GUIDELINES FOR THE CLASSIFICATION OF HAZARDOUS CHEMICALS

DEPARTMENT OF OCCUPATIONAL SAFETY AND HEALTH
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PREFACE

These guidelines may be cited as the Guidelines for the Classification of Hazardous Chemicals (hereinafter referred to as "the Guidelines".

The purpose of the Guidelines is to elaborate on and explain the requirements of Regulation 4 of the Occupational Safety and Health (Classification, Packaging and Labelling of Hazardous Chemicals) Regulations 1997 [P.U. (A) 143] (hereinafter referred to as "the Regulations") which stipulates the duty of a supplier of hazardous chemicals to classify each hazardous chemicals according to the specific nature of the risk involved in the use and handling of the chemicals at work. The Guidelines also recommend appropriate risk and safety phrases to be assigned to the chemical and which must be included on the label of the packaging of the hazardous chemicals and which must be included on the label of the packaging of the hazardous chemicals as required by Regulation 7 (1) (d) of the Regulations.

Suppliers of hazardous chemicals are advised to familiarize themselves with the Guidelines and follow these closely in classifying hazardous chemicals. When there is any conflict or inconsistency between the Guidelines and the Regulations, then the provisions of the Regulations will prevail. A supplier, however, may choose to interpret the requirements of the Regulation differently but in such a case he has to prove to the Director General of Occupational Safety and Health that his interpretation is, in effect, at least on a par with the interpretation given in the Guidelines. The Guidelines must be read in conjunction eith the Regulations, the Guidelines for Labelling of Hazardous Chemicals, and the Guidelines for the Formulation of a Chemical Safety Data Sheet.

These Guidelines will be reviewed from time to time. Suppliers are welcome to respond with feedback to the Department in writing with a view to making the Guidelines more comprehensive and user-friendly.

Director General
Department of Occupational Safety and Health
Malaysia

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Glossary

Acute health risk	risk which may result in adverse effect that occurs immediately or shortly after exposure
Boiling point	the temperature of a liquid at which the vapour pressure (i.e. the pressure characteristic at any given temperature
Chemical	any chemical element, compound or mixture thereof, whether natural or synthetic, but not including any microorganism
CAS Number	Chemical Abstracts Service Registry Number; the unique number assigned to a chemical by the Chemical Abstracts Service, Columbus, Ohio, USA.
Carcinogenic	substances or preparations which if inhaled or ingested or penetrated into the skin, may include cancer in human or increase its incidence
Chronic health risk	risk which may result in an adverse effect that occurs after repeated or prolonged exposure
Flash point	the lowest temperature in degrees Celsius at which a liquid will produce enough vapour to ignite
Hazardous chemical	any chemical possessing any of the properties described in Parts A or B of Schedule I of the Regulations or for which relevant information exists to indicate that chemical is hazardous
LC_{50}	a concentration of a chemical in air which is estimated to produce death in 50% of an experimental animal population on inhalation over a specified short period of time
LD_{50}	a dose of a chemical applied through ingestion, injection or skin application which is estimated to produce death in 50% of an experimental animal population
Mutagenic	substances or preparations which if inhaled or ingested or penetrated into the skin may induce genetic changes in spermatozoa or ovum cells or increase their incidence
Teratogenic	substances or preparation which if inhaled or ingested or penetrated into the skin of a pregnant woman, may induce deformation in the foetus or increase its incidence

UN Number

United Nation Number, a system of four digit number assigned by the United Nation Committee of Experts on the Transport of Dangerous Goods. UN Number are assigned to one substances or to a group of substances with similar characteristics. They are not necessarily unique to one chemical, and may cover a group of chemicals with similar hazardous properties, for example, Organophosphorus pesticides, liquid, toxic - UN No. 3018.

1. INTRODUCTION

1.1. Regulation 4 stipulates the duty of a supplier of hazardous chemicals to classify each hazardous chemical according to the *specific nature of the risk* involved during use and handling of the chemical at work.

1.2. The Regulations define "specific nature of the risk" in relation to classification of chemicals to mean the explosive, oxidising, extremely flammable, highly flammable, flammable, very toxic, toxic, harmful, corrosive, irritant, carcinogenic, teratogenic or mutagenic nature of a particular chemical.

1.3. Schedule I of the Regulations categorises a chemical as hazardous based on:

(i) its physicochemical properties (Part A of Schedule I), i.e. explosive, oxidising, extremely flammable, highly flammable or flammable; or

(ii) its health effects (Part B of Schedule I), i.e. very toxic, toxic, harmful, corrosive, irritant, carcinogenic, teratogenic or mutagenic.

1.4. Chemicals which are carcinogenic, teratogenic or mutagenic are classified as either toxic or harmful. Paragraphs 3.2.4, 3.2.5 and 3.2.6 will give more information on the classification of these class of chemicals.

1.5. Chemicals characterised by more than one specific nature of risk within either system mentioned in paragraph 1.3 must be classified under the category which represents the greatest degree of hazard. For chemicals grouped into categories defined in Part A of Schedule I, explosive is more hazardous than oxidising; oxidising is more hazardous than extremely flammable; extremely flammable is more hazardous than highly flammable; highly flammable is more hazardous than flammable. While for those grouped into categories defined in Part B of Schedule I, very toxic is more hazardous than toxic; toxic is more hazardous than corrosive; corrosive is more hazardous than harmful; harmful is more hazardous than irritant.

2. CLASSIFICATION BASED ON PHYSICOCHEMICAL PROPERTIES

2.1 GENERAL

Classification of chemicals based on physicochemical properties must be done using methods specified in **Annex V (A) to Directive 67/548/EEC** (hereinafter referred to as **"the Directive"**) and as amended in the subsequent Directives. A chemical is considered as hazardous and should be classified as either explosive, oxidising, extremely flammable, highly flammable or flammable when the results of tests carried out according to the Directive satisfy one or more of the specific nature of the risk definitions in Part A of Schedule 1 of the Regulations. Figure I summarises the criteria of chemical classification according to physicochemical properties.

Figure 1

SUMMARY OF THE CRITERIA OF CHEMICAL CLASSIFICATION

ACCORDING TO PHYSICOCHEMICAL PROPERTIES

CLASSIFICATION	PHYSICOCHEMICAL PROPERTIES
Explosive	chemicals and preparations which may explode under the effect of flame or sensitive to shocks or friction than dinitrobenzene
Oxidising	chemicals and preparations which give rise to highly exothermic reaction when in contact with other chemicals, particularly flammable chemicals
Extremely Flammable	liquid chemicals and preparations with a flash point $< 0^{o}$ C and boiling point $\leq 35^{o}$ C
Highly Flammable	(i) chemicals and preparations which may become hot and finally catch fire in contact with air at ambient temperature without any application of energy; (ii) solid substances and preparations which may readily catch fire after brief contact with a source of ignition and which continue to burn or be consumed after removal of the source of ignition; (iii) liquid substances and preparations having a flash point below 21^{o} C but which are not extremely flammable. (iv) gaseous substances and preparations which are flammable in air at normal pressure; or (v) substances and preparations which, when in contact with water or damp air, evolve highly flammable gases in dangerous quantities.
Flammable	liquid substances and preparations having a flash point $\geq$ than 21^{o} C and $\leq 55^{o}$ C.

2.2 RISK-PHRASES FOR CHEMICALS CLASSIFIED ACCORDING TO THE PHYSICO-CHEMICAL PROPERTIES

2.2.1 Explosive

A chemical or preparation which is classified as explosive must carry at least one risk-phrase i.e. either R2 or R3. The choice of which risk-phrase to be assigned should be guided by the test results in accordance to the Directives or as follows -

RISK PHRASE	PROPERTIES
R2 *(Risk of explosion by shock, friction, fire or other sources of ignition)*	All explosive chemicals or preparations, including certain organic peroxides, except for those chemicals or preparations set for risk-phrase R3 below.
R3 *(Extreme risk of explosion by shock, friction, fire or other sources of ignition*).	All substances or preparations which are particularly sensitive such as picric acid salts, pentaerythritetetranitrate (PETN) and certain undiluted organic peroxides such as dibenzoyl peroxide.

