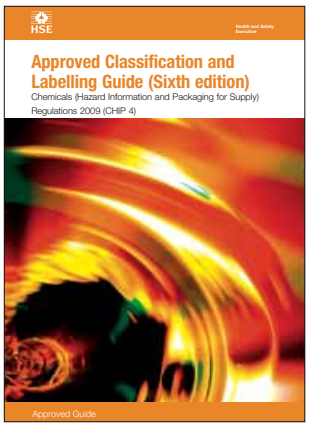
# Approved Classification and Labelling Guide (Sixth edition)

## Chemicals (Hazard Information and Packaging for Supply) Regulations 2009 (CHIP 4)

## Approved Guide

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This Approved Guide (Sixth edition) sets out the general principles of classification and labelling for supply as required by the Chemicals (Hazard Information and Packaging for Supply) Regulations 2009 (CHIP 4).

It is addressed to manufacturers, importers and other suppliers who have responsibilities for the classification and labelling of dangerous substances and preparations and closely follows the European Commission's labelling guide (Annex VI to Directive 67/548/EEC).

The changes in this Guide since the previous (fifth) edition reflect:

- the introduction of European Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures;
- the effect of Directive 2006/121/EC, which amends Annex V of the Dangerous Substances Directive;
- the withdrawal of the Approved Supply List now that the list of substances with harmonised classifications and labels is established in direct-acting Community legislation; and
- the transfer of the substantive provisions relating to safety data sheets to the Registration, Evaluation, Authorisation and Restriction of Chemicals Regulation (REACH).

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# Contents

# Notice of Approval

The Board of the Health and Safety Executive has approved the publication of this document, *Approved Classification and Labelling Guide*, for the purposes of the Chemicals (Hazard Information and Packaging for Supply) Regulations 2009 ('CHIP 4').[1]

This Approved Classification and Labelling Guide shall have effect from the date on which CHIP 4 comes into force, 6 April 2009.

On that date the Approved Classification and Labelling Guide (Fifth edition) (approved by the Health and Safety Commission on 16 April 2002 for the purposes of the Chemicals (Hazard Information and Packaging for Supply) Regulations 2002[2] shall cease to have effect.

Approved,

Board of the Health and Safety Executive
3 March 2009

# Preface

This Approved Classification and Labelling Guide is based on Commission Directive 2001/59/EC[3] which sets out Annex VI to the Dangerous Substances Directive (67/548/EEC).[4] The purpose of Annex VI is to provide a harmonised basis for the classification and labelling of dangerous substances and preparations in member states.

The Chemicals (Hazard Information and Packaging for Supply) Regulations 2009 ('CHIP 4') impose requirements by reference to this Guide and to that extent it is legally binding.

# Introduction

1 This Approved Guide sets out the general principles of classification and labelling for supply as required by the Chemicals (Hazard Information and Packaging for Supply) Regulations 2009 (known as 'CHIP 4'). It is addressed to manufacturers, importers and other suppliers who have responsibilities for the classification and labelling of dangerous substances and preparations and closely follows the European Commission's 'labelling guide', ie Annex VI to Directive 67/548/EEC.

## Introduction to recent changes to European classification and labelling legislation

2 The changes in this Approved Guide since the previous (fifth) edition reflect:

(a) the introduction of European Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures (see paragraphs 3–8);
(b) the effect of Directive 2006/121/EC, which amends Annex V of the Dangerous Substances Directive (see paragraph 9);
(c) the withdrawal of the Approved Supply List now that the list of substances with harmonised classifications and labels is established in direct-acting Community legislation (see paragraphs 10–12 below); and
(d) the transfer of the substantive provisions relating to safety data sheets to the REACH Regulation (Registration, Evaluation, Authorisation and Restriction of Chemicals).

## European Regulation (EC) No 1272/2008 on the Classification, Labelling and Packaging of Substances and Mixtures (the 'CLP Regulation')

3 The main purpose of the CLP Regulation is to adopt, within the European Community, the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) published by the UN Social and Economic Council and known as the Purple Book.[5] The GHS addresses the need for the creation of a globally harmonised classification and compatible labelling system, including material safety data sheets and easily understood symbols. The GHS sets out internationally accepted definitions and criteria to identify the hazards of chemicals and to communicate those hazards via labels and safety data sheets. The GHS is a voluntary international agreement and allows for implementation over a period of years within certain limitations. Countries may keep national requirements that are not covered by the GHS provided they do not contradict it.

4 The CLP Regulation adopts the majority of the GHS hazard classes and categories. It also retains a few aspects of the existing EU system, where these do not contradict the GHS, to maintain existing EU standards. It replaces certain provisions of the Dangerous Substances Directive (67/548/EEC) and the Dangerous Preparations Directive[6] (1999/45/EC) relating to the classification, packaging and labelling of substances and preparations through a phase-in approach, allowing a transitional period until 1 June 2015. The CLP Regulation introduces new classification criteria, hazard symbols and labelling phrases, known as hazard statements and precautionary statements, while taking account of elements which are part of the earlier Community legislation (such as harmful to the ozone layer).

5 The CLP Regulation also takes over certain provisions of European Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals ('REACH')[7] relating to the notification of classifications, the establishment

of a list of harmonised classifications and the creation of a classification and labelling inventory.

6 Subject to the transitional arrangements set out below, the CLP Regulation entered into legal effect throughout the UK, and all other European Union Member States, on 20 January 2009.

## Transitional arrangements in the CLP Regulation

7 The new requirements will enter into force over a phased transitional period, ultimately replacing the CHIP Regulations and its parent European legislation in June 2015.

8 The specific transitional arrangements are as follows:

### *Substances*

| | |
|---|---|
| 20 January 2009 – 1 December 2010 | Suppliers must classify substances according to CHIP, and may continue to label and package them according to regulations 6–11 of CHIP. However, they may as an alternative choose to classify, label and package substances according to CLP. In this case, they must, in addition, continue to classify under regulation 4 of CHIP, but the requirements on labelling and packaging in regulations 6–11 of CHIP no longer apply. |
| 1 December 2010 – 1 June 2015 | Suppliers must classify substances according to both CHIP and CLP. They must label and package according to CLP. |
| 1 June 2015 onwards | Suppliers must classify, label and package according to CLP. |

### *Preparations*

| | |
|---|---|
| 20 January 2009 – 1 June 2015 | Suppliers must classify preparations according to CHIP, and may continue to label and package them according to regulations 6–11 of CHIP. However, they may, as an alternative, choose to classify, label and package mixtures according to CLP. In this case, they must in addition continue to classify in addition under regulation 4 of CHIP, but the requirements on labelling and packaging in regulations 6–11 of CHIP no longer apply. |
| 1 June 2015 onwards | Suppliers must classify, label and package according to CLP. |

There are certain limited circumstances where these transitional arrangements for substances and preparations can be extended. The re-labelling and re-packaging of substances and mixtures which are already labelled and packaged and in the supply chain ('on the shelves') on the above compliance dates, may be postponed until 1 December 2012 and 1 June 2017 respectively.

## European Directive 2006/121/EC

9 One of the key changes required by European Directive 2006/121/EC[8] is to replace references to the test methods set out in Annex V of the Dangerous Substances Directive with references to the European Commission Regulation on test methods.[9] Consequently, the references to test methods have been amended throughout this Approved Guide.

### Withdrawal of the Approved Supply List

10 Table 3.2, Part 3 of Annex VI to the CLP Regulation, gives the list of harmonised classifications and labelling requirements agreed at European level, which apply for the purposes of the CHIP 4 Regulations. Previously, in Great Britain, Annex I of the Dangerous Substances Directive, which lists the harmonised classifications and labelling requirements, has been published through the Approved Supply List.

11 Annex 1 of the Dangerous Substances Directive ceased to have legal effect on 20 January 2009, on the entry into force of the CLP Regulation. From this date, the list of harmonised classifications and labelling requirements that appeared in Annex 1 was immediately transferred to Table 3.2, Part 3 of Annex VI to the CLP Regulation and re-enacted. Consequently, the Approved Supply List has been withdrawn.

12 References to the Approved Supply List throughout this Approved Guide have been replaced with references to Table 3.2, Part 3 of Annex VI to the CLP Regulation. Table 3.2, Part 3 of Annex VI can be found at http://ecb.jrc.ec.europa.eu/documents/Classification-Labelling/Table_3-2.doc.

# Introduction to classification and labelling

13 The purpose of classification is to identify the properties of substances and preparations that may constitute a hazard during normal handling and use. It is important to note that there is a difference between hazard (ie the inherent properties of a chemical) and risk (ie the probability of the hazardous properties of the chemical causing harm to people or the environment). Classification in this Approved Guide is about identification of the hazard not the risk. The properties considered are:

(a) physicochemical properties;
(b) health effects; and
(c) environmental effects.

In practice, classification will be carried out by an individual, and such a person should be competent to perform the task.

14 Once a substance or a preparation has been classified under regulation 4 of CHIP 4 by application of the criteria in paragraphs 35–147, the supply label required by regulation 7 of CHIP 4 is derived using the criteria in paragraphs 148–165.

15 The label is intended to provide a primary means by which people at work and the general public are given essential information about dangerous substances and preparations. It draws the attention of users to the inherent hazards of such materials so that the necessary precautionary measures can be taken. The label may also serve to draw attention to more comprehensive product information on safety such as the supplier's safety data sheet.

16 The label should take account of all hazards that are likely to be present in normal handling and use of a dangerous substance or preparation in the form in which it is supplied, although not necessarily in any different form in which it may

ultimately be used, eg diluted. The information on the label includes (see regulation 7 of CHIP):

(a) symbols and general indications of danger which highlight the most severe hazards;
(b) standard risk phrases (R-phrases), which specify the hazards arising from (a) and from other dangerous properties; and
(c) standard safety phrases (S-phrases) which give advice on the necessary precautions.

17 Supply labels derived by a manufacturer or supplier in accordance with this Approved Guide for a substance not yet listed in Table 3.2, Part 3 of Annex VI of the CLP Regulation remain valid until the substance is listed in Table 3.2, Part 3, or until a decision has been taken not to classify and label it in accordance with the agreed European procedure.

