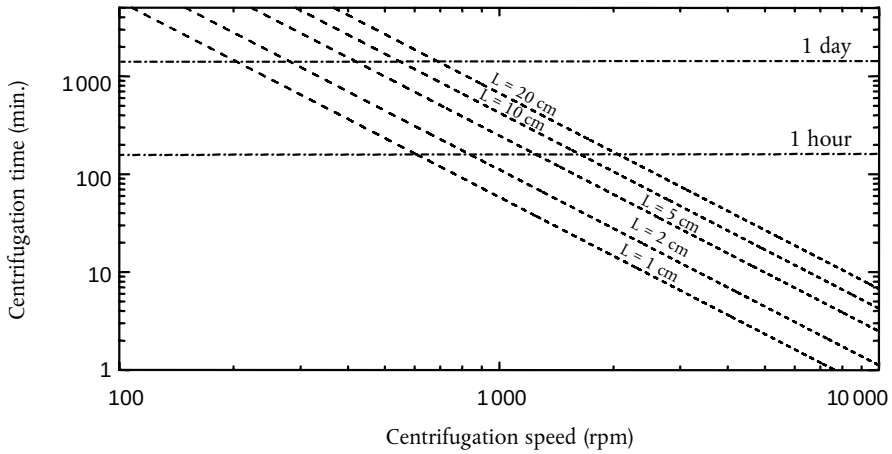
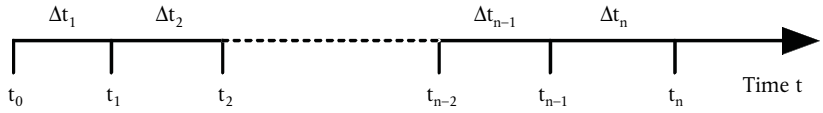



**Fig. 1b.** Variations of centrifugation time (t) versus centrifugation speed (rpm) for different lengths of the mixture in the centrifuge tube ($R_b$-$R_t$) = L; $R_t$ = 10 cm, $\eta$ = 8,95 × $10^{-3}$ g $s^{-1}$ $cm^{-1}$, $\rho_{aq}$ = 1,0 g $cm^{-3}$ at 25 °C and $\rho_s$ = 2,0 g $cm^{-3}$.

*APPENDIX 5*

**CALCULATION OF ADSORPTION A (%) AND DESORPTION D (%)**

The time scheme of the procedure is:




For all the calculations it is assumed that the test substance is stable and does not adsorb significantly to the container walls.

ADSORPTION A (A%)

(a) *Parallel method*

The percentage adsorption is calculated for each test tube (i) at each time point ($t_i$), according to the equation:

$$A_{t_i} = \frac{m_s^{ads}(t_i) \cdot 100}{m_0} (\%) \qquad (1)\ (^1)$$

The terms of this equation may be calculated as follows:

$$m_0 = C_0 \cdot V_0\ (\mu g) \qquad (2)$$

$$m_s^{ads}(t_i) = m_0 - C_{aq}^{ads}(t_i) \cdot V_0\ (\mu g) \qquad (3)$$

where:

$A_{t_i}$ = adsorption percentage (%) at the time point $t_i$

$m_s^{ads}(t_i)$ = mass of the test substance on soil at the time $t_i$ that the analysis is performed (μg)

$m_0$ = mass of test substance in the test tube, at the beginning of the test (μg)

$C_0$ = initial mass concentration of the test solution in contact with the soil (μg $cm^{-3}$)

$C_{aq}^{ads}(t_i)$ = mass concentration of the substance in the aqueous phase at the time $t_i$ that the analysis is performed (μg $cm^{-3}$); this concentration is analytically determined taking into account the values given by the blanks

$V_0$ = initial volume of the test solution in contact with the soil ($cm^3$).

The values of the adsorption percentage $A_{t_i}$ or $C_{aq}^{ads}(t_i)$ are plotted versus time and the time after which the sorption equilibrium is attained is determined. Examples of such plots are given in Fig. 1 and Fig. 2 respectively.

(1) Equation applicable to both direct and indirect methods. All the other equations are applicable only to indirect method.

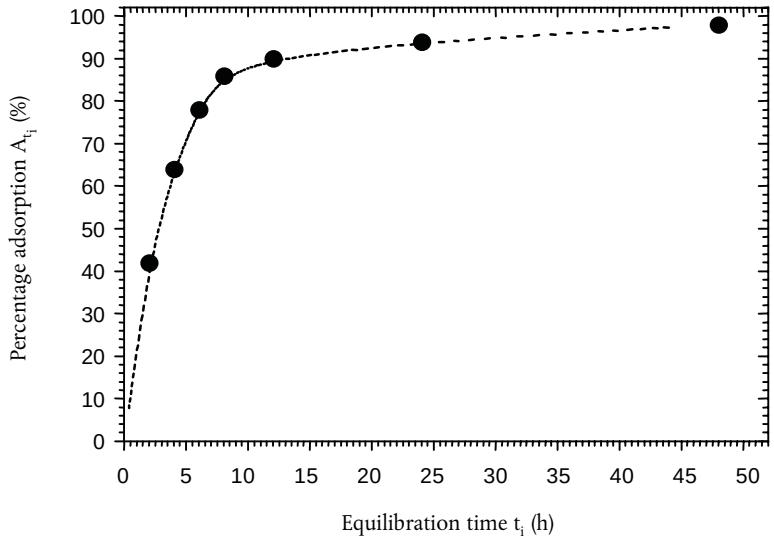



**Fig. 1.** Adsorption equilibrium plot

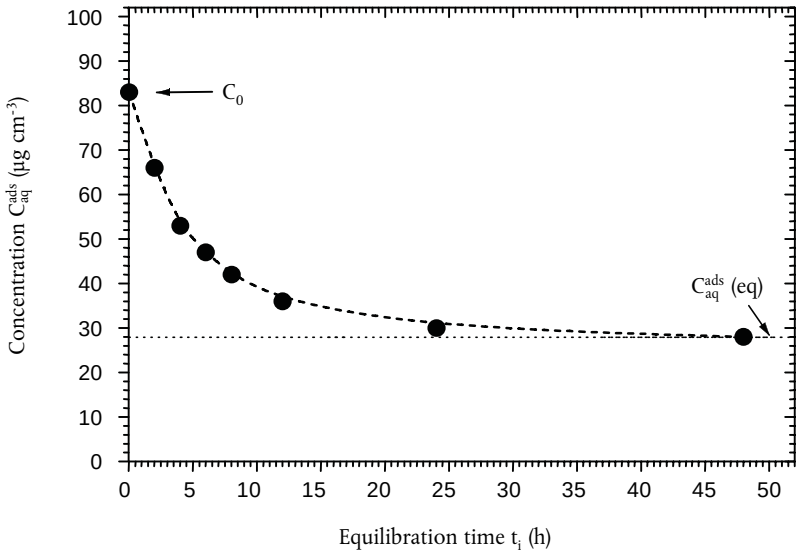



**Fig. 2.** Mass concentration of the test substance in the aqueous phase ($C_{aq}$) versus time

(b) *Serial method*

The following equations take into account that the adsorption procedure is carried out by measurements of the test substance in small aliquots of the aqueous phase at specific time intervals.

— During each time interval the amount of the substance adsorbed on the soil is calculated as follows:

— for the first time interval $\Delta t_i = t_i - t_0$

$$m_s^{ads}(\Delta t_1) = m_0 - m_m^{ads}(t_1) \cdot \left(\frac{V_0}{v_a^A}\right) \quad (4)$$

— for the second time interval $\Delta t_2 = t_2 - t_1$

$$m_s^{ads}(\Delta t_2) = m_m^{ads}(t_1) \cdot \left(\frac{V_0}{v_a^A}\right) - m_m^{ads}(t_2) \cdot \left(\frac{V_0 - v_a^A}{v_a^A}\right) \quad (5)$$

— for the third time interval $\Delta t_3 = t_3 - t_2$

$$m_s^{ads}(\Delta t_3) = m_m^{ads}(t_2) \cdot \left(\frac{V_0 - v_a^A}{v_a^A}\right) - m_m^{ads}(t_3) \cdot \left(\frac{V_0 - 2 \cdot v_a^A}{v_a^A}\right) \quad (6)$$

— for the $n^{th}$ time interval $\Delta t_n = t_n - t_{n-1}$

$$m_s^{ads}(\Delta t_n) = m_m^{ads}(t_{n-1}) \cdot \left(\frac{V_0 - (n-2) \cdot v_a^A}{v_a^A}\right) - m_m^{ads}(t_n) \cdot \left(\frac{(V_0 - (n-1) \cdot v_a^A)}{v_a^A}\right) \quad (7)$$

— The percentage of adsorption at each time interval, $A_{\Delta t_i}$, is calculated using the following equation:

$$A_{\Delta t_i} = \frac{m_s^{ads}(\Delta t_i)}{m_0} \cdot 100\ (\%) \quad (8)\ (1)$$

while the percentage of adsorption ($A_{t_i}$) at a time point $t_i$ is given by the equation:

$$A_{t_i} = \frac{\sum_{j=\Delta t_1}^{\Delta t_i} m_s^{ads}(j)}{m_0} \cdot 100\ (\%) \quad (9)\ (1)$$

The values of the adsorption $A_{t_i}$ or $A_{\Delta t_i}$ (with respect to the needs of the study) are plotted versus time and the time after which the sorption equilibrium is attained is determined.

— At the equilibration time $t_{eq}$:

— the mass of the test substance adsorbed on the soil is:

$$m_s^{ads}(eq) = \sum_{\Delta t_i = 1}^{n} m_s^{ads}(\Delta t_i) \quad (10)\ (1)$$

— the mass of the test substance in the solution is:

$$m_{aq}^{ads}(eq) = m_0 - \sum_{\Delta t_i = 1}^{n} m_s^{ads}(\Delta t_i) \quad (11)\ (1)$$

— and the percentage of adsorption at equilibrium is:

$$A_{eq} = \frac{m_s^{ads}(eq)}{m_0} \cdot 100\ (\%) \quad (12)\ (1)$$

The parameters used above are defined as:

$m_s^{ads}(\Delta t_1)$, $m_s^{ads}(\Delta t_2)$, …, $m_s^{ads}(\Delta t_n)$ = mass of the substance adsorbed on the soil during the time intervals $\Delta t_1$, $\Delta t_2$, …, $\Delta t_n$ respectively (μg)

$m_m^{ads}(t_1)$, $m_m^{ads}(t_2)$, …, $m_n^{ads}(t_n)$ = mass of the substance measured in an aliquot $v_a^A$ at the time points $t_1$, $t_2$, …, $t_n$ respectively (μg)

$m_s^{ads}(eq)$ = mass of the substance adsorbed on the soil at adsorption equilibrium (μg)

$m_{aq}^{ads}(eq)$ = mass of the substance in the solution at adsorption equilibrium (μg)

$v_a^A$ = volume of the aliquot in which the test substance is measured ($cm^3$)

$A_{\Delta t_i}$ = percentage of adsorption corresponding at a time interval $\Delta t_i$ (%)

$A_{eq}$ = percentage of adsorption at adsorption equilibrium (%).

(1) Equation applicable to both direct and indirect methods. All the other equations are applicable only to indirect method.

DESORPTION D (%)

The time $t_0$ that the desorption kinetics experiment begins, is considered as the moment that the maximal recovered volume of the test substance solution (after that the adsorption equilibrium is attained) is replaced by an equal volume of 0,01 M $CaCl_2$ solution.

(a) *Parallel method*

At a time point $t_i$, the mass of the test substance is measured in the aqueous phase taken from the tube i ($V_r^i$), and the mass desorbed is calculated according to the equation:

$$m_{aq}^{des}(t_i) = m_m^{des}(t_i) \cdot \left(\frac{V_0}{v_r^i}\right) - m_{aq}^A \tag{13}$$

At desorption equilibrium $t_i = t_{eq}$ and therefore $m_{aq}^{ads}(t_i) = m_{aq}^{ads}(eq)$.

The mass of the test substance desorbed during a time interval ($\Delta t_i$) is given by the equation:

$$m_{aq}^{des}(\Delta t_i) = m_{aq}^{des}(t_i) - \sum_{j=1}^{i-1} m_{aq}^{des}(j) \tag{14}$$

The percentage of desorption is calculated:

— at a time point $t_i$ from the equation:

$$D_{t_i} = \frac{m_{aq}^{des}(t_i)}{m_s^{ads}(eq)} \cdot 100\ (\%) \tag{15}$$

— and during a time interval ($\Delta t_i$) from the equation:

$$D_{\Delta t_i} = \frac{m_{aq}^{des}(\Delta t_i)}{m_s^{ads}(eq)} \cdot 100\ (\%) \tag{16}$$

where:

$D_{t_i}$ = desorption percentage at a time point $t_i$ (%)

$D_{\Delta t_i}$ = desorption percentage corresponding to a time interval $\Delta t_i$ (%)

$m_{aq}^{des}(t_i)$ = mass of the test substance desorbed at a time point $t_i$, (μg)

$m_{aq}^{des}(\Delta t_i)$ = mass of the test substance desorbed during a time interval $\Delta t_i$ (μg)

$m_m^{des}(t_i)$ = mass of the test substance analytically measured at a time $t_i$ in a solution volume $V_r^i$, which is taken for the analysis (μg)

$m_{aq}^A$ = mass of the test substance left over from the adsorption equilibrium due to incomplete volume replacement (μg)

$$m_{aq}^A = m_{aq}^{ads}\ (eq) \cdot \left(\frac{V_0 - V_R}{V_0}\right) \tag{17}$$

$m_{aq}^{ads}(eq)$ = mass of the test substance in the solution at adsorption equilibrium (μg)

$V_R$ = volume of the supernatant removed from the tube after the attainment of adsorption equilibrium and replaced by the same volume of a 0,01 M $CaCl_2$ solution ($cm^3$)

$V_r^i$ = volume of the solution taken from the tube (i) for the measurement of the test substance, in desorption kinetics experiment ($cm^3$).

The values of desorption $D_{t_i}$ or $D_{\Delta t_i}$ (according to the needs of the study) are plotted versus time and the time after which the desorption equilibrium is attained is determined.

(b) *Serial method*

The following equations take into account that the adsorption procedure, which was preceded, was carried out by measurement of test substance in small aliquots ($v_a^A$) of the aqueous phase (serial method in 1.9. Performance of the test). It is assumed that: (a) the volume of the supernatant removed from the tube after the adsorption kinetics experiment was replaced by the same volume of 0,01 M $CaCl_2$ solution ($V_R$) and (b) and the total volume of the aqueous phase in contact with the soil ($V_T$) during the desorption kinetics experiment remains constant and is given by the equation:

$$V_T = V_0 - \sum_{i=1}^{n} v_a^A(i) \tag{18}$$

At a time point $t_i$:

— the mass of the test substance is measured in a small aliquot ($v_a^D$) and the mass desorbed is calculated, according to the equation:

$$m_{aq}^{des}(t_i) = m_m^{des}(t_i) \cdot \left(\frac{V_T}{v_a^D}\right) - m_{aq}^A \cdot \left(\frac{(V_T - (i-1) \cdot v_a^D)}{V_T}\right) \tag{19}$$

— at desorption equilibrium $t_i = t_{eq}$ and therefore $m_{aq}^{des}(t_i) = m_{aq}^{des}(eq)$.

— the percentage of desorption $D_{t_i}$ is calculated, from the following equation:

$$D_{t_i} = \frac{m_{aq}^{des}(t_i)}{m_s^{ads}(eq)} \cdot 100\ (\%) \tag{20}$$

At a time interval ($\Delta t_i$):

During each time interval the amount of the substance desorbed is calculated as follows:

— for the first time interval $\Delta t_1 = t_1 - t_0$

$$m_{aq}^{des}(\Delta t_1) = m_m^{des}(t_1) \cdot \left(\frac{V_T}{v_a^D}\right) - m_{aq}^A \quad \text{and} \quad m_s^{des}(t_1) = m_s^{aq}(eq) - m_{aq}^{des}(\Delta t_1) \tag{21}$$

— for the second time interval $\Delta t_2 = t_2 - t_1$

$$m_{aq}^{des}(\Delta t_2) = m_m^{des}(t_2) \cdot \left(\frac{V_T}{v_a^D}\right) - m_{aq}^{des}(\Delta t_1) \cdot \left(\frac{(V_T - v_a^D)}{V_T}\right) - m_{aq}^A \cdot \left(\frac{(V_T - v_a^D)}{V_T}\right) \text{ and}$$

$$m_s^{des}(t_2) = m_s^{ads}(eq) - \left[m_{aq}^{des}(\Delta t_1) + m_{aq}^{des}(\Delta t_2)\right] \tag{22}$$

— for the nth interval $\Delta t_n = t_n - t_{n-1}$

$$m_{aq}^{des}(\Delta t_n) = \left[m_m^{des}(t_n) \cdot \left(\frac{V_T}{v_a^D}\right) - m_{aq}^A \cdot \left(\frac{(V_T - (n-1) \cdot v_a^D)}{V_T}\right) - \sum_{i=1,\, n\neq 1}^{n-1} \left(\frac{(V_T - (n-i) \cdot v_a^D)}{V_T} \cdot m_{aq}^{des}(\Delta t_i)\right)\right] \text{ and}$$

$$m_s^{des}(t_n) = m_s^{ads}(eq) - \sum_{i=1,\, n\neq 1}^{n} m_{aq}^{des}(\Delta t_i) \tag{23}$$

Finally, the percentage of desorption at each time interval, $D_{\Delta t_i}$, is calculated using the following equation:

$$D_{\Delta t_i} = \frac{m_{aq}^{des}(\Delta t_i)}{m_s^{ads}(eq)} \cdot 100\ (\%) \tag{24}$$

while the percentage of desorption $D_{t_i}$ at a time point $t_i$ is given by the equation:

$$D_{t_i} = \frac{\sum_{j=\Delta t_1}^{\Delta t_i} m_{aq}^{des}(j)}{m_s^{ads}(eq)} \cdot 100 = \frac{m_{aq}^{des}(t_i)}{m_s^{ads}(eq)} \cdot 100\ (\%) \tag{25}$$

where the above used parameters are defined as:

$m_s^{des}(\Delta t_1)$, $m_s^{des}(\Delta t_2)$, …, $m_s^{des}(\Delta t_n)$ = mass of the substance remaining adsorbed on the soil after the time intervals $\Delta t_1$, $\Delta t_2$, …, $\Delta t_n$ respectively (μg)

$m_{aq}^{des}(\Delta t_1)$, $m_{aq}^{des}(\Delta t_2)$, …, $m_{aq}^{des}(\Delta t_n)$ = mass of the test substance desorbed during the time intervals $\Delta t_1$, $\Delta\ t_2$, …, $\Delta t_n$ respectively (μg)

$m_m^{des}(t_1)$, $m_m^{des}(t_2)$, … $m_m^{des}(t_n)$ = mass of the substance measured in an aliquot $v_a^D$ at time points $t_1$, $t_2$, …, $t_n$, respectively (μg)

$V_T$ = total volume of the aqueous phase in contact with the soil during the desorption kinetics experiment performed with the serial method ($cm^3$)

$m_{aq}^A$ = mass of the test substance left over from the adsorption equilibrium due to incomplete volume replacement (μg)

$$m_{aq}^A = \left( \frac{\left( V_0 - \sum_{i=1}^{n} v_a^A(i) \right) - V_R}{\left( V_0 - \sum_{i=1}^{n} v_a^A(i) \right)} \right) \cdot m_{aq}^{ads}(eq) \tag{26}$$

$V_R$ = volume of the supernatant removed from the tube after the attainment of adsorption equilibrium and replaced by the same volume of a 0,01 M $CaCl_2$ solution ($cm^3$)

$v_a^D$ = volume of the aliquot sampled for analytical purpose from the tube (i), during the desorption kinetics experiment performed with the serialmethod ($cm^3$)

$$v_a^D \leq 0{,}02 \cdot V_T \tag{27}$$

*APPENDIX 6*

**ADSORPTION-DESORPTION IN SOILS: DATA REPORTING SHEETS**

Substance tested:

Soil tested:

Dry mass content of the soil (105 °C, 12 h): . . . . . %

Temperature: . . . . . °C

**Suitability of the analytical method**

| | | |
|---|---|---|
| Weighed soil | g | |
| Soil: dry mass | g | |
| Volume $CaCl_2$ solution | $cm^3$ | |
| Nominal concentration final solution | $\mu g\ cm^{-3}$ | |
| Analytical concentration final solution | $\mu g\ cm^{-3}$ | |

Principle of the analytical method used:

Calibration of the analytical method:

Substance tested:

Soil tested:

Dry mass content of the soil (105 °C, 12 h): . . . . . %

Temperature: . . . . . °C

Analytical methodology followed: Indirect ☐ Parallel ☐ Serial ☐

Direct ☐

**Adsorption test: test samples**

| | Symbol | Units | Equilibration time | | Equilibration time | | Equilibration time | | Equilibration time | |
|---|---|---|---|---|---|---|---|---|---|---|
| Tube No | | | | | | | | | | |
| Weighed soil | — | g | | | | | | | | |
| Soil: dry mass | $m_{soil}$ | g | | | | | | | | |
| Water volume in weighed soil (calculated) | $V_{WS}$ | $cm^3$ | | | | | | | | |
| Volume 0,01 M $CaCl_2$ solution to equilibrate the soil | | $cm^3$ | | | | | | | | |
| Volume of stock solution | | $cm^3$ | | | | | | | | |
| Total volume of aqueous phase in contact with soil | $V_0$ | $cm^3$ | | | | | | | | |
| Initial concentration test solution | $C_0$ | $\mu g\ cm^{-3}$ | | | | | | | | |
| Mass test substance at beginning of test | $m_0$ | µg | | | | | | | | |
| **After agitation and centrifugation** | | | | | | | | | | |
| **Indirect method** | | | | | | | | | | |
| **Parallel method** | | | | | | | | | | |
| Concentration test substance aqueous phase, blank correction included | $C_{aq}^{ads}(t_i)$ | $\mu g\ cm^{-3}$ | | | | | | | | |
| **Serial method** | | | | | | | | | | |
| Measured mass test substance in aliquot $V_a^A$ | $m_{aq}^{ads}(t_i)$ | µg | | | | | | | | |
| **Direct method** | | | | | | | | | | |
| Mass test substance adsorbed on soil | $m_s^{ads}(t_i)$ | µg | | | | | | | | |
| **Calculation of adsorption** | | | | | | | | | | |
| Adsorption | $A_{t_i}$ | % | | | | | | | | |
| | $A_{\Delta t_i}$ | % | | | | | | | | |
| Means | | | | | | | | | | |
| Adsorption coefficient | $K_d$ | $cm^3\ g^{-1}$ | | | | | | | | |
| Means | | | | | | | | | | |
| Adsorption coefficient | $K_{oc}$ | $cm^3\ g^{-1}$ | | | | | | | | |
| Means | | | | | | | | | | |

Substance tested:

Soil tested:

Dry mass content of the soil (105 °C, 12 h): . . . . . %

Temperature: . . . . . °C

**Adsorption test: blanks and control**

| | Symbol | Units | Blank | | Blank | | Control | |
|---|---|---|---|---|---|---|---|---|
| Tube No | | | | | | | | |
| Weighed soils | | g | | | | | 0 | 0 |
| Water amount in weighed soil (calculated) | | $cm^3$ | | | | | — | — |
| Volume of 0,01 M $CaCl_2$ solution added | | $cm^3$ | | | | | | |
| Volume of stock solution of test substance added | | $cm^3$ | 0 | 0 | | | | |
| Total volume of aqueous phase (calculated) | | $cm^3$ | | | | | — | — |
| Initial concentration of test substance in aqueous phase | | $\mu g\ cm^{-3}$ | | | | | | |
| **After agitation and centrifugation** | | | | | | | | |
| Concentration in aqueous phase | | $\mu g\ cm^{-3}$ | | | | | | |

Remark: Add columns if necessary.

Substance tested:

Soil tested:

Dry mass content of the soil (105 °C, 12 h): . . . . . %

Temperature: . . . . . °C

**Mass balance**

| | Symbol | Units | | | | |
|---|---|---|---|---|---|---|
| Tube No | | | | | | |
| Weighed soil | — | g | | | | |
| Soil: dry mass | $m_{soil}$ | g | | | | |
| Water volume in weighed soil (calculated) | $V_{WS}$ | ml | | | | |
| Volume 0,01 M $CaCl_2$ solution to equilibrate soil | | ml | | | | |
| Volume of stock solution | | $cm^3$ | | | | |
| Total volume of aqueous phase in contact with soil | $V_0$ | $cm^3$ | | | | |
| Initial concentration test solution | $C_0$ | µg $cm^{-3}$ | | | | |
| Equilibration time | — | h | | | | |
| **After agitation and centrifugation** | | | | | | |
| Concentration test substance aqueous phase at adsorption, equilibrium blank correction included | $C_{aq}^{ads}(eq)$ | µg $cm^{-3}$ | | | | |
| Equalibration time | $t_{eq}$ | h | | | | |
| **1st dilution with solvent** | | | | | | |
| Removed volume aqueous phase | $V_{rec}$ | $cm^3$ | | | | |
| Added volume of solvent | $\Delta V$ | $cm^3$ | | | | |
| **1st extraction with solvent** | | | | | | |
| Signal analysed in solvent | $S_{E1}$ | var. | | | | |
| Concentration test substance in solvent | $C_{E1}$ | µg $cm^{-3}$ | | | | |
| Mass of substance extracted from soil and vessel walls | $m_{E1}$ | µg | | | | |
| **2nd dilution with solvent** | | | | | | |
| Removed volume of solvent | $\Delta V_s$ | $cm^3$ | | | | |
| Added volume of solvent | $\Delta V'$ | $cm^3$ | | | | |
| **2nd extraction with solvent** | | | | | | |
| Signal analysed in solvent phase | $S_{E2}$ | var. | | | | |
| Concentration test substance in solvent | $C_{E2}$ | µg $cm^{-3}$ | | | | |
| Mass of substance extracted from soil and vessel walls | $m_{E2}$ | µg | | | | |
| Total mass test substance extracted in two steps | $m_E$ | µg | | | | |
| Mass balance | MB | % | | | | |

Substance tested:

Soil tested:

Dry mass content of the soil (105 °C, 12 h): . . . . . %

Temperature: . . . . . °C

**Adsorption isotherms**

| | Symbol | Units | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Tube No | | | | | | | | | | |
| Weighed soil | — | g | | | | | | | | |
| Soil: dry mass | E | g | | | | | | | | |
| Water volume in weighed soil (calculated) | $V_{WS}$ | $cm^3$ | | | | | | | | |
| Volume 0,01 M $CaCl_2$ solution to equilibrate soil | | $cm^3$ | | | | | | | | |
| Volume of stock solution added | | $cm^3$ | | | | | | | | |
| Total volume of aqueous phase in contact with soil (calculated) | $V_0$ | $cm^3$ | | | | | | | | |
| Concentration solution | $C_0$ | $\mu g\ cm^{-3}$ | | | | | | | | |
| Equilibration time | — | h | | | | | | | | |
| **After agitation and centrifugation** | | | | | | | | | | |
| Concentration substance aqueous phase, blank correction included | $C_{aq}^{ads}$ (eq) | $\mu g\ cm^{-3}$ | | | | | | | | |
| Temperature | | °C | | | | | | | | |
| Adsorption mass per unit soil | $C_s^{ads}$ (eq) | $\mu g\ g^{-1}$ | | | | | | | | |

Regression analysis:

value of $K_F^{ads}$:

value of l/n:

regression coefficient $r^2$:

Substance tested:

Soil tested:

Dry mass content of the soil (105 °C, 12 h): . . . . . %

Temperature: . . . . . °C

Analytical methodology followed: Indirect ☐ Parallel ☐ Serial ☐

**Desorption test**

| | | Symbol | Units | Time interval | Time interval | Time interval | Time interval |
|---|---|---|---|---|---|---|---|
| Tube No coming from adsorption step | | | | | | | |
| Mass of substance adsorbed on soil at adsorption equilibrium | | $m_s^{ads}$ (eq) | µg | | | | |
| Removed volume aqueous phase, replaced by 0,01 M $CaCl_2$ | | $V_R$ | $cm^3$ | | | | |
| Total volume of aqueous phase in contact with soil | PM<br>SM | $V_0$<br>$V_T$ | $cm^3$<br>$cm^3$ | | | | |
| Mass test substance left over the adsorption equilibrium due to incomplete volume replacement | | $m_{aq}^A$ | µg | | | | |
| **Desorption kinetics** | | | | | | | |
| Measured mass of substance desorbed from soil at time $t_i$ | | $m_m^{des}$ ($t_i$) | µg | | | | |
| Volume of the solution taken from the tube (i) for the measurement of the test substance | PM | $V_r^i$ | $cm^3$ | | | | |
| | SM | $V_a^D$ | $cm^3$ | | | | |
| Mass of substance desorbed from soil at time $t_i$ (calculated) | | $m_{aq}^{des}$ ($t_i$) | µg | | | | |
| Mass of substance desorbed from soil during time interval $\Delta t_i$ (calculated) | | $m_{aq}^{des}$ ($\Delta t_i$) | µg | | | | |
| **Desorption percentage** | | | | | | | |
| Desorption at time $t_i$ | | $D_{t_i}$ | % | | | | |
| Desorption at time interval $\Delta t_i$ | | $D_{\Delta t_i}$ | % | | | | |
| Apparent desorption coefficient | | $K_{des}$ | | | | | |

PM: Parallel method

SM: Serial method

## C.19. ESTIMATION OF THE ADSORPTION COEFFICIENT ($K_{OC}$) ON SOIL AND ON SEWAGE SLUDGE USING HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

### 1. METHOD

This method is a replicate of OECD TG121 (2000).

### 1.1. INTRODUCTION

The sorption behavior of substances in soils or sewage sludges can be described through parameters experimentally determined by means of the test method C.18. An important parameter is the adsorption coefficient which is defined as the ratio between the concentration of the substance in the soil/sludge and the concentration of the substance in the aqueous phase at adsorption equilibrium. The adsorption coefficient normalised to the organic carbon content of the soil $K_{oc}$ is a useful indicator of the binding capacity of a chemical on organic matter of soil and sewage sludge and allows comparisons to be made between different chemicals. This parameter can be estimated through correlations with the water solubility and the n-octanol/water partition coefficient (1) (2) (3) (4) (5) (6) (7).