2.2.2 Oxidising

A chemical or preparation which is classified as oxidising must carry at least one of the following risk-phrases i.e. R11, R8 or R9. The choice of which risk-phrase to choose must be guided by the results of the test in accordance to the Directives or as follows -

RISK PHRASE	PROPERTIES
R11 *(Highly flammable)*	*Organic peroxides which has flammable properties even when not in contact with other combustible material.
R8 *(Contact with combustible material may cause fire)*	Other oxidising chemicals or preparations including inorganic peroxides, which may cause fire or enhance the risk of fire when in contact with combustible material.
R9 *(Explosive when mixed with combustible material)*	Other oxidising chemicals or preparations including inorganic peroxides,which become explosive when mixed with combustible materials such as certain chlorates.

***Note on peroxides:** Organic peroxides classified as hazardous on the basis of their structure (e.g R-O-O-H ; R1-O-O-R2) are generally classified as oxidising, and should be labeled as oxidising chemical under paragraph 2.2.2. However, if the test results carried out in accordance with the Directives showed that the organic peroxide (in the form in which it is placed on the market) have explosive properties, then paragraph 2.2.1 will apply.*

2.2.3 Extremely Flammable, Highly Flammable and Flammable

Substances or preparations which are classified as extremely flammable, highly flammable, very flammable or flammable must carry risk-phrases determined by the test results in accordance to the Directives or as follows -

CLASS	RISK PHRASE	PROPERTIES
Extremely flammable	R12 *(Extremely flammable)*	Liquid substances or preparations which have a flash point lower than 0 °C and a boiling point lower than or equal to 35°C.
Highly flammable	R11 *(Highly flammable)*	Solid substances or 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 or preparations having a flash point below 21° C but which are not extremely flammable.
	R12 *(Extremely flammable)*	Gaseous substances or preparations which are flammable in air at normal pressure.
	R13 *(Extremely flammable liquefied gas)*	Gaseous substances or preparations which are flammable in air at normal pressure when put on the market in liquefied form.
	R15 *(Contact with water liberates highly flammable gases)*	Substances or preparations which in contact with water or damp air, evolve highly flammable gases in dangerous quantities, at minimum rate of one liter per kilogram per hour.
	R17 *(Spontaneous flammable in air)*	Substances or preparations which become hot and finally catch fire in contact with air at ambient temperature without any input of energy.

CLASS	RISK PHRASE	PROPERTIES
Flammable	R10 *(Flammable)*	Liquid substances and preparations having flash point equal or greater than 21° C, and less than or equal to 55 ° C.

		However, in practice, it has been shown that a preparation having a flash point equal to or greater than 21° C and less than or equal to 55 ° C need not be classified as flammable if the preparation could not in any way support combustion.

2.2.4 Other physico-chemical properties

Additional risk-phrases should be assigned to a substance and preparation which has been classified by virtue of paragraph 2.2.1 to 2.2.3 inclusive, if test results in accordance with the Directives or information from other sources showed that the substance or preparation has other inherent hazardous properties. The substance or preparation should carry additional risk-phrases and the phrases should be chosen according to the following guide -

RISK PHRASE	PROPERTIES
R1 *(Explosive when dry)*	Explosive substances and preparations which are put on the market in solution or in wetted form e.g nitrocellulose with more than 12.6% nitrogen.
R4 *(Forms very sensitive explosive metallic compound)*	Substances or preparations which may form sensitive explosive metallic derivatives e.g picric acid, styphnic acid.
R5 *(Heating may cause an explosion)*	For thermally unstable substances and preparations not classified as explosive e.g. perchloric acid > 50%.
R6 *(Explosive with or without contact with air)*	For substances or preparations which are unstable at ambient temperatures e.g. acetylene
R11 *(Highly flammable)*	Organic peroxides which have flammable properties even when not in contact with other combustible material.
R14 *(Reacts violently with water)*	Substances or preparations which react violently with water, e.g. acetyl chloride, alkali metals, titanium tetrachloride.
R16 (*Explosive when mixed with oxidising substances*)	For substances or preparations which react explosively with an oxidising agent, e.g red phosphorus.

RISK PHRASE	PROPERTIES
R18 (*In use, may form flammable/explosive vapour-air mixture)*	Preparations not in themselves classified as flammable, which contain volatile components which are flammable in air.

R19 *(May form explosive peroxides)*	Substances or preparations which may form explosive peroxides during storage, e.g diethyl ether, 1,4- dioxan.
R30 *(Can become highly flammable in use)*	Preparations not in themselves classified as flammable, which become flammable due to the loss of non-flammable volatile components.
R44 *(Risk of explosion if heated under confinement)*	Substances or preparations not in themselves classified as explosive in accordance with paragraph 2.2.1 but which may nevertheless display explosive properties in practice if heated under sufficient confinement. For example, certain substances which would decomposed explosively if heated in a steel drum do not show this effect if heated in less-strong containers.

3. CLASSIFICATION BASED ON HEALTH EFFECTS

3.1 GENERAL

Figure 2 summarised the criteria used to classify chemicals based on their health effects as stipulated in Part B of Schedule I of the Regulations. The criteria set in the Regulations may, however, be inadequate to classify a chemical or preparation according to the specific nature of the risk. These guidelines contain additional information to address these gaps using guidance adopted by the European Communities (EC). The EC criteria take into consideration both short and long term health effects, and are applicable to both pure substances as well as preparations or mixtures.

Substances which have been classified according to the Directive and which do not contradict the requirements of the Regulations is deemed to have been classified as required by Regulation 4 of the Regulations.

3.2 HEALTH EFFECTS CRITERIA AND RISK-PHRASES

The toxicity data stipulated in Part B of Schedule I of the Regulations (Figure 2) refer to acute animal test data only which may not be adequate to classify a chemical. As mention in paragraph 3.1, these Guidelines elaborate on the criteria given in the Regulations by giving additional information on other toxicological testing data as well as other relevant data which can be used by suppliers to assist them in classifying a chemical. The following are the combined health effects criteria (both stipulated and non-stipulated criteria in the Regulations) which are recommended for use in classifying a chemical according to its health effects.

3.2.1. Very Toxic, Toxic and Harmful Effects

Classification of a chemical or preparation into the very toxic, toxic or harmful classes depends on the different types of toxicity data which have been generated for the particular chemical. For the purpose of these Guidelines, three different types of toxicity data are considered:

(a) Acute Lethal Effects

A chemical or preparation which is considered to be hazardous as a result of its acute lethal effects can be classified as either very toxic, toxic or harmful according to its LD_{50} /LC_{50} values for three routes of exposure as described below:

(i) Oral (through the mouth)

LD_{50} < 25mg/kg absorbed orally in rat - **very toxic (R28).**

LD_{50} between 25 and 200mg/kg absorbed orally in rat **- toxic (R25).**
LD_{50} between 200 and 500mg/kg absorbed orally in rat - **harmful (R22).**

(ii) Dermal (through the skin)

LD_{50} < 50 mg/kg percutaneous absorption in rat or rabbit - **very toxic (R27).**

LD_{50} between 50 and 400 mg/kg percutaneous absorption in rat or rabbit - **toxic (R24).**

LD_{50} between 400 and 2000 mg/kg percutaneous absorption in rat or rabbit - **harmful (R21).**

(iii) Inhalation

LC_{50} < 0.5 mg/litre inhalation in rat per 4 hours - **very toxic (R26).**

LC_{50} between 0.5 and 2.0 mg/litre inhalation in rat per 4 hours - **toxic (R23).**

LC_{50} between 2 and 20 mg/litre inhalation in rat per 4 hours - **harmful (R20).**

(b) Non-Lethal Irreversible Effects After a Single Exposure

A chemical or preparation capable of causing severe irreversible effects (other than carcinogenesis, mutagenesis or teratogenesis) after a single exposure is considered to be a hazardous chemical. Such irreversible effects can include central nervous system effects, kidney necrosis, liver lesions, anemia or paralysis.