18 The Carriage of Dangerous Goods and Use of Transportable Pressure Equipment Regulations 2007[10] and CHIP Regulations 8 and 9show how, under certain circumstances, the labelling details for supply and for carriage may be combined.

### Scope

19 This Approved Guide applies to dangerous substances and preparations within the scope of CHIP 4 and should be read in the context of those Regulations. This Approved Guide does not apply to classifications determined under the CLP Regulation. Where a supplier classifies their substance and/or mixtures by applying the criteria set out in the CLP Regulation, the supplier should seek instruction from the technical Annexes to that Regulation.

20 This Approved Guide will cease to have legal effect from 1 June 2015.

# Data for classification and labelling

21 For **substances**, the data required for classification and labelling can be obtained from a number of different sources. In the case of substances that have been registered within the meaning of the European REACH Regulation, some of the necessary data for classification and labelling will already be available from the European Chemical Agency, which manages a database of information meeting the requirements set out for substance registration in Annexes VI to X of that Regulation. The classification and labelling should be reviewed, however, if further information becomes available (REACH Article 22). For other substances the necessary data may come from:

(a) the results of previous tests;
(b) information required by international rules on the transport of dangerous goods;
(c) reference works or scientific and technical literature;
(d) practical experience; or
(e) the results of validated structure-activity relationships and expert judgement may also be taken into account where appropriate.

22 For **preparations**, the physicochemical, health effect and ecotoxicological data required for classification and labelling shall be obtained by application of the

test methods specified in the European Commission Regulation (EC) No 440/2008 (unless, in the case of preparations which are subject to the Plant Protection Products Regulations 2005,[11] other internationally recognised methods are acceptable in accordance with the provisions of those Regulations). In the case of health effects and environmental effects, the classification may also be obtained by application of the conventional method as set out in Schedule 3 to CHIP 4, or in the case of R65, by application of the rules in the section on 'Aspiration hazard' in paragraph 64.

**Note**, however, that the conventional method must always be used for the evaluation of carcinogenicity, mutagenicity and reproductive toxicity.

23 The criteria in this Approved Guide are directly applicable when the data have been obtained from test methods equivalent to those described in European Commission Regulation (EC) No 440/2008 (see exception in paragraph 22 for preparations subject to the Plant Protection Products Regulations 2005). In other cases, the available data should be assessed by comparing the test methods used with those in the above Commission Regulation and by applying the criteria in this Guide to determine the classification and label.

24 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 or preparation on the basis of an assessment of the evidence by a competent person.

25 In the case of a substance, and 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 Table 3.2, Part 3 of Annex VI to the CLP Regulation, which lists European agreed harmonised classifications. The proposal should be made to the Health and Safety Executive and should be accompanied by appropriate scientific data (see also paragraphs 130 and 131). A similar procedure may be followed when information is identified which gives cause for concern over the accuracy of an existing entry in Table 3.2, Part 3 of Annex VI.

## Animal tests

26 The performance of animal tests to establish experimental data is subject to the Animals (Scientific Procedures) Act 1986,[12] which implements Directive 86/609/EEC,[13] regarding the protection of animals used for experimental purposes.

## Application of the criteria in this Guide

27 Classification of substances and preparations should include consideration of all the physicochemical, toxicological and ecotoxicological properties covered in this Approved Guide. R-phrases should be selected to ensure that all the potential dangers identified in the classification are properly reflected on the label. When selecting symbols and R-phrases, it is important, therefore, to consider in turn each of the criteria in this Approved Guide.

28 The criteria in this Approved Guide are also applicable to gaseous substances and preparations in so far as they are subject to the packaging and labelling provisions of CHIP. Gaseous preparations are covered explicitly in paragraphs 166–168 and 171–180.

## Classification of substances containing impurities, additives or individual constituents

29 Where a substance contains an impurity or additive, or an individual constituent has been identified, its presence should be taken into account in the classification if the concentration of the impurity, additive or individual constituent is equal to or exceeds:

(a) 0.1% for substances classified as very toxic, toxic, carcinogenic (Category 1 or 2), mutagenic (Category 1 or 2), toxic for reproduction (Category 1 or 2), or dangerous for the environment (either assigned the symbol 'N' for the aquatic environment or classified as dangerous for the ozone layer);
(b) 1% for substances classified as harmful, corrosive, irritant, sensitising, carcinogenic (Category 3), mutagenic (Category 3), toxic for reproduction (Category 3), or dangerous for the environment (not assigned the symbol 'N', ie harmful to aquatic organisms and/or may cause long-term adverse effects);

unless lower values have been specified in Table 3.2, Part 3 of Annex VI.

30 With the exception of those substances listed in Table 3.2, Part 3 of Annex VI, classification of substances containing impurities, additives or individual constituents for physicochemical properties, health effects and environmental effects should be carried out in accordance with the requirements of Schedule 3 to CHIP 4.

31 Labelling for these substances should be carried out in accordance with regulation 7(2) and Schedule 4 Part I of CHIP 4, as if the substance was a preparation.

32 In the case of asbestos, this general rule does not apply until a concentration limit has been set in Table 3.2, Part 3 of Annex VI. Substances in which asbestos is present should be classified and labelled according to the principles in regulation 4(3) and (4) of CHIP.

## Preparations or substances containing impurities, additives or individual constituents which are used as constituents of another preparation

33 The labelling of such preparations should be in accordance with regulation 7(3) of CHIP 4. However, in certain cases, the information on the label of the preparation or substance described in paragraphs 29–31 may be 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 it is recommended that the supplier should provide all necessary data concerning the dangerous substances present to enable correct classification and labelling of the new preparation. These data are also necessary to enable the person responsible for supplying the new preparation to comply with other requirements of CHIP 4.

34 The classification and labelling details derived in accordance with this Approved Guide may need to be revised from time to time as the EC classification system for dangerous substances and preparations evolves and as more information on hazards becomes available.

# Classification on the basis of physicochemical properties

## Criteria for classification, choice of symbols, indication of danger and choice of risk phrases

35 In general the test methods for explosive, oxidising and flammable properties set out in Commission Regulation No 440/2008 give specific criteria for classification under the physicochemical properties defined in Schedule 1 to CHIP 4.

36 However, certain of the test methods for the determination of flashpoint given in Commission Regulation No 440/2008 may not be suitable in certain circumstances, as they can give widely differing results. Care should be taken, therefore, to apply the most appropriate test to the particular substance or preparation being classified. Advice on the correct test method to use can be sought on a case-by-case basis by contacting the Health and Safety Laboratory at www.hsl.gov.uk/capabilities/fire-safety.htm or Business Development Group, Health and Safety Laboratory, Harpur Hill, Buxton, Derbyshire SK17 9JN.

37 If adequate information is available to demonstrate in practice that the physicochemical properties of substances and preparations (apart from the oxidising properties of organic peroxides) are different from those revealed by the test methods in Commission Regulation No 440/2008 then such substances and preparations should be classified according to the hazard (if any) they present to those handling the substances and preparations or to other people.

38 Full testing of preparations for explosive, oxidising and flammable properties may not be necessary if none of the constituent substances possess such properties – see paragraph 3 of Part I of Schedule 3 to CHIP 4.

### Explosive

39 Substances and preparations should be classified as explosive and assigned the corresponding symbol ‘E’ with the indication of danger ‘explosive’ in accordance with the results of the tests in Commission Regulation No 440/2008 and in so far as the substances and preparations are explosive as supplied. One R-phrase is obligatory and should be assigned as follows:

**R2** *Risk of explosion by shock, friction, fire or other sources of ignition*
Substances and preparations including certain organic peroxides but excepting those assigned R3.

**R3** *Extreme risk of explosion by shock, friction, fire or other sources of ignition*
Substances and preparations which are particularly sensitive such as picric acid salts or PETN.

### Oxidising

40 Substances and preparations should be classified as oxidising and assigned the corresponding symbol ‘O’ with the indication of danger ‘oxidising’ in accordance with the results of the tests in Commission Regulation No 440/2008. One R-phrase is obligatory. It should be assigned 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 organic 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 organic peroxides which become explosive when mixed with combustible materials, eg certain chlorates.

## Comments regarding peroxides

41 For the explosive properties, an organic peroxide, or a preparation containing organic peroxides, in the form in which it is supplied is classified according to the criteria in paragraph 39 on the basis of tests carried out in accordance with the methods given in Commission Regulation No 440/2008.

42 For the oxidising properties, the existing methods in Commission Regulation No 440/2008 cannot be applied to organic peroxides. For substances, organic peroxides not already classified as explosive are classified as oxidising on the basis of their structure (eg R-O-O-H; $R_1$-O-O-$R_2$). Preparations not already classified as explosive should be classified using the calculation method based on the percentage of active oxygen shown in paragraphs 182 and 183. Any organic peroxide, or preparation containing organic peroxides, not already classified as explosive is classified as oxidising, if the peroxide or the preparation contains:

(a) more than 5% of organic peroxides; or
(b) more than 0.5% available oxygen from the organic peroxides, and more than 5% hydrogen peroxide.

## Extremely flammable

43 Substances and preparations should be classified as extremely flammable and assigned the corresponding symbol ‘F+’ with the indication of danger ‘extremely flammable’ in accordance with the results of the tests in Commission Regulation No 440/2008 (see also paragraph 36). The R-phrase should be assigned as follows:

**R12** *Extremely flammable*
Liquid substances and preparations which have a flash point lower than 0 °C and a boiling point (or, in the 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.

## Highly flammable

44 Substances and preparations should be classified as highly flammable and assigned the corresponding symbol ‘F’ with the indication of danger ‘highly flammable’ in accordance with the results of the tests referred to in paragraph 43. R-phrases should be assigned as follows:

**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 flashpoint 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 l/kg 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.

## Flammable

45 Substances and preparations should be classified as flammable in accordance with the results of the tests referred to in paragraph 43. The R-phrase should be assigned as follows:

**R10** *Flammable*
For liquid substances and preparations having a flashpoint equal to or greater than 21 °C, and less than or equal to 55 °C.

46 However, a preparation having a flashpoint 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 the preparation or to other persons.