The experimental method described in this test uses HPLC for the estimation of the adsorption coefficient $K_{oc}$ in soil and in sewage sludge (8). The estimates are of higher reliability than those from QSAR calculations (9). As an estimation method it cannot fully replace batch equilibrium experiments used in the test method C18. However, the estimated $K_{oc}$ may be useful for choosing appropriate test parameters for adsorption/desorption studies according to the test method C.18 by calculating $K_d$ (distribution coefficient) or $K_f$ (Freundlich adsorption coefficient) according to the equation 3 (see section 1.2).

### 1.2. DEFINITIONS

**$K_d$:** Distribution coefficient is defined as the ratio of equilibrium concentrations C of a dissolved test substance in a two phase system consisting of a sorbent (soil or sewage sludge) and an aqueous phase; it is a dimensionless value when concentrations in both phases are expressed on a weight/weight base. In case the concentration in the aqueous phase is given on a weight/volume base then the units are $ml \cdot g^{-1}$. $K_d$ can vary with sorbent properties and can be concentration dependent.

$$K_d = \frac{C_{soil}}{C_{aq}} \text{ or } \frac{C_{sludge}}{C_{aq}} \quad (1)$$

where:

$C_{soil}$ = concentration of test substance in soil at equilibrium ($\mu g \cdot g^{-1}$)

$C_{sludge}$ = concentration of test substance in sludge at equilibrium ($\mu g \cdot g^{-1}$)

$C_{aq}$ = concentration of test substance in aqueous phase at equilibrium ($\mu g \cdot g^{-1}$, $\mu g \cdot ml^{-1}$).

**$K_f$:** Freundlich adsorption coefficient is defined as the concentration of the test substance in soil or sewage sludge (x/m) when the equilibrium concentration $C_{aq}$ in the aqueous phase is equal to one; units are $\mu g \cdot g^{-1}$ sorbent. The value can vary with sorbent properties.

$$\log \frac{x}{m} = \log K_f + \frac{1}{n} \cdot \log C_{aq} \quad (2)$$

where:

x/m = amount of test substance x (μg) adsorbed on amount of sorbent m (g) at equilibrium

1/n = slope of Freundlich adsorption isotherm

$C_{aq}$ = concentration of test substance in aqueous phase at equilibrium ($\mu g \cdot ml^{-1}$)

At $C_{aq} = 1$; $\log K_f = \log \frac{x}{m}$

**$K_{oc}$:** Distribution coefficient ($K_d$) or Freundlich adsorption coefficient ($K_f$) normalised to the organic carbon content ($f_{oc}$) of a sorbent; particularly for non-ionised chemicals, it is an approximate indicator for the extent of adsorption between a substance and the sorbent and allows comparisons to be made between different chemicals. Depending on the dimensions of $K_d$ and $K_f$, $K_{oc}$ can be dimensionless or have the units $ml \cdot g^{-1}$ or $\mu g \cdot g^{-1}$ organic matter.

$$K_{oc} = \frac{K_d}{f_{oc}} \text{ (dimensionless or } ml \cdot g^{-1}) \text{ or } \frac{K_f}{f_{oc}} (\mu g \cdot g^{-1}) \quad (3)$$

The relationship between $K_{oc}$ and $K_d$ is not always linear and thus $K_{oc}$ values can vary from soil to soil but their variability is greatly reduced compared to $K_d$ or $K_f$ values.

The adsorption coefficient ($K_{oc}$) is deduced from the capacity factor (k′) using a calibration plot of log k′ versus log $K_{oc}$ of the selected reference compounds.

$$k' = \frac{t_R - t_0}{t_0} \quad (4)$$

where:

$t_R$: HPLC retention time of test and reference substance (minutes)

$t_0$: HPLC dead time (minutes) (see section 1.8.2).

**$P_{OW}$:** The octanol-water partition coefficient is defined as the ratio of the concentrations of dissolved substance in n-octanol and water; it is a dimensionless value.

$$P_{ow} = \frac{C_{octanol}}{C_{aq}} (= K_{ow}) \quad (5)$$

1.3. REFERENCE SUBSTANCES

The structural formula, the purity and the dissociation constant (if appropriate) should be known before using the method. Information on solubility in water and organic solvents, on octanol-water partition coefficient and on hydrolysis characteristics is useful.

To correlate the measured HPLC-retention data of a test substance with its adsorption coefficient $K_{oc}$, a calibration graph of log $K_{oc}$ versus log k' has to be established. A minimum of six reference points, at least one above and one below the expected value of the test substance should be used. The accuracy of the method will be significantly improved if reference substances that are structurally related to the test substance are used. If such data are not available, it is up to the user to select the appropriate calibration substances. A more general set of structurally heterogeneous substances should be chosen in this case. Substances and $K_{oc}$-values which may be used are listed in the Appendix in Table 1 for sewage sludge and in Table 3 for soil. The selection of other calibration substances should be justified.

1.4. PRINCIPLE OF THE TEST METHOD

HPLC is performed on analytical columns packed with a commercially available cyanopropyl solid phase containing lipophilic and polar moieties. A moderately polar stationary phase based on a silica matrix is used:

| $-O-Si$ | $-CH_2-CH_2-CH_2$ | $-CN$ |
|---|---|---|
| silica | non-polar spacer | polar moiety |

The principle of the test method is similar to testing method A.8 (partition coefficient, HPLC method). While passing through the column along with the mobile phase the test substance interacts with the stationary phase. As a result o partitioning between mobile and stationary phases the test substance is retarded. The dual composition of the stationary phase having polar and non-polar sites allows for interaction of polar and non-polar groups of a molecule in a similar way as is the case for organic matter in soil or sewage sludge matrices. This enables the relationship between the retention time on the column and the adsorption coefficient on organic matter to be established.

pH has a significant influence on sorption behavior in particular for polar substances. For agricultural soils or tanks of sewage treatment plants pH normally varies between pH 5,5 and 7,5. For ionisable substances, two tests should be performed with both ionised and non-ionised forms in appropriate buffer solutions but only in cases where at least 10 % of the test compound will be dissociated within pH 5,5 to 7,5.

Since only the relationship between the retention on the HPLC column and the adsorption coefficient is employed for the evaluation, no quantitative analytical method is required and only the determination of the retention time is necessary. If a suitable set of reference substances is available and standard experimental conditions can be used, the method provides a fast and efficient way to estimate the adsorption coefficient $K_{oc}$.

1.5. APPLICABILITY OF THE TEST

The HPLC method is applicable to chemical substances (unlabelled or labelled) for which an appropriate detection system (e.g. spectrophotometer, radioactivity detector) is available and which are sufficiently stable during the duration of the experiment. It may be particularly useful for chemicals which are difficult to study in other experimental systems (i.e. volatile substances; substances which are not soluble in water at a concentration which can be measured analytically; substances with a high affinity to the surface of incubation systems). The method can be used for mixtures which give unresolved elution bands. In such a case, upper and lower limits of the log $K_{oc}$ values of the compounds of the test mixture should be stated.

Impurities may sometimes cause problems for interpretation of HPLC results, but they are of minor importance as long as the test substance can analytically be clearly identified and separated from the impurities.

The method is validated for the substances listed in Table 1 in the Appendix and was also applied to a variety of other chemicals belonging to the following chemical classes:

— aromatic amines (e.g. trifluralin, 4-chloroaniline, 3,5-dinitroaniline, 4-methylaniline, N-methylaniline, 1-naphthylamine),

— aromatic carboxilic acid esters (e.g. benzoic acid methylester, 3,5-dinitrobenzoic acid ethylester),

— aromatic hydrocarbons (e.g. toluene, xylene, ethylbenzene, nitrobenzene),

— aryloxyphenoxypropionic acid esters (e.g. diclofop-methyl, fenoxaprop-ethyl, fenoxaprop-P-ethyl),

— benzimidazole and imidazole fungicides (e.g. carbendazim, fuberidazole, triazoxide),

— carboxilic acid amides (e.g. 2-chlorobenzamide, N,N-dimethylbenzamide, 3,5-dinitrobenzamide, N-methylbenzamide, 2-nitrobenzamide, 3-nitrobenzamide),

— chlorinated hydrocarbons (e.g. endosulfan, DDT, hexachlorobenzene, quintozene, 1,2,3-trichlorobenzene),

— organophosphorus insecticides (e.g. azinphos-methyl, disulfoton, fenamiphos, isofenphos, pyrazophos, sulprofos, triazophos),

— phenols (e.g. phenol, 2-nitrophenol, 4-nitrophenol, pentachlorophenol, 2,4,6-trichlorophenol, 1-naphthol),

— phenylurea derivatives (e.g. isoproturon, monolinuron, pencycuron),

— pigment dyestuffs (e.g. Acid Yellow 219, Basic Blue 41, Direct Red 81),

— polyaromatic hydrocarbons (e.g. acenaphthene, naphthalene),

— 1,3,5-triazine herbicides (e.g. prometryn, propazine, simazine, terbutryn),

— triazole derivatives (e.g. tebuconazole, triadimefon, tradimenol, triapenthenol).

The method is not applicable for substances which react either with the eluent or the stationary phase. It is also not applicable for substances that interact in a specific way with inorganic components (e.g. formation of cluster complexes with clay minerals). The method may not work for surface active substances, inorganic compounds and moderate or strong organic acids and bases. Log $K_{oc}$ values ranging from 1,5 to 5,0 can be determined. Ionisable substances must be measured using a buffered mobile phase, but care has to be taken to avoid precipitation of buffer components or test substance.

1.6. QUALITY CRITERIA

1.6.1. **Accuracy**

Normally, the adsorption coefficient of a test substance can be estimated to within ± 0,5 log unit of the value determined by the batch equilibrium method (see Table 1 in the Appendix). Higher accuracy may be achieved if the reference substances used are structurally related to the test substance.

1.6.2. **Repeatability**

Determinations should be run at least in duplicate. The values of log $K_{oc}$ derived from individual measurements should be within a range of 0,25 log unit.

1.6.3. **Reproducibility**

Experience gained so far in the application of the method is supportive of its validity. An investigation of the HPLC method, using 48 substances (mostly pesticides) for which reliable data on $K_{oc}$ on soils were available gave a correlation coefficient of R = 0,95 (10) (11).

An inter-laboratory comparison test with 11 participating laboratories was performed to improve and validate the method (12). Results are given in Table 2 of the Appendix.

1.7. DESCRIPTION OF THE TEST METHOD

1.7.1. **Preliminary estimation of the adsorption coefficient**

The octanol-water partition coefficient $P_{ow}$ (= $K_{ow}$) and, to some extent, the water solubility can be used as indicators for the extent of adsorption, particularly for non-ionised substances, and thus may be used for preliminary range finding. A variety of useful correlations have been published for several groups of chemicals (1) (2) (3) (4) (5) (6) (7).

1.7.2. **Apparatus**

A liquid chromatograph, fitted with a pulse-free pump and a suitable detection device is required. The use of an injection valve with an injection loop is recommended. Commercial cyanopropyl chemically bound resins on a silica base shall be used (e.g. Hypersil and Zorbax CN). A guard column of the same material may be positioned between the injection system and the analytical column. Columns from different suppliers may vary considerably in their separation efficiency. As a guidance, the following capacity factors k′ should be reached: log k′ > 0,0 for log $K_{oc}$ = 3,0 and log k′ > 0,4 for log $K_{oc}$ = 2,0 when using methanol/water 55/45 % as mobile phase.

1.7.3. **Mobile phases**

Several mobile phases have been tested, and the following two are recommended:

— methanol/water (55/45 % v/v),

— methanol/0,01M citrate-buffer pH 6,0 (55/45 % v/v).

HPLC grade methanol and distilled water or citrate buffer are used to prepare the eluting solvent. The mixture is degassed before use. Isocratic elution should be employed. If methanol/water mixtures are not appropriate, other organic solvent/water mixtures may be tried, e.g. ethanol/water or acetonitrile/water mixtures. For ionisable compounds the use of buffer solution is recommended to stabilise pH. Care must be taken to avoid salt precipitation and column deterioration, which may occur with some organic phase/buffer mixtures.

No additives such as ion pair reagents may be used because they can affect the sorption properties of the stationary phase. Such changes of the stationary phase may be irreversible. For this reason, it is mandatory that experiments using additives are carried out on separate columns.

1.7.4. **Solutes**

Test and reference substances should be dissolved in the mobile phase.

1.8. PERFORMANCE OF THE TEST

1.8.1. **Test condition**

The temperature during the measurements should be recorded. The use of a temperature controlled column compartment is highly recommended to guarantee constant conditions during calibration and estimation runs and measurement of the test substance.

1.8.2. **Determination of dead time $t_o$**

For the determination of the dead time $t_o$ two different methods may be used (see also section 1.2).

1.8.2.1. *Determination of the dead time $t_o$ by means of a homologous series*

This procedure has proven to yield reliable and standardised $t_o$ values. For details see testing method A.8: partition coefficient (n-octanol/water), HPLC method.

1.8.2.2. *Determination of the dead time $t_o$ by inert substances which are not retained by the column*

This technique is based on the injection of solutions of formamide, urea or sodium nitrate. Measurements should be performed at least in duplicate.

1.8.3. **Determination of the retention times $t_R$**

Reference substances should be selected as described in section 1.3. They may be injected as a mixed standard to determine their retention times, provided it has been confirmed that the retention time of each reference standard is unaffected by the presence of the other reference standards. The calibration should be performed at regular intervals at least twice daily in order to account for unexpected changes in column performance. For best practice the calibration injections should be carried out before and after injections of the test substance to confirm retention times have not drifted. The test substances are injected separately in quantities as small as possible (to avoid column overload) and their retention times are determined.

In order to increase the confidence in the measurement, at least duplicate determinations should be made. The values of log $K_{oc}$ derived from individual measurements should fall within a range of 0,25 log unit.

1.8.4. **Evaluation**

The capacity factors k′ are calculated from the dead time $t_o$ and retention times $t_R$ of the selected reference substances according to equation 4 (see section 1.2). The log k′ data of the reference substances are then plotted against their log $K_{oc}$ values from batch equilibrium experiments given in Tables 1 and 3 of the Appendix. Using this plot, the log k′ value of a test substance is then used to determine its log $K_{oc}$ value. If the actual results show that the log $K_{oc}$ of the test substance is outside the calibration range the test should be repeated using different, more appropriate reference substances.

2. **DATA AND REPORTING**

The report must include the following information:

— identity of test and reference substances and their purity, and $pK_a$ values if relevant,

— description of equipment and operating conditions, e.g. type and dimension of analytical (and guard) column, means of detection, mobile phase (ratio of components and pH), temperature range during measurements,

— dead time and the method used for its determination,

— quantities of test and reference substances introduced in the column,

— retention times of reference compounds used for calibration,

— details of fitted regression line (log k′ vs log $K_{oc}$) and a graph of the regression line,

— average retention data and estimated d log $K_{oc}$ value for the test compound.

— chromatograms.

3. **REFERENCES**

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*APPENDIX*

TABLE 1

**Comparison of $K_{oc}$ values for soils and sewage sludges, and calculated values by the HPLC screening method** ([1]) ([2])

| Substance | CAS No | Log $K_{oc}$ sewage sludges | Log $K_{oc}$ HPLC | Δ | Log $K_{oc}$ soils | Log $K_{oc}$ HPLC | Δ |
|---|---|---|---|---|---|---|---|
| Atrazine | 1912-24-9 | 1,66 | 2,14 | 0,48 | 1,81 | 2,20 | 0,39 |
| Linuron | 330-55-2 | 2,43 | 2,96 | 0,53 | 2,59 | 2,89 | 0,30 |
| Fenthion | 55-38-9 | 3,75 | 3,58 | 0,17 | 3,31 | 3,40 | 0,09 |
| Monuron | 150-68-5 | 1,46 | 2,21 | 0,75 | 1,99 | 2,26 | 0,27 |
| Phenanthrene | 85-01-8 | 4,35 | 3,72 | 0,63 | 4,09 | 3,52 | 0,57 |
| Benzoic acid phenylester | 93-99-2 | 3,26 | 3,03 | 0,23 | 2,87 | 2,94 | 0,07 |
| Benzamide | 55-21-0 | 1,60 | 1,00 | 0,60 | 1,26 | 1,25 | 0,01 |
| 4-Nitrobenzamide | 619-80-7 | 1,52 | 1,49 | 0,03 | 1,93 | 1,66 | 0,27 |
| Acetanilide | 103-84-4 | 1,52 | 1,53 | 0,01 | 1,26 | 1,69 | 0,08 |
| Aniline | 62-53-3 | 1,74 | 1,47 | 0,27 | 2,07 | 1,64 | 0,43 |
| 2,5-Dichloroaniline | 95-82-9 | 2,45 | 2,59 | 0,14 | 2,55 | 2,58 | 0,03 |

([1]) W. Kördel, D. Hennecke, M. Herrmann (1997). Application of the HPLC-screening method for the determination of the adsorption coefficient on sewage sludges. Chemosphere, 35(1/2), pp. 121-128.
([2]) W. Kördel, D. Hennecke, C. Franke (1997). Determination of the adsorption-coefficients of organic substances on sewage sludges. Chemosphere, 35 (1/2), pp. 107-119.

TABLE 2

**Results of a laboratory inter-comparison test (11 participating laboratories) performed to improve and validate the HPLC-method** ([1])

| Substance | CAS No | Log $K_{oc}$ (OECD 106) | $K_{oc}$ | Log $K_{oc}$ |
|---|---|---|---|---|
| | | | [HPLC method] | |
| Atrazine | 1912-24-9 | 1,81 | 78 ± 16 | 1,89 |
| Monuron | 150-68-5 | 1,99 | 100 ± 8 | 2,00 |
| Triapenthenol | 77608-88-3 | 2,37 | 292 ± 58 | 2,47 |
| Linuron | 330-55-2 | 2,59 | 465 ± 62 | 2,67 |
| Fenthion | 55-38-9 | 3,31 | 2062 ± 648 | 3,31 |

([1]) W. Kördel, G. Kotthoff, J. Müller (1995). HPLC-screening method for the determination of the adsorption coefficient on soil-results of a ring test. Chemosphere, 30(7), pp. 1373-1384.

TABLE 3

**Recommended reference substances for the HPLC screening method based on soil adsorption data**

| Reference substance | CAS No | Log $K_{oc}$ mean values from batch equilibrium | Number of $K_{oc}$ data | Log S.D. | Source |
|---|---|---|---|---|---|
| Acetanilide | 103-84-4 | 1,25 | 4 | 0,48 | [a] |
| Phenol | 108-95-2 | 1,32 | 4 | 0,70 | [a] |
| 2-Nitrobenzamide | 610-15-1 | 1,45 | 3 | 0,90 | [b] |
| N.N-dimethylbenzamide | 611-74-5 | 1,52 | 2 | 0,45 | [a] |
| 4-Methylbenzamide | 619-55-6 | 1,78 | 3 | 1,76 | [a] |
| Methylbenzoate | 93-58-3 | 1,80 | 4 | 1,08 | [a] |
| Atrazine | 1912-24-9 | 1,81 | 3 | 1,08 | [c] |
| Isoproturon | 34123-59-6 | 1,86 | 5 | 1,53 | [c] |
| 3-Nitrobenzamide | 645-09-0 | 1,95 | 3 | 1,31 | [b] |
| Aniline | 62-53-3 | 2,07 | 4 | 1,73 | [a] |
| 3,5-Dinitrobenzamide | 121-81-3 | 2,31 | 3 | 1,27 | [b] |
| Carbendazim | 10605-21-7 | 2,35 | 3 | 1,37 | [c] |
| Triadimenol | 55219-65-3 | 2,40 | 3 | 1,85 | [c] |
| Triazoxide | 72459-58-6 | 2,44 | 3 | 1,66 | [c] |
| Triazophos | 24017-47-8 | 2,55 | 3 | 1,78 | [c] |
| Linuron | 330-55-2 | 2,59 | 3 | 1,97 | [c] |
| Naphthalene | 91-20-3 | 2,75 | 4 | 2,20 | [a] |
| Endosulfan-diol | 2157-19-9 | 3,02 | 5 | 2,29 | [c] |
| Methiocarb | 2032-65-7 | 3,10 | 4 | 2,39 | [c] |
| Acid Yellow 219 | 63405-85-6 | 3,16 | 4 | 2,83 | [a] |
| 1,2,3-Trichlorobenzene | 87-61-6 | 3,16 | 4 | 1,40 | [a] |
| γ-HCH | 58-89-9 | 3,23 | 5 | 2,94 | [a] |
| Fenthion | 55-38-9 | 3,31 | 3 | 2,49 | [c] |
| Direct Red 81 | 2610-11-9 | 3,43 | 4 | 2,68 | [a] |
| Pyrazophos | 13457-18-6 | 3,65 | 3 | 2,70 | [c] |
| α-Endosulfan | 959-98-8 | 4,09 | 5 | 3,74 | [c] |
| Diclofop-methyl | 51338-27-3 | 4,20 | 3 | 3,77 | [c] |
| Phenanthrene | 85-01-8 | 4,09 | 4 | 3,83 | [a] |
| Basic Blue 41 (mix) | 26850-47-5 | 4,89 | 4 | 4,46 | [a] |
| | 12270-13-2 | | | | |
| DDT | 50-29-3 | 5,63 | 1 | — | [b] |

[a] W. Kördel, J. Müller (1994). Bestimmung des Adsorptionskoeffizienten organischer Chemikalien mit der HPLC. UBA R & D Report No 106 01 044 (1994).
[b] B.V. Oepen, W. Kördel, W. Klein (1991). Chemosphere, 22, pp. 285-304.
[c] Data provided by industry.

## C.20. *DAPHNIA MAGNA* REPRODUCTION TEST

### 1. METHOD

This reproduction toxicity test method is a replicate of the OECD TG 211 (1998).

#### 1.1. INTRODUCTION

The primary objective of the test is to assess the effect of chemicals on the reproductive output of *Daphnia magna*.

#### 1.2. DEFINITIONS AND UNITS

**Parent animals**: are those female *Daphnia* present at the start of the test and of which the reproductive output is the object of the study.

**Offspring**: are the young *Daphnia* produced by the parent animals in the course of the test.

**Lowest observed effect concentration (LOEC)**: is the lowest tested concentration at which the substance is observed to have a statistically significant effect on reproduction and parent mortality (at $p < 0,05$) when compared with the control, within a stated exposure period. However, all test concentrations above the LOEC must have a harmful effect equal to or greater than those observed at the LOEC. When these two conditions cannot be satisfied, a full explanation must be given for how the LOEC (and hence the NOEC) has been selected.

**No observed effect concentration (NOEC)**: is the test concentration immediately below the LOEC, which when compared with the control, has no statistically significant effect ($p < 0,05$), within a stated exposure period.

**$EC_x$**: is the concentration of the test substance dissolved in water that results in an x % reduction in reproduction of *Daphnia magna* within a stated exposure period.

**Intrinsic rate of increase**: is a measure of population growth which integrates reproductive output and age-specific mortality (20) (21) (22). In steady state populations it will be zero. For growing populations it will be positive and for shrinking populations it will be negative. Clearly, the latter is not sustainable and ultimately will lead to extinction.

**Limit of detection**: is the lowest concentration that can be detected but not quantified.

**Limit of determination**: is the lowest concentration that can be measured quantitatively.

**Mortality**: an animal is recorded as dead when it is immobile, i.e. when it is not able to swim, or if there is no observed movement of appendages or post-abdomen, within 15 seconds after gentle agitation of the test container. (If another definition is used, this must be reported together with its reference.)

#### 1.3. PRINCIPLE OF THE TEST METHOD

Young female *Daphnia* (the parent animals), aged less than 24 hours at the start of the test, are exposed to the test substance added to water at a range of concentrations. The test duration is 21 days. At the end of the test, the total number of living offspring produced per parent animal alive at the end of the test is assessed. This means that juveniles produced by adults that die during the test are excluded from the calculations. Reproductive output of parent animals can be expressed in other ways (e.g. number of living offspring produced per animal per day from the first day offspring were observed) but these should be reported in addition to the total number of juveniles produced per parent alive at the end of the test. The reproductive output of the animals exposed to the test substance is compared to that of the control(s) in order to determine the lowest observed effect concentration (LOEC) and hence the no observed effect concentration (NOEC). In addition, and as far as possible, the data are analysed using a regression model in order to estimate the concentration that would cause an x % reduction in reproductive output (i.e. the $EC_{50}$, $EC_{20}$, or $EC_{10}$).

The survival of the parent animals and time to production of first brood must also be reported. Other substance-related effects on parameters such as growth (e.g. length) and possibly intrinsic rate of increase, may also be examined.

1.4. INFORMATION ON THE TEST SUBSTANCE

Results of an acute toxicity test (see method C.2, Part I) performed with *Daphnia magna* should be available. The result may be useful in selecting an appropriate range of test concentrations in the reproduction tests. The water solubility and the vapour pressure of the test substance should be known and a reliable analytical method for the quantification of the substance in the test solutions with reported recovery efficiency and limit of determination should be available.

Information on the test substance which may be useful in establishing the test conditions includes the structural formula, purity of the substance, stability in light, stability under the conditions of the test, pKa, $P_{ow}$ and results of the test for ready biodegradability (see method C.4).

1.5. VALIDITY OF THE TEST

For a test to be valid, the following performance criteria should be met in the control(s):

— the mortality of the parent animals (female *Daphnia*) does not exceed 20 % at the end of the test,

— the mean number of live offspring produced per parent animal surviving at the end of the test is ≥ 60.

1.6. DESCRIPTION OF THE TEST METHOD

1.6.1. **Apparatus**

Test vessels and other apparatus which will come into contact with the test solutions should be made entirely of glass or other chemically inert material. The test vessels will normally be glass beakers.

In addition, some or all of the following equipment will be required:

— oxygen meter (with microelectrode or other suitable equipment for measuring dissolved oxygen in low volume samples),

— adequate apparatus for temperature control,

— pH meter,

— equipment for the determination of the hardness of water,

— equipment for the determination of the total organic carbon concentration (TOC) of water or equipment for the determination of the chemical oxygen demand (COD),

— adequate apparatus for the control of the lighting regime and the measurement of light intensity.

1.6.2. **Test organism**

The species to be used in the test is *Daphnia magna* Straus. Other *Daphnia* species may be used providing they meet the validity criteria as appropriate (the validity criterion relating to the reproductive output in the controls should be relevant for the *Daphnia* species). If other species of *Daphnia* are used they must be clearly identified and their use justified.

Preferably, the clone should have been identified by genotyping. Research (1) has shown that the reproductive performance of Clone A (which originated from IRCHA in France) (3) consistently meets the validity criterion of a mean of ≥ 60 offspring per parent animal surviving when cultured under the conditions described in this method. However, other clones are acceptable provided that the *Daphnia* culture is shown to meet the validity criteria for a test.

At the start of the test, the animals should be less than 24 hours old and must not be first brood progeny. They should be derived from a healthy stock (i.e. showing no signs of stress such as high mortality, presence of males and ephippia, delay in the production of the first brood, discoloured animals etc.). The stock animals must be maintained in culture conditions (light, temperature, medium, feeding and animals per unit volume) similar to those to be used in the test. If the *Daphnia* culture medium to be used in the test is different from that used for routine *Daphnia* culture, it is good practice to include a pre-test acclimation period of normally about three weeks (i.e. one generation) to avoid stressing the parent animals.

1.6.3. **Test medium**

It is recommended that a fully defined medium be used in this test. This can avoid the use of additives (e.g. seaweed, soil extract, etc.), which are difficult to characterise, and therefore improves the opportunities for standardisation between laboratories. Elendt M4 (4) and M7 media (see Appendix 1) have been found to be suitable for this purpose. However, other media (e.g. (5) (6)) are acceptable providing the performance of the *Daphnia* culture is shown to meet the validity criteria for the test.

If media are used which include undefined additives, these additives should be specified clearly and information should be provided in the test report on composition, particularly with regard to carbon content as this may contribute to the diet provided. It is recommended that the total organic carbon (TOC) and/or chemical oxygen demand (COD) of the stock preparation of the organic additive is determined and an estimate of the resulting contribution to the TOC/COD in the test medium made. It is recommended that TOC levels in the medium (i.e. before addition of the algae) be below 2 mg/l (7).

When testing substances containing metals, it is important to recognise that the properties of the test medium (e.g. hardness, chelating capacity) may have a bearing on the toxicity of the test substance. For this reason, a fully defined medium is desirable. However, at present, the only fully defined media which are known to be suitable for long-term culture of *Daphnia magna* are Elendt M4 and M7. Both media contain the chelating agent EDTA. Work has shown (2) that the 'apparent toxicity' of cadmium is generally lower when the reproduction test is performed in M4 and M7 media than in media containing no EDTA. M4 and M7 are not, therefore, recommended for testing substances containing metals, and other media containing known chelating agents should also be avoided. For metal-containing substances it may be advisable to use an alternative medium such as, for example, ASTM reconstituted hard fresh water (7), which contains no EDTA, with added seaweed extract (8). This combination of ASTM reconstituted hard fresh water and seaweed extract is also suitable for long-term culture and testing of *Daphnia magna* (2), although it still exerts a mild chelating action due to the organic component in the added seaweed extract.

At the beginning and during the test, the dissolved oxygen concentration should be above 3 mg/l. The pH should be within the range 6-9, and normally it should not vary by more than 1,5 units in any one test. Hardness above 140 mg/l (as $CaCO_3$) is recommended. Tests at this level and above have demonstrated reproductive performance in compliance with the validity criteria (9) (10).

1.6.4. **Test solutions**

Test solutions of the chosen concentrations are usually prepared by dilution of a stock solution. Stock solutions should preferably be prepared by dissolving the substance in test medium.