These substances are subdivided into three categories:

- Very Toxic (R39).
- Toxic (R39).
- Harmful (R40).

For oral, dermal and inhalation routes, the same dose ranges as for acute lethal effects apply for very toxic, toxic and harmful hazard classifications, as in sub-paragraph (a). An additional risk phrase is assigned to indicate oral, dermal or inhalation route of administration/exposure, that is:

- Very Toxic (R26,R27 or R28).
- Toxic (R23, R24 or R25).
- Harmful (R20, R21 or R22).

(c) Severe Effects After Repeated or Prolonged Exposure

A chemical or preparation capable of causing serious damage to health is considered to be hazardous. Serious damage in this context means a clear functional disturbance or morphological change of toxicological significance resulting from repeated or prolonged exposure by an appropriate route. Such a substance can be classified as either toxic or harmful according to the following criteria:

(i) Toxic

A chemical or preparation for which danger of serious damage to health is likely from repeated or prolonged exposure by an appropriate route at dosage levels significantly lower than those for harmful substances should be classified as toxic (R48).

(ii) Harmful

A chemical or preparation for which danger of serious damage to health is likely from repeated or prolonged exposure by the following routes at the following dose ranges should be classified as harmful (R48).

- LD_{50} between 200 and 500 mg/kg absorbed orally in rat.
- LD_{50} between 400 and 2000 mg/kg percutaneous absorption in rat or rabbit.
- LC_{50} between 2 and 20 mg/litre inhalation in rat per 4 hours.

3.2.2 Corrosive Effects

A chemical or a preparation is considered to be corrosive if, when it is applied to healthy intact animal skin, it produces full thickness destruction of skin tissue on at least one animal during the test for skin irritation cited in the Directives or during an equivalent method or if the results can be predicted, for example from strong acid or alkaline reactions. Classification can be based on the results of validated in-vitro tests. The chemical or preparation shall be classified as corrosive. Risk phrases shall be assigned in accordance with the following criteria:

Causes severe burns *(35)*
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

Causes burns *(34)*
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.

3.2.3 Irritant Effects

A chemical or preparation is determined to be hazardous and classified as irritant if it causes :

- inflammation of the skin (R38)
- eye irritation (R36)
- serious eye effects (R41)

- irritation to the respiratory system (R37); or
- sensitising effect s (R43 or R42)

Substances which are strongly acidic or alkaline are usually not tested for irritant effects, owing to their predictable corrosive properties.
The following criteria are to be used when testing the whole substance, whether it is a mixture or pure substance, for its irritant effects. Firstly the scientific literature should be used to determine whether an accepted causal relationship exists between the substance and irritant effects in humans. However if the evidence from the scientific literature is inadequate, then the criteria to be used are stated below:

a). Inflammation of the skin

Substances are considered to be skin irritants (R38) if:

- when applied to healthy intact animal skin for up to 4 hours, significant inflammation occurs which persists for 24 hours or more after the end of the exposure period; or
- practical experience shows they are capable of causing inflammation in a substantial number of persons.

b) Eye contact - irritating to eyes

Substances are considered to be eye irritants (R36) if:

- when applied to the eye of the animal, they cause significant ocular lesions (within 72 hours following exposure) which present for 24 hours or more after instillation of the test material; or
- practical experience shows they are capable of causing eye irritation in a substantial number of persons.

c) Eye contact - serious eye effects

Substances are considered to present risk of serious damage to eyes (R41) if, when applied to the eye of the animal, they cause severe ocular lesions which present 24 hours or more after instillation of the test material.

Substances which can cause serious damage to the eyes pose a greater risk than the substances classified as eye irritants.

d) Inhalation - irritation to the respiratory system

The designation of substances which cause serious irritation to the respiratory system (R37) is normally based on practical observation in humans and reports in scientific literature which have led to the establishment of an accepted causal relationship between a substance and a respiratory irritation effect on persons who have inhaled the substance. However, animal test results may be used where available and classified for irritant potential.

e) Sensitising effects

Substances which causes sensitisation by either skin contact (R43) or by inhalation (R42) are determined to be hazardous substances, and classified as Irritant and Harmful respectively.

The following criteria shall be used when testing the whole substance, whether it is a mixture or pure substance, for its health effects. First, the scientific literature should be used to determine whether there are reports which have led to the establishment of an accepted causal relationship between the

substance and a sensitisation effects on persons exposed. However, if evidence for this is inadequate, then the criterias below are to be applied.

i) Skin sensitisers

Substances are considered to be skin sensitisers (R43) if:

- practical experience shows that the substances are capable of inducing a sensitisation reaction by skin contact in a substantial number of persons; or
- there is a positive response in an appropriate animal study.

ii) Sensitisation by inhalation

Substances which can cause sensitisation by inhalation (R42) are those where practical evidence is available which shows that they are capable of inducing a sensitisation reaction in humans at a greater frequency than would be expected from the response of a general population. There are currently no standard animal testing procedures for determining sensitisation by inhalation.

3.2.4 Carcinogenic Effects

A chemical or preparation is considered to be carcinogenic if it is suspected to cause or have caused cancer in humans or animals upon prolonged exposure. A carcinogen may be categorized into either of the following categories:

Category 1
substances known to be carcinogen to humans;

Category 2
substances regarded as if they are carcinogen to humans; and

Category3
substances which cause concern for humans owing to possible
carcinogen effects, but in respect of which the available information is not adequate
for making a satisfactory assessment.
Note: The placing of a substance into Category 1 is done on the basis of epidemiological data. The placement of substances into Category 2 and Category 3 is based primarily on animal experiments.

Category 1

a) A substance is included in Category 1 and classified as Toxic (R45 or R49) if there is sufficient evidence to establish a causal association between human exposure and the development of cancer on the basis of epidemiological data. The existence of a causal relationship would be supported by any of the following:

- an increased incidence of one or more cancer types in an exposed population in comparison with a non-exposed population;

- evidence of dose-time-response relationships, that is, an increased cancer incidence associated with higher exposure levels or with increasing exposure duration;

- an association between exposure and increased risk observed in more than one study ;

- demonstration of a decline in risk after reduction of exposure; and

- specificity of any association, defined as an increased occurrence of cancer at one target organ or of one morphological type.

b) For a substance which presents a carcinogenic risk only when inhaled, for example, as dust, vapour or fumes, the specific risk phrase R49 should be used instead of R45.

Category 2

a) A substance is included in Category 2 and classified as Toxic (R45 or R49) if there is sufficient evidence, on the basis of appropriate long term animal studies or other relevant information, to provide a strong presumption that human exposure to that substance may result in the development of cancer.

b) For Category 2 classification, 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 carcinogen, or data from epidemiological studies suggesting an association.

c) Human data providing suspicions of carcinogen potential may warrant a Category 2 classification irrespective of the nature of any animal data . Increased confidence in the credibility of a causal relationship would be provided by evidence of carcinogenicity in animals and/or of genotoxicity potential in short term screening tests.

Category 3

A substance is included in Category 3 and classified as Harmful (R40) if there is some evidence from appropriate animal studies that human exposure can result in the development of cancer, but this evidence is sufficient to place the substance in Category 2. Category 3 substances comprise two subcategories:

a) Substances which are well investigated, but for which the evidence of tumour inducing effects 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 they raise concern for humans. This classification is provisional and further experiments are necessary before a final decision can be made.