## Other physicochemical properties

47 Additional R-phrases should be assigned to substances and preparations which have been classified by virtue of paragraphs 39–46, 62–126 or 138–147, in accordance with the following criteria:

**R1** *Explosive when dry*
For explosive substances and preparations supplied in solution or in a wetted form, eg 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, eg picric acid, styphnic acid.

**R5** *Heating may cause an explosion*
For thermally unstable substances and preparations not classified as explosive, eg perchloric acid 50%.

**R6** *Explosive with or without contact with air*
For substances and preparations which are unstable at ambient temperatures, eg acetylene.

**R7** *May cause fire*
For reactive substances and preparations, eg fluorine, sodium hydrosulphite.

**R14** *Reacts violently with water*
For substances and preparations which react violently with water, eg acetyl chloride, alkali metals, titanium tetrachloride.

**R16** *Explosive when mixed with oxidising substances*
For substances and preparations which react explosively with an oxidising agent, eg 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, eg 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 paragraph 40 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.

48 For other additional R-phrases see paragraph 132.

# Classification on the basis of health effects

## Criteria for classification, choice of symbols, indication of danger and choice of risk phrases

49 Classification is concerned with both the acute and long-term effects of substances and preparations, whether resulting from a single instance of exposure or from repeated or prolonged exposure.

50 Where it can be demonstrated by epidemiological studies, by scientifically valid case studies as specified in this Approved Guide or by statistically backed experience (such as the assessment of data from poison information units or concerning occupational diseases), that the toxicogical effect of a substance or preparation on humans is, or is likely to be, different from that suggested by the experimental results obtained in animal tests or by the application of the conventional method in Part I of Schedule 3 to CHIP 4, then the substance or preparation should be classified according to its toxicity in humans. However, tests on humans should be discouraged and should not normally be used to negate positive animal data.

51 **Substances** should be classified on the basis of available experimental data in accordance with the scheme set out in paragraphs 62–132. This scheme covers:

(a) acute lethal effects – paragraphs 62–64;
(b) non-lethal irreversible effects after a single exposure – paragraphs 62–64;
(c) severe effects after repeated or prolonged exposure – paragraphs 63 and 64;
(d) corrosive effects – paragraphs 71 and 72;
(e) irritant effects – paragraphs 73–75;
(f) sensitising effects – paragraphs 76–90;
(g) carcinogenic, mutagenic and toxic for reproduction effects – paragraphs 91–129;
(h) other toxicological properties – paragraph 132.

52 **Preparations** should be classified:

(a) in the absence of experimental data, by application of the conventional method in Part I of Schedule 3 to CHIP 4. In this case the classification should be based on the individual concentration limits taken either:

  (i) from Table 3.2, Part 3 of Annex VI to the CLP Regulation; or
  (ii) from Part II of Schedule 3 to CHIP if the substance or substances do not appear in Table 3.2 or appear in it without concentration limits; or

(b) where experimental data are available in accordance with the scheme in paragraph 51 with the exception of carcinogenic, mutagenic and toxic for reproduction properties, which must be evaluated by the conventional method in Part I of Schedule 3 to CHIP.

53 Without prejudice to the requirements of the Plant Protection Products Regulations 2005, only where it can be scientifically demonstrated by the person responsible for supplying a preparation that the toxicological properties of the preparation cannot correctly be determined by application of the conventional method, or on the basis of existing test results on animals, may tests be performed on animals for the purpose of applying the criteria in this Approved Guide. Note that the performance of animal tests to establish experimental data is subject to the Animals (Scientific Procedures) Act 1986, which implements Directive 86/609/EEC, regarding the protection of animals used for experimental purposes.

54 Whichever method is used for the evaluation of the danger of a preparation, all the dangerous effects on health as defined in Part I of Schedule 3 to CHIP must be taken into consideration.

55 When the classification is to be established from experimental results obtained in animal tests, the results should have validity for humans in that the tests reflect, in an appropriate way, the risks to humans.

56 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 procedure) or by determining the range of exposure where lethality is expected (the acute toxic class method).

57 The discriminating dose is the dose which causes evident toxicity but not mortality and must be one of the four dosage levels specified in Commission Regulation (EC) No 440/2008 (5, 50, 500, or 2000 mg/kg/body weight).

58 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 may be either:

(a) less than 100% survival;
(b) 100% survival, but evident toxicity;
(c) 100% survival, but no evident toxicity.

The test method requires in some cases testing at higher or lower doses if not already tested at the relevant dose level. (Refer to the description of the test method in Commission Regulation No 440/2008).

59 In the criteria below for very toxic, toxic and harmful, only the final test result is shown. The 2000 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.

60 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 2000 mg/kg/body weight) is used.

61 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 to the description of the test method in Commission Regulation No 440/2008).

## Very toxic

62 Substances and preparations should be classified as very toxic, assigned the corresponding symbol 'T+' with the indication of danger 'very toxic' and the appropriate R-phrases in accordance with the following criteria:

### *Acute lethal effects*

**R28** *Very toxic if swallowed*
Acute toxicity results:

$LD_{50}$ oral, rat:
≤ 25 mg/kg; or

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 Commission Regulation No 440/2008).

**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/l/4 hr

$LC_{50}$ inhalation, rat, for gases and vapours:
≤ 0.5 mg/l/4 hr

### *Non-lethal irreversible effects after a single exposure*

**R39** *Danger of very serious irreversible effects*
Strong evidence that irreversible damage (other than the effects referred to in paragraphs 91–129) is likely to be caused by a single exposure by an appropriate route, generally in the above dose ranges (see also paragraphs 51–52).

To indicate the route of administration/exposure one of the following combinations of R-phrases shall be used: R39/26, R39/27, R39/28, R39/26/27, R39/26/28, R39/27/28, R39/26/27/28.

## Toxic

63 Substances and preparations should be classified as toxic, assigned the corresponding symbol 'T' with the indication of danger 'toxic' and the appropriate R-phrases in accordance with the following criteria:

### *Acute lethal effects*

**R25** *Toxic if swallowed*
Acute toxicity results:

$LD_{50}$ oral, rat:
$25 < LD_{50} \leq 200$ mg/kg; or

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 Commission Regulation No 440/2008).

**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/l/4 hr

$LC_{50}$ inhalation, rat, for gases and vapours:
$0.5 < LC_{50} \leq 2$ mg/l/4 hr

### *Non-lethal irreversible effects after a single exposure*

**R39** *Danger of very serious irreversible effects*
Strong evidence that irreversible damage (other than the effects referred to in paragraphs 91–129) is likely to be caused by a single exposure by an appropriate route, generally in the above dose ranges (see also paragraphs 51–52).

To indicate the route of administration/exposure one of the following combinations of R-phrases shall be used: R39/23, R39/24, R39/25, R39/23/24, R39/23/25, R39/24/25, R39/23/24/25.

### *Severe effects after repeated or prolonged exposure*

**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 toxic with R48 when these effects are observed at levels of the order of:

oral, rat: ≤ 5 mg/kg (body weight)/day

dermal, rat or rabbit: ≤ 10 mg/kg (body weight)/day

inhalation, rat: ≤ 0.025 mg/l 6 hr/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 three fold. 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. Further information on the use of R48 is given in paragraphs 66–70.

To indicate the route of administration/exposure one of the following combinations of R-phrases shall be used: R48/23, R48/24, R48/25, R48/23/24, R48/23/25, R48/24/25, R48/23/24/25.

## Harmful

64 Substances and preparations should be classified as harmful, assigned the corresponding symbol 'Xn' with the indication of danger 'harmful' and the appropriate R-phrases in accordance with the following criteria:

### *Acute lethal effects*

**R22** *Harmful if swallowed*
Acute toxicity results:

$LD_{50}$ oral, rat:
$200 < LD_{50} \leq 2000$ mg/kg; or

discriminating dose, oral, rat, 50 mg/kg: 100% survival but evident toxicity; or

less than 100% survival at 500 mg/kg, rat by the fixed dose procedure. Refer to the evaluation table in the test method in Commission Regulation No 440/2008; or

high mortality in the dose range > 200 to ≤ 2000 mg/kg oral, rat, by the acute toxic class method (for test result interpretation see flow charts in Commission Regulation No 440/2008).

**R21** *Harmful in contact with skin*
Acute toxicity results:

$LD_{50}$, dermal, rat or rabbit:
$400 < LD_{50} \leq 2000$ mg/kg

**R20** *Harmful by inhalation*
Acute toxicity results:

$LC_{50}$ inhalation, rat, for aerosols or particulates:
$1 < LC_{50} \leq 5$ mg/l/4 hr

$LC_{50}$ inhalation, rat, for gases and vapours:
$2 < LC_{50} \leq 20$ mg/l/4 hr

### *Aspiration hazard*

**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:

(i) a flow time of less than 30 seconds in a 3 mm ISO cup according to BS EN ISO 2431 relating to *Paints and varnishes. Determination of flow time by use of flow cups*,[14] or
(ii) a kinematic viscosity measured by a calibrated glass capillary viscometer in accordance with ISO 3104/3105 of less than $7 \times 10^{-6}$ $m^2/s$ at 40 °C (ISO 3104, relating to *Petroleum products. Transparent and opaque liquids. Determination of kinematic viscosity and calculation of dynamic viscosity*;[15] ISO 3105, relating to glass capillary kinematic viscometers – *Specifications and operating instructions*),[16] or
(iii) a kinematic viscosity derived from measurements of rotational viscometry in accordance with ISO 3219[17] of less than $7 \times 10^{-6}$ $m^2/s$ at 40 °C; or

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 Commission Regulation No 440/2008.

(b) for substances and preparations based on practical experience in humans.

### *Non-lethal irreversible effects after a single exposure*

**R68** *Possible risk of irreversible effects*
Strong evidence that irreversible damage (other than the effects referred to in paragraphs 91–129) is likely to be caused by a single exposure by an appropriate route, generally in the above dose ranges (see also paragraphs 51–52).

To indicate the route of administration/exposure one of the following combinations of R-phrases shall be used: R68/20, R68/21, R68/22, R68/20/21, R68/20/22, R68/21/22, R68/20/21/22.