The use of organic solvents or dispersants may be required in some cases in order to produce a suitably concentrated stock solution, but every effort should be made to avoid the use of such materials. Examples of suitable solvents are acetone, ethanol, methanol, dimethylformamide and triethylene glycol. Examples of suitable dispersants are Cremophor RH40, methylcellulose 0,01 % and HCO-40. In any case, the test substance in the test solutions should not exceed the limit of solubility in the test medium.

Solvents are used to produce a stock solution which can be dosed accurately into water. At the recommended solvent concentration in the final test medium (i.e. ≤ 0,1 ml/l), the solvents listed above will not be toxic and will not increase the water solubility of a substance.

Dispersants may assist in accurate dosing and dispersion. At the recommended concentration in the final test medium (≤ 0,1 ml/l), the dispersants listed above will not be toxic and will not increase the water solubility of a substance.

1.7. TEST DESIGN

Treatments should be allocated to the test vessels and all subsequent handling of the test vessels should be done in a random fashion. Failure to do this may result in bias that could be construed as being a concentration effect. In particular, if experimental units are handled in treatment or concentration order, then some time-related effect, such as operator fatigue or other error, could lead to greater effects at the higher concentrations. Furthermore, if the test results are likely to be affected by an initial or environmental condition of the test, such as position in the laboratory, then consideration should be given to blocking the test.

1.8. PROCEDURE

1.8.1. **Conditions of exposure**

1.8.1.1. *Duration*

The test duration is 21 days.

1.8.1.2. *Loading*

Parent animals are maintained individually, one per test vessel, with 50-100 ml of medium in each vessel.

Larger volumes may sometimes be necessary to meet requirements of the analytical procedure used for determination of the test substance concentration, although pooling of replicates for chemical analysis is also allowable. If volumes greater than 100 ml are used, the ration given to the *Daphnia* may need to be increased to ensure adequate food availability and compliance with the validity criteria. For flow-through tests, alternative designs may, for technical reasons, be considered (e.g. four groups of 10 animals in a larger test volume), but any changes to the test design should be reported.

1.8.1.3. *Number of animals*

For semi-static tests, at least 10 animals individually held at each test concentration and at least 10 animals individually held in the control series.

For flow-through tests, 40 animals divided into four groups of 10 animals at each test concentration has been shown to be suitable (1). A smaller number of test organisms may be used and a minimum of 20 animals per concentration divided into two or more replicates with an equal number of animals (e.g. four replicates each with five daphnids) is recommended. Note that for tests where animals are held in groups, it will not be possible to express the reproductive output as the total number of living offspring produced per parent animal alive at the end of the test, if parent animals die. In these cases reproductive output should be expressed as 'total number of living offspring produced per parent present at the beginning of the test'.

1.8.1.4. *Feeding*

For semi-static tests, feeding should preferably be done daily, but at least three times per week (i.e. corresponding to media changes). Deviations from this (e.g. for flow-through tests) should be reported.

During the test the diet of the parent animals should preferably be living algal cells of one or more of the following: *Chlorella* sp., *Selenastrum capricornutum* (now *Pseudokirchneriella subcapitata* (11)) and *Scenedesmus subspicatus*. The supplied diet should be based on the amount of organic carbon (C) provided to each parent animal. Research (12) has shown that, for *Daphnia magna*, ration levels of between 0,1 and 0,2 mg C/*Daphnia*/day are sufficient for achieving the required number of offspring to meet the test validity criteria. The ration can be supplied either at a consistent rate throughout the period of the test, or, if desired, a lower rate can be used at the beginning and then increased during the test to take account of growth of the parent animals. In this case, the ration should still remain within the recommended range of 0,1-0,2 mg C/*Daphnia*/day at all times.

If surrogate measures, such as algal cell number or light absorbance, are to be used to feed the required ration level (i.e. for convenience since measurement of carbon content is time consuming), each laboratory must produce its own nomograph relating the surrogate measure to carbon content of the algal culture (see Appendix 2 for advice on nomograph production). Nomographs should be checked at least annually and more frequently if algal culture conditions have changed. Light absorbance has been found to be a better surrogate for carbon content than cell number (13).

A concentrated algal suspension should be fed to the *Daphnia* to minimise the volume of algal culture medium transferred to the test vessels. Concentration of the algae can be achieved by centrifugation followed by resuspension in distilled water, deionised water or *Daphnia* culture medium.

1.8.1.5. *Light*

16 hours light at an intensity not exceeding 15-20 $\mu E \cdot m^{-2} \cdot s^{-1}$.

1.8.1.6. *Temperature*

The temperature of the test media should be within the range 18-22 °C. However, for any one test, the temperature should not, if possible, vary by more than 2 °C within these limits (e.g. 18-20, 19-21 or 20-22 °C). It may be appropriate to use an additional test vessel for the purposes of temperature monitoring.

1.8.1.7. *Aeration*

The test vessels must not be aerated during the test.

1.8.2. **Test concentration**

Normally, there should be at least five test concentrations arranged in a geometric series with a separation factor preferably not exceeding 3,2, and the appropriate number of replicates for each test concentration should be used (see section 1.8.1.3). Justification should be provided if fewer than five concentrations are used. Substances should not be tested above their solubility limit in the test medium.

In setting the range of concentrations, the following should be borne in mind:

(i) if the aim is to obtain the LOEC/NOEC, the lowest test concentration must be low enough so that the fecundity at that concentration is not significantly lower than that in the control. If this is not the case, the test will have to be repeated with a reduced lowest concentration;

(ii) if the aim is to obtain the LOEC/NOEC, the highest test concentration must be high enough so that the fecundity at that concentration is significantly lower than that in the control. If this is not the case, the test will have to be repeated with an increased highest concentration;

(iii) if the $EC_X$ for effects on reproduction is estimated, it is advisable that sufficient concentrations are used to define the $EC_X$ with an appropriate level of confidence. If the $EC_{50}$ for effects on reproduction is estimated, it is advisable that the highest test concentration is greater than this $EC_{50}$. Otherwise, although it will still be possible to estimate the $EC_{50}$, the confidence interval for the $EC_{50}$ will be very wide and it may not be possible to satisfactorily assess the adequacy of the fitted model;

(iv) the range of test concentration should preferably not include any concentrations that have a statistically significant effect on adult survival since this would change the nature of the test from simply a reproduction test to a combined reproduction and mortality test requiring much more complex statistical analysis.

Prior knowledge of the toxicity of the test substance (e.g. from an acute test and/or from range-finding studies) should help in selecting appropriate test concentrations.

Where a solvent or dispersant is used to aid preparation of test solutions (see section 1.6.4), its final concentration in the test vessels should not be greater than 0,1 ml/l and should be the same in all test vessels.

1.8.3. **Controls**

One test-medium control series and also, if relevant, one control series containing the solvent or dispersant should be run in addition to the test series. When used, the solvent or dispersant concentration should be the same as that used in the vessels containing the test substance. The appropriate number of replicates should be used (see section 1.8.1.3).

Generally, in a well-run test, the coefficient of variation around the mean number of living offspring produced per parent animal in the control(s) should be ≤ 25 %, and this should be reported for test designs using individually held animals.

1.8.4. **Test medium renewal**

The frequency of medium renewal will depend on the stability of the test substance, but should be at least three times per week. If, from preliminary stability tests (see section 1.4) the test substance concentration is not stable (i.e. outside the range 80-120 % of nominal or falling below 80 % of the measured initial concentration) over the maximum renewal period (i.e. three days), consideration should be given to more frequent medium renewal, or to the use of a flow-through test.

When the medium is renewed in semi-static tests, a second series of test vessels are prepared and the parent animals transferred to them by, for example, a glass pipette of suitable diameter. The volume of medium transferred with the *Daphnia* should be minimised.

1.8.5. **Observations**

The results of the observations made during the test should be recorded on data sheets (see examples in Appendices 3 and 4). If other measurements are required (see 1.3 and 1.8.8) additional observations may be required.

1.8.6. **Offspring**

The offspring produced by each parent animal should preferably be removed and counted daily from the appearance of the first brood, to prevent them consuming food intended for the adult. For the purpose of this method it is only the number of living offspring that needs to be counted, but the presence of aborted eggs or dead offspring should be recorded.

1.8.7. **Mortality**

Mortality among the parent animals should be recorded preferably daily, at least at the same times as offspring are counted.

1.8.8. **Other parameters**

Although this method is designed principally to assess effects on reproduction, it is possible that other effects may also be sufficiently quantified to allow statistical analysis. Growth measurements are highly desirable since they provide information on possible sublethal effects, which may be more useful than reproduction measurement alone; the measurement of the length of the parent animals (i.e. body length excluding the anal spine) at the end of the test is recommended. Other parameters that can be measured or calculated include time to production of first brood (and subsequent broods), number and size of broods per animal, number of aborted broods, presence of males or ephippia and the intrinsic rate of population increase.

1.8.9. **Frequency of analytical determinations and measurements**

Oxygen concentration, temperature, hardness and pH values should be measured at least once a week, in fresh and old media, in the control(s) and in the highest test substance concentration.

During the test, the concentrations of test substance are determined at regular intervals.

In semi-static tests where the concentration of the test substance is expected to remain within ± 20 % of the nominal (i.e. within the range 80-120 % — see 1.4 and 1.8.4), it is recommended that, as a minimum, the highest and lowest test concentrations be analysed when freshly prepared and at the time of renewal on one occasion during the first week of the test (i.e. analyses should be made on a sample from the same solution — when freshly prepared and at renewal). These determinations should be repeated at least at weekly intervals thereafter.

For tests where the concentration of the test substance is not expected to remain within ± 20 % of the nominal, it is necessary to analyse all test concentrations, when freshly prepared and at renewal. However, for those tests where the measured initial concentration of the test substance is not within ± 20 % of nominal but where sufficient evidence can be provided to show that the initial concentrations are repeatable and stable (i.e. within the range 80-120 % of initial concentrations), chemical determinations could be reduced in weeks 2 and 3 of the test to the highest and lowest test concentrations. In all cases, determination of test substance concentrations prior to renewal need only be performed on one replicate vessel at each test concentration.

If a flow-through test is used, a similar sampling regime to that described for semi-static tests is appropriate (but measurement of 'old' solutions is not applicable in this case). However, it may be advisable to increase the number of sampling occasions during the first week (e.g. three sets of measurements) to ensure that the test concentrations are remaining stable. In these types of test, the flow-rate of diluent and test substance should be checked daily.

If there is evidence that the concentration of the substance being tested has been satisfactorily maintained within ± 20 % of the nominal or measured initial concentration throughout the test, then results can be based on nominal or measured initial values. If the deviation from the nominal or measured initial concentration is greater than ± 20 %, results should be expressed in terms of the time-weighed mean (see Appendix 5).

## 2. DATA AND REPORTING

### 2.1. TREATMENT OF RESULTS

The purpose of this test is to determine the effect of the test substance on the total number of living offspring produced per parent animal alive at the end of the test. The total number of offspring per parent animal should be calculated for each test vessel (i.e. replicate). If, in any replicate the parent animal dies during the test or turns out to be male, then the replicate is excluded from the analysis. The analysis will then be based on a reduced number of replicates.

For the estimation of the LOEC, and hence the NOEC, for effects of the chemical on reproductive output, it is necessary to calculate the mean reproductive output across replicates for each concentration and the pooled residual standard deviation, and this can be done using analysis of variance (ANOVA). The mean for each concentration must then be compared with the control mean using an appropriate multiple comparison method. Dunnett's or Williams' tests may be useful (14) (15) (16) (17). It is necessary to check whether the ANOVA assumption of homogeneity of variance holds. It is recommended that this be done graphically rather than via a formal significance test (18); a suitable alternative is to run a Bartlett's test. If this assumption does not hold, then consideration should be given to transforming the data to homogenise variances prior to performing the ANOVA, or to carrying out a weighted ANOVA. The size of the effect detectable using ANOVA (i.e. the least significant difference) should be calculated and reported.

For the estimation of the concentration which would cause a 50 % reduction in reproductive output (i.e. the $EC_{50}$), a suitable curve, such as the logistic curve, should be fitted to the data using a statistical method such as least squares. The curve could be parameterised so that the $EC_{50}$ and its standard error can be estimated directly. This would greatly ease the calculation of the confidence limits about the $EC_{50}$. Unless there are good reasons to prefer different confidence levels, two-sided 95 % confidence limits should be quoted. The fitting procedure should preferably provide a means for assessing the significance of the lack of fit. This can be done graphically or by dividing the residual sum of squares into 'lack of fit' and 'pure error components' and performing a significance test for lack of fit. Since treatments giving high fecundity are likely to have greater variance in the number of juveniles produced than treatments giving low fecundity, consideration to weighting the observed values to reflect the different variances in the different treatment groups should be given (see for background information reference (18)).

In the analysis of the data from the final ring test (2), a logistic curve was fitted using the following model, although other suitable models can be used:

$$Y = \frac{c}{1 + \left(\frac{x}{x_0}\right)^b}$$

where:

Y: the total number of juveniles per parent animal alive at the end of the test (calculated for each vessel)

x: the substance concentration

c: the expected number of juveniles when x = 0

$x_0$: the $EC_{50}$ in the population

b: the slope parameter.

This model is likely to be adequate in a large number of situations, but there will be tests for which it is not appropriate. A check should be made on the validity of the model as suggested above. In some cases, a hormesis model in which low concentrations give enhanced effects may be appropriate (19).

Other effect concentrations, such as the $EC_{10}$ or $EC_{20}$ can also be estimated, although it may be preferable to use a different parameterisation of the model from that used to estimate the $EC_{50}$.

2.2. TEST REPORT

The test report must include the following:

2.2.1. **Test substance:**

— physical nature and relevant physicochemical properties,

— chemical identification data, including purity.

2.2.2. **Test species:**

— the clone (whether it has been genetically typed), supplier or source (if known) and the culture conditions used. If a different species to *Daphnia magna* is used, this should be reported and justified.

2.2.3. **Test conditions:**

— test procedure used (e.g. semi-static or flow-through, volume, loading in number of *Daphnia* per litre),

— photoperiod and light intensity,

— test design (e.g. number of replicates, number of parents per replicate),

— details of culture medium used,

— if used, additions of organic material including the composition, source, method of preparation, TOC/COD of stock preparations, estimation of resulting TOC/COD in test medium,

— detailed information on feeding, including amount (in mg C/*Daphnia*/day) and schedule (e.g. type of food(s), including for algae the specific name(species) and, if known, the strain, the culture conditions),

— method of preparation of stock solutions and frequency of renewal (the solvent or dispersant and its concentration must be given, when used).

2.2.4. **Results:**

— results from any preliminary studies on the stability of the test substance,

— the nominal test concentrations and the results of all analyses to determine the concentration of the test substance in the test vessels (see example data sheets in Appendix 4); the recovery efficiency of the method and the limit of determination should also be reported,

— water quality within the test vessels (i.e. pH, temperature and dissolved oxygen concentration, and TOC and/or COD and hardness where applicable) (see example data sheet in Appendix 3),

— the full record of living offspring by each parent animal (see example data sheet in Appendix 3),

— the number of deaths among the parent animals and the day on which they occurred (see example data sheet in Appendix 3),

— the coefficient of variation for control fecundity (based on total number of living offspring per parent animal alive at the end of the test),

— plot of total number of living offspring per parent animal (for each replicate) alive at the end of the test vs concentration of the test substance,

— the lowest observed effect concentration (LOEC) for reproduction, including a description of the statistical procedures used and an indication of what size of effect could be detected and the no observed effect concentration (NOEC) for reproduction; where appropriate, the LOEC/NOEC for mortality of the parent animals should also be reported,

— where appropriate, the $EC_x$ for reproduction and confidence intervals and a graph of the fitted model used for its calculation, the slope of the dose-response curve and its standard error,

— other observed biological effects or measurements: report any other biological effects which were observed or measured (e.g. growth of parent animals) including any appropriate justification,

— an explanation for any deviation from the test method.

3. **REFERENCES**

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*APPENDIX 1*

**PREPARATION OF FULLY DEFINED ELENDT M7 AND M4 MEDIA**

**Acclimation to Elendt M7 and M4 media**

Some laboratories have experienced difficulty in directly transferring *Daphnia* to M4 (1) and M7 media. However, some success has been achieved with gradual acclimation, i.e. moving from own medium to 30 % Elendt, then to 60 % Elendt and then to 100 % Elendt. The acclimation periods may need to be as long as one month.

PREPARATION

**Trace elements**

Separate stock solutions (I) of individual trace elements are first prepared in water of suitable purity, e.g. deionised, distilled or reverse osmosis. From these different stock solutions (I) a second single stock solution (II) is prepared, which contains all trace elements (combined solution), i.e.:

| Stock solutions I (single substance) | Amount added to water (mg/l) | Concentration (in relation to medium M4) (fold) | To prepare the combined stock-solution II add the following amount of stock solution I to water (ml/l) | |
|---|---|---|---|---|
| | | | M 4 | M 7 |
| $H_3BO_3$ | 57 190 | 20 000 | 1,0 | 0,25 |
| $MnCl_2$ * 4 $H_2O$ | 7 210 | 20 000 | 1,0 | 0,25 |
| LiCl | 6 120 | 20 000 | 1,0 | 0,25 |
| RbCl | 1 420 | 20 000 | 1,0 | 0,25 |
| $SrCl_2$ * 6 $H_2O$ | 3 040 | 20 000 | 1,0 | 0,25 |
| NaBr | 320 | 20 000 | 1,0 | 0,25 |
| $Na_2MoO_4$ * 2 $H_2O$ | 1 260 | 20 000 | 1,0 | 0,25 |
| $CuCl_2$ * 2 $H_2O$ | 335 | 20 000 | 1,0 | 0,25 |
| $ZnCl_2$ | 260 | 20 000 | 1,0 | 1,0 |
| $CoCl_2$ * 6 $H_2O$ | 200 | 20 000 | 1,0 | 1,0 |
| KI | 65 | 20 000 | 1,0 | 1,0 |
| $Na_2SeO_3$ | 43,8 | 20 000 | 1,0 | 1,0 |
| $NH_4VO_3$ | 11,5 | 20 000 | 1,0 | 1,0 |
| $Na_2EDTA$ * 2 $H_2O$ | 5 000 | 2 000 | – | – |
| $FeSO_4$ * 7 $H_2O$ | 1 991 | 2 000 | – | – |

Both $Na_2EDTA$ and $FeSO_4$ solutions are prepared singly, poured together and autoclaved immediately. This gives:

| | | | | |
|---|---|---|---|---|
| 21 Fe-EDTA solution | | 1 000 | 20,0 | 5,0 |

**M4 and M7 media**

M4 and M7 media are prepared using stock solution II, the macro-nutrients and vitamins as follows:

| | Amount added to water (mg/l) | Concentration (related to medium M4) (fold) | Amount of stock solution added to prepare medium (ml/l) | |
|---|---|---|---|---|
| | | | M 4 | M 7 |
| Stock solution II combined trace elements | | 20 | 50 | 50 |
| Macro-nutrient stock solutions (single substance) | | | | |
| $CaCl_2 * 2 H_2O$ | 293 800 | 1 000 | 1,0 | 1,0 |
| $MgSO_4 * 7 H_2O$ | 246 600 | 2 000 | 0,5 | 0,5 |
| KCl | 58 000 | 10 000 | 0,1 | 0,1 |
| $NaHCO_3$ | 64 800 | 1 000 | 1,0 | 1,0 |
| $Na_2SiO_3 * 9 H_2O$ | 50 000 | 5 000 | 0,2 | 0,2 |
| $NaNO_3$ | 2 740 | 10 000 | 0,1 | 0,1 |
| $KH_2PO_4$ | 1 430 | 10 000 | 0,1 | 0,1 |
| $K_2HPO_4$ | 1 840 | 10 000 | 0,1 | 0,1 |
| Combined vitamin stock | – | 10 000 | 0,1 | 0,1 |
| The combined vitamin stock solution is prepared by adding the 3 vitamins to 1 litre water as shown below: | | | | |
| Thiamine hydrochloride | 750 | 10 000 | – | – |
| Cyanocobalamine ($B_{12}$) | 10 | 10 000 | – | – |
| Biotine | 7,5 | 10 000 | – | – |

The combined vitamin stock is stored frozen in small aliquots. Vitamins are added to the media shortly before use.

Notes: To avoid precipitation of salts when preparing the complete media, add the aliquots of stock solutions to about 500-800 ml deionised water and then fill up to 1 litre.

The first publication of the M4 medium can be found in Elendt, B.P. (1990). Selenium deficiency in crustacea; an ultrastructural approach to antennal damage in *Daphnia magna* Straus. Protoplasma, 154, pp. 25-33.

*APPENDIX 2*

**TOTAL ORGANIC CARBON (TOC) ANALYSIS AND PRODUCTION OF A NOMOGRAPH FOR TOC CONTENT OF ALGAL FEED**

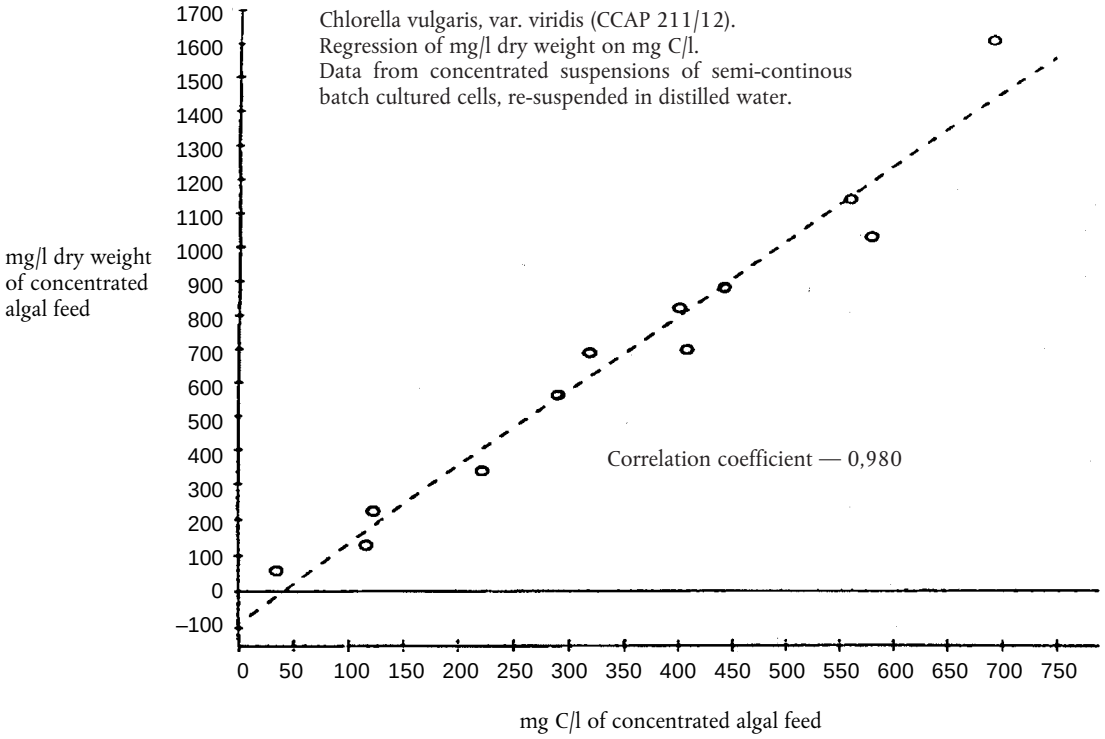
It is recognised that the carbon content of the algal feed will not normally be measured directly but from correlations (i.e. nomographs) with surrogate measures such as algal cell number or light absorbance).

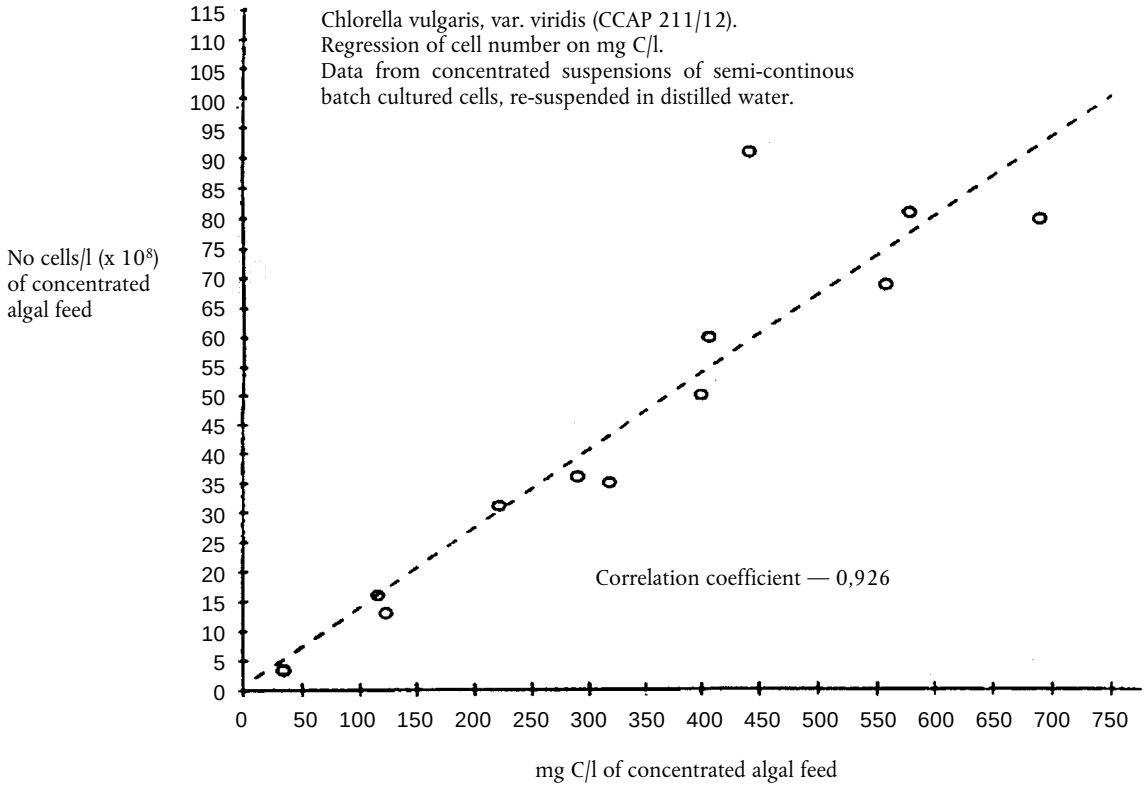
TOC should be measured by high temperature oxidation rather than by UV or persulphate methods. (See: The Instrumental Determination of Total Organic Carbon, Total Oxygen Demand and Related Determinands 1979, HMSO 1980; 49 High Holborn, London WC1V 6HB).

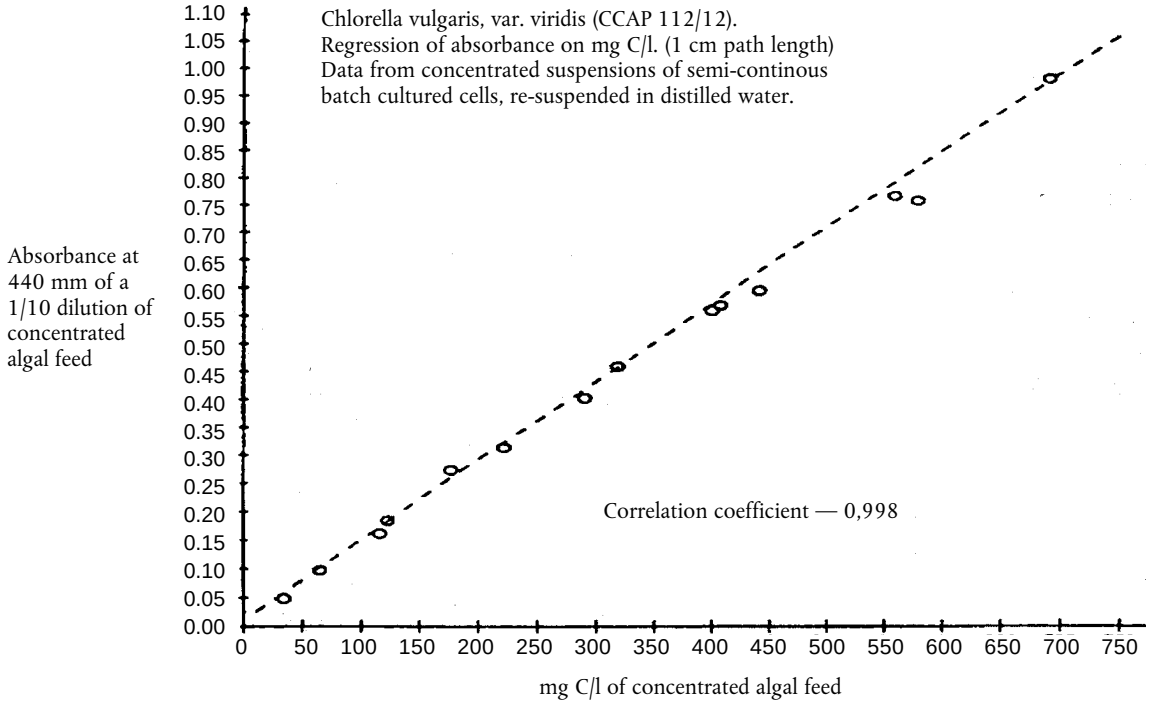
For nomograph production, algae should be separated from the growth medium by centrifugation followed by resuspension in distilled water. Measure the surrogate parameter and TOC concentration in each sample in triplicate. Distilled water blanks should be analysed and the TOC concentration deducted from that of the algal sample TOC concentration.

Nomograph should be linear over the required range of carbon concentrations. Examples are shown below.

NB: These should not be used for conversions; it is essential that laboratories prepare their own nomographs.