For a distinction between Category 2 and Category 3, the arguments listed below are relevant which reduce the significance of experimental tumour induction in view of possible human exposure. These arguments, especially in combination, would lead in most cases to classification in Category 3, even though tumours have been induced in animals:

a) Carcinogen effects only at very high dose levels exceeding the 'maximal tolerated dose'. The maximal tolerated dose is characterised by toxic effects which, although not reducing lifespan, go along with physical changes such as about 10% retardation in weight gain.

b) Appearance of tumor, especially at high dose levels, only in particular organ of certain species known to be susceptible to a high spontaneous tumor formation.

c) Appearance of tumors, only at the sight of application, in very sensitive test system, for example, intra peritoneal or subcutaneous application of certain locally active compound, if the particular target is not relevant to humans.

- Lack of genotoxicity in short term tests in vivo and in vitro.

- Existence of a secondary mechanism of action with the implementation of a practical threshold above a certain dose level, for example, hormonal effects on target organs or on mechanisms of physiological regulation and chronic stimulation of cell proliferation.

- Existence of a species-specific mechanism of tumour formation, for example, by specific metabolic pathways irrelevant for humans.

For a distinction between Category 3 and no classification, arguments are relevant which demonstrate that the available animal data are not relevant to humans, for example:

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.

a) If the only available tumour data are liver tumors in certain sensitive strains of mice, without any supplementary evidence, the substance may not be classified in any of the categories.

b) 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.

3.2.5 Mutagenic Effects

A mutagen is an agent that give rise to an enhanced occurrence of mutations. A mutation is a permanent change in the amount structure of the genetic material in an organism, resulting in a change of the phenotypic characteristic 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 a 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.

Substances are determined to be hazardous due to mutagenic effects if they fall into the following categories:

Category 1
substances known to be mutagenic to humans;

Category 2
substances which should be regarded as if they are mutagenic to humans; and

Category 3
substances which cause concern for humans owing to possible mutagenic effects, but in respect of which available information does not satisfactorily demonstrate heritable genetic damage.

It should be noted that substances are classified as mutagens with specific reference to inherited genetic damage. However, mutagenicity assays which show 'induction of genetically relevant events in somatic cells' are generally also regarded as an alert for possible carcinogenic activity .

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

Category 1

a) A substance is included in Category 1 and classified as Toxic (R46) if there is sufficient evidence to establish a causal association between human exposure and heritable genetic damage.

b) To place a substance in Category 1, positive evidence from human mutation epidemiology studies will be needed. It is recognised that it is extremely difficult to obtain reliable information from

studies of the incidence of mutations in human populations, or on possible increases in their frequencies. Examples of such substances are not known to date.

Category 2

a) A substance is included in Category 2 and classified as Harmful if there is sufficient evidence, generally on the basis of appropriate animal studies and other relevant information, to provide a strong presumption that human exposure can result in the development of heritable genetic damage.

b) To place a substance in Category 2, positive results are needed from assays showing: (a) mutagenic effects; or (b) other cellular interactions relevent to mutagenicity, in germ cells of *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.

c) With respect to placement in Category 2, at present the following methods are appropriate:

i) *In vivo* germ cell mutagenicity assays:

- specific locus mutation tests,
- heritable translocation test, and
- dominant lethal mutation test.

These assays actually demonstrate the appearance of affected progeny or a defect in the developing embryo.

ii) *In vivo* assays showing relevent 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,
- test for unscheduled DNA synthesis,
    - assays of (covalent) binding of mutagen to germ cell DNA, and
    - assaying other kinds of DNA damage.

These assays provide evidence of a more or less indirect nature. Positive results in this assays would normally be supported by positive results from *in vivo* somatic cell mutagenicity assays in mammals or in humans (see under Category 3).

iii) In vivo assays showing mutagen effects in somatic cells of mammals (see subsection under Category 3). In combination with toxicokinetic methods or other methodologies capable of demonstrating that the compound or a relevant metabolite reaches the germ cells.

For subsection under Category 2 i) and ii), positive results from host-mediated assays or the demonstration of unequivocal effects in *in vitro* mutagenicity assays can be considered as supporting evidence.

Category 3

a) A substance is included in Category 3 and classified as Harmful (R40) if there is evidence, from appropriate mutagenicity studies, of concern that human exposure can result in the development of heritable damage , but that this evidence is insufficient to place the substance in Category 2.

b) 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 of mammals *in vivo*. The latter, especially, would normally be supported by positive results from *in vitro* mutagenicity assays.

c) For effects in somatic cells in vivo, at present the following methods are appropriate:

i) In vivo somatic cell mutagenicity assays:

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

ii) In vivo somatic cell DNA interaction assays:

- test for sister chromatid exchanges in somatic cells,
- test for unscheduled DNA synthesis in somatic cells,
- assay for the (covalent) binding of mutagen to somatic cell DNA, and
- assay for DNA damage in somatic cells, for example, by alkaline elution.

d) Substances showing positive results only in *in vitro* mutagenicity assays should normally not be classified. Their further investigation using *in vivo* assays, however, is strongly indicated. In exceptional cases, for example, 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.

3.2.6 Teratogenic Effects

Substances are determined to be hazardous due to teratogenic effects if they fall into the following categories:

Category 1
substances known to be teratogenic to humans; and

Category 2
substances which can be regarded as if they are teratogenic to humans.

The risk phrase R47 applies to both categories.

Category 1

A substance is included in Category 1 and classified as Toxic (R47) if there is sufficient evidence to establish a causal association between human exposure and subsequent no-heritable birth defects in offspring.

Category 2

A substance is included in Category 2 and classified as Harmful (R47) if there are sufficient evidence, generally on the basis of appropriate animal studies and other relevant information, to provide strong presumption that human exposure to the substance may result in non-heritable birth defects in offspring.

3.3 CHOICE OF RISK PHRASES

The choice for the core risk-phrases for each specific nature of risk for chemicals classified according to their health effects recommended in paragraph 3.2 are summarised in Appendix VI. In addition, additional phrases or combination of phrases are identified to accompany the core phrase if the substance or preparation exhibit the properties described.

Figure 2

CHEMICAL CLASSIFICATION ACCORDING TO HEALTH EFFECTS CRITERIA AS STIPULATED IN PART B OF SCHEDULE I OF THE REGULATIONS

CLASSIFICATION	HEALTH EFFECTS	TOXICITY DATA
Very Toxic	substances and preparations which if inhaled or ingested or penetrated into the skin or inhaled may involve extremely serious acute or chronic health risks or even death	LD_{50} < 25 mg/kg oral absorption in rat LD_{50} < 50 mg/kg skin absorption in rat or rabbit LC_{50} < 0.5 mg/litre (4-hour) inhalation in rat
Toxic	substances and preparations which if inhaled or ingested or penetrated into the skin may involve serious acute or chronic health risks or even death substances and preparations which are defined as carcinogenic, tetratogenic or mutagenic	LD_{50} between 25 and 200 mg/kg oral absorption in rat LD_{50} between 50 and 400 mg/kg skin absorption in rat or rabbit LC_{50} between 0.5 to 2 mg/litre (4-hour) inhalation in rat
Corrosive	substances and preparations which may, on contact with living tissues, destroy them	
Harmful	substances and preparations which if inhaled or ingested or penetrated into the skin may involve limited health risk	LD_{50} between 200 and 500 mg/litre oral absorption in rat LD_{50} between 400 and 2000 mg/kg skin absorption in rat or rabbit LC_{50} between 2 and 20 mg/litre (4-hour) in rat

Irritant	non-corrosive substances and preparations which, through immediate, prolonged or repeated contact with the skin or mucous membrane, can cause inflammation	

4. LISTED HAZARDOUS CHEMICALS BASED ON HEALTH EFFECTS

4.1. A limited number of hazardous chemicals are listed in Appendix VII to assist suppliers in classifying pure or single-ingredient chemicals or multi-ingredient mixtures. There are two types of information fields contained in the list namely:

- chemical identification information which consist of three fields, namely the chemical name, CAS number, and the United Nation number; and
- hazard classification data which consist of three fields, namely concentration cut-off levels, risk phrases and safety phrases.