### *Severe effects after repeated or prolonged exposure*

**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 with R48 when these effects are observed at levels of the order of:

oral, rat: ≤ 50 mg/kg (body weight)/day

dermal, rat or rabbit: ≤ 100 mg/kg (body weight)/day

inhalation, rat: ≤ 0.25 mg/l 6 hr/day

See also the explanation under R48 in paragraph 66. Further information on the use of R48 is given in paragraphs 66–70.

To indicate the route of administration/exposure one of the following combinations of R-phrases shall be used: R48/20, R48/21, R48/22, R48/20/21, R48/20/22, R48/21/22, R48/20/21/22.

## Comments regarding very volatile substances

65 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 or covered by paragraph 132. 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 Table 3.2, Part 3 of Annex VI to the CLP Regulation may be necessary.

## Criteria for use of R48

66 Use of this R-phrase refers to the specific range of biological effects within the terms described below. For application of this R-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.

67 When assessing whether there is evidence for these types of effects, reference should be made to the guidelines in paragraphs 68–70.

### *Evidence indicating that R48 should be applied*

68 The evidence includes:

(a) substance-related deaths;
(b) major functional changes in:

  (i) the central or peripheral nervous systems, including sight, hearing and the sense of smell, assessed by clinical observations or other appropriate methods (eg electrophysiology);
  (ii) 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 in microscopic examination following autopsy:

(i) widespread or severe necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity (eg liver);
(ii) severe morphological changes that are potentially reversible but are clear evidence of marked organ dysfunction (eg severe fatty change in the liver, severe acute tubular nephrosis in the kidney, ulcerative gastritis);
(iii) evidence of appreciable cell death in vital organs incapable of regeneration (eg fibrosis of the myocardium or dying back of a nerve) or in stem cell populations (eg aplasia or hypoplasia of the bone marrow).

69 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.

### *Evidence indicating that R48 should not be applied*

70 The use of this R-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 body weight 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) adaptive responses (eg 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';
(e) where a species-specific mechanism of toxicity (eg by specific metabolic pathways) has been demonstrated.

## Corrosive

71 A substance or preparation should be classified as corrosive, assigned the corresponding symbol 'C' with the indication of danger 'corrosive' in accordance with the following criteria:

(a) if, when 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 described in Commission Regulation No 440/2008 or during an equivalent method; or
(b) it gives a positive result in a validated *in vitro* test, such as that described in Commission Regulation No 440/2008 (Skin corrosion: rat skin transcutaneous electrical resistance assay and human skin model assay); or
(c) if corrosivity can be predicted, for example, from strongly acidic 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[18] may also be taken into consideration. If consideration of acid/alkali 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.

72 R-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.

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 on consideration of extreme pH alone, R35 should be applied.

## Irritant

73 Substances and preparations should be classified as irritant, assigned the corresponding symbol 'Xi' with the indication of danger 'irritant' and the appropriate R-phrases in accordance with the following criteria:

**R38** *Irritating to skin*
If they 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 Commission Regulation No 440/2008.

Inflammation of the skin is significant if one of the following criteria is met:

(a) the mean value of the scores for either erythema and eschar formation or oedema formation, calculated over all animals tested, is two or more; or
(b) in the case where the Commission Regulation test has been completed using three animals, either erythema and eschar formation or oedema formation equivalent to a mean value of two or more calculated for each animal separately, has been observed in two or more animals; or

(In (a) and (b) all scores at each of the reading times (24, 48, 72 hours) for an effect should be used in calculating the respective mean values.)

(c) it persists in at least two animals at the end of the observation time. Particular effects, eg hyperplasia, scaling, discoloration, fissures, scabs and alopecia should be taken into account.

Relevant data may also be available from non-acute animal studies (see comments on R48, paragraph 70(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.

Parathesia:
Parathesia 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.

**R36** *Irritating to eyes*
If when applied to the eye of the animal, significant ocular lesions occur within 72 hours after exposure and persist for at least 24 hours.

Ocular lesions are significant if they correspond to the following mean values determined on the rabbit according to the eye irritation test described in Commission Regulation No 440/2008. Either:

(a) the mean value of the scores for each type of lesion, calculated over all animals tested, is one of the following:

| | |
|---|---|
| cornea opacity | $2 \leq$ score $< 3$ |
| iris lesion | $1 \leq$ score $\leq 1.5$ |
| redness of conjunctiva | $\geq 2.5$ |
| oedema of conjunctiva | $\geq 2$; or |

(b) in the case where the Commission Regulation test has been completed using three animals, a lesion equivalent to one of the mean values quoted below, but calculated for each animal separately, has been observed in two or more animals:

| | |
|---|---|
| cornea opacity | $2 \leq$ score $< 3$ |
| iris lesion | $1 \leq$ score $\leq 2$ |
| redness of conjunctiva | $\geq 2.5$ |
| oedema of conjunctiva | $\geq 2$ |

(In (a) and (b) 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*
If when applied to the eye of the animal severe ocular lesions are caused which occur within 72 hours after exposure and which are present 24 hours or more after instillation of the test material.

Ocular lesions are severe if:

(a) the means of the scores calculated over all the animals tested have any of the values:

| | |
|---|---|
| cornea opacity | $\geq 3$ |
| iris lesion | $> 1.5$; or |

(b) the test has been completed using three animals if these lesions, on two or more animals, have any of the values:

| | |
|---|---|
| cornea opacity | $\geq 3$ |
| iris lesion | $= 2$; or |

(In (a) and (b) 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.)

(c) when they are still present at the end of the observation time; or
(d) if the substance or preparation causes irreversible coloration 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.

#### *Respiratory system irritation*

**R37** *Irritating to respiratory system*
For substances and preparations which cause serious irritation to the respiratory system, normally based on:

(a) practical observation in humans;
(b) positive results from appropriate animal tests.

### Comments regarding the use of R37

74 In interpreting practical observations in humans, care should be taken to distinguish between effects which lead to classification with R48 (see paragraphs 66–70) from those leading to classification with R37. Conditions normally leading to classification with R37 are reversible and usually limited to the upper airways.

75 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.

### Sensitising

#### *Sensitisation by inhalation*

76 Substances and preparations should be classified as sensitising and assigned the symbol 'Xn', with the indication of danger 'harmful', and the R-phrase R42 in accordance with the following criteria:

**R42** *May cause sensitisation by inhalation*

(a) If there is evidence that the substance or preparation can induce specific respiratory hypersensitivity; or;
(b) where there are positive results from appropriate animal tests; or
(c) if the substance is an isocyanate, unless there is evidence that the substance does not cause respiratory hypersensitivity.

### Comments regarding the use of R42

#### *Human evidence*

77 Evidence that the substance 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.

78 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:

(a) the size of the population exposed;
(b) 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) a chemical structure related to substances known to cause respiratory hypersensitivity;
(b) *in vivo* immunological test (eg skin prick test);
(c) *in vitro* immunological test (eg serological analysis);
(d) studies that may indicate other specific but non-immunological mechanisms of action (eg repeated low-level irritation, pharmacologically mediated effects); or
(e) data from a positive bronchial challenge test with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.

79 Clinical history should include both medical and occupational history to determine a relationship between exposure to a specific substance 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.

80 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.

81 Substances that elicit symptoms of asthma by irritation only in people with bronchial hyperreactivity should not be assigned R42.

### *Animal studies*

82 Data from tests which may be indicative of the potential of a substance to cause sensitisation by inhalation in humans may include:

(a) IgE measurements (eg in mice);
(b) specific pulmonary responses in guinea pigs.

## Sensitisation by skin contact

83 Substances and preparations should be classified as sensitising and assigned the symbol 'Xi' with the indication of danger 'irritant' and the appropriate R-phrase in accordance with the following criteria:

**R43** *May cause sensitisation by skin contact*
If practical experience shows the substances and preparations to be capable

of inducing a sensitisation reaction in a substantial number of people. Where there are positive results from an appropriate animal test.

## Comments regarding the use of R43

### *Human evidence*

84 The following evidence (practical experience) is sufficient to classify a substance with R43:

(a) positive data from appropriate patch testing, normally in more than one dermatological clinic; or
(b) epidemiological studies showing allergic contact 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
(c) positive data from experimental studies on humans (see also paragraph 50).

85 The following is sufficient to classify a substance with R43 when there is supportive evidence:

(a) isolated episodes of allergic contact dermatitis; or
(b) epidemiological studies where chance, bias or confounders have not been ruled out fully with reasonable confidence.

86 Supportive evidence may include:

(a) 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
(b) data from non-standard methods; or
(c) appropriate structure-activity relationships.

### *Animal studies*

87 Positive results from appropriate animal tests are:

(a) in the case of the adjuvant-type test method for skin sensitisation detailed in Commission Regulation No 440/2008; or in the case of other adjuvant-type test methods, a response of at least 30% of the animals; or
(b) for any other test method, a response of at least 15% of the animals.

## Immunological contact urticaria

88 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.

89 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.

90 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).

**Note:** that if the symbol 'Xn' and the indication of danger 'harmful' are assigned, the symbol 'Xi' and the indication of danger 'irritant' are optional.

# Carcinogenic, mutagenic and toxic for reproduction

91 Substances that may be carcinogenic, mutagenic or toxic for reproduction should be classified in accordance with the criteria below (see also paragraphs 29–32). Preparations that contain one or more substances classified as carcinogenic, mutagenic or toxic for reproduction should be classified using the conventional method (see paragraph 52).

## Carcinogenic substances

92 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*

93 These are substances known to be carcinogenic to humans. There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.

### *Category 2*

94 These are substances which should be regarded as if they are carcinogenic to humans. 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:

(a) appropriate long-term animal studies;
(b) other relevant information.

### *Category 3*

95 These are substances which cause concern for humans 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.

96 The following symbols and specific risk phrases apply:

### *Categories 1 and 2*

Substances classified as carcinogenic category 1 or 2 should be assigned the symbol 'T' and the R-phrase:

**R45** *May cause cancer*

97 However, for substances and preparations which present a carcinogenic risk only when inhaled, for example, as dust, vapour or fumes (other routes of exposure such as swallowing or contact with skin do not present any carcinogenic risk) should be assigned the symbol 'T' and the R-phrase:

**R49** *May cause cancer by inhalation*

### *Category 3*

Substances classified as carcinogenic category 3 should be assigned the symbol 'Xn' and the R-phrase:

**R40** *Limited evidence of a carcinogenic effect*

## Criteria for the categorisation of carcinogenic substances

98 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.