Chlorella vulgaris, var. viridis (CCAP 211/12).
Regression of cell number on mg C/l.
Data from concentrated suspensions of semi-continous batch cultured cells, re-suspended in distilled water.
No cells/l (x 10⁸) of concentrated algal feed
Correlation coefficient — 0,926
mg C/l of concentrated algal feed


Chlorella vulgaris, var. viridis (CCAP 112/12).
Regression of absorbance on mg C/l. (1 cm path length)
Data from concentrated suspensions of semi-continous batch cultured cells, re-suspended in distilled water.
Absorbance at 440 mm of a 1/10 dilution of concentrated algal feed
Correlation coefficient — 0,998
mg C/l of concentrated algal feed

*APPENDIX 3*

**EXAMPLE DATA SHEET RECORDING MEDIUM RENEWAL, PHYSICAL/CHEMICAL MONITORING DATA, FEEDING, DAPHNIA REPRODUCTION AND ADULT MORTALITY**

Experiment No: Data started: Clone: Medium: Type of food: Test substance: Nominal conc.:

| Day | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Medium renewal (tick) | | | | | | | | | | | | | | | | | | | | | | | | |
| PH (1) | | | | | | | | | | | | | | | | | | | | | | | new | |
| | | | | | | | | | | | | | | | | | | | | | | | old | |
| $O_2$ mg/l (1) | | | | | | | | | | | | | | | | | | | | | | | new | |
| | | | | | | | | | | | | | | | | | | | | | | | old | |
| Temperature (°C) (1) | | | | | | | | | | | | | | | | | | | | | | | new | |
| | | | | | | | | | | | | | | | | | | | | | | | old | |
| Food provided (tick) | | | | | | | | | | | | | | | | | | | | | | | | |
| No live offspring (2) | | | | | | | | | | | | | | | | | | | | | | | | Total |
| Vessel 1 | | | | | | | | | | | | | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | | | | | | | | | | | | | |
| 3 | | | | | | | | | | | | | | | | | | | | | | | | |
| 4 | | | | | | | | | | | | | | | | | | | | | | | | |
| 5 | | | | | | | | | | | | | | | | | | | | | | | | |
| 6 | | | | | | | | | | | | | | | | | | | | | | | | |
| 7 | | | | | | | | | | | | | | | | | | | | | | | | |
| 8 | | | | | | | | | | | | | | | | | | | | | | | | |
| 9 | | | | | | | | | | | | | | | | | | | | | | | | |
| 10 | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | Total | |
| Cumulative adult mortality (3) | | | | | | | | | | | | | | | | | | | | | | | | |

(1) Indicate which vessel was used for the experiment.
(2) Record aborted broods as 'AB' in relevant box.
(3) Record mortality of any adult animals as 'M' in relevant box.

*APPENDIX 4*

**EXAMPLE DATA SHEET FOR RECORDING RESULTS OF CHEMICAL ANALYSIS**

(a) **Measured concentrations**

| Nominal conc. | Week 1 sample | | Week 2 sample | | Week 3 sample | |
|---|---|---|---|---|---|---|
| | Fresh | Old | Fresh | Old | Fresh | Old |
| | | | | | | |

(b) **Measured concentrations as a percentage of nominal**

| Nominal conc. | Week 1 sample | | Week 2 sample | | Week 3 sample | |
|---|---|---|---|---|---|---|
| | Fresh | Old | Fresh | Old | Fresh | Old |
| | | | | | | |

*APPENDIX 5*

## CALCULATION OF A TIME-WEIGHTED MEAN

### Time-weighted mean

Given that the concentration of the test substance can decline over the period between medium renewals, it is necessary to consider what concentration should be chosen as representative of the range of concentrations experienced by the parent *Daphnia*. The selection should be based on biological considerations as well as statistical ones. For example, if reproduction is thought to be affected mostly by the peak concentration experienced, then the maximum concentration should be used. However, if the accumulated or longer term effect of the toxic substance is considered to be more important, then an average concentration is more relevant. In this case, an appropriate average to use is the time-weighted mean concentration, since this takes account of the variation in instantaneous concentration over time.

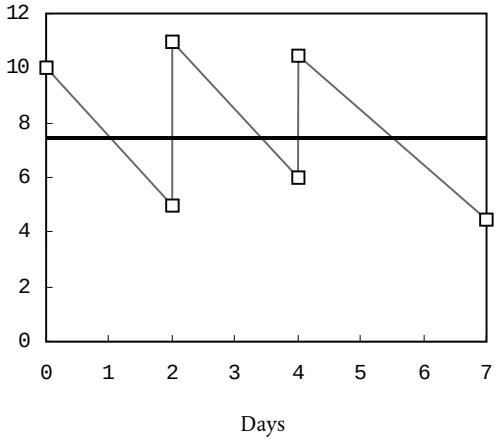



**Figure 1: Example of time-weighted mean**

Figure 1 shows an example of a (simplified) test lasting seven days with medium renewal at days 0, 2 and 4.

— The thin zig-zag line represents the concentration at any point in time. The fall in concentration is assumed to follow an exponential decay process.

— The six plotted points represent the observed concentrations measured at the start and end of each renewal period.

— The thick solid line indicates the position of the time-weighted mean.

The time-weighted mean is calculated so that the area under the time-weighted mean is equal to the area under the concentration curve. The calculation for the above example is illustrated in Table 1.

**Table 1: Calculation of time-weighted mean**

| Renewal No | Days | Conc0 | Conc1 | Ln(Conc0) | Ln(Conc1) | Area |
|---|---|---|---|---|---|---|
| 1 | 2 | 10,000 | 4,493 | 2,303 | 1,503 | 13,767 |
| 2 | 2 | 11,000 | 6,037 | 2,398 | 1,798 | 16,544 |
| 3 | 3 | 10,000 | 4,066 | 2,303 | 1,403 | 19,781 |
| Total days: 7 | | | | | Total area | 50,091 |
| | | | | | TW mean | 7,156 |

'Days' is the number of days in the renewal period.

'Conc0' is the measured concentration at the start of each renewal period.

'Conc1' is the measured concentration at the end of each renewal period.

'Ln(Conc0)' is the natural logarithm of Conc0.

'Ln(Conc1)' is the natural logarithm of Conc1.

'Area' is the area under the exponential curve for each renewal period. It is calculated by:

$$\text{Area} = \frac{\text{Conc0} - \text{Conc1}}{\text{Ln(Conc0)} - \text{Ln(Conc1)}} \times \text{Days}$$

The time-weighted mean ('TW mean') is the 'Total area' divided by the 'Total days'.

Of course, for the *Daphnia* reproduction test the table would have to be extended to cover 21 days.

It is clear that when observation are taken only at the start and end of each renewal period, it is not possible to confirm that the decay process is, in fact, exponential. A different curve would result in a different calculation for 'Area'. However, an exponential decay process is not implausible and is probably the best curve to use in the absence of other information.

However, a work of caution is required if the chemical analysis fails to find any substance at the end of the renewal period. Unless it is possible to estimate how quickly the substance disappeared from the solution, it is impossible to obtain a realistic area under the curve, and hence it is impossible to obtain a reasonable time-weighted mean.

*ANNEX 6*

*ANNEX VI*

# GENERAL CLASSIFICATION AND LABELLING REQUIREMENTS FOR DANGEROUS SUBSTANCES AND PREPARATIONS

**Contents**

COMMISSION STATEMENT

1. GENERAL INTRODUCTION

1.1. The object of classification is to identify all the physico-chemical, toxicological and ecotoxicological properties of substances and preparations which may constitute a risk during normal handling or use. Having identified any hazardous properties, the substance or preparation must then be labelled to indicate the hazard(s) in order to protect the user, the general public and the environment.

1.2. This Annex sets out the general principles governing the classification and labelling of substances and preparations referred to in Article 4 of this Directive and in Article 4 of Directive 1999/45/EC and other relevant Directives on dangerous preparations.

It is addressed to all those concerned (manufacturers, importers, national authorities) with methods of classifying and labelling dangerous substances and preparations.

1.3. The requirements of this Directive and of Directive 1999/45/EC are intended to provide a primary means by which the general public and persons at work are given essential information about dangerous substances and preparations. The label draws the attention of persons handling or using substances and preparations to the inherent danger of certain such materials.

The label may also serve to draw attention to more comprehensive product information on safety and use available in other forms.

1.4. The label takes account of all potential hazards which are likely to be faced in the normal handling and use of dangerous substances and preparations when in the form in which they are placed on the market, but not necessarily in any different form in which they may finally be used, e.g. diluted. The most severe hazards are highlighted by symbols, such hazards and those arising from other dangerous properties are specified in standard risk phrases, and safety phrases give advice on necessary precautions.

In the case of substances, the information is completed by the name of the substance under an internationally recognised chemical nomenclature, the preferred name being the one used in the European Inventory of Existing Commercial Chemical Substances (Einecs), or in the European List of Notified Chemical Substances (Elincs), the EC number and the name, address and telephone number of the person established in the Community who is responsible for placing the substance on the market.

In the case of preparations, the information in accordance with Article 10(2) of Directive 1999/45/EC, is completed by:

— the trade name or the designation of the preparation,

— the chemical name of the substance or substances present in the preparation, and

— the name, full address and telephone number of the person established in the Community who is responsible for placing the preparation on the market.

1.5. Article 6 requires that manufacturers, distributors and importers of dangerous substances which appear in the Einecs but which have not yet been introduced into Annex I shall be obliged to carry out an investigation to make themselves aware of the relevant and accessible data which exist concerning the properties of such substances. On the basis of this information, they shall package and provisionally label these substances according to the rules laid down in Articles 22 to 25 and the criteria in this Annex.

1.6. **Data required for classification and labelling**

1.6.1. For substances the data required for classification and labelling may be obtained:

(a) as regards substances for which the information specified in Annex VII is required, most of the necessary data for classification and labelling appear in the 'base set'. This classification and labelling must be reviewed, if necessary, when further information is available (Annex VIII);

(b) as regards other substances (e.g. those referred to in section 1.5), the data required for classification and labelling may, if necessary, be obtained from a number of different sources, for example:

— the results of previous tests,

— information required by international rules on the transport of dangerous substances,

— information taken from reference works and the literature, or

— information derived from practical experience.

The results of validated structure-activity relationships and expert judgement may also be taken into account where appropriate.

1.6.2. For preparations, normally the data required for classification and labelling may be obtained:

(a) if it concerns physicochemical data, by the application of the methods specified in Annex V. This applies also to preparations covered by Directive 91/414/EEC unless other internationally recognised methods are acceptable in accordance with the provisions of Annexes II and III to Directive 91/414/EEC (Article 5(5) of Directive 1999/45/EC). For gaseous preparations a calculation method may be used for flammable and oxidising properties (see 9.1.1.1 and 9.1.1.2). For non-gaseous preparations containing organic peroxides a calculation method may be used for oxidising properties (see 2.2.2.1);

(b) if it concerns data on health effects:

— by the application of the methods specified in Annex V, unless, in the case of plant protection products, other internationally recognised methods are acceptable in accordance with the provisions of Annexes II and III to Directive 91/414/EEC (Article 6(1) (b) of Directive 1999/45/EC),

— and/or by the application of a conventional method referred to in Article 6 of and Annex II, Parts A.1-6 and B.1-5, to Directive 1999/45/EC, or,

— in the case of R65, by the application of the rules under 3.2.3,

— however, if it concerns the evaluation of the carcinogenic, mutagenic and reproductive toxicity properties, by the application of a conventional method referred to in Article 6 of and Annex II, Parts A.7-9 and B.6, to Directive 1999/45/EC;

(c) if it concerns data on ecotoxicological properties:

(i) for aquatic toxicity only:

— by the application of the methods specified in Annex V, subject to the conditions referred to in Annex III, Part C, to Directive 1999/45/EC, unless, in the case of plant protection products, other internationally recognised methods are acceptable in accordance with the provisions of Annexes II and III to Directive 91/414/EEC (Article 7(1)(b) of Directive 1999/45/EC), or

— by application of a conventional method referred to in Article 7 of and Annex III, Parts A and B, to Directive 1999/45/EC;

(ii) for the evaluation of the potential for (or actual) bioaccumulation through the determination of log Pow (or BCF), or the evaluation of degradability, by application of a conventional method referred to in Article 7 of and Annex III, Parts A and B, to Directive 1999/45/EC;

(iii) for dangers of the ozone layer by application of a conventional method referred to in Article 7 of and Annex III, Parts A and B, to Directive 1999/45/EC.

Note concerning the performance of animal tests:

The performance of animal tests to establish experimental data is subject to the provisions of Directive 86/609/EEC regarding the protection of animals used for experimental purposes.

Note concerning physicochemical properties:

For organic peroxides and organic peroxide preparations data may be derived from the calculation method set out in section 9.5. For gaseous preparations a calculation method may be used for flammable and oxidising properties (see section 9).

1.7. **Application of the guide criteria**

Classification must cover the physicochemical, toxicological and ecotoxicological properties of substances and preparations.

Classification of substances and preparations is made according to section 1.6, on the basis of the criteria in sections 2 to 5 (substances) and sections 2, 3, 4.2.4 and 5 of this Annex. All types of hazard must be considered. For instance, classification under 3.2.1 does not imply that the sections such as 3.2.2 or 3.2.4 can be ignored.

The choice of symbol(s) and risk phrase(s) is made on the basis of the classification in order to ensure that the specific nature of the potential dangers identified in classification is expressed on the label.

Notwithstanding the criteria given under 2.2.3, 2.2.4 and 2.2.5, substances and preparations in the form of aerosols shall be subject to the provisions of Directive 75/324/EEC as amended and adapted to technical progress.

1.7.1. Definitions

'Substances' means chemical elements and their compounds in the natural state or obtained by any production process, including any additive necessary to preserve the stability of the product, and any impurity deriving from the production process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition.

A substance may be chemically very well defined (e.g. acetone) or a complex mixture of constituents of variable composition (e.g. aromatic distillates). For certain complex substances, some individual constituents have been identified.

'Preparations' means mixtures or solutions composed of two or more substances.

1.7.2. Application of the guide criteria for substances

The guidance criteria set out in this Annex are directly applicable when the data in question have been obtained from test methods comparable with those described in Annex V. In other cases, the available data must be evaluated by comparing the test methods employed with those indicated in Annex V and the rules specified in this Annex for determining the appropriate classification and labelling.

In some cases there may be doubt over the application of the relevant criteria, especially where these require the use of expert judgement. In such cases the manufacturer, distributor or importer should provisionally classify and label the substance on the basis of an assessment of the evidence by a competent person.

Without prejudice to Article 6, where the above procedure has been followed and there is concern over possible inconsistencies then a proposal may be submitted for the entry of the provisional classification into Annex I. The proposal should be made to one of the Member States and should be accompanied by appropriate scientific data (see also section 4.1).

A similar procedure may be followed when information is identified which gives cause for concern over the accuracy of an existing entry in Annex I.

1.7.2.1. *Classification of substances containing impurities, additives or individual constituents*

Where impurities, additives or individual constituents of substances have been identified, they shall be taken into account if their concentration is greater than or equal to the limits specified:

— 0,1 % for substances classified as very toxic, toxic, carcinogenic (category 1 or 2), mutagenic (category 1 or 2), toxic to reproduction (category 1 or 2), or dangerous for the environment (assigned the symbol 'N' for the aquatic environment, dangerous for the ozone layer),

— 1 % for substances classified as harmful, corrosive, irritant sensitising, carcinogenic (category 3), mutagenic (category 3), toxic to reproduction (category 3), or dangerous for the environment (not assigned the symbol 'N', i.e. harmful to aquatic organisms, may cause long-term adverse effects),

unless lower values have been specified in Annex I.

With the exception of substances listed specifically in Annex I, classification should be carried out according to the requirements of Articles 5, 6 and 7 of Council Directive 1999/45/EC.

In the case of asbestos (650-013-00-6) this general rule does not apply until a concentration limit has been fixed in Annex I. Substances in which asbestos is present must be classified and labelled according to the principles in Article 6 of this Directive.

1.7.3. Application of the guide criteria for preparations

The guidance criteria set out in this Annex are directly applicable when the data in question have been obtained from test methods comparable with those described in Annex V with the exception of the criteria of section 4 for which only the conventional method is applicable. A conventional method is also applicable in relation to the criteria of section 5, with the exception of aquatic toxicity, subject to the conditions referred to

in Annex III, Part C, to Directive 1999/45/EC. For preparations covered by Directive 91/414/EEC data for classification and labelling are also acceptable from other internationally recognised methods (see special provisions in section 1.6 of this Annex). In other cases, the available data must be evaluated by comparing the test methods employed with those indicated in Annex V and the rules specified in this Annex for determining the appropriate classification and labelling.

Where the health and environmental hazards are assessed by applying a conventional method referred to in Articles 6 and 7 and Annexes II and III to Directive 1999/45/EC the individual concentration limits to be used are those set out either:

— in Annex I to this Directive, or

— in Annex II, Part B, and/or Annex III, Part B, to Directive 1999/45/EC where the substance or substances do not appear in Annex I to this Directive or appear in it without concentration limits.

In the case of preparations containing mixtures of gases, classification with respect to the health and environmental effects will be established by the calculation method on the basis of the individual concentration limits from Annex I to this Directive or when these limits are not in Annex I on the basis of the criteria of Annexes II and III to Directive 1999/45/EC.

1.7.3.1. *Preparations or substances described in section 1.7.2.1 used as constituents of another preparation*

The labelling of such preparations must be in conformity with the provisions of Article 10 according to the principles set out in Articles 3 and 4 of Directive 1999/45/EC. However, in certain cases, the information on the label of the preparation or substance described in section 1.7.2.1 is insufficient to enable other manufacturers who wish to use it as a constituent of their own preparation(s) to carry out the classification and labelling of their preparation(s) correctly.

In these cases, the person established within the Community responsible for placing the original preparation or substance described in section 1.7.2.1 on the market, whether it be the manufacturer, the importer or the distributor shall supply upon justified request and as soon as possible all necessary data concerning the dangerous substances present to enable correct classification and labelling of the new preparation. This data is also necessary to enable the person responsible for placing the new preparation on the market to comply with other requirements of Directive 1999/45/EC.

## 2. CLASSIFICATION ON THE BASIS OF PHYSICOCHEMICAL PROPERTIES

### 2.1. **Introduction**

The test methods relating to explosive, oxidising and flammable properties included in Annex V serve to give specific meaning to the general definitions given in Article 2(2)(a) to (e). Criteria follow directly from the test methods in Annex V as far as they are mentioned.

If adequate information is available to demonstrate in practice that the physico-chemical properties of substances and preparations (apart from organic peroxides) are different from those revealed by the test methods given in Annex V, then such substances and preparations should be classified according to the hazard they present, if any, to those handling the substances and preparations or to other persons.

### 2.2. **Criteria for classification, choice of symbols, indication of danger and choice of risk phrases**

In the case of preparations, the criteria referred to in Article 5 of Directive 1999/45/EC need to be taken into consideration.

#### 2.2.1. Explosive

Substances and preparations shall be classified as explosive and assigned the symbol 'E' and the indication of danger 'explosive' in accordance with the results of the tests given in Annex V and in so far as the substances

and preparations are explosive as placed on the market. One risk phrase is obligatory, it is to be specified on the basis of the following:

R2 Risk of explosion by shock, friction, fire or other sources of ignition

— Substances and preparations except those set out below.

R3 Extreme risk of explosion by shock, friction, fire or other source of ignition

— Substances and preparations which are particularly sensitive such as picric acid salts or PETN.

2.2.2. Oxidising

Substances and preparations shall be classified as oxidising and assigned the symbol 'O' and the indication of danger 'oxidising' in accordance with the results of the tests given in Annex V. One risk phrase is obligatory, it is to be specified on the basis of the test results but subject to the following:

R7 May cause fire

— Organic peroxides which have flammable properties even when not in contact with other combustible material.

R8 Contact with combustible material may cause fire

— Other oxidising substances and preparations, including inorganic peroxides, which may cause fire or enhance the risk of fire when in contact with combustible material.

R9 Explosive when mixed with combustible material

— Other substances and preparations, including inorganic peroxides, which become explosive when mixed with combustible materials, e.g. certain chlorates.

2.2.2.1. *Remarks concerning peroxides*

For the explosive properties, an organic peroxide or preparation thereof in the form in which it is placed on the market is classified according to the criteria in section 2.2.1 on the basis of tests carried out in accordance with the methods given in Annex V.

For the oxidising properties the existing methods in Annex V cannot be applied to organic peroxides.

For substances, organic peroxides not already classified as explosive are classified as dangerous on the basis of their structure (e.g. R-O-O-H; $R_1$-O-O-$R_2$).

Preparations not already classified as explosive shall be classified using the calculation method based on the percentage of active oxygen shown in section 9.5.

Any organic peroxide or preparation thereof not already classified as explosive is classified as oxidising, if the peroxide or its formulation contains:

— more than 5 % of organic peroxides, or

— more than 0,5 % available oxygen from the organic peroxides, and more than 5 % hydrogen peroxide.

2.2.3. Extremely flammable

Substances and preparations shall be classified as extremely flammable and assigned the symbol 'F+' and the indication of danger 'extremely flammable' in accordance with the results of the tests given in Annex V. The risk phrase shall be assigned in accordance with the following criteria:

R12 Extremely flammable

— Liquid substances and preparations which have a flash point lower than 0 °C and a boiling point (or in case of a boiling range the initial boiling point) lower than or equal to 35 °C.

— Gaseous substances and preparations which are flammable in contact with air at ambient temperature and pressure.

2.2.4. Highly flammable

Substances and preparations shall be classified as highly flammable and assigned the symbol 'F' and the indication of danger 'highly flammable' in accordance with the results of the tests given in Annex V. Risk phrases shall be assigned in accordance with the following criteria:

R11 Highly flammable

— Solid substances and preparations which may readily catch fire after brief contact with a source of ignition and which continue to burn or to be consumed after removal of the source of ignition.

— Liquid substances and preparations having a flash point below 21 °C but which are not extremely flammable.

R15 Contact with water liberates extremely flammable gases

— Substances and preparations which, in contact with water or damp air, evolve extremely flammable gases in dangerous quantities, at a minimum rate of 1 litre per kilogram per hour.

R17 Spontaneously flammable in air

— Substances and preparations which may become hot and finally catch fire in contact with air at ambient temperature without any input of energy.

2.2.5. Flammable

Substances and preparations shall be classified as flammable in accordance with the results of the tests given in Annex V. The risk phrase shall be assigned in accordance with the criteria mentioned below.

R10 Flammable

— Liquid substances and preparations having a flash point equal to or greater than 21 °C, and less than or equal to 55 °C.

However, in practice it has been shown that a preparation having a flash point equal to or greater than 21 °C and less than or equal to 55 °C need not be classified as flammable if the preparation could not in any way support combustion and only so long as there is no reason to fear risks to those handling these preparations or to other persons.

2.2.6. Other physico-chemical properties

Additional risk phrases shall be assigned to substances and preparations which have been classified by virtue of sections 2.2.1 to 2.2.5 or by sections 3, 4 and 5, in accordance with the following criteria (based on experience obtained during compilation of Annex I):

R1 Explosive when dry

For explosive substances and preparations put on the market in solution or in a wetted form, e.g. nitrocellulose with more than 12,6 % nitrogen.

R4 Forms very sensitive explosive metallic compounds

For substances and preparations which may form sensitive explosive metallic derivatives, e.g. picric acid, styphnic acid.

R5 Heating may cause an explosion

For thermally unstable substances and preparations not classified as explosive, e.g. perchloric acid > 50 %.

R6 Explosive with or without contact with air

For substances and preparations which are unstable at ambient temperatures, e.g. acetylene.

R7 May cause fire

For reactive substances and preparations, e.g. fluorine, sodium hydrosulphite.

R14 Reacts violently with water

For substances and preparations which react violently with water, e.g. acetyl chloride, alkali metals, titanium tetrachloride.

R16 Explosive when mixed with oxidising substances

For substances and preparations which react explosively with an oxidising agent, e.g. red phosphorus.

R18 In use, may form flammable/explosive vapour-air mixture

For preparations not in themselves classified as flammable, which contain volatile components which are flammable in air.

R19 May form explosive peroxides

For substances and preparations which may form explosive peroxides during storage, e.g. diethyl ether, 1,4-dioxan.

R30 Can become highly flammable in use

For preparations not in themselves classified as flammable, which may become flammable due to the loss of non-flammable volatile components.

R44 Risk of explosion if heated under confinement

For substances and preparations not in themselves classified as explosive in accordance with section 2.2.1 above but which may nevertheless display explosive properties in practice if heated under sufficient confinement. For example, certain substances which would decompose explosively if heated in a steel drum do not show this effect if heated in less-strong containers.

For other additional risk phrases see section 3.2.8.

## 3. CLASSIFICATION ON THE BASIS OF TOXICOLOGICAL PROPERTIES

### 3.1. **Introduction**

3.1.1. Classification is concerned with both the acute and long-term effects of substances and preparations, whether resulting from a single instance of exposure or repeated or prolonged exposure.

Where it can be demonstrated by epidemiological studies, by scientifically valid case studies as specified in this Annex or by statistically backed experience, such as the assessment of data from poison information units or concerning occupational diseases, that toxicological effects on man differ from those suggested by the application of the methods outlined in section 1.6 of this Annex, then the substance or preparation shall be classified according to its effects on man. However, tests on man should be discouraged and should not normally be used to negate positive animal data.

Directive 86/609/EEC seeks to protect animals used for experimental and other scientific purposes. For several endpoints there are validated *in vitro* test methods in Annex V to this Directive and these tests should be used where appropriate.

3.1.2. The classification of substances must be made on the basis of the experimental data available in accordance with the following criteria which take into account the magnitude of these effects:

(a) for acute toxicity (lethal and irreversible effects after a single exposure), the criteria under sections 3.2.1 to 3.2.3 are to be used;

(b) for subacute, subchronic or chronic toxicity the criteria under sections 3.2.2 to 3.2.4 are to be used;

(c) for corrosive and irritant effects the criteria under sections 3.2.5 and 3.2.6 are to be used;

(d) for sensitising effects the criteria under section 3.2.7 are to be used;

(e) for specific effects on health (carcinogenicity, mutagenicity and reproductive toxicity), the criteria in section 4 are to be used.

3.1.3. For preparations, the classification relating to dangerous for health is carried out:

(a) on the basis of a conventional method referred to in Article 6 of and Annex II to Directive 1999/45/EC in the absence of experimental data. In this case, the classification is based on the individual concentration limits:

— either taken from Annex I to this Directive, or

— from Annex II, Part B, to Directive 1999/45/EC where the substance or substances do not appear in Annex I to this Directive or appear in it without concentration limits;

(b) or when experimental data are available, according to the criteria described under section 3.1.2 excluding the carcinogenic, mutagenic and toxic to reproduction properties referred to under 3.1.2(e) which must be evaluated by a conventional method referred to in Article 6 of and Annex II, Parts A.7-9 and B.6, to Directive 1999/45/EC.

Note: Without prejudice to requirements of Directive 91/414/EEC, only where it can be scientifically demonstrated by the person responsible for placing the preparation on the market that the toxicological properties of the preparation cannot correctly be determined by the method outlined in paragraph 3.1.3(a), or on the basis of existing test results on animals, the methods outlined in paragraph 3.1.3(b) may be used, provided they are justified or specifically authorised under Article 12 of Directive 86/609/EEC.

Whichever method is used for the evaluation of the danger of a preparation, all the dangerous effects on health as defined in Annex II, Part B, to Directive 1999/45/EC must be taken into consideration.

3.1.4. When the classification is to be established from experimental results obtained in animal tests the results should have validity for man in that the tests reflect, in an appropriate way, the risks to man.

3.1.5. The acute oral toxicity of substances or preparations placed on the market may be established either by a method permitting assessment of the $LD_{50}$ value, or by determining the discriminating dose (the fixed dose method, or by determining the range of exposure where lethality is expected (the acute toxic class method).

3.1.5.1. The discriminating dose is the dose which causes evident toxicity but not mortality and must be one of the four dosage levels specified in Annex V (5, 50, 500 or 2 000 mg per kg body weight).

The concept 'evident toxicity' is used to designate toxic effects, after exposure to the substance tested, which are so severe that exposure to the next highest fixed dose would probably lead to mortality.

The results of testing at a particular dose following the fixed dose method may be either:

— less than 100 % survival,

— 100 % survival, but evident toxicity,

— 100 % survival, but no evident toxicity.

In the criteria in sections 3.2.1, 3.2.2 and 3.2.3 only the final test result is shown. The 2 000 mg/kg dose should be used primarily to obtain information on the toxic effects of substances which are of low acute toxicity and which are not classified on the basis of acute toxicity.

The fixed dose method requires in some cases testing at higher or lower doses, if not already tested at the relevant dose level. Refer also to the evaluation table in test method B.1 *bis*.

3.1.5.2. The range of exposure where lethality is expected is derived from the observed absence or presence of substance related mortality following the acute toxic class method. For initial testing one of three fixed starting doses (25, 200 or 2 000 mg per kg body weight) is used.

The acute toxic class method requires in some cases testing at higher or lower doses, if not already tested at the relevant dose level. Refer also to the test procedure flow charts in test method B.1 *ter* of Annex V.

3.2. **Criteria for classification, choice of symbols, indication of danger, choice of risk phrases**

3.2.1. Very toxic

Substances and preparations shall be classified as very toxic, and assigned the symbol 'T+' and indication of danger 'very toxic' in accordance with the criteria specified below.

Risk phrases shall be assigned in accordance with the following criteria:

R28 Very toxic if swallowed

Acute toxicity results:

— $LD_{50}$ oral, rat ≤ 25 mg/kg,

— less than 100 % survival at 5 mg/kg oral, rat by the fixed dose procedure, or

— high mortality at doses ≤ 25 mg/kg oral, rat, by the acute toxic class method (for test result interpretation see flow charts in Appendix 2 to test method B.1 *ter* of Annex V).

R27 Very toxic in contact with skin

Acute toxicity results:

— $LD_{50}$ dermal, rat or rabbit: ≤ 50 mg/kg.

R26 Very toxic by inhalation

Acute toxicity results:

— $LC_{50}$ inhalation, rat, for aerosols or particulates: ≤ 0,25 mg/litre/4h,

— $LC_{50}$ inhalation, rat, for gases and vapours: ≤ 0,5 mg/litre/4h.

R39 Danger of very serious irreversible effects

— Strong evidence that irreversible damage other than the effects referred to in section 4 is likely to be caused by a single exposure by an appropriate route, generally in the above-mentioned dose range.