4.2. Concentration cut-off levels are levels which have been determined to assist suppliers to classify single-ingredient chemicals or multi-ingredient chemical mixtures by comparing the concentration(s) of the ingredient(s) with the cut-off levels for that particular ingredient of concern.

A chemical mixture is regarded as hazardous if any ingredient is present at a concentration above its lowest relevant concentration cut-off level shown in the list. The hazard class as well as the risk and safety phrases for the ingredient will be assigned as prescribed in the list. The overall hazard class of a mixture should be based on the highest degree of hazard exhibited by any ingredient. Note that the concentration cut-off levels are designed to provide a practical level of protection and a convenient amount of information, and it should not be construed that an effect cannot occur below these levels.

4.3. If the concentration of each ingredient in the mixture lies below its corresponding cut-off level and the health effects of the ingredients are additive, classification of the chemical should be done using the appropriate formula from among the several given in Appendix I. These formulae are applicable only for chemicals which have irritant, corrosive or acute lethal effects.

5. NON-LISTED HAZARDOUS CHEMICALS BASED ON HEALTH EFFECTS

5.1 Classification of a chemical which is not listed in Appendix VII should be based on the health effects criteria described in section 3. Once a chemical has been classified, the appropriate risk phrase for the chemical can be obtained with the aid of the table given in Appendix II.

5.2 For a multi-ingredient mixture containing ingredients which are not listed in Appendix VI, each ingredient should be classified using the health effects criteria discussed in paragraph 3. Once all the ingredients have been classified then the hazard class for the mixture can be determined with the aid of Tables 1 to 14 of Appendix IV.

6. PROCEDURE FOR CLASSIFYING CHEMICALS BASED ON HEALTH EFFECTS

6.1 GENERAL

The flow chart in Appendix III depicts the various steps for classifying a chemical based on its health effects. The important starting point is to get relevant information on the chemical before it can be classified and supplied to the end user. These data include:

(i) data on the health effects of a chemical (for a pure chemical) or its individual constituent ingredients (for a multi-ingredient chemical mixture) including any information on the additive effect of the ingredients; and

(ii) data on the concentrations of ingredients in the mixture.

The responsibility to classify chemicals is on the supplier which can be either manufacturer , formulator or importer. It is important that the classification of hazardous chemicals are carried out by a person who has the competency in this area.

The following is a step by step account of the procedure for classifying a chemical in line with the flow chart shown in Appendix III.

6.2 CLASSIFICATION PROCEDURE FOR PURE CHEMICALS

Step 1: Use the List of Hazardous Chemical

(i) Refer to the List and check the chemical identity against the List.

(ii) Use the List to classify the chemical if at least one entry is found under the columns with symbols Xn, T, T+, Xi, C. If not go to Step 2.

(iii) Compare chemical concentration with the concentration cut-off levels.

(iv) Determine the hazard category(ies) by looking-up the column under which the chemical concentration equals or exceeds the cut-off level. The result may give one category from among the three acute lethal effect columns (Xn, T, T+) or one category from either of the irritant or corrosive effect columns (Xi and C) or one category from each group (Xn, T or T+ and Xi or C).

(v) Assign risk and safety phrases by looking up the columns for risk and safety phrases. Then go to Step 3.

(vi) If the chemical concentration does not exceed the lowest concentration cut-off level, then the chemical is not considered as a hazardous chemical.

Step 2: Apply the Health Effects Criteria

(i) Determine the hazard category(ies) by comparing the chemical health effects with the health effects criteria described in section 3.

(ii) Assign appropriate risk phrases based on the chemical health effects. Then go to Step 3.

Step 3: Determine Overall Hazard Classification

(i) If the chemical falls under more than one hazard category, the overall hazard classification is based on the hazard category that poses the greatest degree of hazard.

6.3 CLASSIFICATION PROCEDURE FOR MIXTURES

Step 1: Use the List of Hazardous Chemicals

(i) Refer to the List and check the identity of an ingredient against the List.

(ii) Use the List to classify the ingredient if at least one entry is found under columns Xn to C. If not go to Step 3.

(iii) Compare the ingredient concentration with its appropriate cut-off levels.

(iv) If the ingredient concentration < lowest cut-off level, the ingredient is considered as non-hazardous and go to (vi). Otherwise proceed.

(v) Determine the hazard category(ies) for the ingredient by looking-up the column under which the ingredient concentration equals or exceeds the cut-off level. The result may give one category from among the three acute lethal effect columns (Xn, T or T+) or one category from either of the irritant or corrosive effect columns (Xi or C) or one category from each group (Xn, Tor T+ and Xi or C).

(vi) Repeat procedures (i) to (iv) for the next ingredient until all ingredients are considered. If each ingredient in the mixture is at a concentration below its concentration cut-off level, go to Step 2. Otherwise proceed.

(vii) Determine the hazard category(ies) of the mixture by comparing the hazard category(ies) of each individual hazardous ingredient against the appropriate table from among Tables 1-14 in Appendix IV. Then go to Step 4.

Step 2: Use the Formulae

(i) If the ingredients do not act additively or do not have acute lethal, irritant or corrosive effects, then consider the mixture as non-hazardous and terminate the procedure. Otherwise proceed.

(ii) Use the appropriate formula from among the several given in Appendix I to determine the hazard category of the mixture.

(iil) Assign appropriate risk phrases. Then go to Step 4

Step 3: Apply the Health Effects Criteria

(i) Determine the hazard category(ies) of each ingredient by comparing the health effects of each ingredient with the health effects criteria describe in section 3.

(ii) If no ingredient meets the health effects criteria then consider the mixture as non-hazardous and terminate the procedure. Otherwise, assign the appropriate risk phrases based on the health effects of each hazardous ingredient. Then go to Step 4.

Step 4: Determine Overall Hazard Classification

(i) If the chemical falls under more than one hazard category, the overall hazard classification is based on the hazard category that poses the greatest degree of hazard.

6.4 CLASSIFYING A MIXTURE USING THE CUT-OFF LEVEL CONCEPT

Appendix V gives examples of how to classify a chemical mixture using the cut-off concept for references purposes.

REFERENCES

1. Worksafe Standard Australia - List of Designated Hazardous Substances NOHSC:0007(1994).

2. Worksafe Standard Australia - Approved Criteria For Classifying Hazardous Substances - NOHSC:1008(1994).

3. Official Journal of the European Community - Council Directive 79/831/EEC.

4. Official Journal of the European Community - Council Directive 67/548/EEC.

5. Official Journal of the European Community - Council Directive 91/325/EEC.

6. Occupational Safety and Health (Classification, Packaging and Labeling of Hazardous Chemicals) Regulations 1997.

7. Worksafe Standard Australia - List of Designated Hazardous Substances NOHSC:10005(1994).

APPENDIX I

FORMULAE FOR CLASSIFICATION OF MIXTURES WITH INGREDIENT CONCENTRATIONS BELOW CUT-OFF LEVELS AND HAVING ADDITIVE EFFECTS

This appendix applies to a mixture all of whose ingredients are present at concentrations below their cut-off levels and these ingredients have additive health effects. The formulae are relevant only for irritant, corrosive and acute lethal effects. For irritant and corrosive mixtures the formulae are used only for the purpose of assigning R-phrases:

I.1 Acute lethal effects

(i) Very toxic mixtures

A mixture containing more than one very toxic ingredient is classified as very toxic if:

$$\sum (\% A/CCL_A) \geq 1$$

where

% A = percentage by weight of each very toxic ingredient
CCL_A = concentration cut-off level for each very toxic ingredient

(ii) Toxic mixtures

A mixture containing more than one very toxic or toxic ingredient is classified as toxic if:

$$\sum (\%A/CCL_A + \%B/CCL_B) \geq 1$$

where

%B = percentage by weight of each toxic ingredient
CCL_B = concentration cut-off level for each toxic ingredient