99 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.

100 Category 3 actually comprises two sub-categories:

(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 data are inadequate, but raise concern for humans. This classification is provisional; further experiments are necessary before a final decision can be made.

101 Relevant arguments to distinguish between Categories 2 and 3 are listed below. Their effect is to reduce the significance of experimental tumour induction for possible human exposure as, especially in combination, they lead in most cases to classification in Category 3, even though tumours have been induced in animals:

(a) 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 life span, are associated with physical changes such as about 10% retardation in weight gain;
(b) 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;
(c) appearance of tumours only at the site of application, in very sensitive test systems (eg, i.p. or s.c. application of certain locally active compounds), if the particular target is not relevant to humans;
(d) lack of genotoxicity in short-term tests *in vivo* and *in vitro*;
(e) existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (eg hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation);
(f) existence of a species-specific mechanism of tumour formation (eg by specific metabolic pathways) irrelevant for humans.

102 Relevant arguments to distinguish between Category 3 and no classification are those which exclude a concern for humans:

(a) 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 humans;
(b) 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;
(c) 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.

## Mutagenic substances

103 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*

104 These are substances known to be mutagenic to humans. There is sufficient evidence to establish a causal association between human exposure to a substance and heritable genetic damage.

### *Category 2*

105 These are substances which should be regarded as if they are mutagenic to humans. 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:

(a) appropriate animal studies;
(b) other relevant information.

### *Category 3*

106 These are substances which cause concern for humans owing to possible mutagenic effects. There is evidence from appropriate mutagenicity studies, but this is insufficient to place the substance in Category 2.

107 The following symbols and specific R-phrases apply:

### *Categories 1 and 2*

Substances classified as mutagenic category 1 or 2 should be assigned the symbol 'T' and the R-phrase:

**R46** *May cause heritable genetic damage*

### *Category 3*

Substances classified as mutagenic category 3 should be assigned the symbol 'Xn' and the R-phrase:

**R68** *Possible risk of irreversible effects*

## Criteria for the categorisation of mutagenic substances

### *Definition of terms*

108 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.

109 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.

110 Method development for mutagenicity testing is an ongoing process. For many new tests no standardised protocols and evaluation criteria are presently available. To evaluate the mutagenicity data, the quality of the test performance and the degree of validation of the test method have to be considered.

### *Category 1*

111 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*

112 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. At present the following methods (2a, 2b and 2c) are appropriate:

(2a) *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.

(2b) *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 humans (see under Category 3, preferably methods as under 3a).

(2c) *In vivo* assays showing mutagenic effects in somatic cells of mammals (see under 3a), in combination with toxicokinetic methods, or other methodologies capable of demonstrating that the compound or a relevant metabolite reaches the germ cells.

For 2b and 2c, positive results from host-mediated assays or the demonstration of unequivocal effects *in vitro* assays can be considered as supporting evidence.

### *Category 3*

113 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:

(3a) *In vivo* somatic cell mutagenicity assays:

- bone marrow micronucleus test or metaphase analysis;
- metaphase analysis of peripheral lymphocytes;
- mouse coat colour spot test.

(3b) *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, eg by alkaline elution, in somatic cells.

114 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, eg 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.

## Substances toxic for reproduction

115 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*

(a) 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.
(b) 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*

(a) 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:

(i) 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;
(ii) other relevant information.

(b) 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:

(i) 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;
(ii) other relevant information.

***Category 3***

(a) Substances which cause concern for human fertility, generally on the basis of:

(i) 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 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, but where the evidence is insufficient to place the substance in Category 2;
(ii) other relevant information.

(b) Substances which cause concern for humans owing to possible developmental toxic effects, generally on the basis of:

(i) 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;
(ii) other relevant information.

116 The following symbols and specific R-phrases apply:

***Category 1***

For substances that impair fertility in humans:

Substances classified as toxic for reproduction category 1 should be assigned the symbol ‘T’ and the R-phrase:

**R60** *May impair fertility*

For substances that cause developmental toxicity:

Substances classified as toxic for reproduction category 1 should be assigned the symbol ‘T’ and the R-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 for reproduction category 2 should be assigned the symbol 'T' and the R-phrase:

**R60** *May impair fertility*

For substances that should be regarded as if they cause developmental toxicity in humans:

Substances classified as toxic for reproduction category 2 should be assigned the symbol 'T' and the R-phrase:

**R61** *May cause harm to the unborn child*

### *Category 3*

For substances which cause concern for human fertility:

Substances classified as toxic for reproduction category 3 should be assigned the symbol 'Xn' and the R-phrase:

**R62** *Possible risk of impaired fertility*

For substances which cause concern for humans owing to possible developmental toxic effects:

Substances classified as toxic for reproduction category 3 should be assigned the symbol 'Xn' and the R-phrase:

**R63** *Possible risk of harm to the unborn child*

## Comments regarding the categorisation of substances toxic for reproduction

117 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 (a) Effects on male or female fertility and (b) Developmental toxicity.

(a) 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.

(b) 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.

118 Classification of chemicals as 'toxic for 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 for 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 for reproduction at exposure levels which do not produce other signs of toxicity.

119 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 into 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.

120 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.

121 European Commission Regulation No 440/2008 specifies a limit test in the case of substances of low toxicity. If a dose level of at least 1000 mg/kg orally produces no evidence of effects toxic for 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, these 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 for reproduction.

## Effects on fertility

122 For the classification of a substance into 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.

123 Since impaired fertility may occur as a non-specific accompaniment to severe generalised toxicity or where there is severe inanition, classification into 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 into Category 2, it would normally be necessary to have evidence on the mechanism of action to interpret whether any adverse effect such as alteration in pattern of hormonal release would be likely to occur in humans.

## Developmental toxicity

124 For classification into 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.

125 Classification into 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.

126 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

127 Substances which are classified as toxic for reproduction and which also cause concern due to their effects on lactation should in addition be labelled with R64 (see criteria in paragraph 132). 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 for reproduction', unless such effects result in impaired development of the offspring. Substances which are not classified as toxic for reproduction but which cause concern due to toxicity when transferred to the baby during the period of lactation should be labelled with R64. This R-phrase may also be appropriate for substances which affect the quantity or quality of the milk.

128 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 lactation period.

129 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.

## Harmonised classification and labelling of carcinogens, mutagens and substances toxic for reproduction

130 Regulation 4(4)(c) of CHIP 4 requires that a manufacturer, distributor or importer who has information available indicating that a substance should be classified and labelled in accordance with the criteria in paragraphs 91–129 should classify and label the substance accordingly, on the basis of the assessment of the evidence by a competent person. This classification and label remains valid until an agreed entry is included in Part 3 of Annex VI to the CLP Regulation. Furthermore, regulation 4(6) requires the manufacturer, distributor or importer to send to the Health and Safety Executive a document summarising the information on which the classification and label was based, unless such information has already been submitted to an authority nominated for that purpose in another member state in which the substance has been supplied. The summary document should include a

bibliography containing all relevant references, including any relevant unpublished data.

131 The Health and Safety Executive will forward to the European Commission or the European Chemicals Agency the summary documents received. In practice, manufacturers, distributors or importers who have new information on the classification of substances as carcinogenic, mutagenic and toxic to reproduction, or on other key hazardous properties, are encouraged to contact the UK REACH Competent Authority Helpdesk at ukreachca@hse.gsi.gov.uk and seek advice on how to proceed.

## Other health effects

132 Additional R-phrases should be assigned to substances and preparations classified by virtue of paragraphs 39–46, 62–126 and 138–147.

**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, eg 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, eg 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, eg 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.

**R64** *May cause harm to breast-fed 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 breast-fed child.

For comments on the use of this R-phrase (and in some cases R33) see paragraphs 128–129 and Schedule 4 to CHIP 4.

**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:

(a) practical observation after normal handling and use; or
(b) relevant evidence concerning their predicted effects on the skin.

See also paragraphs 21, 24 and 25.

**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, R40/20, R39/23 or R39/26).

The following evidence may be used:

(a) data from animal studies showing clear signs of central nervous system (CNS) depression such as narcotic effects, lethargy, lack of co-ordination (including loss of righting reflex) and ataxia either:

(i) at concentrations/exposure times not exceeding 20 mg/l/4 hour; or
(ii) for which the ratio of the effect concentration at ≤ 4 hour to the saturated vapour concentration (SVC) at 20 °C is ≤ 1/10; or

(b) practical experience in humans (eg narcosis, drowsiness, reduced alertness, loss of reflexes, lack of co-ordination, vertigo) from well-documented reports under comparable exposure conditions to the effects specified above for animals.

See also paragraphs 21, 24 and 25 and regulation 7 and Schedule 4 to CHIP 4.

133 For other additional R-phrases see paragraph 47.

# Classification on the basis of environmental effects

## Criteria for classification, indication of danger and choice of risk phrases

134 The primary objective of classifying substances and preparations as dangerous for the environment is to alert the user to the hazards these substances and preparations present to ecosystems. Although the present criteria refer largely 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.

135 The criteria set out in paragraphs 138–147 follow directly from the test methods set out in Commission Regulation No 440/2008 in so far as they are mentioned. The information derived from these test methods may be insufficient for an appropriate classification. Classification may require additional data derived from Annexes VI to X of the REACH Regulation or other equivalent studies. Furthermore, classified substances may be subject to review in the light of other new data.

136 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.

137 The classification of substances is usually made on the basis of experimental data for acute aquatic toxicity, degradation, and log $P_{ow}$ (or BCF (biological

concentration factor) if available). The classification of preparations should normally be done on the basis of the conventional method referred to in Schedule 3 to CHIP 4. 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 may only modify the classification for acute aquatic toxicity which would have been obtained by application of the conventional method. If such tests are chosen by the person responsible for placing on the market, it must be ensured that the quality criteria of Commission Regulation No 440/2008 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 Approved Classification and Labelling Guide (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.

## Aquatic environment

138 The following classification criteria only apply to preparations where they have been tested in accordance with paragraph 137.