In order to indicate the route of administration/exposure one of the following combinations shall be used: R39/26, R39/27, R39/28, R39/26/27, R39/26/28, R39/27/28, R39/26/27/28.

3.2.2. Toxic

Substances and preparations shall be classified as toxic and assigned the symbol 'T' and the indication of danger 'toxic' in accordance with the criteria specified below. Risk phrases shall be assigned in accordance with the following criteria.

R25 Toxic if swallowed

Acute toxicity results:

— $LD_{50}$ oral, rat: $25 < LD_{50} \leq 200$ mg/kg,

— discriminating dose, oral, rat, 5 mg/kg: 100 % survival but evident toxicity, or

— high mortality in the dose range > 25 to ≤ 200 mg/kg oral, rat, by the acute toxic class method (for test result interpretation see flow charts in Appendix 2 to test method B.1 *ter* of Annex V).

R24 Toxic in contact with skin

Acute toxicity results:

— $LD_{50}$ dermal, rat or rabbit: $50 < LD_{50} \leq 400$ mg/kg.

R23 Toxic by inhalation

Acute toxicity results:

— $LC_{50}$ inhalation, rat, for aerosols or particulates: $0,25 < LC_{50} \leq 1$ mg/litre/4h,

— $LC_{50}$ inhalation, rat, for gases and vapours: $0,5 < LC_{50} \leq 2$ mg/litre/4h.

R39 Danger of very serious irreversible effects

— strong evidence that irreversible damage other than the effects referred to in section 4 is likely to be caused by a single exposure by an appropriate route, generally in the above-mentioned dose range.

In order to indicate the route of administration/exposure one of the following combinations shall be used: R39/23, R39/24, R39/25, R39/23/24, R39/23/25, R39/24/25, R39/23/24/25.

R48 Danger of serious damage to health by prolonged exposure

— serious damage (clear functional disturbance or morphological change which have toxicological significance) is likely to be caused by repeated or prolonged exposure by an appropriate route.

Substances and preparations are classified at least as toxic when these effects are observed at levels of one order of magnitude lower (i.e. 10-fold) than those set out for R48 in section 3.2.3.

In order to indicate the route of administration/exposure one of the following combinations shall be used: R48/23, R48/24, R48/25, R48/23/24, R48/23/25, R48/24/25, R48/23/24/25.

3.2.3. Harmful

Substances and preparations shall be classified as harmful and assigned the symbol 'Xn' and the indication of danger 'harmful' in accordance with the criteria specified below. Risk phrases shall be assigned in accordance with the following criteria:

R22 Harmful if swallowed

Acute toxicity results:

— $LD_{50}$ per oral, rat: $200 < LD_{50} \leq 2\,000$ mg/kg,

— discriminating dose, oral, rat, 50 mg/kg: 100 % survival but evident toxicity,

— less than 100 % survival at 500 mg/kg, rat oral by the fixed dose procedure. Refer to the evaluation table in the test method B.1 *bis* of Annex V, or

— high mortality in the dose range > 200 to ≤ 2 000 mg/kg oral, rat, by the acute toxic class method (for test result interpretation see flow charts in Appendix 2 of test method B.1 *ter* of Annex V).

R21 Harmful in contact with skin

Acute toxicity results:

— $LD_{50}$ dermal, rat or rabbit: $400 < LD_{50} \leq 2\,000$ mg/kg.

R20 Harmful by inhalation

Acute toxicity results:

— $LC_{50}$ inhalation, rat, for aerosols or particulates: $1 < LC_{50} \leq 5$ mg/litre/4h,

— $LC_{50}$ inhalation, rat, for gases or vapours: $2 < LC_{50} \leq 20$ mg/litre/4h.

R65 Harmful: may cause lung damage if swallowed

Liquid substances and preparations presenting an aspiration hazard in humans because of their low viscosity:

(a) for substances and preparations containing aliphatic, alicyclic and aromatic hydrocarbons in a total concentration equal to or greater than 10 % and having either:

— a flow time of less than 30 sec. in a 3 mm ISO cup according to ISO 2431 (April 1996/July 1999 edition) relating to 'Paints and varnishes — Determination of flow time by use of flow cups',

— a kinematic viscosity measured by a calibrated glass capillary viscometer in accordance with ISO 3104/3105 of less than $7 \times 10^{-6}$ $m^2$/sec. at 40 °C (ISO 3104, 1994 edition, relating to 'Petroleum products — Transparent and opaque liquids — Determination of kinematic viscosity and calculation of dynamic viscosity'; ISO 3105, 1994 edition, relating to 'Glass capillary kinematic viscometers — Specifications and operating instructions'), or

— a kinematic viscosity derived from measurements of rotational viscometry in accordance with ISO 3219 of less than $7 \times 10^{-6}$ $m^2$/sec. at 40 °C (ISO 3219, 1993 edition, relating to 'Plastics — Polymers/resins in the liquid state or as emulsions or dispersions — Determination of viscosity using a rotational viscometer with defined shear rate').

Note that substances and preparations meeting these criteria need not be classified if they have a mean surface tension greater than 33 mN/m at 25 °C as measured by the du Nouy tensiometer or by the test methods shown in Annex V, Part A.5;

(b) for substances and preparations, based on practical experience in humans.

R68 Possible risk of irreversible effects

— strong evidence that irreversible damage other than the effects referred to in section 4 is likely to be caused by a single exposure by an appropriate route, generally in the above-mentioned dose range.

In order to indicate route of administration/exposure one of the following combinations shall be used: R68/20, R68/21, R68/22, R68/20/21, R68/20/22, R68/21/22, R68/20/21/22.

R48 Danger of serious damage to health by prolonged exposure

— serious damage (clear functional disturbance or morphological change which has toxicological significance) is likely to be caused by repeated or prolonged exposure by an appropriate route.

Substances and preparations are classified at least as harmful when these effects are observed at levels of the order of:

— oral, rat ≤ 50 mg/kg (bodyweight)/day,

— dermal, rat or rabbit ≤ 100 mg/kg (bodyweight)/day,

— inhalation, rat ≤ 0,25 mg/l, 6 h/day.

These guide values can apply directly when severe lesions have been observed in a subchronic (90 days) toxicity test. When interpreting the results of a subacute (28 days) toxicity test these figures should be increased approximately threefold. If a chronic (two years) toxicity test is available it should be evaluated on a case-by-case basis. If results of studies of more than one duration are available, then those from the study of the longest duration should normally be used.

In order to indicate route of administration/exposure one of the following combinations shall be used: R48/20, R48/21, R48/22, R48/20/21, R48/20/22, R48/21/22, R48/20/21/22.

3.2.3.1. *Comments regarding volatile substances*

For certain substances with a high saturated vapour concentration evidence may be available to indicate effects that give cause for concern. Such substances may not be classified under the criteria for health effects in this guide (3.2.3) or not covered by section 3.2.8. However, where there is appropriate evidence that such substances may present a risk in normal handling and use, then classification on a case-by-case basis in Annex I may be necessary.

3.2.4. Comments regarding the use of R48

Use of this risk phrase refers to the specific range of biological effects within the terms described below. For application of this risk phrase serious damage to health is to be considered to include death, clear functional disturbance or morphological changes which are toxicologically significant. It is particularly important when

these changes are irreversible. It is also important to consider not only specific severe changes in a single organ or biological system but also generalised changes of a less severe nature involving several organs, or severe changes in general health status.

When assessing whether there is evidence for these types of effects reference should be made to the following guidelines:

1. Evidence indicating that R48 should be applied:

   (a) substance-related deaths;

   (b) (i) major functional changes in the central or peripheral nervous systems, including sight, hearing and the sense of smell, assessed by clinical observations or other appropriate methods (e.g. electrophysiology);

   (ii) major functional changes in other organ systems (for example the lung);

   (c) any consistent changes in clinical biochemistry, haematology or urinalysis parameters which indicate severe organ dysfunction. Haematological disturbances are considered to be particularly important if the evidence suggests that they are due to decreased bone marrow production of blood cells;

   (d) severe organ damage noted on microscopic examination following autopsy:

   (i) widespread or severe necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity (e.g. liver);

   (ii) severe morphological changes that are potentially reversible but are clear evidence of marked organ dysfunction (e.g. severe fatty change in the liver, severe acute tubular nephrosis in the kidney, ulcerative gastritis); or

   (iii) evidence of appreciable cell death in vital organs incapable of regeneration (e.g. fibrosis of the myocardium or dying back of a nerve) or in stem cell populations (e.g. aplasia or hypoplasia of the bone marrow).

   The above evidence will most usually be obtained from animal experiments. When considering data derived from practical experience special attention should be given to exposure levels.

2. Evidence indicating that R48 should not be applied:

   The use of this risk phrase is restricted to 'serious damage to health by prolonged exposure'. A number of substance-related effects may be observed in both humans and animals that would not justify the use of R48. These effects are relevant when attempting to determine a no-effect level for a chemical substance.

   Examples of well-documented changes which would not normally justify classification with R48, irrespective of their statistical significance, include:

   (a) clinical observations or changes in bodyweight gain, food consumption or water intake, which may have some toxicological importance but which do not, by themselves, indicate 'serious damage';

   (b) small changes in clinical biochemistry, haematology or urinalysis parameters which are of doubtful or minimal toxicological importance;

   (c) changes in organ weights with no evidence of organ dysfunction;

   (d) adaptative responses (e.g. macrophage migration in the lung, liver hypertrophy and enzyme induction, hyperplastic responses to irritants). Local effects on the skin produced by repeated dermal application of a substance which are more appropriately classified with R38 'irritating to skin'; or

   (e) where a species-specific mechanism of toxicity (e.g. specific metabolic pathways) has been demonstrated.

3.2.5. Corrosive

The substance or preparation shall be classified as corrosive and assigned the symbol 'C' and the indication of danger 'corrosive' in accordance with the following criteria:

— a substance or a preparation is considered to be corrosive if, when it is applied to healthy intact animal skin, it produces full thickness destruction of skin tissue on at least one animal during the test for skin irritation cited in Annex V or during an equivalent method,

— classification can be based on the results of a validated *in vitro* test, such as that cited in Annex V (B.40. Skin corrosion: rat skin transcutaneous electrical resistance assay and human skin model assay),

— a substance or a preparation should also be considered corrosive if the result can be predicted, for example from strongly acid or alkaline reactions indicated by a pH of 2 or less or 11,5 or greater. However, where extreme pH is the basis for classification, acid/alkali reserve ([1]) may also be taken into consideration. If consideration of alkali/acid reserve suggests the substance or preparation may not be corrosive then further testing should be carried out to confirm this, preferably by use of an appropriate validated *in vitro* test. Consideration of acid/alkali reserve should not be used alone to exonerate substances or preparations from classification as corrosive.

Risk phrases shall be assigned in accordance with the following criteria:

R35 Causes severe burns

— if, when applied to healthy intact animal skin, full thickness destruction of skin tissue occurs as a result of up to three minutes exposure, or if this result can be predicted.

R34 Causes burns

— if, when applied to healthy intact animal skin, full thickness destruction of skin tissue occurs as a result of up to four hours exposure, or if this result can be predicted,

— organic hydroperoxides, except where evidence to the contrary is available.

Notes:

Where classification is based on results of a validated in vitro test R35 or R34 should be applied according to the capacity of the test method to discriminate between these.

Where classification is based upon consideration of extreme pH alone, R35 should be applied.

3.2.6. Irritant

Substances and preparations shall be classified as irritant and assigned the symbol 'Xi' and the indication of danger 'irritant' in accordance with the criteria given below.

3.2.6.1. *Inflammation of the skin*

The following risk phrase shall be assigned in accordance with the criteria given:

R38 Irritating to skin

— Substances and preparations which cause significant inflammation of the skin which persists for at least 24 hours after an exposure period of up to four hours determined on the rabbit according to the cutaneous irritation test method cited in Annex V.

Inflammation of the skin is significant if:

(a) the mean value of the scores for either erythema and eschar formation or oedema formation, calculated over all the animals tested, is 2 or more; or

(b) in the case where the Annex V test has been completed using three animals, either erythema and eschar formation or oedema formation equivalent to a mean value of 2 or more calculated for each animal separately has been observed in two or more animals.

In both cases all scores at each of the reading times (24, 48 and 72 hours) for an effect should be used in calculating respective mean values.

Inflammation of the skin is also significant if it persists in at least two animals at the end of the observation time. Particular effects e.g. hyperplasia, scaling, discoloration, fissures, scabs and alopecia should be taken into account.

([1]) J. R. Young, M. J. How, A. P. Walker and W. M. H. Worth (1988), 'Classification as corrosive or irritant to skin of preparations containing acidic or alkaline substances, without testing on animals', *Toxic. In Vitro* 2(1): pp. 19-26.

Relevant data may also be available from non-acute animal studies (see comments on R48, section 2.d). These are considered significant if the effects seen are comparable to those described above.

— Substances and preparations which cause significant inflammation of the skin, based on practical observations in humans on immediate, prolonged or repeated contact.

— Organic peroxides, except where evidence to the contrary is available.

Paresthesia:

Paresthesia caused in humans by skin contact with pyrethroid pesticides is not regarded as an irritant effect justifying classification as Xi; R38. The S-phrase S24 should however be applied for substances seen to cause this effect.

3.2.6.2. *Ocular lesions*

The following risk phrases shall also be assigned in accordance with the criteria given:

R36 Irritating to eyes

— Substances and preparations which, when applied to the eye of the animal, cause significant ocular lesions which occur within 72 hours after exposure and which persist for at least 24 hours.

Ocular lesions are significant if the mean scores of the eye irritation test cited in Annex V have any of the following values:

— cornea opacity equal to or greater than 2 but less than 3,

— iris lesion equal to or greater than 1 but not greater than 1,5,

— redness of the conjunctivae equal to or greater than 2,5,

— oedema of the conjunctivae (chemosis) equal to or greater than 2,

or, in the case where the Annex V test has been completed using three animals if the lesions, on two or more animals, are equivalent to any of the above values except that for iris lesion the value should be equal to or greater than 1 but less than 2 and for redness of the conjunctivae the value should be equal to or greater than 2,5.

In both cases all scores at each of the reading times (24, 48 and 72 hours) for an effect should be used in calculating the respective mean values.

— Substances or preparations which cause significant ocular lesions, based on practical experience in humans.

— Organic peroxides except where evidence to the contrary is available.

R41 Risk of serious damage to eyes

— Substances and preparations which, when applied to the eye of the animal cause severe ocular lesions which occur within 72 hours after exposure and which persist for at least 24 hours.

Ocular lesions are severe if the means of the scores of the eye irritation test in Annex V have any of the values:

— cornea opacity equal to or greater than 3,

— iris lesion greater than 1,5.

The same shall be the case where the test has been completed using three animals if these lesions, on two or more animals, have any of the values:

— cornea opacity equal to or greater than 3,

— iris lesion equal to 2.

In both cases all scores at each of the reading times (24, 48 and 72 hours) for an effect should be used in calculating the respective mean values.

Ocular lesions are also severe when they are still present at the end of the observation time.

Ocular lesions are also severe if the substance or preparation causes irreversible colouration of the eyes.

— Substances and preparations which cause severe ocular lesions, based on practical experience in humans.

Note:

When a substance or preparation is classified as corrosive and assigned R34 or R35, the risk of severe damage to eyes is considered implicit and R41 is not included in the label.

3.2.6.3. *Respiratory system irritation*

The following risk phrase shall be assigned in accordance with the criteria given:

R37 Irritating to respiratory system

Substances and preparations which cause serious irritation to the respiratory system based on:

— practical observation in humans

— positive results from appropriate animal tests.

Comments regarding the use of R37:

In interpreting practical observations in humans, care should be taken to distinguish between effects which lead to classification with R48 (see section 3.2.4) from those leading to classification with R37. Conditions normally leading to classification with R37 are reversible and usually limited to the upper airways.

Positive results from appropriate animal tests may include data obtained in a general toxicity test, including histopathological data from the respiratory system. Data from the measurement of experimental bradypnea may also be used to assess airway irritation.

3.2.7. Sensitisation

3.2.7.1. *Sensitisation by inhalation*

Substances and preparations shall be classified as sensitising and assigned the symbol 'Xn', the indication of danger 'Harmful' and the risk phrase R42 in accordance with the criteria given below.

R42 May cause sensitisation by inhalation

— if there is evidence that the substance or preparation can induce specific respiratory hypersensitivity,

— where there are positive results from appropriate animal tests, or

— if the substance is an isocyanate, unless there is evidence that the specific isocyanate does not cause respiratory hypersensitivity.

Comments regarding the use of R42:

Human evidence

Evidence that the substance or preparation can induce specific respiratory hypersensitivity will normally be based on human experience. In this context hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated.

When considering the evidence from human exposure, it is necessary for a decision on classification to take into account in addition to the evidence from the cases:

— the size of the population exposed,

— the extent of exposure.

The evidence referred to above could be:

— clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include:

  — a chemical structure related to substances known to cause respiratory hypersensitivity,

  — an *in vivo* immunological test (e.g. skin prick test),

  — an *in vitro* immunological test (e.g. serological analysis),

  — studies indicating other specific but non-immunological mechanisms of action, e.g. repeated low-level irritation, pharmacologically mediated effects, or

  — data from a positive bronchial challenge test with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.

Clinical history should include both medical and occupational history to determine a relationship between exposure to a specific substance or preparation and development of respiratory hypersensitivity. Relevant information includes aggravating factors both in the home and workplace, the onset and progress of the disease, family history and medical history of the patient in question. The medical history should also include a note of other allergic or airway disorders from childhood, and smoking history.

The results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own. It is however recognised that in practice many of the examinations listed above will already have been carried out.

Substances that elicit symptoms of asthma by irritation only in people with bronchial hyperreactivity should not be assigned R42.

Animal studies

Data from tests which may be indicative of the potential of a substance or preparation to cause sensitisation by inhalation in humans may include:

— IgE measurements (e.g. in mice), or

— specific pulmonary responses in guinea pigs.

3.2.7.2. *Sensitisation by skin contact*

Substances and preparations shall be classified as sensitising and assigned the symbol 'Xi', the indication of danger 'Irritant' and the risk phrase R43 in accordance with the criteria given below:

R43 May cause sensitisation by skin contact

— if practical experience shows the substance or preparation to be capable of inducing a sensitisation by skin contact in a substantial number of persons, or

— where there are positive results from an appropriate animal test.

Comments regarding the use of R43:

Human evidence

The following evidence (practical experience) is sufficient to classify a substance or preparation with R43:

— positive data from appropriate patch testing, normally in more than one dermatological clinic, or

— epidemiological studies showing allergic contacts dermatitis caused by the substance or preparation. Situations in which a high proportion of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small, or

— positive data from experimental studies in man (see also 3.1.1).

The following is sufficient to classify a substance with R43 when there is supportive evidence:

— isolated episodes of allergic contact dermatitis, or

— epidemiological studies where chance, bias or confounders have not been ruled out fully with reasonable confidence.

Supportive evidence may include:

— data from animal tests performed according to existing guidelines, with a result that does not meet the criteria given in the section on animal studies but is sufficiently close to the limit to be considered significant, or

— data from non-standard methods, or

— appropriate structure-activity relationships.

Animal studies

Positive results from appropriate animal tests are:

— in the case of the adjuvant type test method for skin sensitisation detailed in Annex V or in the case of other adjuvant-type test methods, a response of at least 30 % of the animals is considered positive,

— for any other test method a response of at least 15 % of the animals is considered positive.

3.2.7.3. *Immunological contact urticaria*

Some substances or preparations, which meet the criteria for R42 may in addition cause immunological contact urticaria. In these cases, information concerning contact urticaria should be included by the use of appropriate S-phrases, usually S24 and S36/37, and in the safety data sheet.

For substances or preparations, which produce signs of immunological contact urticaria which do not fulfil the criteria for R42, consideration should be given to classification with R43.

There is no recognised animal model available to identify substances which cause immunological contact urticaria. Therefore, classification will normally be based on human evidence which will be similar to that for skin sensitisation (R43).

3.2.8. Other toxicological properties

Additional risk phrases shall be assigned in accordance with the following criteria (based on experience obtained during compilation of Annex I) to substances and preparations classified by virtue of 2.2.1 to 3.2.7 and/or sections 4 and 5:

R29 Contact with water liberates toxic gas

For substances and preparations which in contact with water or damp air, evolve very toxic/toxic gases in potentially dangerous amounts, e.g. aluminium phosphide, phosphorus pentasulphide.

R31 Contact with acids liberates toxic gas

For substances and preparations which react with acids to evolve toxic gases in dangerous amounts, e.g. sodium hypochlorite, barium polysulphide. For substances used by members of the general public, the use of S50 (do not mix with … (to be specified by the manufacturer)) would be more suitable.

R32 Contact with acids liberates very toxic gas

For substances and preparations which react with acids to evolve very toxic gases in dangerous amounts; e.g. salts of hydrogen cyanide, sodium azide. For substances used by members of the general public, the use of S50 (do not mix with … (to be specified by the manufacturer)) would be more suitable.

R33 Danger of cumulative effects

For substances and preparations when accumulation in the human body is likely and may cause some concern which, however, is not sufficient to justify the use of R48.

For comments on the use of this R-phrase see section 4.2.3.3 for substances and Annex V, Part A.3, to Directive 1999/45/EC for preparations.

R64 May cause harm to breastfed babies

For substances and preparations which are absorbed by women and may interfere with lactation or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child.

For comments on the use of this R-phrase see section 4.2.3.3 for substances and Annex V, Part A.4, to Directive 1999/45/EC for preparations.

R66 Repeated exposure may cause skin dryness or cracking

For substances and preparations which may cause concern as a result of skin dryness, flaking or cracking but which do not meet the criteria for R38 based on either:

— practical observation after normal handling and use, or

— relevant evidence concerning their predicted effects on the skin.

See also sections 1.6 and 1.7.

R67 Vapours may cause drowsiness and dizziness

For volatile substances and preparations containing such substances which cause clear symptoms of central nervous system depression by inhalation and which are not already classified with respect to acute inhalation toxicity (R20, R23, R26 , R68/20, R39/23 or R39/26).

The following evidence may be used:

(a) data from animal studies showing clear signs of CNS depression such as narcotic effects, lethargy, lack of coordination (including loss of righting reflex) and ataxia either:

— at concentrations/exposure times not exceeding 20 mg/l/4h or,

— for which the ratio of the effect concentration at ≤ 4 h to the saturated vapour concentration (SVC) at 20 °C is ≤ 1/10;

(b) practical experience in humans (e.g. narcosis, drowsiness, reduced alertness, loss of reflexes, lack of coordination, vertigo) from well documented reports under comparable exposure conditions to the effects specified above for animals.

See also sections 1.6 and 1.7.

For other supplementary risk phrases, see section 2.2.6.

## 4. CLASSIFICATION ON THE BASIS OF SPECIFIC EFFECTS ON HUMAN HEALTH

### 4.1. **Introduction**

4.1.1. This chapter sets out the procedure for the classification of substances which may have the effects mentioned below. For preparations see section 4.2.4.

4.1.2. If a manufacturer, distributor or importer has information available which indicates that a substance should be classified and labelled in accordance with the criteria given in section 4.2.1, 4.2.2 or 4.2.3, he shall provisionally label the substance in accordance with these criteria, on the basis of the assessment of the evidence by a competent person.

4.1.3. The manufacturer, distributor or importer shall submit as soon as possible a document summarising all relevant information to one Member State in which the substance is placed on the market. Relevant information in this context comprises in particular all available published and unpublished information required for appropriate classification of the substance in question, on the basis of the intrinsic properties according to the categories laid down in Article 2(2) and in accordance with the criteria in this Annex. The submitted summary document should include a bibliography containing all relevant references, including any relevant unpublished data.

4.1.4. Furthermore, a manufacturer, distributor or importer who has new data which are relevant to the classification and labelling of a substance in accordance with the criteria given in section 4.2.1, 4.2.2 or 4.2.3, shall submit this data as soon as possible to one Member State in which the substance is placed on the market.

4.1.5. To obtain as quickly as possible a harmonised classification for the Community by the procedure defined in Article 28 of this Directive, Member States which have relevant information available justifying the classification of a substance in one of these categories, whether submitted by the manufacturer or not, should forward such information together with suggestions for classification and labelling, to the Commission as soon as possible.

The Commission will forward to the other Member States the classification and labelling proposal that it receives. Any Member State may ask the Commission for the information it has received.

Any Member State which has good reason to believe that the suggested classification and labelling is inappropriate as far as the carcinogenic, mutagenic or reproductive toxicity effects are concerned shall notify the Commission thereof.

4.2. **Criteria for classification, indication of danger, choice of risk phrases**

4.2.1. Carcinogenic substances

For the purpose of classification and labelling, and having regard to the current state of knowledge, such substances are divided into three categories:

Category 1

Substances known to be carcinogenic to man. There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.

Category 2

Substances which should be regarded as if they are carcinogenic to man. There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of:

— appropriate long-term animal studies,

— other relevant information.

Category 3

Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in category 2.

4.2.1.1. *The following symbols and specific risk phrases apply:*

Categories 1 and 2:

Substances classified carcinogenic category 1 or 2 shall be assigned the symbol 'T' and the risk phrase

R45 May cause cancer

However, substances and preparations which present a carcinogenic risk only when inhaled, for example, as dust, vapour or fumes, (other routes of exposure e.g. by swallowing or in contact with skin do not present any carcinogenic risk), shall be assigned the symbol 'T' and the risk phrase

R49 May cause cancer by inhalation

Categories 3:

Substances classified as carcinogenic category 3 shall be assigned the symbol 'Xn' and the risk phrase

R40 Limited evidence of a carcinogenic effect

4.2.1.2. *Comments regarding the categorisation of carcinogenic substances*

The placing of a substance into category 1 is done on the basis of epidemiological data; placing into categories 2 and 3 is based primarily on animal experiments.

For classification as a category 2 carcinogen either positive results in two animal species should be available or clear positive evidence in one species, together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association.

Category 3 actually comprises 2 subcategories:

(a) substances which are well investigated but for which the evidence of a tumour-inducing effect is insufficient for classification in category 2. Additional experiments would not be expected to yield further relevant information with respect to classification;

(b) substances which are insufficiently investigated. The available date are inadequate, but they raise concern for man. This classification is provisional; further experiments are necessary before a final decision can be made.

For a distinction between categories 2 and 3 the arguments listed below are relevant which reduce the significance of experimental tumour induction in view of possible human exposure. These arguments, especially in combination, would lead in most cases to classification in category 3, even though tumours have been induced in animals:

— carcinogenic effects only at very high dose levels exceeding the 'maximal tolerated dose'. The maximal tolerated dose is characterised by toxic effects which, although not yet reducing lifespan, go along with physical changes such as about 10 % retardation in weight gain,

— appearance of tumours, especially at high dose levels, only in particular organs of certain species known to be susceptible to a high spontaneous tumour formation,

— appearance of tumours, only at the site of application, in very sensitive test systems (e.g. i.p. or s.c. application of certain locally active compounds), if the particular target is not relevant to man,

— lack of genotoxicity in short-term tests *in vivo* and *in vitro*,

— existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (e.g., hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation),

— existence of a species-specific mechanism of tumour formation (e.g. by specific metabolic pathways) irrelevant for man.

For a distinction between category 3 and no classification arguments are relevant which exclude a concern for man:

— a substance should not be classified in any of the categories if the mechanism of experimental tumour formation is clearly identified, with good evidence that this process cannot be extrapolated to man,

— if the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories,

— particular attention should be paid to cases where the only available tumour data are the occurrence of neoplasms at sites and in strains where they are well known to occur spontaneously with a high incidence.

4.2.2. Mutagenic substances

4.2.2.1. For the purposes of classification and labelling, and having regard to the current state of knowledge, such substances are divided into three categories:

Category 1

Substances known to be mutagenic to man.

There is sufficient evidence to establish a causal association between human exposure to a substance and heritable genetic damage.

Category 2

Substances which should be regarded as if they are mutagenic to man.

There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in the development of heritable genetic damage, generally on the basis of:

— appropriate animal studies,

— other relevant information.

Category 3

Substances which cause concern for man owing to possible mutagenic effects. There is evidence from appropriate mutagenicity studies, but this is insufficient to place the substance in category 2.

4.2.2.2. *The following symbols and specific risk phrases apply:*

Categories 1 and 2:

Substances classified as mutagenic category 1 or 2 shall be assigned the symbol 'T' and the risk phrase

R46 May cause heritable genetic damage

Categories 3:

Substances classified as mutagenic category 3 shall be assigned the symbol 'Xn' and the risk phrase

R68 Possible risk of irreversible effects.

4.2.2.3. *Comments regarding the categorisation of mutagenic substances*

Definition of terms:

A mutation is a permanent change in the amount or structure of the genetic material in an organism, resulting in a change of the phenotypic characteristics of the organism. The alterations may involve a single gene, a block of genes, or a whole chromosome. Effects involving single genes may be a consequence of effects on single DNA bases (point mutations) or of large changes, including deletions, within the gene. Effects on whole chromosomes may involve structural or numerical changes. A mutation in the germ cells in sexually reproducing organisms may be transmitted to the offspring. A mutagen is an agent that gives rise to an enhanced occurrence of mutations.

It should be noted that substances are classified as mutagens with specific reference to inherited genetic damage. However, the type of results leading to classification of chemicals in category 3: 'induction of genetically relevant events in somatic cells' is generally also regarded as an alert for possible carcinogenic activity.

Method development for mutagenicity testing is an ongoing process. For many new tests no standardised protocols and evaluation criteria are presently available. For the evaluation of mutagenicity data the quality of the test performance and the degree of validation of the test method have to be considered.

Category 1

To place a substance in category 1, positive evidence from human mutation epidemiology studies will be needed. Examples of such substances are not known to date. It is recognised that it is extremely difficult to

obtain reliable information from studies on the incidence of mutations in human populations, or on possible increases in their frequencies.