(iii) Harmful mixtures

A mixture containing more than one very toxic, toxic or harmful is classified as harmful if:

$$\sum (\%A/CCL_A + \%B/CCL_B + \%C/CCL_C) \geq 1$$

where

%C = percentage by weight of each harmful ingredient
CCL_C = concentration cut-off level for each harmful ingredient

I.2 Corrosive effects

(i) Very corrosive mixtures

A mixture containing more than one very corrosive ingredient (risk phrase R35) is classified as very corrosive if:

$$\sum (\%D/CCL_D) \geq 1$$

where

%D = percentage by weight of each very corrosive ingredient
CCL_D = concentration cut-off level for each very corrosive ingredient

(ii) Corrosive mixtures

A mixture containing more than one very corrosive (risk phrase R35) or corrosive (risk phrase R34) ingredient is classified as corrosive if:

$$\sum (\%D/CCL_D + \%E/CCL_E) \geq 1$$

where

%E = percentage by weight of each corrosive ingredient
CCL_E = concentration cut-off level for each corrosive ingredient

I.3. Irritant effects

(i) Irritant mixtures with risk of serious eye damage

A mixture containing more than one irritant ingredient with risk of serious eye damage (risk phrase R41) is classified as irritant if:

$$\sum (\%F/CCL_F) \geq 1$$

where

%F = percentage by weight of each irritant ingredient with risk of serious eye damage
CCL_F = concentration cut-off level for each irritant ingredient with risk of serious eye damage

(ii) Skin irritant mixtures

A mixture containing more than one very corrosive, corrosive or skin irritant ingredient (risk phrase R38) is classified as skin irritant if:

$\sum (\%D/CCL_D + \%E/ CCL_E + \%G/CCL_G) \geq 1$

where

%G = percentage by weight of each skin irritant ingredient
CCL_G = concentration cut-off level for each skin irritant ingredient

(iii) Eye irritant mixtures

A mixture containing more than one irritant ingredient with risk of serious eye damage (risk phrase 41) or eye irritant ingredient (risk phrase R36) is classified as eye irritant if:

$\sum (\%F/CCL_F + \%H/CCL_H) \geq 1$

where

%H = percentage by weight of each eye irritant ingredient
CCL_H = concentration cut-off level for each eye irritant ingredient

(iv) Respiratory irritant mixtures

A mixture containing more than one respiratory irritant ingredient (risk phrase R37) is classified as respiratory irritant if:

$\sum (\%J/CCL_J) \geq 1$

where

%J = percentage by weight of each respiratory irritant ingredient
CCL_J = concentration cut-off level for each respiratory irritant ingredient

APPENDIX II

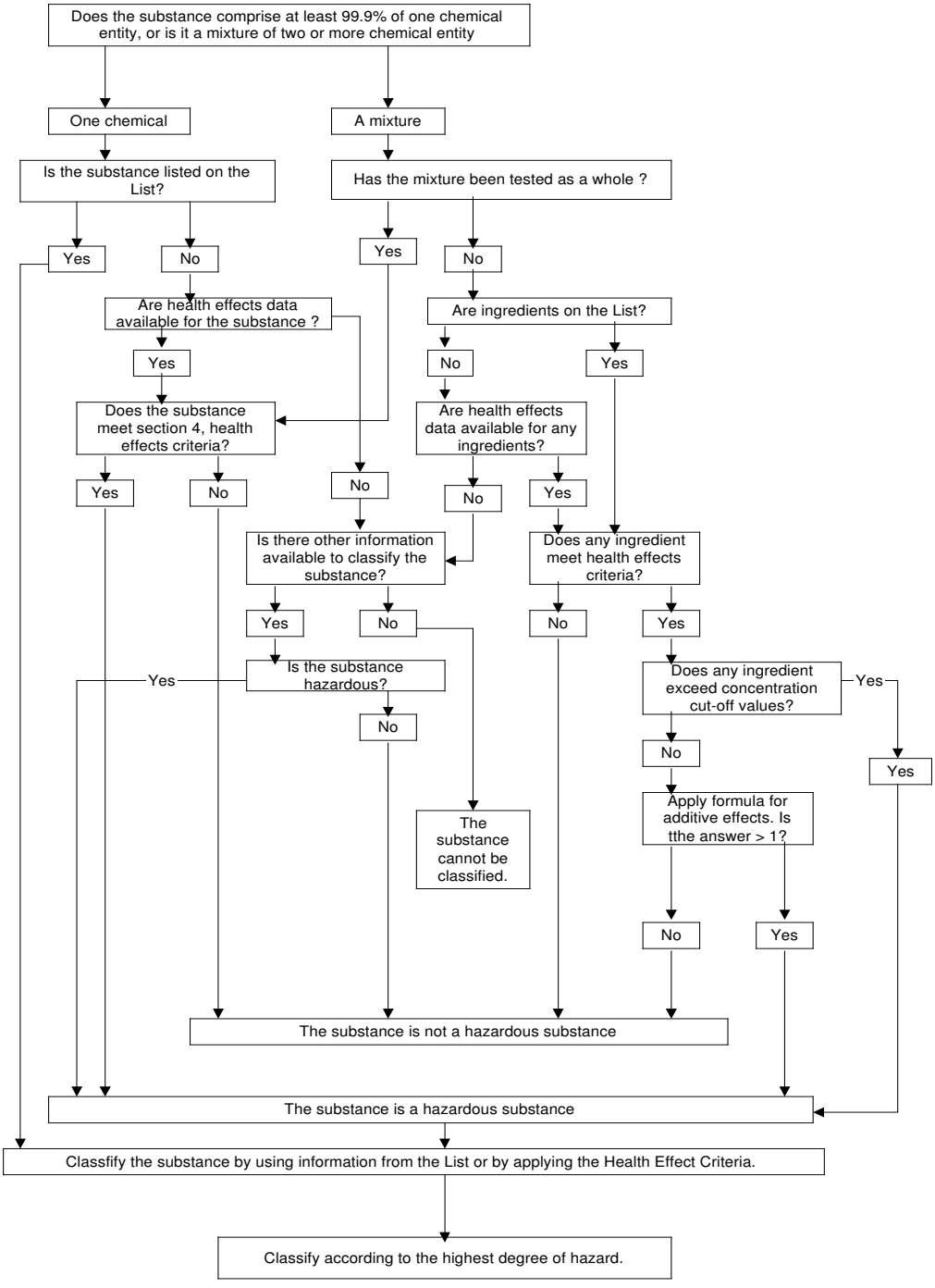
RECOMMENDED RISK PHRASES FOR CLASSIFICATIONS BASED ON HEALTH EFFECTS

CLASSIFICATION	RISK PHRASE	R-NUMBER
Very Toxic	very toxic if swallowed	R28
	very toxic in contact with skin	R27
	very toxic by inhalation	R26
Toxic	toxic if swallowed	R25
	toxic in contact with skin	R24
	toxic by inhalation	R23
	may cause cancer	R45
	may cause heritable genetic damage	R46
	may cause birth defects	R47

Corrosive	causes severe burns	R35
	causes burns	R34
Harmful	harmful if swallowed	R22
	harmful in contact with skin	R21
	harmful by inhalation	R20
	may cause sensitization by inhalation	R42
Irritant	irritating to skin	R38
	irritating to eyes	R36
	may cause sensitization by skin contact	R43

APPENDIX III

PROCESS OF DETERMINING WHETHER A SUBSTANCE IS HAZARDOUS



APPENDIX IV

HEALTH-EFFECTS BASED CLASSIFICATION OF NON-LISTED CHEMICALS AND RECOMMENDED RISK PHRASES

This appendix applies to a chemical which is not listed in Appendix VII and which have been classified using the health effects criteria in described in paragraph 3. It lists the recommended risk and safety phrases which should accompany the hazardous chemical. The appendix should be used as follows:

(i) Classify the chemical in the left hand vertical column of the tables.

(ii) Compare the concentration of the chemical with its concentration cut-off level listed in the table row.