139 Substances should be classified as dangerous for the environment, assigned the corresponding symbol 'N' with the indication of danger 'dangerous for the environment' and the appropriate R-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 hr $LC_{50}$ (for fish):
≤ 1 mg/l; or

48 hr $EC_{50}$ (for daphnia):
≤ 1 mg/l; or

72 hr $IC_{50}$ (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 hr $LC_{50}$ (for fish):
≤ 1 mg/l; or

48 hr $EC_{50}$ (for daphnia):
≤ 1 mg/l; or

72 hr $IC_{50}$ (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 hr $LC_{50}$ (for fish):
1 mg/l < $LC_{50}$ ≤ 10 mg/l; or

48 hr $EC_{50}$ (for daphnia):
1 mg/l < $EC_{50}$ ≤ 10 mg/l; or

72 hr $IC_{50}$ (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)

Substances should be classified as dangerous for the environment and assigned the appropriate R-phrases 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 hr $LC_{50}$ (for fish):
10 mg/l < $LC_{50}$ ≤ 100mg/l; or

48 hr $EC_{50}$ (for daphnia):
10 mg/l < $EC_{50}$ ≤ 100mg/l; or

72 hr $IC_{50}$ (for algae):
10 mg/l < $IC_{50}$ ≤ 100mg/l
and

the substance is not readily degradable.

140 This criterion applies unless there is sufficient additional scientific evidence concerning degradation and/or toxicity sufficient to provide 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 in Annexes VI to X of the REACH Regulation or studies of equivalent value, and could include:

(a) a proven potential to degrade rapidly in the aquatic environment;
(b) an absence of chronic toxicity effects at 1 mg/l, or at the solubility limit if less, eg where the no-observed effect concentration determined in a prolonged toxicity study with fish or daphnia is greater than the solubility limit.

141 Substances not falling under the criteria in paragraphs 139 and 140 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 should be assigned:

**R52** *Harmful to aquatic organisms*

142 Substances not falling under the criteria listed in paragraphs 139 and 140, 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 should be assigned:

**R53** *May cause long-term adverse effects in the aquatic environment*

For example, poorly water soluble substances, ie substances with a solubility of less than 1 mg/l will be covered by these criteria if:

(a) they are not readily degradable; and
(b) the log $P_{ow} \geq 3.0$ (unless the experimentally determined BCF ≤ 100).

143 The criteria in (a) and (b) above apply unless there is sufficient additional scientific evidence concerning degradation and/or toxicity sufficient to provide 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 or studies of equivalent value, and could include:

(a) a proven potential to degrade rapidly in the aquatic environment;
(b) an absence of chronic toxicity effects at the solubility limit, eg where the no-observed effect concentration determined in a prolonged toxicity study with fish or daphnia is greater than the solubility limit.

## Comments on the determination of $IC_{50}$ for algae and of degradability

144 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 72 hr $IC_{50}$ for algae should not be used as a basis for classification.

145 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:

    (i) in tests based upon dissolved organic carbon: 70%;
    (ii) in tests based upon oxygen depletion or carbon dioxide generation: 600 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 or $BOD_5$ data are available when the ratio of $BOD_5$/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.

### Non-aquatic environment

146 Substances should be classified as dangerous for the environment, assigned the corresponding symbol 'N' with the indication of danger 'dangerous for the environment' and assigned R-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 which on the basis of the available evidence concerning their properties, 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 in paragraphs 139–145. Detailed criteria will be elaborated later.

147 Substances should be classified as dangerous for the environment, assigned the corresponding symbol 'N' with the indication of danger 'dangerous for the environment' and assigned an R-phrase 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 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[19] and its subsequent amendments.

Preparations shall be classified on the basis of the conventional method set out in Schedule 3 to CHIP 4.

# Labelling

148 When a substance or preparation has been classified, the appropriate label is determined with reference to the requirements of regulations 7(2) and (3) of CHIP for substances and preparations respectively. This section explains how the label is determined and, in particular, gives guidance on how to select the appropriate risk and safety phrases.

149 For substances and preparations the risk phrases (R-phrases) form part of the classification assigned in accordance with the criteria in paragraphs 35–48 for physicochemical effects, paragraphs 49–133 for health effects and paragraphs 134–147 for environmental effects. The prescribed safety phrases (S-phrases) for substances and preparations are listed in Appendix 1, together with the conditions that determine their application and use.

150 The label should contain the following information:

(a) for preparations, the trade name or other designation;
(b) for substances, the name of the substance and for preparations, the names of

the substances present in the preparation in accordance with regulation 7(3) and Part I of Schedule 4 to CHIP 4;
(c) the name, address and telephone number of the person responsible for placing the substance or preparation on the market;
(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 Table 3.2, Part 3 of Annex VI to the CLP Regulation, the words 'EC label';
(h) for preparations intended for sale to the general public, the nominal quantity of the contents.

**Note:** For certain preparations there are additional labelling requirements which are set out in Part II of Schedule 4 to CHIP 4.

## Choice of danger symbols

151 The design of the danger symbols and the wording of the indications of danger should comply with those laid down in Schedule 2 to CHIP 4. The symbol should be printed in black on an orange–yellow background.

152 For substances appearing in Table 3.2, Part 3 of Annex VI to the CLP Regulation the danger symbols and indications of danger should be those shown in the list.

153 For dangerous substances not yet appearing in the Table 3.2, Part 3 of Annex VI and for preparations, the danger symbols and indications of danger shall be assigned according to the rules laid down in Part I of Schedule 4 to CHIP 4.

## Risk phrases

154 The wording of the R-phrases should comply with that laid down in Part V. The combined R-phrases should be used where applicable.

155 For **substances**, the R-phrases that appear on the label should be selected according to the following criteria and priorities:

(a) in the case of health effects:

  (i) the R-phrases corresponding to the category of danger illustrated by a symbol. These phrases must appear on the label;
  (ii) the R-phrases corresponding to other categories of danger not illustrated by a symbol;

(b) in the case of dangers arising from physicochemical properties the criteria described under (a) above are applicable, except that the R-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 the R-phrases corresponding to the classification category 'dangerous for the environment' (these phrases must appear on the label).

156 For **preparations**, the R-phrases that appear on the label should be selected according to the following criteria and priorities:

(a) in the case of dangers which give rise to health effects:

(i) the R-phrases which correspond to the category of danger illustrated by a symbol. In certain cases the R-phrases should be adapted according to the tables in Part II of Schedule 3 to CHIP. 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) the R-phrases which correspond to the other categories of danger that have been attributed to the constituents but which are not illustrated by a symbol;

(b) in the case of dangers arising from physicochemical properties the criteria described under (a) are applicable, except that the R-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 the R-phrases corresponding to the classification category 'dangerous for the environment' must appear on the label.

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 R53 alone, the combined R-phrase R50/53 shall be used.

157 As a general rule applying to preparations, a maximum of six R-phrases should suffice to describe the dangers (although in some cases the obligation to use certain R-phrases may result in more than six R-phrases being used). For this purpose the combined phrases listed in Part V should be regarded as single phrases. The R-phrases should cover all the principal hazards associated with the preparation. In some cases more than six R-phrases may be necessary.

## Safety phrases

158 The wording of safety phrases should comply with that laid down in Part V. The combined S-phrases should be used where applicable.

159 For substances appearing in Table 3.2, Part 3 of Annex VI the S-phrases should be those shown in Table 3.2. Where no S-phrases are shown the supplier may include any appropriate S-phrase. For substances not appearing in Table 3.2 and for preparations, the supplier shall include S-phrases in accordance with the criteria given in Appendix 1 to this Approved Classification and Labelling Guide.

160 The final choice of S-phrases should have regard to the R-phrases indicated on the label and to the intended use of the substance or preparation:

(a) As a general rule, a maximum of six S-phrases shall suffice to formulate the most appropriate safety advice (although in some cases the obligation to use certain S-phrases will result in more than six S-phrases being used). For this purpose the combined phrases listed in Table 3.2, Part 3 of Annex VI shall be regarded as single phrases.
(b) 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.
(c) 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 should appear on the label only if it is intended to emphasise a specific warning.
(d) Particular attention should be given, in the choice of S-phrases, to the foreseen conditions of use of certain substances and preparations,

eg spraying or other aerosol effects. Phrases should be chosen with the intended use in view.

(e) The S-phrases S1, S2 and S45 are obligatory for all very toxic, toxic and corrosive substances and preparations sold to the general public.

(f) The S-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 Appendix 1 result in redundancy or ambiguity or are clearly unnecessary given the specific product/ package then some phrases may be deleted.

## Final choice of R- and S-phrases

161 Although the final choice of the most appropriate R- and S-phrases is primarily governed by the need to give all necessary information, consideration should also be given to the clarity and impact of the label. With clarity in mind, the necessary information should be expressed in a minimum number of phrases. Where it is physically impossible to include the advice on the safety label or package itself, the package shall be accompanied by safety advice on the use of the preparation.

**Note:** Regulation 7(7), (8) and (9) of CHIP 4 allows some derogations for certain substances and preparations which are supplied in quantities of 125 ml or less.

## Other information to be provided on the label

162 For substances, the information is completed by the name of the substance, 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.

163 For substances listed in Table 3.2, Part 3 of Annex VI to the CLP Regulation, the name on the label should be one of those given in the list for that substance. For substances not shown in Table 3.2, the name should be the one used in the European Inventory of Existing Commercial Substances (EINECS), or the European List of Notified Chemical Substances (ELINCS),[20] or, if it is not so listed, an internationally recognised name.

164 For preparations, the information is completed by the designation or the trade name of the preparation, the chemical names of the substances present in the preparation (paragraph 2 in Part I of Schedule 4 to CHIP 4) and the name, address and telephone number of the person established in the Community who is responsible for placing the preparation on the market.

**Note:** In the case of concentrate preparations which are intended for the perfume industry and which may be sensitisers:

(a) 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;

(b) 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.

165 Certain preparations attract additional labelling requirements as set out in regulation 10 and Part II of Schedule 4 to CHIP 4.