Category 2

To place a substance in category 2, positive results are needed from assays showing (a) mutagenic effects, or (b) other cellular interactions relevant to mutagenicity, in germ cells of mammals *in vivo*, or (c) mutagenic effects in somatic cells of mammals *in vivo* in combination with clear evidence that the substance or a relevant metabolite reaches the germ cells.

With respect to placement in category 2, at present the following methods are appropriate:

2(a) *In vivo* germ cell mutagenicity assays:

— specific locus mutation test,

— heritable translocation test,

— dominant lethal mutation test.

These assays actually demonstrate the appearance of affected progeny or a defect in the developing embryo.

2(b) *In vivo* assays showing relevant interaction with germ cells (usually DNA):

— assays for chromosomal abnormalities, as detected by cytogenetic analysis, including aneuploidy, caused by malsegregation of chromosomes,

— test for sister chromatid exchanges (SCEs),

— test for unscheduled DNA synthesis (UDS),

— assay of (covalent) binding of mutagen to germ cell DNA,

— assaying other kinds of DNA damage.

These assays provide evidence of a more or less indirect nature. Positive results in these assays would normally be supported by positive results from *in vivo* somatic cell mutagenicity assays, in mammals or in man (see under category 3, preferably methods as under 3(a)).

2(c) *In vivo* assays showing mutagenic effects in somatic cells of mammals (see under 3(a)), in combination with toxicokinetic methods, or other methodologies capable of demonstrating that the compound or a relevant metabolite reaches the germ cells.

For 2(b) and 2(c), positive results from host-mediated assays or the demonstration of unequivocal effects in *in vitro* assays can be considered as supporting evidence.

Category 3

To place a substance in category 3, positive results are needed in assays showing (a) mutagenic effects or (b) other cellular interaction relevant to mutagenicity, in somatic cells in mammals *in vivo*. The latter especially would normally be supported by positive results from *in vitro* mutagenicity assays.

For effects in somatic cells *in vivo* at present the following methods are appropriate:

3(a) *In vivo* somatic cell mutagenicity assays:

— bone marrow micronucleus test or metaphase analysis,

— metaphase analysis of peripheral lymphocytes,

— mouse coat colour spot test.

3(b) *In vivo* somatic cell DNA interaction assays:

— test for SCEs in somatic cells,

— test for UDS in somatic cells,

— assay for the (covalent) binding of mutagen to somatic cell DNA,

— assay for DNA damage, e.g. by alkaline elution, in somatic cells.

Substances showing positive results only in one or more *in vitro* mutagenicity assays should normally not be classified. Their further investigation using *in vivo* assays, however, is strongly indicated. In exceptional cases, e.g. for a substance showing pronounced responses in several *in vitro* assays, for which no relevant *in vivo* data are available, and which shows resemblance to known mutagens/carcinogens, classification in category 3 could be considered.

4.2.3. Substances toxic to reproduction

4.2.3.1. For the purposes of classification and labelling and having regard to the present state of knowledge, such substances are divided into three categories:

Category 1

*Substances known to impair fertility in humans*

There is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility.

*Substances known to cause developmental toxicity in humans*

There is sufficient evidence to establish a causal relationship between human exposure to the substance and subsequent developmental toxic effects in the progeny.

Category 2

*Substances which should be regarded as if they impair fertility in humans*

There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in impaired fertility on the basis of:

— clear evidence in animal studies of impaired fertility in the absence of toxic effects, or, evidence of impaired fertility occurring at around the same dose levels as other toxic effects but which is not a secondary non-specific consequence of the other toxic effects,

— other relevant information.

*Substances which should be regarded as if they cause developmental toxicity to humans*

There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in developmental toxicity, generally on the basis of:

— clear results in appropriate animal studies where effects have been observed in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of the other toxic effects,

— other relevant information.

Category 3

*Substances which cause concern for human fertility*

Generally on the basis of:

— results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of impaired fertility in the absence of toxic effects, or evidence of impaired fertility occuring at around the same dose levels as other toxic effects, but which is not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in category 2,

— other relevant information.

*Substances which cause concern for humans owing to possible developmental toxic effects*

Generally on the basis of:

— results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of developmental toxicity in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in category 2,

— other relevant information.

4.2.3.2. *The following symbols and specific risk phrases apply:*

Category 1:

for substances that impair fertility in humans:

Substances classified as toxic to reproduction category 1 shall be assigned the symbol 'T' and the risk phrase

R60 May impair fertility

for substances that cause developmental toxicity:

Substances classified as toxic to reproduction category 1 shall be assigned the symbol 'T' and the risk phrase

R61 May cause harm to the unborn child

Category 2:

for substances that should be regarded as if they impair fertility in humans:

Substances classified as toxic to reproduction category 2 shall be assigned the symbol 'T' and the risk phrase

R60 May impair fertility

for substances that should be regarded as if they cause developmental toxicity in humans:

Substances classified as toxic to reproduction category 2 shall be assigned the symbol 'T' and the risk phrase

R61 May cause harm to the unborn child

Category 3:

for substances which cause concern for human fertility:

Substances classified as toxic to reproduction category 3 shall be assigned the symbol 'Xn' and the risk phrase

R62 Possible risk of impaired fertility

for substances which cause concern for humans owing to possible developmental toxic effects:

Substances classified as toxic to reproduction category 3 shall be assigned the symbol 'Xn' and the risk phrase

R63 Possible risk of harm to the unborn child.

4.2.3.3. *Comments regarding the categorisation of substances toxic to reproduction*

Reproductive toxicity includes impairment of male and female reproductive functions or capacity and the induction of non-inheritable harmful effects on the progeny. This may be classified under two main headings of 1. Effects on male or female fertility; 2. Developmental toxicity.

1 Effects on male or female fertility, includes adverse effects on libido, sexual behaviour, any aspect of spermatogenesis or oogenesis, or on hormonal activity or physiological response which would interfere with the capacity to fertilise, fertilisation itself or the development of the fertilised ovum up to and including implantation.

2 Developmental toxicity, is taken in its widest sense to include any effect interfering with normal development, both before and after birth. It includes effects induced or manifested prenatally as well as those manifested postnatally. This includes embrytoxic/fetotoxic effects such as reduced body weight, growth and developmental retardation, organ toxicity, death, abortion, structural defects (teratogenic effects), functional defects, peri-postnatal defects, and impaired postnatal mental or physical development up to and including normal pubertal development.

Classification of chemicals as toxic to reproduction is intended to be used for chemicals which have an intrinsic or specific property to produce such toxic effects. Chemicals should not be classified as toxic to reproduction where such effects are solely produced as a non-specific secondary consequence of other toxic effects. Chemicals of most concern are those which are toxic to reproduction at exposure levels which do not produce other signs of toxicity.

The placing of a compound in category 1 for effects on fertility and/or developmental toxicity is done on the basis of epidemiological data. Placing in categories 2 or 3 is done primarily on the basis of animal data. Data from *in vitro* studies, or studies on avian eggs, are regarded as 'supportive evidence' and would only exceptionally lead to classification in the absence of *in vivo* data.

In common with most other types of toxic effect, substances demonstrating reproductive toxicity will be expected to have a threshold below which adverse effects would not be demonstrated. Even when clear effects have been demonstrated in animal studies the relevance for humans may be doubtful because of the doses administered, for example, where effects have been demonstrated only at high doses, or where marked toxicokinetic differences exist, or the route of administration is inappropriate. For these or similar reasons it may be that classification in category 3, or even no classification, will be warranted.

Annex V to the Directive specifies a limit test in the case of substances of low toxicity. If a dose level of at least 1 000 mg/kg orally produces no evidence of effects toxic to reproduction, studies at other dose levels may not be considered necessary. If data are available from studies carried out with doses higher than the above limit dose, this data must be evaluated together with other relevant data. Under normal circumstances it is considered that effects seen only at doses in excess of the limit dose would not necessarily lead to classification as 'Toxic to reproduction'.

EFFECTS ON FERTILITY

For the classification of a substance in category 2 for impaired fertility, there should normally be clear evidence in one animal species, with supporting evidence on mechanism of action or site of action, or chemical relationship to other known anti-fertility agents or other information from humans which would lead to the conclusion that effects would be likely to be seen in humans. Where there are studies in only one species without other relevant supporting evidence then classification in category 3 may be appropriate.

Since impaired fertility may occur as a non-specific accompaniment to severe generalised toxicity or where there is severe inanition, classification in category 2 should only be made where there is evidence that there is some degree of specificity of toxicity for the reproductive system. If it was demonstrated that impaired fertility in animal studies was due to failure to mate, then for classification in category 2, it would normally be necessary to have evidence on the mechanism of action in order to interpret whether any adverse effect such as alteration in pattern of hormonal release would be likely to occur in humans.

DEVELOPMENTAL TOXICITY

For classification in category 2 there should be clear evidence of adverse effects in well conducted studies in one or more species. Since adverse effects in pregnancy or postnatally may result as a secondary consequence of maternal toxicity, reduced food or water intake, maternal stress, lack of maternal care, specific dietary deficiencies, poor animal husbandry, intercurrent infections, and so on, it is important that the effects observed should occur in well conducted studies and at dose levels which are not associated with marked maternal toxicity. The route of exposure is also important. In particular, the injection of irritant material intraperitoneally may result in local damage to the uterus and its contents, and the results of such studies must be interpreted with caution and on their own would not normally lead to classification.

Classification in category 3 is based on similar criteria as for category 2 but may be used where the experimental design has deficiencies which make the conclusions less convincing, or where the possibility that the effects may have been due to non-specific influences such as generalised toxicity cannot be excluded.

In general, classification in category 3 or no category would be assigned on an ad hoc basis where the only effects recorded are small changes in the incidences of spontaneous defects, small changes in the proportions of common variants such as are observed in skeletal examinations, or small differences in postnatal developmental assessments.

*Effects during lactation*

Substances which are classified as toxic to reproduction and which also cause concern due to their effects on lactation should in addition be labelled with R64 (see criteria in section 3.2.8).

For the purpose of classification, toxic effects on offspring resulting only from exposure via the breast milk, or toxic effects resulting from direct exposure of children will not be regarded as 'Toxic to reproduction', unless such effects result in impaired development of the offspring.

Substances which are not classified as toxic to reproduction but which cause concern due to toxicity when transferred to the baby during the period of lactation should be labelled with R64 (see criteria in section 3.2.8). This R-phrase may also be appropriate for substances which affect the quantity or quality of the milk.

R64 would normally be assigned on the basis of:

(a) toxicokinetic studies that would indicate the likelihood that the substance would be present in potentially toxic levels in breast milk; and/or

(b) on the basis of results of one or two generation studies in animals which indicate the presence of adverse effects on the offspring due to transfer in the milk; and/or

(c) on the basis of evidence in humans indicating a risk to babies during the lactational period.

Substances which are known to accumulate in the body and which subsequently may be released into milk during lactation may be labelled with R33 and R64.

4.2.4. Procedure for the classification of preparations concerning specific effects on health

If a preparation contains one or more substances classified with respect to the criteria laid out above, it must be classified according to the criteria referred to in Annex II, Part A.7-9 and Part B.6, to Directive 1999/45/EC (the concentration limits are either in Annex I to this Directive, or in Annex II, Part B.6, to Directive 1999/45/EC where the substance or substances under consideration do not appear in Annex I or appear in it without concentration limits).

5. CLASSIFICATION ON THE BASIS OF ENVIRONMENTAL EFFECTS

5.1. **Introduction**

The primary objective of classifying substances and preparations dangerous for the environment is to alert the user to the hazards these substances and preparations present to ecosystems. Although the present criteria refer to aquatic ecosystems it is recognised that certain substances and preparations may simultaneously or alternatively affect other ecosystems whose constituents may range from soil microflora and microfauna to primates.

The criteria set out below follow directly from the test methods set out in Annex V in so far as they are mentioned. The test methods required for the 'base set' referred to in Annex VII are limited and the information derived from them may be insufficient for an appropriate classification. Classification may require additional data derived from level 1 (Annex VIII) or other equivalent studies. Furthermore, classified substances may be subject to review in the light of other new data.

For the purposes of classification and labelling and having regard to the current state of knowledge such substances and preparations are divided into two groups according to their acute and/or long-term effects in aquatic systems or their acute and/or long-term effects in non-aquatic systems.

5.1.1. The classification of substances is usually made on the basis of experimental data for acute aquatic toxicity, degradation, and log $P_{ow}$ (or BCF if available).

5.1.2. The classification of preparations shall normally be carried out on the basis of a conventional method referred to in Article 7 of and Annex III, Parts A and B, to Directive 1999/45/EC. In this case, the classification is based on the individual concentration limits

— in Annex I to this Directive

— or in Annex III, Part B, to Directive 1999/45/EC where the substance or substances do not appear in Annex I to this Directive or appear in it without concentration limits.

5.1.3. Normally, the classification of a preparation is made on the basis of a conventional method. However, for the determination of the acute aquatic toxicity, there may be cases for which it is appropriate to carry out tests on the preparation. The result of these tests on the preparation may only modify the classification concerning acute aquatic toxicity which would have been obtained by the application of a conventional method. If such tests are chosen by the person responsible for the placing on the market, it must be ensured that the quality criteria of the test methods in Part C of Annex V to this Directive have been complied with. Furthermore, the tests are to be carried out on all three groups of species in conformity with the criteria in this Annex (algae, daphnia and fish), unless the highest hazard classification relating to acute aquatic toxicity has been assigned to the preparation after testing on one of the species or a test result was already available before Directive 1999/45/EC entered into force.

5.2. **Criteria for classification, indication of danger, choice of risk phrases**

The classification criteria for substances in section 5.2.1 only apply to preparations where they have been tested in accordance with 5.1.3.

5.2.1. Aquatic environment

5.2.1.1. Substances shall be classified as dangerous for the environment and assigned the symbol 'N' and the appropriate indication of danger, and assigned risk phrases in accordance with the following criteria:

R50 Very toxic to aquatic organisms, and

R53 May cause long-term adverse effects in the aquatic environment

| | | | |
|---|---|---|---|
| Acute toxicity: | | 96 h $LC_{50}$ (for fish) | ≤ 1 mg/l |
| | or | 48 h $EC_{50}$ (for daphnia) | ≤ 1 mg/l |
| | or | 72 h $IC_{50}$ (for algae) | ≤ 1 mg/l |

and:

— the substance is not readily degradable, or

— the log $P_{ow}$ (log octanol/water partition coefficient) ≥ 3,0 (unless the experimentally determined BCF ≤ 100).

R50 Very toxic to aquatic organisms

| | | | |
|---|---|---|---|
| Acute toxicity: | | 96 h $LC_{50}$ (for fish) | ≤ 1 mg/l |
| | or | 48 h $EC_{50}$ (for daphnia) | ≤ 1 mg/l |
| | or | 72 h $IC_{50}$ (for algae) | ≤ 1 mg/l |

R51 Toxic to aquatic organisms, and

R53 May cause long-term adverse effects in the aquatic environment

| | | | |
|---|---|---|---|
| Acute toxicity: | | 96 h $LC_{50}$ (for fish) | 1 mg/l < $LC_{50}$ ≤ 10 mg/l |
| | or | 48 h $EC_{50}$ (for daphnia) | 1 mg/l < $EC_{50}$ ≤ 10 mg/l |
| | or | 72 h $IC_{50}$ (for algae) | 1 mg/l < $IC_{50}$ ≤ 10 mg/l |

and:

— the substance is not readily degradable, or

— the log $P_{ow}$ ≥ 3,0 (unless the experimentally determined BCF ≤ 100).

5.2.1.2. Substances shall be classified as dangerous for the environment in accordance with the criteria set out below. Risk phrases shall also be assigned in accordance with the following criteria

R52 Harmful to aquatic organisms, and

R53 May cause long-term adverse effects in the aquatic environment

| | | | |
|---|---|---|---|
| Acute toxicity: | | 96 h $LC_{50}$ (for fish) | 10 mg/l < $LC_{50}$ ≤ 100 mg/l |
| | or | 48 h $EC_{50}$ (for daphnia) | 10 mg/l < $EC_{50}$ ≤ 100 mg/l |
| | or | 72 h $IC_{50}$ (for algae) | 10 mg/l < $IC_{50}$ ≤ 100 mg/l |

and:

the substance is not readily degradable.

This criterion applies unless there exists additional scientific evidence concerning degradation and/or toxicity sufficient to provide an adequate assurance that neither the substance nor its degradation products will constitute a potential long-term and/or delayed danger to the aquatic environment. Such additional scientific evidence should normally be based on the studies required at level 1 (Annex VIII), or studies of equivalent value, and could include:

(i) a proven potential to degrade rapidly in the aquatic environment;

(ii) an absence of chronic toxicity effects at a concentration of 1,0 mg/litre, e.g. a no-observed effect concentration of greater than 1,0 mg/litre determined in a prolonged toxicity study with fish or daphnia.

R52 Harmful to aquatic organisms

Substances not falling under the criteria listed above in this chapter, but which on the basis of the available evidence concerning their toxicity may nevertheless present a danger to the structure and/or functioning of aquatic ecosystems.

R53 May cause long-term adverse effects in the aquatic environment

Substances not falling under the criteria listed above in this chapter, but which, on the basis of the available evidence concerning their persistence, potential to accumulate, and predicted or observed environmental fate and behaviour may nevertheless present a long-term and/or delayed danger to the structure and/or functioning of aquatic ecosystems.

For example, poorly water-soluble substances, i.e. substances with a solubility of less than 1 mg/l will be covered by this criterion if:

(a) they are not readily degradable; and

(b) the log $P_{ow} \geq 3,0$ (unless the experimentally determined BCF ≤ 100).

This criterion applies to substances unless there exists additional scientific evidence concerning degradation and/or toxicity sufficient to provide an adequate assurance that neither the substance nor its degradation products will constitute a potential long-term and/or delayed danger to the aquatic environment.

Such additional scientific evidence should normally be based on the studies required at level 1 (Annex VIII), or studies of equivalent value, and could include

(i) a proven potential to degrade rapidly in the aquatic environment;

(ii) an absence of chronic toxicity effects at the solubility limit e.g. a no-observed effect concentration of greater than the solubility limit determined in a prolonged toxicity study with fish or daphnia.

5.2.1.3. *Comments on the determination of $IC_{50}$ for algae and of degradability*

— where it can be demonstrated in the case of highly coloured substances that algal growth is inhibited solely as a result of a reduction in light intensity, then the 72h $IC_{50}$ for algae should not be used as a basis for classification,

— substances are considered readily degradable if the following criteria hold true.

(a) if in 28-day biodegradation studies the following levels of degradation are achieved

— in tests based upon dissolved organic carbon: 70 %,

— in tests based upon oxygen depletion or carbon dioxide generation: 60 % of the theoretical maxima.

These levels of biodegradation must be achieved within 10 days of the start of degradation, which point is taken as the time when 10 % of the substance has been degraded; or

(b) if in those cases where only COD and BOD5 data are available when the ratio of BOD5/COD is greater than or equal to 0,5; or

(c) if other convincing scientific evidence is available to demonstrate that the substance can be degraded (biotically and/or abiotically) in the aquatic environment to a level of > 70 % within a 28-day period.

5.2.2. Non-aquatic environment

5.2.2.1. Substances and preparations shall be classified as dangerous for the environment and assigned the symbol 'N' and the appropriate indication of danger, and assigned risk phrases in accordance with the following criteria:

R54 Toxic to flora

R55 Toxic to fauna

R56 Toxic to soil organisms

R57 Toxic to bees

R58 May cause long-term adverse effects in the environment

Substances and preparations which on the basis of the available evidence concerning their toxicity, persistence, potential to accumulate and predicted or observed environmental fate and behaviour may present a danger, immediate or long-term and/or delayed, to the structure and/or functioning of natural ecosystems other than those covered under 5.2.1. Detailed criteria will be elaborated later.

5.2.2.2. Substances and preparations shall be classified as dangerous for the environment, and assigned the symbol 'N' and the appropriate indication of danger, where applicable, and assigned risk phrases in accordance with the following criteria:

R59 Dangerous for the ozone layer

Substances which on the basis of the available evidence concerning their properties and their predicted or observed environmental fate and behaviour may present a danger to the structure and/or the functioning of the stratospheric ozone layer. This includes the substances which are listed in Annex I to Council Regulation (EC) No 2037/2000 on substances that deplete the ozone layer (OJ L 244, 29.9.2000, p.1) and its subsequent amendments.

Preparations shall be classified on the basis of a conventional method referred to in Article 7 of and Annex III, Parts A and B, to Directive 1999/45/EC.

6. CHOICE OF SAFETY ADVICE PHRASES

6.1. **Introduction**

Safety advice phrases (S-phrases) shall be assigned to dangerous substances and preparations in accordance with the following general criteria. In addition, for certain preparations, the safety advice listed in Annex V to Directive 1999/45/EC is mandatory.

Whenever the manufacturer is mentioned in Chapter 6 it refers to the person responsible for placing the substance or preparation on the market.

6.2. **Safety phrases for substances and preparations**

S1 *Keep locked up*

— Applicability:

— very toxic, toxic and corrosive substances and preparations.

— Criteria for use:

— *obligatory* for those substances and preparations mentioned above if sold to the general public.

S2 *Keep out of the reach of children*

— Applicability:

— all dangerous substances and preparations.

— Criteria for use:

— *obligatory* for all dangerous substances and preparations sold to the general public, except for those only classified as dangerous for the environment.

S3 *Keep in a cool place*

— Applicability:

— organic peroxides,

— other dangerous substances and preparations having a boiling point of ≤ 40 °C.

— Criteria for use:

— *obligatory* for organic peroxides unless S47 is used,

— recommended for other dangerous substances and preparations having a boiling point of ≤ 40 °C.

S4 *Keep away from living quarters*

— Applicability:

— very toxic and toxic substances and preparations.

— Criteria for use:

— normally limited to very toxic and toxic substances and preparations when desirable to supplement S13; for example when there is an inhalation risk and the substance or preparation should be stored away from living quarters. The advice is not intended to preclude proper use of the substance or preparation in living quarters.

S5 *Keep contents under … (appropriate liquid to be specified by the manufacturer)*

— Applicability:

— spontaneously flammable solid substances and preparations.

— Criteria for use:

— normally limited to special cases, e.g. sodium, potassium or white phosphorous.

S6 *Keep under … (inert gas to be specified by the manufacturer)*

— Applicability:

— dangerous substances and preparations which must be kept under an inert atmosphere.

— Criteria for use:

— normally limited to special cases, e.g. certain organo-metallic compounds.

S7 *Keep container tightly closed*

— Applicability:

  — organic peroxides,

  — substances and preparations which can give off very toxic, toxic, harmful or extremely flammable gases,

  — substances and preparations which in contact with moisture give off extremely flammable gases,

  — highly flammable solids.

— Criteria for use:

  — *obligatory* for organic peroxides,

  — recommended for the other fields of application mentioned above.

S8 *Keep container dry*

— Applicability:

  — substances and preparations which may react violently with water,

  — substances and preparations which on contact with water liberate extremely flammable gases,

  — substances and preparations which on contact with water liberate very toxic or toxic gases.

— Criteria for use:

  — normally limited to the fields of application mentioned above when necessary to reinforce warnings given by R14, R15 in particular, and R29.

S9 *Keep container in a well-ventilated place*

— Applicability:

  — volatile substances and preparations which may give off very toxic, toxic or harmful vapours,

  — extremely flammable or highly flammable liquids and extremely flammable gases.

— Criteria for use:

  — recommended for volatile substances and preparations which may give off very toxic, toxic or harmful vapours,

  — recommended for extremely flammable or highly flammable liquids or extremely flammable gases.

S12 *Do not keep the container sealed*

— Applicability:

  — substances and preparations which will by giving off gases or vapours be liable to burst the container.

— Criteria for use:

  — normally limited to the special cases mentioned above.

S13 *Keep away from food, drink and animal feedingstuffs*

— Applicability:

  — very toxic, toxic and harmful substances and preparations.

— Criteria for use:

  — recommended when such substances and preparations are likely to be used by the general public.

S14 *Keep away from … (incompatible materials to be indicated by the manufacturer)*

— Applicability:

  — organic peroxides.

— Criteria for use:

  — *obligatory* for and normally limited to organic peroxides. However, may be useful in exceptional cases when incompatibility is likely to product a particular risk

S15 *Keep away from heat*

— Applicability:

  — substances and preparations which may decompose or which may react spontaneously under the effect of heat.

— Criteria for use:

  — normally limited to special cases, e.g. monomers, but not assigned if risk phrases R2, R3 and/or R5 have already been applied.

S16 *Keep away from sources of ignition — No smoking*

— Applicability:

  — extremely flammable or highly flammable liquids and extremely flammable gases.

— Criteria for use:

  — recommended for the substances and preparations mentioned above but not assigned if risk phrases R2, R3 and/or R5 have already been applied.

S17 *Keep away from combustible material*

— Applicability:

  — substances and preparations which may form explosive or spontaneously flammable mixtures with combustible material.

— Criteria for use:

  — available for use in special cases, e.g. to emphasise R8 and R9.

S18 *Handle and open container with care*

— Applicability:

  — substances and preparations liable to produce an overpressure in the container,

  — substances and preparations which may form explosive peroxides.

— Criteria for use:

  — normally limited to the abovementioned cases when there is risk of damage to the eyes and/or when the substances and preparations are likely to be used by the general public.

S20 *When using do not eat or drink*

— Applicability:

  — very toxic, toxic and corrosive substances and preparations.

— Criteria for use:

— normally limited to special cases (e.g. arsenic and arsenic compounds; fluoracetates) in particular when any of these are likely to be used by the general public.

S21 *When using do not smoke*

— Applicability:

— substances and preparations which produce toxic products on combustion.

— Criteria for use:

— normally limited to special cases (e.g. halogenated compounds).

S22 *Do not breathe dust*

— Applicability:

— all solid substances and preparations dangerous for health.

— Criteria for use:

— *obligatory* for those substances and preparations mentioned above to which R42 is assigned,

— recommended for those substances and preparations mentioned above which are supplied in the form of an inhalable dust and for which the health hazards following inhalation are not known.

S23 *Do not breathe gas/fumes/vapour/spray (appropriate wording to be specified by the manufacturer)*

— Applicability:

— all liquid or gaseous substances and preparations dangerous to health.

— Criteria for use:

— *obligatory* for those substances and preparations mentioned above to which R42 is assigned,

— *obligatory* for substances and preparations intended for use by spraying. Either S38 or S51 must be ascribed in addition,

— recommended when it is necessary to draw the attention of the user to inhalation risks not mentioned in the risk phrases which have to be ascribed.

S24 *Avoid contact with skin*

— Applicability:

— all substances and preparations dangerous for health.

— Criteria for use:

— *obligatory* for those substances and preparations to which R43 has been ascribed, unless S36 has also been ascribed,

— recommended when it is necessary to draw the attention of the user to skin contact risks not mentioned in the risk phrases (e.g. paresthesia) which have to be ascribed. However, may be used to emphasise such risk phrases.

S25 *Avoid contact with eyes*

— Applicability:

— all substances and preparations dangerous to health.

— Criteria for use:

— recommended when it is necessary to draw the attention of the user to eye contact risks not mentioned in the risk phrases which have to be applied. However, may be used to emphasise such risk phrases,

— recommended for substances ascribed R34, R35, R36 or R41 which are likely to be used by the general public.

S26 *In case of contact with eyes, rinse immediately with plenty of water and seek medical advice*

— Applicability:

— corrosive or irritant substances and preparations.

— Criteria for use:

— *obligatory* for corrosive substances and preparations and those to which R41 has already been ascribed,

— recommended for irritant substances and preparations to which the risk phrase R36 has already been ascribed.

S27 *Take off immediately all contaminated clothing*

— Applicability:

— very toxic, toxic or corrosive substances and preparations.

— Criteria for use:

— *obligatory* for very toxic substances and preparations to which R27 has been ascribed and which are likely to be used by the general public,

— recommended for very toxic substances and preparations to which R27 has been ascribed used in industry. However, this safety phrase should not be used if S36 has been ascribed,

— recommended for toxic substances and preparations to which R24 has been ascribed as well as corrosive substances and preparations which are likely to be used by the general public.

S28 *After contact with skin, wash immediately with plenty of … (to be specified by the manufacturer)*

— Applicability:

— very toxic, toxic or corrosive substances and preparations.

— Criteria for use:

— *obligatory* for very toxic substances and preparations,

— recommended for the other substances and preparations mentioned above, in particular when water is not the most appropriate rinsing fluid,

— recommended for corrosive substances and preparations which are likely to be used by the general public.

S29 *Do not empty into drains*

— Applicability:

— extremely or highly flammable liquids immiscible with water,

— very toxic and toxic substances and preparations,

— substances and preparations dangerous for the environment.

— Criteria for use:

— *obligatory* for substances and preparations dangerous for the environment and assigned the symbol 'N', which are likely to be used by the general public, unless this is the intended use,

— recommended for other substances and preparations mentioned above which are likely to be used by the general public, unless this is the intended use.

S30 *Never add water to this product*

— Applicability:

— substances and preparations which react violently with water.

— Criteria for use:

— normally limited to special cases (e.g. sulphuric acid) and may be used, as appropriate, to give the clearest possible information, either to emphasise R14 or as an alternative to R14.

S33 *Take precautionary measures against static discharges*

— Applicability:

— extremely or highly flammable substances and preparations.

— Criteria for use:

— recommended for substances and preparations used in industry which do not absorb moisture. Virtually never used for substances and preparations as placed on the market for use by the general public.

S35 *This material and its container must be disposed of in a safe way*

— Applicability:

— all dangerous substances and preparations.

— Criteria for use:

— recommended for substances and preparations where special guidance is needed to ensure proper disposal.

S36 *Wear suitable protective clothing*

— Applicability:

— organic peroxides,

— very toxic, toxic or harmful substances and preparations,

— corrosive substances and preparations.

— Criteria for use:

— *obligatory* for very toxic and corrosive substances and preparations,

— *obligatory* for those substances and preparations to which either R21 or R24 has been ascribed,

— *obligatory* for category 3 carcinogens, mutagens and substances toxic to reproduction unless the effects are produced solely by inhalation of the substance or preparation,

— *obligatory* for organic peroxides,

— recommended for toxic substances and preparations if the $LD_{50}$ dermal value is unknown but the substance or preparation is likely to be toxic through skin contact,

— recommended for substances and preparations used in industry which are liable to damage health by prolonged exposure.