(iii) Determine the mixture classification by reading the column heading for the concentration range matching the ingredient concentration in the mixture.

1. Acute lethal effects

Table 1: Solid and Liquid Mixtures

	Ingredient	Very Toxic	Toxic	Harmful
1.	Very Toxic R26, R27, R28	≥ 7% R26,R27,R28	1% ≤ conc. ≤7% R23,R24,R25	0.1 ≤ conc. ≤1% R20,R21,R22
2.	Toxic R23, R24, R25		≥ 25% R23,R24,R25	3% ≤conc. ≤25% R20,R21,R22
3.	Harmful R20, R21, R22			≥ 25% R20,R21,R22

concentrations are in % w/w

Table 2: Gaseous Mixtures

	Ingredient	Very Toxic	Toxic	Harmful
1.	Very Toxic R26	≥ 1% R26	0.2% ≤conc. ≤ 1% R23	0.02% ≤ conc. ≤0.2% R20
2.	Toxic R23		≥ 5% R23	0.5% ≤conc. ≤5% R20
3.	Harmful R20			≥ 5% R20

concentrations are in % v/v

2. Non-lethal irreversible effects after a single exposure

Table 3: Solid and Liquid Mixtures

	Ingredient	Very Toxic	Toxic	Harmful
1.	Very Toxic R39	≥10% R39	1%≤ conc.≤10%	0.1% ≤conc.≤1%

			R39	R40
2.	Toxic R39		≥10% R39	1%≤conc.≤10% R40
3.	Harmful R40			≥10% R40

concentrations are in % w/w

Table 4: Gaseous Mixtures

	Ingredient	Very Toxic	Toxic	Harmful
1.	Very Toxic R39	≥1% R39	0.2%≤ conc.≤1% R39	0.02≤ conc.≤0.2% R40
2.	Toxic R39		≥5% R39	0.5%≤conc.≤5% R40
3.	Harmful R40			≥5% R40

concentrations are in % v/v

3. Severe effects after repeated or prolonged exposure

Table 5: Solid and Liquid Mixtures

	Ingredient	Toxic	Harmful
1.	Toxic R48	≥10% R48	1%≤ conc.≤10% R48
2.	Harmful R48		≥10% R48

concentrations are in % w/w

Table 6: Gaseous Mixtures

	Ingredient	Toxic	Harmful
1.	Toxic R48	≥5% R48	0.5%≤ conc.≤5% R48
2.	Harmful R48		≥5% R48

concentrations are in % v/v

4. Corrosive and irritant effects

Table 7 : Solid and liquid mixtures

Ingredient	Very corrosive	Corrosive	Irritant serious eye damage	Irritant
1. Very corrosive R35	≥ 10% R35	5% ≤ conc. < 10% R34		1% ≤ conc. < 5% R36,R38
2. Corrosive R34		≥ 10% R34		5% ≤ conc. < 10% R36,R38
3. Irritant (Serious eye damage) R41			≥ 10% R41	5% ≤ conc. < 10% R36
4. Irritant R36,R37,R38				≥ 20% R36,R37,R38

concentrations are in % w/w.

Table 8 : Gaseous mixtures

Ingredient	Very corrosive	Corrosive	Irritant (serious eye damage)	Irritant
1. Very corrosive R35	≥ 1% R35	0.2% ≤ conc.<1% R34		0.02% ≤conc.<0.2% R37
2. Corrosive R34		≥ 5% R34		0.5% ≤ conc. < 5% R37
3. Irritant (Serious eye damage) R41			≥ 5% R41	0.5% ≤ conc. < 5% R36
4. Irritant R36,R37,R38				≥ 5% R37,(R36,R38)

concentrations are in % v/v.

5. Sensitising effects

Table 9: Solid and liquid mixtures

Ingredient	Harmful 42	Irritant R43
1. Respiratory sensitising R42	≥ 1% R42	
2. Skin sensitising R43		≥ 1% R43
3. Skin and respiratory sensitising R42/43	≥ 1% R42/43	

concentrations are in % w/w.

Table 10: Gaseous mixtures

Ingredient	Harmful R42
1. Respiratory sensitising R42	≥ 0.2% R42
2. Skin and respiratory sensitising	≥ 0.2% R42/43

concentrations are in % v/v.

6. Carcinogenic effects

The concentration cut-off levels for a gaseous mixture is the same as for solid and liquid mixtures.

Table 11: Solid, Liquid and Gaseous Mixtures

	Ingredient	Toxic	Harmful R42
1.	Category 1 R45 or R49	≥0.1% R45 or R49	
2.	Category 2 R45 or R49	≥0.1% R45 or R49	
3.	Category 3 R40.		≥1% R40

concentrations are in % w/w for solids and liquids, and in v/v for gases.

7. Mutagenic effects

The concentration cut-off levels for a gaseous mixture is the same as for solid and liquid mixtures.

Table 12: Solid, Liquid and Gaseous Mixtures

	Ingredient	Toxic	Harmful
1.	Category 1 R46	≥0.1% R46	
2.	Category 2 R46	≥0.1% R46	
3.	Category 3 R40		≥1% R40

concentrations are in % w/w for solids and liquids, and in v/v for gases

8. Teratogenic effects

Table 13: Solid and Liquid Mixtures

	Ingredient	Toxic	Harmful
1.	Category 1 R47	≥0.5% R47	
2.	Category 2 R47		≥5% R47

concentrations are in % w/w

Table 14: Gaseous Mixtures.

	Ingredient	Toxic	Harmful
1.	Category 1 R47	≥0.2% R47	
2.	Category 2 R47		≥1% R47

concentrations are in % v/v

APPENDIX V

CLASSIFYING A MIXTURE USING THE CONCENTRATION CUT-OFF LEVEL CONCEPT

Example. 1: A substance containing 0.5% w/w Paraquat

I. The data shows that paraquat is Very Toxic on the basis of its acute lethal effects (risk phrase R26/R27/R28).

II. Therefore, Paraquat meets health effects criteria. The concentration cut-off levels of Appendix IV should now be applied.

III. According to Table 1, a mixture with 0.5% w/w of a Very Toxic substance is to be classified as Harmful, as the concentration is below the concentration cut-off level for a Very Toxic mixture (7%). It is also below the concentration cut-off level for a Toxic mixture (1%), but within the range (0.1-1%) for a Harmful mixture . The substance is therefore a hazardous substance and is classified as Harmful, with R20/21/22 the most appropriate risk phrase.

Example 2: **A substance containing 7% w/w Acrylic acid**

I. The data show that Acrylic acid is Corrosive (risk phrase R34).

II. Therefore, Acrylic acid meets the health effects criteria of section 3. The concentration cut-off levels of Appendix IV should now be applied.

III. According to Table 7, a mixture with 7% w/w of a Corrosive substance is to be classified as Irritant, as the concentration is in the range 5-10%, but below the cut-off level for a level for a Corrosive mixture (10%). The substance is therefore a hazardous substance and is classified as Irritant, with R36/38 the most appropriate risk phrase.

Example 3: A substance containing 70% w/w 2-Hydroxyethylamine and 30% w/w Amyl alcohol.

I. As the substance is a mixture, its classification depends on whether the mixture has been tested as a whole and whether it has health effects that meet the criteria in Appendix 1. If the mixture has not been tested as a whole, the availability of the health effects data on the ingredients (2-Hydroxyethylamine and Amyl alcohol) needs to be considered.

II. The data available for 2-Hydroxyethylamine and Amyl alcohol show that:

III. 2- Hydroxyethylamine is Harmful by inhalation on the basis of its acute lethal effects (risk phrase R20) and is an Irritant (risk phrase R36/37/38); and

IV. Amyl alcohol is harmful by inhalation on the basis of its acute lethal effects (risk phrase R20).

V. Therefore, both 2-Hydroxyethylamine and Amyl alcohol meet the health effects criteria of paragraph 3. The concentration cut-off levels of Appendix IV should now be applied.