# Special cases

## Mobile gas cylinders

166 For mobile gas cylinders the requirements concerning labelling are considered to be satisfied when they are in agreement with regulations 7 and 10 of CHIP 4, including the arrangements for combined carriage and supply labelling. However, by way of derogation from regulations 10(2), (4) and (5) of CHIP 4, one of the following alternatives can be used for gas cylinders with a water capacity of less than or equal to 150 l:

(a) The format and dimensions of the label can follow the prescriptions of the ISO Standard ISO/DP 7225 relating to *Gas cylinders. Precautionary labels*, in which case, for preparations, the label can bear the generic name or industrial (commercial) name of the preparation provided the dangerous component substances of the preparation are shown on the body of the gas cylinder in a clear and indelible way.

Or

(b) The information specified in regulation 7(2) or (3) of CHIP 4 may be provided on a durable information disc or label held captive on the cylinder.

## Gas containers intended for propane, butane or liquefied petroleum gas (LPG) or for preparations containing stenched propane, butane or LPG

167 Propane, butane and liquefied petroleum gas are classified in Table 3.2, Part 3 of Annex VI. Although these substances (and preparations containing these substances) are classified as hazardous in accordance with regulation 4 of CHIP 4, 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[21] as fuel gases which are only released for combustion.

168 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 by way of a safety data sheet. For the consumer, sufficient information shall be provided to enable them to take all necessary measures for health and safety as described in Article 31 of European Regulation (EC) No 1907/2006 – on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

## Substances and preparations classified with R65

169 Substances and 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.

## Metals in massive form

170 If not already classified in Table 3.2, Part 3 of Annex VI to the CLP Regulation, these substances should be classified in accordance with regulation 4(4) and (5) of CHIP 4. Some of these substances, however, although correctly classified, 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 supplied. Such substances do not require a label under regulation 7 of CHIP 4. However, all the information which should have appeared on the label should be transmitted by the supplier to the user. In general this information will be in the form of a safety data sheet.

## Gaseous preparations (gas mixtures)

171 For gaseous preparations, consideration should be given to the evaluation of:

(a) physicochemical properties;
(b) health hazards;
(c) environmental hazards.

### *Evaluation of physicochemical properties*

#### *Flammability*

172 The flammable properties of these preparations should be determined in accordance with paragraph 3 in Part I of Schedule 3 to CHIP 4. Gaseous preparations should be classified according to the results of the relevant tests in Commission Regulation No 440/2008 and the criteria in this Approved Guide. By way of derogation, however, where these preparations are produced to order in small quantities, the flammability of these gaseous mixtures can be evaluated by the following calculation method.

173 A gaseous mixture may be represented as:

$$A_1F_1 + \ldots + A_iF_i + \ldots + A_nF_n + B_1I_1 + \ldots + B_iI_i + \ldots + B_pI_p$$

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

174 This can also be expressed in a form where all the $I_i$ (inert gases) are replaced by a nitrogen equivalent using a coefficient of equivalency, $K_i$. The equivalent concentration of a flammable gas $A'_i$ is then expressed as follows:

$$A'_i = A_i \times \left(\frac{100}{A_i + K_iB_i}\right)$$

175 The maximum concentration of flammable gases ($T_{ci}$) which, when mixed with nitrogen, gives a concentration that is not flammable in air can be expressed as:

$$\sum_i \frac{A'_i}{T_{ci}} \leq 1$$

If the value of the above expression is greater than one, the gas mixture is flammable and the preparation should be classified as extremely flammable and the R-phrase R12 should be assigned.

176 The values of the coefficients of equivalency ($K_i$) between the inert gases and nitrogen and the values of the maximum content of flammable gas ($T_{ci}$) may be found in Tables 1 and 2 of ISO Standard ISO/DIS 10156. When a $T_{ci}$ value for a flammable gas does not appear in this standard, the corresponding lower explosivity limit (LEL) should be used. If no LEL value exists, the value of $T_{ci}$ should be set at 1% by volume.

177 The expression in paragraph 176 can be used to derive appropriate labelling of gaseous preparations. It should be noted, however, that the expression:

(a) should not be regarded as a substitute for the determination of technical safety parameters by experimental methods;
(b) does not take into account the effects of oxidising gases on the mixture and therefore should not be used to check whether such a gas mixture can be prepared safely;
(c) will not give reliable results if the individual gases interfere with each other to affect the flammability of the mixture. An example of such interference is the effect of adding a halogenated hydrocarbon to a flammable gas.

*Oxidising properties*

178 As Commission Regulation No 440/2008 does not contain a method to determine the oxidising properties of gaseous mixtures, these properties should be estimated by comparing the oxidising potential of gases in a mixture with that of oxygen in air. A gas mixture is considered to be equally or more oxidising than air if:

$$\sum_i x_i C_i \leq 21$$

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 should be assigned.

179 The coefficients of oxygen equivalency are listed in ISO Standard ISO/DIS 10156. They are:

| | |
|---|---|
| $O_2$ | 1 |
| $N_2O$ | 0.6 |

When no value for the $C_i$ coefficient is given in this standard a value of 40 should be assigned.

## *Evaluation of the health effects*

180 The evaluation of the dangers of a preparation for health should be made according to Schedule 3 to CHIP 4. Where evaluation of the health hazards is made according to the conventional method the appropriate individual concentration limits are expressed in per cent by volume and appear either in Table 3.2, Part 3 of Annex VI to the CLP Regulation for the gas(es) considered, or in Part II of Schedule 3 to CHIP 4 when the gas(es) considered are not in Table 3.2, or appear there without concentration limits.

## Alloys, preparations containing polymers, preparations containing elastomers

181 These preparations should be classified and labelled according to the requirements of CHIP 4. Some of these preparations, however, although properly classified under Schedule 3 to CHIP 4 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 supplied. Such preparations do not require a label under regulation 7 or 9 of CHIP 4. However all the information which would have appeared on the label should be transmitted to the user by means of the supplier's safety data sheet.

## Organic peroxides

182 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 Commission Regulation No 440/2008 cannot be applied to organic peroxides. The following calculation method based on the presence of active oxygen must be used.

183 The available oxygen content (%) of an organic peroxide preparation is given by the formula:

$$16 \times \sum_i \left( n_i \times \frac{c_i}{m_i} \right)$$

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

# Appendix 1 Safety phrases for substances and preparations

Safety phrases should be assigned to dangerous substances and preparations in accordance with the general criteria below. In addition, for certain preparations safety advice is given in regulation 10 and Part II of Schedule 4 to CHIP 4. References to the manufacturer include any supplier.

| | | ***Applicability:*** | ***Criteria for use:*** |
|---|---|---|---|
| S1 | *Keep locked up* | - Very toxic, toxic and corrosive substances and preparations. | - *Obligatory* for those substances and preparations mentioned above if sold to the general public. |
| S2 | *Keep out of the reach of children* | - All dangerous substances and preparations. | - *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* | - Organic peroxides.<br>- Other dangerous substances and preparations having a boiling point ≤ 40 °C. | - *Obligatory* for organic peroxides unless S47 is used.<br>- Recommended for other dangerous substances and preparations having a boiling point ≤ 40 °C. |
| S4 | *Keep away from living quarters* | - Very toxic and toxic substances and preparations. | - 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) | - Spontaneously flammable solid substances and preparations. | - Normally limited to special cases, eg sodium, potassium or white phosphorous. |
| S6 | *Keep under ...* (inert gas to be specified by the manufacturer) | - Dangerous substances and preparations which must be kept under an inert atmosphere. | - Normally limited to special cases, eg certain organo-metallic compounds. |

| | | ***Applicability:*** | ***Criteria for use:*** |
|---|---|---|---|
| S7 | *Keep container tightly closed* | - Organic peroxides.<br>- Substances and preparations which can give off very toxic, toxic, harmful or extremely flammable gases.<br>- Substances and preparations which on contact with moisture give off extremely flammable gases.<br>- Highly flammable solids. | - *Obligatory* for organic peroxides.<br>- Recommended for other fields of application mentioned above. |
| S8 | *Keep container dry* | - Substances and preparations which may react violently with water.<br>- Substances and preparations which on contact with water liberate extremely flammable gases.<br>- Substances and preparations which on contact with water liberate very toxic or toxic gases. | - 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* | - Volatile substances and preparations which may give off very toxic, toxic or harmful vapours.<br>- Extremely flammable or highly flammable liquids and extremely flammable gases. | - Recommended for volatile substances and preparations which may give off very toxic, toxic or harmful vapours.<br>- Recommended for extremely flammable or highly flammable liquids or extremely flammable gases. |
| S12 | *Do not keep the container sealed* | - Substances and preparations which will be giving off gases or vapours liable to burst the container. | - Normally limited to special cases mentioned above. |
| S13 | *Keep away from food, drink and animal feedingstuffs* | - Very toxic, toxic and harmful substances and preparations. | - 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) | - Organic peroxides. | - *Obligatory* for and normally limited to organic peroxides. However, may be useful in exceptional cases when incompatibility is likely to produce a particular risk. |
| S15 | *Keep away from heat* | - Substances and preparations which may decompose or which may react spontaneously under the effect of heat. | - Normally limited to special cases, eg monomers, but not assigned if R-phrases R2, R3 and/or R5 have already been applied. |

| | | | |
|---|---|---|---|
| S16 | *Keep away from sources of ignition – No smoking* | - Extremely flammable or highly flammable liquids and extremely flammable gases. | - Recommended for the substances and preparations mentioned above but not assigned if R-phrases R2, R3 and/or R5 have already been applied. |
| S17 | *Keep away from combustible material* | - Substances and preparations which may form explosive or spontaneously flammable mixtures with combustible material. | - Available for use in special cases (eg to emphasise R8 and R9). |
| S18 | *Handle and open container with care* | - Substances and preparations liable to produce an overpressure in the container.<br>- Substances and preparations which may form explosive peroxides. | - Normally limited to the above-mentioned 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* | - Very toxic, toxic and corrosive substances and preparations. | - Normally limited to special cases (eg 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* | - Substances and preparations which produce toxic products on combustion. | - Normally limited to special cases (eg halogenated compounds). |
| S22 | *Do not breathe dust* | - All solid substances and preparations dangerous to health. | - *Obligatory* for those substances and preparations mentioned above to which R42 is assigned.<br>- 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) | - All liquid or gaseous substances and preparations dangerous to health. | - *Obligatory* for those substances and preparations mentioned above to which R42 is assigned.<br>- *Obligatory* for substances and preparations intended for use by spraying. Either S38 or S51 must be ascribed in addition.<br>- Recommended when it is necessary to draw the attention of the user to inhalation risks not mentioned in the R-phrases which have to be ascribed. |