S37 *Wear suitable gloves*

— Applicability:

  — very toxic, toxic, harmful or corrosive substances and preparations,

  — organic peroxides,

  — substances and preparations irritating to the skin or causing sensitisation by skin contact.

— Criteria for use:

  — *obligatory* for very toxic and corrosive substances and preparations,

  — *obligatory* for those substances and preparations to which either R21, R24 or R43 has been ascribed,

  — *obligatory* for category 3 carcinogens, mutagens and substances toxic to reproduction unless the effects are produced solely by inhalation of the substances and preparations,

  — *obligatory* for organic peroxides,

  — recommended for toxic substances and preparations if the $LD_{50}$ dermal value is unknown but the substance or preparation is likely to be harmful by skin contact,

  — recommended for substances and preparations irritating to the skin.

S38 *In case of insufficient ventilation, wear suitable respiratory equipment*

— Applicability:

  — very toxic or toxic substances and preparations.

— Criteria for use:

  — normally limited to special cases involving the use of very toxic or toxic substances and preparations in industry or in agriculture.

S39 *Wear eye/face protection*

— Applicability:

  — organic peroxides,

  — corrosive substances and preparations, including irritants which give rise to risk of serious damage to the eyes,

  — very toxic and toxic substances and preparations.

— Criteria for use:

  — *obligatory* for those substances and preparations to which R34, R35 or R41 have been ascribed,

  — *obligatory* for organic peroxides,

  — recommended when it is necessary to draw the attention of the user to eye contact risks not mentioned in the risk phrases which have to be ascribed,

  — normally limited to exceptional cases for very toxic and toxic substances and preparations, where there is a risk of splashing and they are likely to be easily absorbed by the skin.

S40 *To clean the floor and all objects contaminated by this material use … (to be specified by the manufacturer)*

— Applicability:

  — all dangerous substances and preparations.

— Criteria for use:

— normally limited to those dangerous substances and preparations for which water is not considered to be a suitable cleansing agent (e.g. where absorption by powdered material, dissolution by solvent etc. is necessary) and where it is important for health and/or safety reasons to provide a warning on the label.

S41 *In case of fire and/or explosion do not breathe fumes*

— Applicability:

— dangerous substances and preparations which on combustion give off very toxic or toxic gases.

— Criteria for use:

— normally limited to special cases.

S42 *During fumigation/spraying wear suitable respiratory equipment (appropriate wording to be specified by the manufacturer)*

— Applicability:

— substances and preparations intended for such use but which may endanger the health and safety of the user unless proper precautions are taken.

— Criteria for use:

— normally limited to special cases.

S43 *In case of fire use … (indicate in the space the precise type of fire-fighting equipment. If water increases the risk add: Never use water)*

— Applicability:

— extremely flammable, highly flammable and flammable substances and preparations.

— Criteria for use:

— *obligatory* for substances and preparations which, in contact with water or damp air, evolve extremely flammable gases,

— recommended for extremely flammable, highly flammable and flammable substances and preparations, particularly when they are immiscible with water.

S45 *In case of accident or if you feel unwell seek medical advice immediately (show the label where possible).*

— Applicability:

— very toxic substances and preparations,

— toxic and corrosive substances and preparations,

— substances and preparations causing sensitisation by inhalation.

— Criteria for use:

— *obligatory* for the substances and preparations mentioned above.

S46 *If swallowed, seek medical advice immediately and show this container or label*

— Applicability:

— all dangerous substances and preparations other than those which are very toxic, toxic, corrosive or dangerous to the environment.

— Criteria for use:

— *obligatory* for all dangerous substances and preparations mentioned above which are likely to be used by the general public, unless there is no reason to fear any danger from swallowing, particularly by children.

S47 *Keep at temperature not exceeding … °C (to be specified by the manufacturer)*

— Applicability:

— substances and preparations which become unstable at a certain temperature.

— Criteria for use:

— normally limited to special cases (e.g. certain organic peroxides).

S48 *Keep wetted with … (appropriate material to be specified by the manufacturer)*

— Applicability:

— substances and preparations which may become very sensitive to sparks, friction or impact if allowed to dry out.

— Criteria for use:

— normally limited to special cases, e.g. nitrocelluloses.

S49 *Keep only in the original container*

— Applicability:

— substances and preparations sensitive to catalytic decomposition.

— Criteria for use:

— substances and preparations sensitive to catalytic decomposition, e.g. certain organic peroxides.

S50 *Do not mix with … (to be specified by the manufacturer)*

— Applicability:

— substances and preparations which may react with the specified product to evolve very toxic or toxic gases,

— organic peroxides.

— Criteria for use:

— recommended for substances and preparations mentioned above which are likely to be used by the general public, when it is a better alternative to R31 or R32,

— *obligatory* with certain peroxides which may give violent reaction with accelerators or promoters.

S51 *Use only in well-ventilated areas*

— Applicability:

— substances and preparations likely to or intended to produce vapours, dusts, sprays, fumes, mists, etc. which give rise to inhalation risks or to a fire or explosion risk.

— Criteria for use:

— recommended when use of S38 would not be appropriate. Thus important when such substances and preparations are likely to be used by the general public.

S52 *Not recommended for interior use on large surface areas*

— Applicability:

  — volatile, very toxic, toxic and harmful substances and preparations containing them.

— Criteria for use:

  — recommended when damage to health is likely to be caused by prolonged exposure to these substances and preparations by reason of their volatilisation from large treated surfaces in the home or other enclosed places where persons congregate.

S53 *Avoid exposure — Obtain special instructions before use*

— Applicability:

  — substances and preparations that are carcinogenic, mutagenic and/or toxic to reproduction.

— Criteria for use:

  — *obligatory* for the abovementioned substances and preparations to which at least one of the following R-phrases has been assigned : R45, R46, R49, R60 or R61.

S56 *Dispose of this material and its container to hazardous or special waste collection point*

— Applicability:

  — all dangerous substances and preparations.

— Criteria for use:

  — recommended for all dangerous substances and preparations likely to be used by the general public for which special disposal is required.

S57 *Use appropriate containment to avoid environmental contamination*

— Applicability:

  — substances and preparations which have been assigned the symbol 'N'.

— Criteria for use:

  — normally limited to substances and preparations not likely to be used by the general public.

S59 *Refer to manufacturer for information on recovery/recycling*

— Applicability:

  — all dangerous substances and preparations.

— Criteria for use:

  — *obligatory* for substances and preparations dangerous for the ozone layer,

  — recommended for other substances and preparations for which recovery/recycling is recommended.

S60 *This material and its container must be disposed of as hazardous waste*

— Applicability:

  — all dangerous substances and preparations.

— Criteria for use:

  — recommended for substances and preparations not likely to be used by the general public and where S35 is not assigned.

S61 *Avoid release to the environment. Refer to special instructions/safety data sheet*

— Applicability:

— substances and preparations dangerous for the environment.

— Criteria for use:

— normally used for substances and preparations which have been assigned the symbol 'N',

— recommended for all substances and preparations classified dangerous for the environment not covered above.

S62 *If swallowed, do not induce vomiting: seek medical advice immediately and show this container or label*

— Applicability:

— substances and preparations classified as harmful with R65 in accordance with the criteria in section 3.2.3,

— not applicable to substances and preparations which are placed on the market in aerosol containers (or in containers fitted with a sealed spray attachment), see sections 8 and 9.

— Criteria for use:

— *obligatory* for substances and preparations mentioned above, if sold to, or likely to be used by the general public, except when S45 or S46 are obligatory,

— recommended for the substances and preparations mentioned above when used in industry, except where S45 or S46 are obligatory.

S63 *In case of accident by inhalation: remove casualty to fresh air and keep at rest*

— Applicability:

— very toxic and toxic substances and preparations (gases, vapours, particulates, volatile liquids),

— substances and preparations causing respiratory sensitisation.

— Criteria for use:

— *obligatory* for substances and preparations to which R26, R23 or R42 has been assigned which are likely to be used by the general public in a way which could result in inhalation.

S64 *If swallowed, rinse mouth with water (only if the person is conscious)*

— Applicability:

— corrosive or irritant substances and preparations.

— Criteria for use:

— recommended for the above substances and preparations which are likely to be used by the general public and where the above treatment is suitable.

## 7. LABELLING

7.1. When a substance or preparation has been classified the appropriate label is determined with reference to the requirements of Article 23 of this Directive and Article 10 of Directive 1999/45/EC for substances and preparations respectively. This section explains how the label is determined and, in particular, gives guidance on how to choose the appropriate risk and safety phrases.

The label contains the following information:

(a) for preparations the trade name or designation;

(b) for substances the name of the substance and for preparations the names of the substances present in the preparations in accordance with the rules set out in Article 10(2)(3) of Directive 1999/45/EC;

(c) the name, full address and telephone number of the person responsible for placing the substance or preparation on the market, whether manufacturer, importer or distributor;

(d) the symbol(s) and indication(s) of danger;

(e) phrases indicating particular hazards (R-phrases);

(f) phrases indicating safety advice (S-phrases);

(g) for substances, the EC number, and in addition for substances appearing in Annex I, the word 'EC label';

(h) for preparations offered or sold to the general public the nominal quantity of the contents unless specified elsewhere on the package.

Note:

For certain preparations there are additional labelling requirements set out in Article 10(1)(2) of and Annex V to Directive 1999/45/EC and in Article 20 of Directive 98/8/EC.

7.1.1. Final choice of risk and safety phrases

Although the final choice of the most appropriate risk and safety phrases is primarily governed by the need to give all necessary information, consideration should also be given in the clarity and impact of the label. With clarity in mind, the necessary information should be expressed in a minimum number of phrases.

In the case of substances which are irritant, highly flammable, flammable and oxidising, an indication of R-phrases and S-phrases need not be given where the package does not contain more than 125 ml. This shall also apply in the case of the same volume of harmful substances not retailed to the general public.

For preparations, if the contents of the package do not exceed 125 ml:

— if classified as highly flammable, oxidising, irritant, with the exception of those assigned R41, or dangerous for the environment and assigned the 'N' symbol it shall not be necessary to indicate the R-phrases or the S-phrases,

— if classified as flammable or dangerous to the environment and not assigned the 'N' symbol it shall be necessary to indicate the R-phrases but it shall not be necessary to indicate the S-phrases.

7.1.2. Without prejudice to Article 16(4) of Directive 91/414/EEC and to Directive 98/8/EC, indications such as 'non-toxic', 'non-harmful', 'non-polluting', 'ecological' or any other statement indicating that the substance or preparation is not dangerous or likely to lead to underestimation of the dangers of the substance or preparation in question shall not appear on the label or packaging of substances or preparations subject to this Directive or to Directive 1999/45/EC.

7.2. **Chemical name(s) to be displayed on the label**

7.2.1. For substances listed in Annex I the label shall show the name of the substances under one of the designations given in Annex I.

For substances not listed in Annex I, the name is established according to an internationally recognised chemical nomenclature as defined in section 1.4.

7.2.2. For preparations, the choice of names to be displayed on the label follows the rules of Article 10(2)(3) of Directive 1999/45/EC.

Note:

Subject to Annex V, B.9 to Directive 1999/45/EC,

— the name of the sensitising substance must be chosen in accordance with section 7.2.1 of this Annex,

— in the case of concentrate preparations which are intended for the perfume industry:

— the person responsible for placing them on the market may identify merely the one sensitising substance judged by him to be primarily responsible for the sensitisation hazard,

— in the case of a natural substance, the chemical name may be of the type: 'essential oil of …' 'extract of …', rather than the name of the constituents of that essential oil or extract.

7.3. **Choice of danger symbols**

The design of the danger symbols and the wording of the indications of danger shall comply with those laid down in Annex II. The symbol shall be printed in black on an orange-yellow background.

7.3.1. For substances appearing in Annex I the danger symbols and indications of danger shall be those shown in the Annex.

7.3.2. For dangerous substances not yet appearing in Annex I and for preparations, the danger symbols and indications of danger shall be assigned according to the rules laid down in this Annex.

Where more than one danger symbol is assigned to a substance or preparation:

— the obligation to indicate the symbol 'E' makes the symbols 'F+', 'F' and 'O' optional,

— the obligation to indicate the symbol 'T+' or 'T' makes the symbols 'Xn', 'Xi' and 'C' optional,

— the obligation to indicate the symbol 'C' makes the symbols 'Xn' and 'Xi' optional,

— if the symbol 'Xn' is assigned, the symbol 'Xi' is optional.

7.4. **Choice of risk phrases**

The wording of the R-phrases shall comply with that laid down in Annex III.

The combined R-phrases in Annex III shall be used where applicable.

7.4.1. For substances appearing in Annex I, the R-phrases shall be those shown in the Annex.

7.4.2. For substances not appearing in Annex I, R-phrases will be selected according to the following criteria and priorities:

(a) in the case of dangers which give rise to health effects:

(i) R-phrases corresponding to the category of danger illustrated by a symbol must appear on the label;

(ii) R-phrases corresponding to other categories of danger which are not illustrated by a symbol by virtue of Article 23;

(b) in the case of dangers arising from physicochemical properties:

— R-phrases corresponding to the category of danger illustrated by a symbol must appear on the label;

(c) in the case of dangers for the environment

— the R-phrase(s) corresponding to the classification category 'dangerous for the environment' must appear on the label.

7.4.3. For preparations, R-phrases will be selected according to the following criteria and priorities:

(a) in the case of dangers which give rise to health effects:

(i) R-phrases which correspond to the category of danger illustrated by a symbol. In certain cases the R-phrases must be adopted according to the tables of Annex II, Part B, to Directive 1999/45/EC. More specifically, the R-phrases of the constituent(s) which are responsible for the assignment of the preparation to a danger category must appear on the label;

(ii) R-phrases which correspond to other categories of danger which have been attributed to the constituents but which are not illustrated by a symbol by virtue of Article 10(2)(4) of Directive 1999/45/EC;

(b) in the case of dangers arising from physicochemical properties:

— the criteria described under 7.4.3(a) are applicable, except that the risk phrases 'extremely flammable' or 'highly flammable' need not be indicated where they repeat the wording of the indication of danger used with a symbol;

(c) in the case of dangers for the environment:

(i) the R-phrase(s) corresponding to the classification category 'dangerous for the environment' must appear on the label;

(ii) where the R-phrase R50 has been assigned in addition to a combined R-phrase R51/53 or R52/53 or to the R-phrase 53 alone, the combined R-phrase R50/53 shall be used.

As a general rule, for preparations a maximum of six R-phrases shall suffice to describe the risk; for this purpose the combined phrases listed in Annex III shall be regarded as single phrases. However, if the preparation falls within more than one danger category, those standard phrases shall cover all the principal hazards associated with the preparation. In some cases, more than six R-phrases may be necessary.

7.5. **Safety phrases**

The wording of S-phrases shall comply with that laid down in Annex IV.

The combined S-phrases in Annex IV shall be used where applicable.

7.5.1. For substances appearing in Annex I, the S-phrases shall be those shown in the Annex. Where no S-phrases are shown, the manufacturer/importer may include any appropriate S-phrase(s). For substances not in Annex I and for preparations, the manufacturer shall include S-phrases in accordance with the criteria given in Chapter 6 of this Annex.

7.5.2. Choice of safety phrases

The final choice of safety phrases must have regard to the risk phrases indicated on the label and to the intended use of the substance or preparation:

— as a general rule, a maximum of six S-phrases shall suffice to formulate the most appropriate safety advice; for this purpose the combined phrases listed in Annex IV shall be regarded as single phrases,

— in the case of S-phrases concerning disposal, one S-phrase shall be used, unless it is clear that disposal of the material and its container does not present a danger for human health or the environment. In particular, advice on safe disposal is important for substances and preparations sold to the general public,

— some R-phrases become superfluous if a careful selection is made of S-phrases and vice versa; S-phrases which obviously correspond to R-phrases will appear on the label only if it is intended to emphasise a specific warning,

— particular attention must be given, in the choice of safety phrases, to the foreseen conditions of use of certain substances and preparations, e.g. spraying or other aerosol effects. Phrases should be chosen with the intended use in view,

— the safety phrases S1, S2 and S45 are obligatory for all very toxic, toxic and corrosive substances and preparations sold to the general public,

— the safety phrases S2 and S46 are obligatory for all other dangerous substances and preparations (except those only classified as dangerous for the environment) sold to the general public.

Where the phrases selected according to the strict criteria in 6.2 result in redundancy or ambiguity or are clearly unnecessary given the specific product/package then some phrases may be deleted.

7.6. **EC number**

If a substance named on the label is listed in the European Inventory of Existing Commercial Chemical Substances (Einecs) or in the European List of Notified Substances (Elincs), the Einecs or Elincs number of the substances shall be shown on the label. This requirement does not apply to preparations.

7.7. **Dimensions of the label for preparations**

The dimensions of the label shall be as follows:

| *Capacity of the package* | *Dimensions (in millimetres)* |
|---|---|
| — not exceeding 3 litres: | if possible, at least 52 × 74 |
| — greater than 3 litres but not exceeding 50 litres: | at least 74 × 105 |
| — greater than 50 litres but not exceeding 500 litres: | at least 105 × 148 |
| — greater than 500 litres: | at least 148 × 210. |

Each symbol shall cover at least one-tenth of the surface area of the label but shall not be less than 1cm$^2$. The label shall be firmly affixed to one or more surfaces of the packaging immediately containing the preparation.

The information required on the label shall stand out clearly from its background and shall be of such size and spacing as to be easily read.

8. SPECIAL CASES: SUBSTANCES

8.1. **Mobile gas cylinders**

For mobile gas cylinders the requirements concerning labelling are considered to be satisfied when they are in agreement with Article 23 or Article 24(6)(b).

However, by way of derogation from Article 24(1) and (2), one of the following alternatives can be used for gas cylinders with a water capacity of less than or equal to 150 litres:

— the format and dimensions of the label can follow the prescriptions of the ISO Standard ISO/DP 7225 (1994 edition) relating to 'Gas cylinders — Precautionary labels',

— the information specified in Article 23(2) may be provided on a durable information disc or label held captive on the cylinder.

8.2. **Gas containers intended for propane, butane or liquefied petroleum gas (LPG)**

These substances are classified in Annex I. Although classified in accordance with Article 2, they do not present a danger to human health when they are placed on the market in closed refillable cylinders or in non-refillable cartridges within the scope of EN 417 as fuel gases which are only released for combustion (EN 417, September 1992 edition, relating to 'Non-refillable metallic gas cartridges for liquefied petroleum gases, with or without a valve, for use with portable appliances; construction, inspection, testing and marking').

These cylinders or cartridges must be labelled with the appropriate symbol and the R- and S-phrases concerning flammability. No information concerning the effects on human health is required on the label. However, the information concerning effects on human health which should have appeared on the label shall be transmitted to the professional user by the person responsible for placing the substance on the market in

the format foreseen in Article 27 of the Directive. For the consumer, sufficient information shall be transmitted to enable them to take all necessary measures for health and safety as foreseen in Article 1(3) of Directive 91/155/EEC, as amended by Directive 93/112/EEC.

8.3. **Metals in massive form**

These substances are classified in Annex I or shall be classified in accordance with Article 6. However, some of these substances, although classified in accordance with Article 2 do not present a danger to human health by inhalation, ingestion or contact with skin or to the aquatic environment in the form in which they are placed on the market. Such substances do not require a label according to Article 23. However, all the information which should have appeared on the label shall be transmitted to the user by the person responsible for placing the metal on the market, in a format foreseen in Article 27.

8.4. **Substances classified with R65**

Substances classified as harmful on the basis of an aspiration hazard need not be labelled as harmful with R65 when placed on the market in aerosol containers or in containers fitted with a sealed spray attachment.

9. SPECIAL CASES: PREPARATIONS

9.1. **Gaseous preparations (gas mixtures)**

For gaseous preparations, consideration must be given to:

— the evaluation of the physico-chemical properties,

— the evaluation of health hazards,

— the evaluation of the environmental hazards.

9.1.1. Evaluation of physico-chemical properties

9.1.1.1. *Flammability*

The flammable properties of these preparations are determined in accordance with Article 5 of Directive 1999/45/EC according to the methods specified in Part A of Annex V to this Directive.

These preparations will be classified according to the results of the tests carried out and with respect to the criteria of Annex V and to the criteria of the labelling guide.

However, by derogation, in the case where gaseous preparations are produced to order in small amounts, the flammability of these gaseous mixtures can be evaluated by the following calculation method:

the expression of the gaseous mixture

$$A_1F_1 + \ldots + A_iF_i + \ldots A_nF_n + B_1I_1 + \ldots + B_iI_i + \ldots B_pI_p$$

where: $A_i$ and $B_i$ are the molar fractions

$F_i$ flammable gas

$I_i$ inert gas

n number of flammable gases

p number of inert gases

can be transformed in a form where all the $I_i$ (inert gases) are expressed by a nitrogen equivalent using a coefficient $K_i$ and where the equivalent content of inflammable gas $A'_i$ is expressed as follows:

$$A'_i = A_i \times (100 / (A_i + K_iB_i))$$

By using the value of the maximum content of flammable gas which, in a mixture with nitrogen, gives a composition which is not flammable in air (Tci), the following expression can be obtained:

$$\Sigma_i A'_i / Tci \leq 1$$

The gas mixture is flammable if the value of the above expression is greater than one. The preparation is classified extremely flammable and, the phrase R12 is assigned.

Coefficients of equivalency (Ki)

The values of the coefficients of equivalency Ki, between the inert gases and nitrogen and the values of the maximum contents of flammable gas (Tci) may be found in Tables 1 and 2 of the ISO Standard ISO 10156 edition 15.12.1990 (new: 1996 edition) relating to 'Gases and gas mixtures — Determination of fire potential and oxidising ability for the selection of cylinder valve outlets'.

Maximum content of flammable gas (Tci)

The value of the maximum content of flammable gas (Tci) may be found in Table 2 of the ISO Standard ISO 10156 edition 15.12.1990 (new: 1996 edition) relating to 'Gases and gas mixtures — Determination of fire potential and oxidising ability for the selection of cylinder valve outlets'.

When a Tci value for a flammable gas does not appear in the above standard, the corresponding lower explosivity limit (LEL) will be used. If no LEL value exists, the value of Tci will be set at 1 % by volume.

Remarks:

— the expression above can be used to allow an appropriate labelling of gaseous preparations, however, it should not be regarded as a method for replacing experimentation for the determination of technical safety parameters,

— furthermore, this expression gives no information as to whether a mixture containing oxidising gases can be prepared safely. When estimating flammability these oxidising gases are not taken into account,

— the expression above will give reliable results only if the flammable gases do not influence each other as far as their flammability is concerned. This has to be considered, e.g. with halogenated hydrocarbons.

9.1.1.2. *Oxidising properties*

Given the fact that Annex V to this Directive does not contain a method to determine the oxidising properties of gaseous mixtures, the evaluation of these properties must be realised according to the following estimation method.

The principle of the method is comparison of the oxidising potential of gases in a mixture with that of the oxidising potential of oxygen in air. The concentrations of gases in the mixture are expressed in % vol.

It is considered that the gas mixture is as oxidant as or more oxidant than air, if the following condition is verified:

$$\Sigma_i x_i C_i \geq 21$$

where: $x_i$ is the concentration of gas i in % vol,

$C_i$ is the coefficient of oxygen equivalency.

In this case, the preparation is classified as oxidising and the phrase R8 will be assigned.

Coefficients of equivalency between oxidising gases and oxygen

The coefficients used in the calculation to determine the oxidising capacity of certain gases in a mixture with respect to the oxidising capacity of oxygen in air, listed under 5.2 in the ISO Standard ISO 10156 edition 15.12.1990 (new: 1996 edition) relating to 'Gases and gas mixtures — Determination of fire potential and oxidising ability for the selection of cylinder valve outlets', are the following.

| | |
|---|---|
| $O_2$ | 1 |
| $N_2O$ | 0,6 |

When no value for the $C_i$ coefficient exists for a gas in the cited standard a value of 40 is attributed to this coefficient.

9.1.2. Labelling

For mobile gas containers the requirements concerning labelling are considered to be satisfied when they are in agreement with Article 11(6)(b) of Directive 1999/45/EC.

However, by way of derogation from Article 11(1) and (2), for gas containers with a water capacity of less than or equal to 150 litres, the format and dimensions of the label can follow the prescriptions of the ISO Standard 7225 (1994 edition) relating to 'Gas cylinders — Precautionary labels'. In this case, the label can bear the generic name or industrial/commercial name of the preparation provided that the dangerous component substances of the preparation are shown on the body of the gas cylinder in a clear and indelible way.

The information specified in Article 10 may be provided on a durable information disc or label held captive on the containers.

9.2. **Gas containers intended for preparations containing stenched propane, butane or liquefied petroleum gas (LPG)**

Propane, butane and liquefied petroleum gas are classified in Annex I. Although preparations containing these substances are classified in accordance with Articles 5, 6 and 7 of Directive 1999/45/EC, they do not present a danger to human health when they are placed on the market in closed refillable cylinders or non-refillable cartridges within the scope on EN 417 as fuel gases which are only released for combustion (EN 417, September 1992 edition, relating to 'Non-refillable metallic gas cartridges for liquefied petroleum gases, with or without a valve, for use with portable appliances; construction, inspection, testing and marking').

These cylinders and cartridges must be labelled with the appropriate symbol and the R- and S-phrases concerning flammability. No information concerning the effects on human health is required on the label. However, the information concerning effects on human health which should have appeared on the label shall be transmitted to the professional user by the person responsible for placing the substance on the market in the format foreseen in Article 14 of Directive 1999/45/EC. For the consumer, sufficient information shall be transmitted to enable them to take all necessary measures for health and safety as foreseen in Article 1(3) of Directive 91/155/EEC.

9.3. **Alloys, preparations containing polymers, preparations containing elastomers**

These preparations shall be classified according to the requirements of Articles 5, 6 and 7 and labelled according to the requirements of Article 10 of Directive 1999/45/EC.

However some of these preparations although classified in accordance with Articles 6 and 7 do not present a danger to human health by inhalation, ingestion or contact with the skin or to the aquatic environment in the form in which they are placed on the market. Such preparations do not require a label according to Article 10 or according to Annex V.B.9. However, all the information which would have appeared on the label shall be transmitted to the professional user by means of an information system in a format foreseen in Article 14 of the abovementioned Directive.

9.4. **Preparations classified with R65**

Preparations classified as harmful on the basis of an aspiration hazard need not be labelled as harmful with R65 when placed on the market in aerosol containers or in containers fitted with a sealed spray attachment.

9.5. **Organic peroxides**

Organic peroxides combine the properties of an oxidiser and a combustible substance in one molecule: when an organic peroxide decomposes, the oxidising part of the molecule reacts exothermically with the combustible (oxidisable) part. For the oxidising properties the existing methods in Annex V cannot be applied to the organic peroxides.

The following calculation method based on the presence of active oxygen must be used.

The available oxygen content (%) of an organic peroxide preparation is given by the formula:

$$16 \times \Sigma (n_i \times c_i/m_i)$$

where:

$n_i$ = number of peroxygen groups per molecule of organic peroxide i

$c_i$ = concentration (mass %) of organic peroxide i

$m_i$ = molecular mass of organic peroxide i.

9.6. **Additional labelling requirements for certain preparations**

For certain preparations there are additional labelling requirements set out in Article 10(1)(2) of and Annex V to Directive 1999/45/EC and Article 20 of Directive 98/8/EC.

COMMISSION STATEMENT

With regard to section 4.1.5 and in particular to the last paragraph of section 4.1.5, the Commission states that, should it envisage making use of the procedure of Article 28, it is prepared to consult in advance appropriate experts designated by Members States and having special qualifications with respect to either carcinogenicity, mutagenicity or reproductive toxicity.

This consultation will take place in the framework of the normal consultation procedure with national experts and/or in the framework of existing committees. The same will be the case when substances already included in Annex I must be reclassified in respect of their carcinogenic, mutagenic effects, or effects toxic to reproduction.

*ANNEX 7A*

For intermediates with limited exposure the provisions under point 7 apply.

*ANNEX 7B*

## 7. **Reduced test package for intermediates at quantities ≥1 tonne/annum**

### 1. Definitions

Without prejudice to other Community legislation, the following definitions apply:

— 'intermediate' is a chemical substance that is solely manufactured for and consumed in or used for chemical processing in order to be transformed into another chemical substance(s),

— 'emission' concerns the release of a substance from a system, for example when a system is breached. To guarantee a maximum level of protection for workers and the environment minimisation of emission through rigorous containment of the process must therefore be the primary aim,

— 'exposure' is concerned with what happens to a substance after it has been emitted, whether this is into the wider environment or whether the substance can be potentially inhaled or come in contact with the skin of a member of the workforce. If emissions can be anticipated to occur, rigorous exposure control must be achieved by appropriate techniques, noting the need to adopt the precautionary principle in that physico-chemical, toxicological and ecotoxicological properties which had not been tested shall be assumed as being hazardous,

— 'integrated exhaust ventilation system' is an exhaust ventilation system of closed type which is used in combination with locks, enclosures, housings, containers etc. in order to restrict the chemical agents to the inner part of the closed functional unit. Process-related openings must be as small as possible. The power of extraction and the air ducting must be designed so that there is sufficient underpressure within the extraction unit to ensure that all of the gases, vapours and/or dusts that occur are fully captured and carried away. Back-flow of the extracted hazardous substances into the working area must be prevented. This means that hazardous substances are prevented from escaping from the closed functional unit into the working area,

— 'highly effective exhaust ventilation' is an exhaust ventilation system of open and semi-open type which is dimensioned in such a way that chemical agents remain within the catchment area. This means that the occurrence of chemical agents in the workplace atmosphere can practically be excluded,

— 'effective exhaust ventilation system' is an exhaust ventilation system of open and semi-open type which is dimensioned in such a way that the chemical agents remain within the catchment area, i.e. the occurrence of chemical agents in the workplace atmosphere can be largely excluded or proof of adherence to the limit value is furnished,

— 'other exhaust ventilation system' is an exhaust ventilation system of open and semi-open type which is dimensioned in such a way that the occurrence of chemical agents in the workplace atmosphere cannot be excluded,

— 'low-emission forms of use' are, for example:

  — expendable packaging, i.e. the hazardous substance is enclosed in appropriate packaging and, without opening the packaging, is introduced into a reaction system together with this packaging,

  — change in consistency, i.e. the substance is used, for example, in the form of a paste or a granulate instead of in powder form,

  — master batch; this means that the hazardous substance is surrounded by a plastic matrix which prevents direct contact with the hazardous substance. The plastic matrix itself is not a hazardous substance. Abrasion of the plastic matrix and therefore of the hazardous substance, is, however, possible,

— 'emission-free forms of use' are, for example, master batches without abrasion, i.e. the plastic matrix is so resistant to abrasion that no hazardous substance can be released,

— 'technically leakproof' is applied to a subunit if a leak is not discernible during testing, monitoring or checking for leakproofness, e.g. using foaming agents or leak searching/indicating equipment performed for the particular use. Systems, subsystems and functional elements are technically leakproof, if the rate of leakage is < 0,00001 mbar*l*$s^{-1}$.

2. Application of a reduced test package

For intermediates, the notifier may request the competent authority to grant permission to apply a reduced test package (RTP). This RTP represents a minimum data set designed to produce a first preliminary risk assessment for any chemical intermediate to be placed on the market. Any additional test result might be required, in accordance with Article 16(1), based on the outcome of the risk assessment.

3. Conditions for a application of a reduced test package

The notifier must demonstrate to the satisfaction of the competent authority where the substance is notified that the following conditions are fulfilled:

(a) the substance is solely manufactured for and consumed in or used for chemical processing. Monomers are excluded. When processed the substance is transformed into chemically different molecules, not being polymers;

(b) the substance is restricted to a maximum number of two users' sites. For example, it may be manufactured by one company and then transported to one or two others for processing. Note that if supply is intended to progress to more than two users' sites, the conditions for a RTP are no longer met and the dossier must be upgraded to the appropriate level;

(c) the supply to the enterprise which uses the intermediate for further processing must be directly from the notifier and not through an intermediate supplier;

(d) the substance must be rigorously contained by technical means during its whole lifecycle. This includes production, transportation, purification, cleaning and maintenance, sampling, analysis, loading and unloading of equipment/vessels, waste disposal/purification and storage. In general, an appropriate process would have all functional elements of the plant such as filling ports, emptying equipment, etc. either of a closed construction type with assured leakproofness or of a closed construction type with integrated exhaust ventilation;

(e) where there is the potential for exposure, procedural and control technologies must be used which minimise emission and the resulting exposure;

(f) in case of cleaning and maintenance works special procedures such as purging and washing must be applied before the system is opened or entered;

(g) transport operations will be in compliance with the requirements of Council Directive 94/55/EC as amended from time to time;

(h) in case of accident and where waste is generated following purification or cleaning and maintenance procedures, environmental exposure may occur. In either case, procedural and/or control technologies are used which minimise emissions and the resulting exposures;

(i) a management system must exist which identifies the roles of the individuals in the organisation;

(j) the packaging of the substance will be labelled according to Annex VI to Directive 67/548/EEC and additionally with the following sentence: 'Caution — substance not yet fully tested';

(k) the notifier must operate a system of product stewardship and must monitor the users (a maximum of two) to ensure compliance with the conditions listed above.

4. Technical dossier to be supplied for a reduced test package

A notifier requesting an RTP for a substance must supply the following technical dossier to the competent authority for all production and user sites:

(a) a statement that the notifier and each user accepts the conditions listed in 3;

(b) a description of the technical measures by which rigorous containment of the substance is achieved ([1]), including procedures for charging, sampling, transfer and cleaning. It is not necessary to provide details of the integrity of every seal or efficiency of integrated exhaust ventilation. However, whatever means are used to achieve rigorous containment of the process it is important that the information is available, if needed, to verify that the assertions made for achievement of control are true;

(c) if the criteria for the assessment of closed systems during handling of chemical agents detailed in section 5 below are not fulfilled, the notifier must submit exposure data based on representative monitoring data and/or reliable model calculations to enable the competent authority to make a decision whether to accept an RTP request or not;

(d) a detailed description of the processes at all sites involved in production and use. In particular, it must be stated whether production and/or processing wastes are discharged to waste-water, liquid or solid waste is incinerated, and how the cleaning and maintenance of all equipment is made;

(e) a detailed assessment of the possible emissions and possible exposure to man and the environment during the whole life cycle, including details of the various chemical reactions involved in the process and the ways in which residues are dealt with. Where emissions may lead to exposure, the means by which these are controlled must be described in sufficient detail to enable the competent authority to make a decision whether to accept the statement or to calculate an emission rate according to the EU Technical Guidance Document;

(f) changes which might affect exposure to man or the environment must be notified in advance, e.g. any change in the functional elements of the plant, new user or site;

(g) the information prescribed for the RTP is the following:

Annex VII.B plus the following tests from this Annex:

— vapour pressure (3.4),

— explosive properties (3.11),

— self-ignition temperature (3.12),

— oxidising properties (3.13),

— granulometry (3.15),

— acute toxicity for daphnia (5.1.2).

The notifier must also include other relevant information to enable the competent authority to make an informed decision and to enable proper controls to be put in place by the user at the intermediate processing site. For example, if supplementary physico-chemical and/or toxicological information and/or information about the environmental behaviour is available this data must also be submitted. Additionally, the notifier must review the available toxicity and ecotoxicity data on substances having close structural relationship to the notified substance. If relevant data are available, especially on chronic and reproductive toxicity and carcinogenicity, then a summary of these data must be provided;

(h) identities of the notifier, producer and the user(s).

([1]) The type of construction and the technical specifications (e.g. leakproofness) of the closed functional element determines the effectiveness of the containment. To enable the competent authority to make a decision as to whether rigorous containment is achieved or not, it is essential that the notifier includes details on these aspects. The technical measures must normally fulfil the conditions of the 'Criteria for the assessment of closed systems during handling of chemical agents', which are included for guidance in section 7.5 and Table 1 of this Annex. This must be stated by the notifier, however it is not necessary to address every type of closed functional element in the description provided of the technical measures. Any deviation from the conditions of the criteria must be fully described, with justification.

5. Criteria for the assessment of closed systems during the handling of chemical agents

5.1. *Use*

An assessment index is used in the assessment of the plant. The assessment index classifies the handling of the substance and the resultant process-related exposure potential. The notifier shall examine the plant or plant unit is in order to determine the assessment index. Each individual functional element must be assessed.

Systems are regarded as closed if the assessment of all of the available functional elements corresponds to the assessment index 0,5 and if only functional elements are involved which are of closed type with assured leakproofness and/or equipped with integrated exhaust ventilation. In addition, direct skin contact must be excluded.

In the collection of examples relevant functional elements are indicated by 0,5 in bold type.

Functional elements of partially open type with highly effective exhaust ventilation (also indicated by the assessment index 0,5, but in normal type) are not regarded as closed according to the meaning of this rule.

In the case of functional elements assigned the assessment index 1, the safe adherence to the limit value on a permanent basis is not always assured. Such functional elements are:

1 — closed type, leakproofness not assured

1 — partially open type with effective exhaust ventilation.

In the case of functional elements assigned the assessment indices 2 and 4 the adherence to the limit values is not always assured. Such functional elements are:

2 — of a partially open type, opening as intended with simple exhaust ventilation

2 — open with simple exhaust ventilation

4 — open type or partially open type

4 — natural ventilation.

The catalogue of examples in Table 1 facilitates the classification of the functional elements. Functional elements which are not included in the collection of examples can be classified by means of conclusions drawn by analogy. The plant or plant unit is then classified using the index value of the functional element which has received the highest assessment index.

5.2. *Checking*

Use of this criterion requires adherence to the process parameters which have been laid down as well as the performance of the checks cited in the collection of examples (e.g. inspection and maintenance).

6. Application of a reduced test package

If the competent authority accepts the notifier's application for a RTP, then information from the tests and/or studies set out in point 7.4 shall be required for the technical dossier referred to in Article 7. Note that for quantities below 1 tonne/annum the usual Annex VIIB/VIIC testing requirements apply.

TABLE 1

**Collection of examples**

| No | Functional element | Constructional type | Examples of constructional type | Assessment index | | Explanations |
|---|---|---|---|---|---|---|
| | | | | Without | With additional measures | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 1 | **static seals** | | | | | |
| 1.1 | **static seals** | inseparable connections | — welded | **0,5** | | |
| | | | — soldered | **0,5** | | |
| 1.2 | **static seals** | separable connections | — welded lip seal | **0,5** | | — reduce connections to number required<br>— open connections as little as possible<br>— leak tests prior to resumption of operation<br>— use new seals in case of resumption of operation involving separated connections<br>— where possible, flanges to be opened for operational reasons should not be equipped with tongue and groove (danger of misalignment) |
| | | | — cutting ring and clamping ring connection ≤ DN 32 | **0,5** | | |
| | | | — NPT thread ≤ DN 50, Δ t ≤ 100 °C | **0,5** | | |
| | | | — cutting ring and clamping ring connection > DN 32 | 1 | **0,5 assurance of leakproofness by means of monitoring and repair (*)** | |
| | | | — NPT thread > DN 50, Δ t > 100 °C | 1 | **0,5 assurance of leakproofness by means of monitoring and repair (*)** | |
| | | | — flange with tongue and groove with suitable seal | 1 | **0,5 assurance of leakproofness by means of monitoring and repair (*)** | |
| | | | — flange with projection and recess with suitable seal | 1 | **0,5 assurance of leakproofness by means of monitoring and repair (*)** | |
| | | | — flange with V-groove and suitable V-groove seal | 1 | **0,5 assurance of leakproofness by means of monitoring and repair (*)** | |
| | | | — flange with smooth seal rail and suitable seals | 1 | **0,5 assurance of leakproofness by means of monitoring and repair (*)** | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| 1.3 | **quasi-static seals** | | | | | |
| 1.3.1 | **fittings** | shafts and spindle seals of fittings e.g. ball valves, stopcocks, valves, butterfly valves, slide valves | — stuffing box seals | 2 | 1 in the case of regular monitoring and repair | |
| | | | — stuffing box seals with self-adjustment (spring-loaded) | 1 | **0,5 technically leakproof** | |
| | | | — double stuffing box with barrier seal | 1 | 0,5 with monitoring of the barrier pressure system | by means of regular visual checks or process control technology equipment |
| | | | — O-ring seal | 1 | **0,5 technically leakproof** | |
| | | | — stopcock liner seal | 1 | 0,5 assurance that technically leakproof by means of monitoring and repair | |
| | | | — piston seal | 1 | 0,5 technically leakproof | |
| | | | — bellows seal | **0,5** | | |
| | | | — diaphragm seal | **0,5** | | |
| | | | — magnetic clutch | **0,5** | | |
| 1.3.2 | **others** | control rods | — stuffing box seals | 2 | 1 in the case of regular monitoring and repair | |
| | | | — stuffing box seals with self-adjustment (spring-loaded) | 1 | **0,5 technically leakproof** | |
| | | | — double stuffing box with barrier seal | 1 | **0,5 with monitoring of the barrier pressure system** | by means of regular visual checks or process control technology equipment |
| | | | — O-ring seal | 1 | | |
| | | | — piston seal | 1 | | |
| | | | — bellows seal | **0,5** | | |
| | | | — diaphragm seal | **0,5** | | |
| 2 | **dynamic seals** | | | | | |
| 2.1 | **seals with revolving parts** | hermetically sealed | — canned motor | **0,5** | | |
| | | | — magnetic clutches | **0,5** | | |
| | | seals which are not contactless | — single-axial face seal | 1 | | |
| | | | — double-axial face seal | 1 | | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| | | | — double-axial face seal with barrier fluid | 1 | **0,5 with monitoring of the barrier pressure system by means of regular checking, as a rule, 1 x day or, for example, process control technology equipment with alarm** | |
| | | | — stuffing box seal | 2 | 1 in the case of regular monitoring and repair | |
| | | | — stuffing box seal with self-adjustment (spring-loaded) | 2 | **0,5 technically leakproof** | |
| | | contactless seals | — labyrinth seal | 2 | | |
| | | | — gas-lubricated seal | 1 | **0,5 with monitoring of the gas flow** | |
| 2.2 | **seals for oscillating parts** | — bellows seal | — bellows valves | **0,5** | | |
| | | | — reciprocating pumps with bellows seal | **0,5** | | |
| | | — diaphragm seals | — diaphragm pumps | **0,5** | | |
| | | | — conical diaphragm valves | **0,5** | | |
| | | — cups | — reciprocating pumps | 1 | | |
| | | | — scraper rings | 1 | | |
| 3. | **substance transfer and filling points** | | | | | |
| 3.1 | **for solid substances** | | | | | |
| 3.1.1 | **sacks** | | | | | |
| 3.1.1.1 | **sacks** (emptying) | open manhole, open container | — manual emptying | 4 | 2 with other exhaust ventilation equipment<br>1 with effective exhaust ventilation equipment<br>1 low emission form of use, no further hazardous substance present<br>0,5 with highly effective exhaust ventilation equipment<br>0,5 emission-free form of use (e.g. master batch without abrasion) | if a hazardous substance is present in the container due account must be taken of this |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| | | sack-slitting and emptying machine | | | 0,5 emission-free form of use (e.g. master batch without abrasion) | |
| | | encapsulated sack-slitting and emptying machine with integrated exhaust ventilation equipment | | 1 | **0,5 compression and packing of the empty sacks within the encapsulated area, assurance of leakproofness by means of monitoring and repair** | |
| 3.1.1.2 | **sacks** (filling) | manual filling, open sack filling | — manual filling | 4 | 2 with other exhaust ventilation equipment<br>1 with effective exhaust ventilation equipment<br>1 low emission form of use, no further hazardous substance present<br>0,5 with highly effective exhaust ventilation equipment<br>0,5 emission-free form of use (e.g. master batch without abrasion) | |
| | | sack-filling equipment | — valve-sack filling machine, e.g. pneumatic packer, spiral packer, net filling scales | 4 | 2 with other exhaust ventilation equipment<br>1 with effective exhaust ventilation equipment<br>0,5 with highly effective exhaust ventilation equipment | |
| | | | — vacuum packer | 2 | 1 with effective exhaust ventilation equipment<br>0,5 with highly effective exhaust ventilation equipment | |
| | | | — completely encapsulated filling machine with integrated exhaust ventilation equipment | 1 | **0,5 assurance of leakproofness by means of monitoring and repair (*)** | |
| | | | — bag forming, filling and sealing machine | 1 | **0,5 assurance of leakproofness by means of monitoring and repair (*)** | |
| 3.1.2 | **big bags, intermediate bulk containers** | | | | | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| 3.1.2.1 | **big bags, intermediate bulk containers** (emptying) | open manhole | — manual emptying | 4 | 2 with other exhaust ventilation equipment<br>1 with effective exhaust ventilation equipment<br>1 low emission form of use, no further hazardous substance present<br>0,5 with highly effective exhaust ventilation equipment<br>0,5 emission-free form of use (e.g. master batch without abrasion) | |
| | | big bag emptying equipment | | 4 | 2 with other exhaust ventilation equipment<br>1 with effective exhaust ventilation equipment<br>1 low emission form of use, no further hazardous substance present<br>0,5 with highly effective exhaust ventilation equipment<br>0,5 emission-free form of use (e.g. master batch without abrasion) | |
| 3.1.2.2 | **big bags, intermediate bulk containers** (filling) | filling of open large sacks | — manual filling | 4 | 2 with other exhaust ventilation equipment<br>1 with effective exhaust ventilation equipment<br>1 low emission form of use, no further hazardous substance present<br>0,5 with highly effective exhaust ventilation equipment<br>0,5 emission-free form of use (e.g. master batch without abrasion) | |
| | | big bag filling equipment | — open filling | 4 | 2 with other exhaust ventilation equipment<br>1 with effective exhaust ventilation equipment<br>1 low emission form of use, no further hazardous substance present<br>0,5 with highly effective exhaust ventilation equipment<br>0,5 emission-free form of use (e.g. master batch without abrasion) | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| | | big-bag filling equipment | — completely encapsulated filling machine with integrated exhaust ventilation equipment | 1 | **0,5 with special filling heads (e.g. laterally sealing) dust-free closing technology; late trickling from the filling head is prevented, assurance of leakproofness by means of monitoring and repair** | |
| | | | — large sack scales | 4 | 2 with other exhaust ventilation equipment<br>1 with effective exhaust ventilation equipment<br>1 low emission form of use, no further hazardous substance present<br>0,5 with highly effective exhaust ventilation equipment<br>0,5 emission-free form of use (e.g. master batch without abrasion) | |
| 3.1.3 | **containers** | | | | | |
| 3.1.3.1 | **containers** (emptying) | with closed emptying equipment | | 1 | **0,5 if leakproofness is assured by means of special measures (e.g. monitored self-locking connection) and integrated exhaust ventilation equipment is present, assurance of leakproofness by means of monitoring and repair (*)**<br>0,5 if leakproofness is assured by means of special measures (e.g. monitored self-locking connection) and highly effective exhaust ventilation equipment is present, assurance of leakproofness by means of monitoring and repair | the container's cover seal must meet the demands of 1.2 |
| | | open container | | 4 | 2 with other exhaust ventilation equipment<br>1 with effective exhaust ventilation equipment<br>0,5 with highly effective exhaust ventilation equipment | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| 3.1.3.2 | **container** (filling) | with special filling equipment | | 1 | **0,5 if leakproofness is assured by means of special measures (e.g. monitored self-locking connection), assurance of leakproofness by means of monitoring and repair (*)** | |
| | | open filling | | 4 | 2 with other exhaust ventilation equipment<br>1 with effective exhaust ventilation equipment<br>0,5 with highly effective exhaust ventilation equipment, assurance of leakproofness by means of monitoring and repair (*) | |
| 3.1.4 | **drums** | with emptying equipment | — closed | 1 | **0,5 if leakproofness is assured by means of special measures (e.g. monitored self-locking connection) and integrated exhaust ventilation equipment is present** | |
| 3.1.4.1 | **drums** (emptying) | | — mechanical conveyance, e.g. by spiral conveyor | 4 | 0,5 if leakproofness is assured by means of special measures (e.g. monitored self-locking connection) and exhaust ventilation equipment or highly effective exhaust ventilation equipment is present | |
| | | | — pneumatic conveyance, e.g. air-blaster | 4 | 2 with other exhaust ventilation equipment<br>1 with effective exhaust ventilation equipment<br>0,5 with highly effective exhaust ventilation equipment | |
| | | | | | 2 with other exhaust ventilation equipment<br>1 with effective exhaust ventilation equipment<br>0,5 with highly effective exhaust ventilation equipment | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| | | open container | — mechanical conveyance, e.g. by spiral conveyor | 4 | 2 with other exhaust ventilation equipment | |
| | | | | | 1 with effective exhaust ventilation equipment | |
| | | | | | 0,5 with highly effective exhaust ventilation equipment | |
| | | | — pneumatic conveyance, e.g. air-blaster | | 2 with other exhaust ventilation equipment | |
| | | | | | 1 with effective exhaust ventilation equipment | |
| | | | | 4 | 0,5 with highly effective exhaust ventilation equipment | |
| 3.1.4.2 | **drums** (filling) | with special filling equipment | | 1 | **0,5 if leakproofness is assured by means of special measures (e.g. monitored self-locking connection) and integrated exhaust ventilation equipment is present** | |
| | | open filling | | 4 | 0,5 if leakproofness is assured by means of special measures (e.g. monitored self-locking connection) and highly effective exhaust ventilation equipment is present | |
| | | | | | 2 other exhaust ventilation equipment | |
| | | | | | 1 with effective exhaust ventilation equipment | |
| | | | | | 0,5 with highly effective exhaust ventilation equipment | |
| 3.1.5 | **silo vehicles** | | | | | |
| 3.1.5.1 | **silo vehicles** (emptying) | fixed pipework, articulated arm | | 1 | 0,5 assurance of leakproofness by means of monitoring and repair (*); complete capture of residual quantities during decoupling and coupling processes | |
| | | hose connection | — fixed use (connecting hoses and couplings are provided by the company) | 1 | 0,5 assurance of leakproofness by means of monitoring and repair (*); complete capture of residual quantities during decoupling and coupling processes | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| | | | — other use (connecting hoses and couplings are not provided by the company) | 2 | 1 complete capture of the residual quantities | |
| 3.1.5.2 | **silo vehicles** (filling) | fixed pipework, articulated arm | | 1 | 0,5 assurance of leakproofness by means of monitoring and repair (*); complete capture of residual quantities during decoupling and coupling processes | |
| | | hose connection | — fixed use (connecting hoses and couplings are provided by the company) | 1 | 0,5 assurance of leakproofness by means of monitoring and repair (*); complete capture of residual quantities during decoupling and coupling processes | |
| | | | — other use (connecting hoses and couplings are not provided by the company) | 2 | 1 Complete capture of the residual quantities | |
| 3.1.6 | **inlet and outlet fittings** | for silos, filling equipment, bulk-material containers | — butterfly valves | 1 | **0,5 assurance of leakproofness by means of monitoring and repair (*): regular cleaning** | |
| | | | — cocks and stopcocks | 1 | **0,5 assurance of leakproofness by means of monitoring and repair (*): regular cleaning** | |
| | | | — flat slide valves | 1 | **0,5 assurance of leakproofness by means of monitoring and repair (*): regular cleaning** | |
| | | | — slide valve plate | 1 | **0,5 assurance of leakproofness by means of monitoring and repair (*): regular cleaning** | |
| | | | — pinch valve with soft seal | 1 | | |
| | | | — iris diaphragm valve | 1 | | |
| | | | — hose valve | 1 | | |
| 3.2 | **substance transfer points for liquids** | | | | | |
| 3.2.1 | **small containers and drums** | | | | | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| 3.2.1.1 | **small containers and drums** (emptying) | fixed connections (pipework, hose connections, articulated arm) | — with gas-displacement or gas offtake at a safe point or transfer to a treatment or incineration plant | 1 | **0,5 assurance of leakproofness by means of monitoring and repair (*); leak test after establishing the connection, complete capture of the residual quantities** | with regard to connection elements see 1 |
| | | | — without gas-displacement and without gas offtake at a safe point | 4 | | |
| | | open packing drums | — with drum pump or hose | 4 | 1 in the case of a construction which is free from leaks and drip quantities as well as being equipped with highly effective exhaust ventilation equipment | regular checking of the exhaust ventilation equipment; the small container or drum must be closed immediately after the filling process |
| | | emptying in closed units | — encapsulation | 1 | **0,5 with integrated exhaust ventilation equipment and opening and closing of the packing drums in the closed unit** | regular checking of the exhaust ventilation equipment |
| 3.2.1.2 | **small containers and drums** (filling) | fixed connections (pipework, hose connections, articulated arm) | — with gas-displacement or gas offtake at a safe point or transfer to a treatment or incineration plant | 1 | **0,5 assurance of leakproofness by means of monitoring and repair (*); leak test after establishing the connection, complete capture of the residual quantities** | with regard to connection elements see 1 |
| | | | — without gas-displacement and without gas offtake | 4 | 1 in the case of a construction which is free from leaks and drip quantities as well as being equipped with effective exhaust ventilation equipment | |
| | | open packing drums | — with filling hose | 4 | 0,5 in the case of a construction which is free from leaks and drip quantities as well as being equipped with highly effective exhaust ventilation equipment | regular checking of the exhaust ventilation equipment; the small container or drum must be closed immediately after the filling process |
| | | | — encapsulation | 1 | **0,5 with integrated exhaust ventilation equipment and closing of the packing drums in the closed unit** | regular checking of the exhaust ventilation equipment |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| **3.2.2** | **tanker, tank wagon, large containers** | | | | | |
| **3.2.2.1** | **tanker, tank wagon, large containers** | fixed connection. e.g. fixed pipework, hose connections, steel | — with gas displacement or gas offtake at a safe point or transfer to a treatment or incineration plant | **1** | **0,5 Assurance of leakproofness by means of monitoring and repair (*); leak test after establishing the connection, complete capture of the residual quantities** | with regard to connection elements see 1 |
| | | | — without gas displacement and without gas offtake | **4** | | |
| | | other hose connections | | **2** | 1 complete capture of the residual quantities | |
| **3.2.2.2** | **tankers/tank wagons, large containers** (filling) | fixed pipework, hose connections, steel loading arms | — with gas displacement or gas offtake at a safe point or transfer to a treatment or incineration plant | **1** | 0,5 assurance of leakproofness by means of monitoring and repair, leak test after establishing the connection, complete capture of residual quantities | the containers must be closed immediately after filling |
| | | | — without gas displacement and without gas offtake | **4** | | |
| | | open filling | — filling pipe | **4** | 1 with highly effective exhaust ventilation, complete capture of the residual quantities | the containers must be closed immediately after filling |
| **3.3** | **substance transfer points gases** | | | | | with regard to the functional elements see 1 |
| **3.3.1** | **gases** (filling and emptying) | | | **1** | **0,5 Assurance of leakproofness by means of monitoring and repair (*); leak test after establishing the connection; gas displacement or offtake of residual gas at a safe point or transfer to a treatment or incineration plant** | closed plant systems, parts of units and functional elements must be operated, monitored and maintained in such a way that they remain technically leakproof in the case of the mechanical, chemical and thermal stresses that can be expected for the envisaged type of operation |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| **4** | **sampling points** | | | | | |
| **4.1** | **open sampling** | | valve, stopcock | **4** | 2 with other exhaust ventilation equipment<br>1 with highly effective exhaust ventilation equipment | |
| **4.2** | **closed sampling** | | | **1** | **0,5 assurance of leakproofness by means of monitoring and repair (*)** | sampling must be done by a closed sampling system avoiding uncontrolled escape of product. Uncontrolled escape of product is understood as:<br>— the splashing of liquid during sampling from pressurised plant parts<br>— after-run of liquid from pipe connection pieces of tubes which are mounted on the sampling unit<br>— escape of product vapours<br>— overflow from overfilled sampling vessels |
| 5 | **Storage in packing drums** | | | | | |
| 5.1 | **solid substances, with the exception of certain explosives** | transport packaging according to ADR-regulations | — drums, containers | **0,5** | | with sufficient ventilation (min. twofold change of air) |
| | | | — bags; plastic, textile, paper and multi-layered sacks | 0,5 | | with sufficient ventilation (min. twofold change of air) |
| 5.2 | **solid substances, certain explosives (containing nitro-glycerine)** | transport packaging according to ADR-regulations | | 4 | 2 with other exhaust ventilation equipment<br>1 with effective exhaust ventilation equipment<br>0,5 with highly effective exhaust ventilation equipment | |
| 5.3 | **liquids** | transport packaging according to ADR-regulations | — containers, metal drums, sheet iron cans, plastic drums, tubes, cans, containers | 0,5 | | with sufficient ventilation (min. twofold change of air) |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| 5.4 | **Gases** | transport packaging according to ADR-regulations | compressed gas cylinders,<br><br>compressed gas containers,<br><br>compressed gas drums | 1 | **0,5 assurance of leakproofness by means of monitoring and repair** | with sufficient ventilation (min. twofold change of air)<br><br>with regard to functional elements see 1; closed plant systems, parts of units and functional elements must be operated, monitored and maintained in such a way that they remain technically leakproof in the case of the mechanical, chemical and thermal stresses that can be expected for the envisaged type of operation |

(*) The leakproofness of separable connections between plant units and parts of the equipment can be assured by taking the following measures on a permanent basis:

1. **Monitoring or inspection measures in order to determine and assess the actual state of the separable connection according to EN 13306 (in preparation)**

This must occur at predetermined times and in accordance with a plan geared to the specific needs of the company, the type of connection and its construction as well as to the nature and the properties of the chemical agents which are conveyed. Examples of such measures are:

— leak testing,
— visual examination of the plant to establish clear leakage points such as places where liquids are leaking, examination to establish streaks, odours, noises, the formation of ice, etc.,
— inspection of the plant with mobile leak-indicating and leak-detection devices (e.g. gas test tubes, FID, portable gas detectors),
— the application of foaming agents to the separable connections,
— the use of gas detectors to monitor the atmosphere,
— the use of an automatic leak-testing device at the articulated hose or the loading hose.

2. **Repair measures to restore the desired state of the separable connection according to EN 13306 (in preparation)**

The measures which are possibly required must be planned and performed on an individual basis in accordance with:

— the particular hazardous substance,
— the type and extent of the damage,
— the protection and safety measures which must be taken.

Before the plant returns to operation the repaired connections must be subjected to thorough leak testing.

*ANNEX 8A*

Where, in accordance with the provisions of Annex VII.A related to intermediates, the relevant competent authority has authorised the application of a reduced test package to a chemical substance, the requirements of this section shall be reduced as follows:

— when the quantity of the substance placed on the market reaches 10 tonnes per year per manufacturer or when the total quantity of the substance placed on the market reaches 50 tonnes per manufacturer; in this case the relevant competent authority shall require all those test and studies laid down in points 3 to 6 of Annex VII.A (excepting those already performed); in addition, the relevant competent authority may require those level 1 tests and studies related to aquatic organisms,

— when the quantity of the substance placed on the market reaches 100 tonnes per year per manufacturer or when the total quantity of the substance placed on the market reaches 500 tonnes per manufacturer; in this case the relevant competent authority shall require the level 1 tests or studies related to reproductive toxicity. The relevant competent authority may decide that the classification of the substance as an intermediate qualifying for a reduced test package constitutes a good reason why one or more tests and studies, except those related to reproductive toxicity, are not appropriate.

*ANNEX 8B*

When the quantity of the substance placed on the market reaches 1 000 tonnes per year per manufacturer or when the total quantity of the substance placed on the market reaches 5 000 tonnes per manufacturer, additional studies mentioned in level 1 or 2 would normally not be required. The relevant competent authority should, however, consider additional tests and may require additional tests including the tests laid down in levels 1 and 2 of this Annex.