| | | ***Applicability:*** | ***Criteria for use:*** |
|---|---|---|---|
| S24 | *Avoid contact with skin* | - All substances and preparations dangerous to health. | - *Obligatory* for those substances and preparations to which R43 has been ascribed unless S36 has also been ascribed.<br>- Recommended when it is necessary to draw the attention of the user to skin contact risks not mentioned in the R-phrases (eg parathesia) which have to be ascribed. However, may be used to emphasise such R-phrases. |
| S25 | *Avoid contact with eyes* | - All substances and preparations dangerous to health. | - Recommended when it is necessary to draw the attention of the user to eye contact risks not mentioned in the R-phrases which have to be applied. However, may be used to emphasise such risks.<br>- 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* | - Corrosive or irritant substances and preparations. | - *Obligatory* for corrosive substances and preparations and those to which R41 has already been ascribed.<br>- Recommended for irritant substances to which the R-phrase R36 has already been ascribed. |
| S27 | *Take off immediately all contaminated clothing* | - Very toxic, toxic or corrosive substances and preparations. | - *Obligatory* for very toxic substances and preparations to which R27 has been ascribed and which are likely to be used by the general public.<br>- Recommended for very toxic substances and preparations to which R27 has been ascribed used in industry. However, this S-phrase should not be used if S36 has been ascribed.<br>- 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) | - Very toxic, toxic or corrosive substances and preparations. | - *Obligatory* for very toxic substances and preparations.<br>- Recommended for the other substances and preparations mentioned above, in particular when water is not the most appropriate rinsing fluid.<br>- Recommended for corrosive substances and preparations which are likely to be used by the general public. |

| | | | |
|---|---|---|---|
| S29 | *Do not empty into drains* | - Extremely or highly flammable liquids immiscible with water.<br>- Very toxic and toxic substances and preparations.<br>- Substances dangerous for the environment. | - *Obligatory* for substances 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.<br>- 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* | - Substances and preparations which react violently with water. | - Normally limited to special cases (eg 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* | - Extremely or highly flammable substances and preparations. | - 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* | - All dangerous substances and preparations. | - Recommended for substances and preparations where special guidance is needed to ensure proper disposal. |
| S36 | Wear suitable protective clothing | - Organic peroxides.<br>- Very toxic, toxic or harmful substances and preparations.<br>- Corrosive substances and preparations. | - *Obligatory* for very toxic and corrosive substances and preparations<br>- *Obligatory* for those substances and preparations to which either R21 or R24 has been ascribed.<br>- *Obligatory* for Category 3 carcinogens, mutagens and substances toxic for reproduction unless the effects are produced solely by inhalation of the substance or preparation.<br>- *Obligatory* for organic peroxides.<br>- 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.<br>- Recommended for substances and preparations used in industry which are liable to damage health by prolonged exposure. |

| | | ***Applicability:*** | ***Criteria for use:*** |
|---|---|---|---|
| S37 | *Wear suitable gloves* | - Very toxic, toxic, harmful or corrosive substances and preparations.<br>- Organic peroxides.<br>- Substances and preparations irritating to the skin or causing sensitisation by skin contact. | - *Obligatory* for very toxic and corrosive substances and preparations.<br>- *Obligatory* for those substances and preparations to which either R21, R24 or R43 has been ascribed.<br>- *Obligatory* for Category carcinogens, mutagens and substances toxic for reproduction unless the effects are produced solely by inhalation of the substances and preparations.<br>- *Obligatory* for organic peroxides.<br>- 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.<br>- Recommended for substances and preparations irritating to the skin. |
| S38 | *In case of insufficient ventilation wear suitable respiratory equipment* | - Very toxic or toxic substances and preparations. | - Normally limited to special cases involving the use of very toxic or toxic substances and preparations in industry or in general agriculture. |
| S39 | *Wear eye/face protection* | - Organic peroxides.<br>- Corrosive substances and preparations, including irritants which give rise to risk of serious damage to the eyes.<br>- Very toxic and toxic substances and preparations. | - *Obligatory* for those substances and preparations to which R34, R35 or R41 have been ascribed.<br>- *Obligatory* for organic peroxides.<br>- Recommended when it is necessary to draw the attention of the user to eye contact risks not mentioned in the R-phrases which have to be ascribed.<br>- 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) | - All dangerous substances and preparations. | - Normally limited to those dangerous substances and preparations for which water is not considered to be a suitable cleansing agent (eg 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. |

| | | ***Applicability:*** | ***Criteria for use:*** |
|---|---|---|---|
| S41 | *In case of fire and/or explosion do not breathe fumes* | - Dangerous substances and preparations which on combustion give off very toxic or toxic gases. | - Normally limited to special cases. |
| S42 | *During fumigation/ spraying wear suitable respiratory equipment* (appropriate wording to be specified by the manufacturer) | - Substances and preparations intended for such use but which may endanger the health and safety of the user unless proper precautions are taken. | - 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*) | - Extremely flammable, highly flammable and flammable substances and preparations. | - *Obligatory* for substances and preparations which in contact with water or damp air, evolve extremely flammable gases.<br>- 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) | - Very toxic substances and preparations.<br>- Toxic and corrosive substances and preparations.<br>- Substances and preparations causing sensitisation by inhalation | - *Obligatory* for the substances and preparations mentioned above. |
| S46 | *If swallowed, seek medical advice immediately and show this container or label* | - All dangerous substances and preparations other than those which are very toxic, toxic, corrosive or dangerous to the environment. | - *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) | - Substances and preparations which become unstable at a certain temperature. | - Normally limited to special cases (eg certain organic peroxides). |
| S48 | *Keep wetted with ...* (appropriate material to be specified by the manufacturer) | - Substances and preparations which may become very sensitive to sparks, friction or impact if allowed to dry out. | - Normally limited to special cases, eg nitrocelluloses. |

| | | ***Applicability:*** | ***Criteria for use:*** |
|---|---|---|---|
| S49 | *Keep only in the original container* | - Substances and preparations sensitive to catalytic decomposition. | - Substances and preparations sensitive to catalytic decomposition, eg certain organic peroxides. |
| S50 | *Do not mix with ...* (to be specified by the manufacturer) | - Substances and preparations which may react with the specified product to evolve very toxic or toxic gases.<br>- Organic peroxides. | - Recommended for substances and preparations mentioned above which are likely to be used by members of the general public, when it is a better alternative to R31 or R32.<br>- *Obligatory* with certain peroxides which may give violent reaction with accelerators or promoters. |
| S51 | *Use only in well-ventilated areas* | - 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. | - 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* | - Volatile very toxic, toxic and harmful substances and preparations containing them. | - 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 people congregate. |
| S53 | *Avoid exposure – Obtain special instructions before use* | - Substances and preparations that are carcinogenic, mutagenic and/or toxic for reproduction. | - *Obligatory* for the above-mentioned 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* | - All dangerous substances and preparations. | - 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* | - Substances which have been assigned the symbol ‘N’. | - Normally limited to substances not likely to be used by the general public. |
| S59 | *Refer to manufacturer/ supplier for information on recovery/ recycling* | - All dangerous substances and preparations. | - *Obligatory* for substances dangerous for the ozone layer.<br>- Recommended for other substances and preparations for which recovery/recycling is recommended. |

| | | ***Applicability:*** | ***Criteria for use:*** |
|---|---|---|---|
| S60 | *This material and its container must be disposed of as hazardous waste* | - All dangerous substances and preparations. | - 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* | - Substances and preparations dangerous for the environment. | - 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* | - Substances and preparations classified as harmful with R65 in accordance with the criteria in paragraph 64.<br>- Not applicable to substances or preparations which are placed on the market in aerosol containers (or in containers fitted with a sealed spray attachment). See paragraph 169. | - *Obligatory* for substances and preparations mentioned above, if sold to, or likely to be used by the general public, except where S45 or S46 are obligatory.<br>- 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* | - Very toxic and toxic substances and preparations (gases, vapours, particulates, volatile liquids).<br>- Substances and preparations causing respiratory sensitisation. | - *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)* | - Corrosive or irritant substances and preparations. | - Recommended for the above substances and preparations which are likely to be used by the general public and where the above treatment is suitable. |

# References

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5 *Globally Harmonized System on classification and labelling of chemicals (GHS)* Second revised edition United Nations www.unece.org/trans/danger/publi/ghs/ghs_rev02/02files_e.html

6 Council Directive 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

7 European Regulation of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

8 Council Directive 2006/121/EC of 18 December 2006 amending Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances in order to adapt it to Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and establishing a European Chemicals Agency

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15 ISO 3104:1994 *Methods of test for petroleum and its products. Petroleum products. Transparent and opaque liquids. Determination of kinematic viscosity and calculation of dynamic viscosity*

16 ISO 3105:1994 *Methods of test for petroleum and its products. Kinematic viscosity. Specifications and operating instructions for glass capillary kinematic viscometers*

17 BS EN ISO 3219:1995 *Plastics. Polymers/resins in the liquid state or as emulsions or dispersions. Determination of viscosity using a rotational viscometer with defined shear rate* British Standards Institution

18 Young J R, How M J, Walker A P and Worth W M H 'Classification as corrosive or irritant to skin of preparations containing acidic or alkaline substances, without testing on animals' *Toxic in Vitro 1988* **2**(1) 19–26

19 'Council Regulation (EC) No 2037/2000 on substances that deplete the ozone layer' *Official Journal* L 244 29 September 2000 p 1

20 European Inventory of Existing Commercial Substances (EINECS) available on the Institute for Health and Consumer Protection website at http://ihcp.jrc.ec.europa.eu/

*European List of Notified Chemical Substances (EINECS)* available on the Institute for Health and Consumer Protection website at http://ihcp.jrc.ec.europa.eu/

21 BS EN 417:2003 *Non-refillable metallic gas cartridges for liquefied petroleum gases, with or without a valve, for use with portable appliances. Construction, inspection, testing and marking* British Standards Institution

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