VI. According to Table 7, a mixture containing an Irritant (risk phrase R36/37/38) at a concentration above 20% w/w is a hazardous substance and the mixture is classified as Irritant, with risk phrase R36/37/38 considered appropriate.

VII. Therefore, according to the health effects criteria of section 3 and the concentration cut-off levels of Table1 and Table 7, a 70% 2-Hydroxyethylamine and 30% Amyl alcohol mixture is a hazardous substance and the mixture is classified as Harmful and irritant, with the R20 and R36/37/38 the most appropriate risk phrases. The final classification for this mixture is Harmful.

Example 4: A substance containing 0.5% w/w 3,3- Dichlorobenzidine.

I. The data shows that 3,3- Dichlorobenzidine is:

- a category 2 Carcinogen;
- Harmful by skin contact on the basis of its acute lethal effects; and
- a skin sensitiser.

I. Therefore, 3,3- Dichlorobenzidine meets the health effects criteria of section 3. The concentration cut-off levels of Table 1-14 should now be applied.

II. According to Table 1, a mixture with 0.5% w/w of a Harmful substance is not a hazardous substance on the basis of its acute lethal effects.

III. According to Table 9, a mixture with 0.5% w/w of a skin sensitiser is not a hazardous substance on the basis of its sensitising effects.

IV. According to Table 11, a mixture with 0.5% w/w of a Category 2 Carcinogen is to be classified as Toxic, with risk phrase R45 to be assigned to the mixture. The substance is therefore a hazardous substance and is classified as Toxic with risk phrase R45.

Example 5: A substance containing 10% w/w Methyl mercaptan, 20% w/w n-Pentanol and 2% w/w 2,4,6- Trinitrophenol.

1. The data show that:

- Methyl mercaptan is Harmful by inhalation on the basis of its acute lethal effects (risk phrase R20);

- n-Pentanol is Harmful by inhalation on the basis of its acute lethal effects (risk phrase R20); and

- 2,4,6-Trinitrophenol is Toxic if swallowed on the basis of its acute lethal effects (risk phrase R23/24/25).

1. Therefore, each of the three ingredients in the mixture meets the health effects criteria of section 3. The concentration cut-off levels of Table 1-14 should now be applied.

2. According to Table 1, a mixture with less than 25% w/w of a Harmful ingredients is not classified as hazardous substance on the basis of its acute lethal effects. Similarly, a mixture with less than 3% w/w of a Toxic ingredient is not classified as a hazardous substance on the basis of its acute lethal effects. Since all hazardous ingredients in the mixture are in concentrations below their respective cut-off levels and they have similar health effects, the formulae of Appendix I must be used to determine whether the mixture overall is a hazardous substance.

3. Assuming that the three ingredients have additive health effects, the appropriate formulae in Appendix 1 can be applied.

   Step 1: Consider the concentration cut-off levels for a Toxic mixture. These are in Table 1 for acute lethal effects that is:

   for a Toxic ingredient, 25% w/w;

   for a Harmful ingredient, no concentration cut-off level is given in the table as it is not appropriate.

   Therefore, a mixture is not classified as Toxic as the only toxic ingredient (2,4,6-Trinitrophenol) is present at concentration below 25% w/w, the sum is less than 1, that is:

   %B/conc. = 2/25

   Step 2 : Consider the concentration cut-off levels for a Harmful mixture In Table 1, that is:

   - for a Very Toxic ingredient, 0.1% w/w;
   - for a Toxic ingredient, 3% w/w; and
   - for a Harmful ingredient, 25% w/w.

   Therefore, the formula for a Harmful mixture in Appendix 1 can be applied.
   $\sum (\%A/CCL_A + \%B/CCL_B + \%C/CCL_C) \geq 1$

   where
   %C = percentage by weight of each harmful ingredient
   CCL_C = concentration cut-off level for each harmful ingredient

   There are no Very Toxic ingredients, so there is no %A, that is:
   $CCL_C = 0/0.1$

   2,4,6-Trinitrophenol is the only Toxic ingredient, so:

   $\%B/CCL_B = 2/3$

   Methyl mercaptan and n-Pentanol are both Harmful ingredients, so:

   $\%C/CCL_C = 10/25 + 20/25 + = 30/25$

   Applying the formula:

   $\sum (\%A/CCL_A + \%B/CCL_B + \%C/CCL_C)$

$\sum$ = [0/0.1 + 2/3 + 30/25] = 1.9, which is ≥ 1

Therefore, the mixture is a hazardous substance and is classified as Harmful with R20/21/22 the most appropriate risk phrases.

Example 6: A substance containing 15% w/w 3-Chlorophenol and 10% w/w Bromobenzene.

I. The available data show that:

- 3-Chlorophenol is Harmful on the basis of its acute lethal effects (risk phrase R20/21/22); and
- Bromobenzene is Irritant on contact with the skin (risk phrase R38).

I. Therefore, each of the two ingredients in the mixture meets the health effects criteria of section 4. The concentration cut-off levels in Table1-14 should now be applied.

II. According to Table1, a mixture containing less than 25% w/w of a Harmful ingredients not classified as a hazardous substance on the basis of its acute lethal effects. According to Table 7, a mixture containing less than 20% w/w of an Irritant is not classified as a hazardous substance on the basis of its irritant effects.

III. As the health effects for each ingredient are different, they are not additive, so it is not necessary to apply the formulae in Appendix 1. The mixture is therefore not a hazardous substance.

APPENDIX VI

CHOICE OF RISK PHRASES

CLASS	RISK PHRASE	PROPERTIES
VERY TOXIC SUBSTANCES AND PREPARATIONS	R26 *(Very toxic by inhalation)*	Acute toxicity results LC_{50} inhalation, rat: <0.5 mg/litre per 4 hours.
	R27 *(Very toxic in contact with skin)*	Acute toxicity results LD_{50} dermal, rat or rabbit: < 50 mg/kg.
	R28 *(Very toxic if swallowed)*	Acute toxicity results LD_{50} oral, rat: < 25 mg/kg.
	R39 *(Danger of very serious irreversible effects)*	Strong evidence that irreversible damage other than the effects referred to in paragraph 4 is likely to be caused by a single exposure by an appropriate route, generally in the above mentioned dose range . In order to indicate the route of administration/exposure the following combinations should be used: R39/26, R39/27, R39/28, R39/26/27, R39/26/28, R39/27/28, R39/26/27/28.
TOXIC SUBSTANCES AND PREPARATIONS	R23 *(Toxic by inhalation)*	Acute toxicity results LC_{50} inhalation, rat: 0.5 < LC_{50} < 2mg/litre per 4 hours
	R24 *(Toxic in contact with skin)*	Acute toxicity results LC_{50} inhalation, rat or rabbit : 50 < LD_{50} < 400 mg/kg

	R25 *(Toxic if swallowed)*	Acute toxicity results LD_{50} oral, rat: 25 <LD_{50} <400 mg/kg
	R39 *(Danger of very serious irreversible effects)*	Strong evidence that irreversible damage other than the effects referred to in section 4 is likely to be caused by a single exposure by an appropriate route, generally in the above mentioned dose range. In order to indicate the route of administration/exposure the following combinations should be used: R39/23, R39/24, R39/25, R39/23/24, R39/23/25, R39/24/25, R39/23/24/25.
CLASS	**RISK PHRASE**	**PROPERTIES**
TOXIC SUBSTANCES AND PREPARATIONS	R48 *(Danger of serious damage to health by prolonged exposure)*	Serious damage (clear functional disturbance or morphological change which have toxicological significance) is likely to be caused by repeated or prolonged exposure by an appropriate route. Substances are classified at least as toxic when these effects are observed at levels of one order of magnitude lower (i.e ten fold) than those set out for R48 under harmful classification. In order to indicate the route of administration/exposure the following combinations should be used: R48/23, R48/24, R48/25, R48/23/24, R48/23/25, R48/24/25, R48/23/24/25.
HARMFUL SUBSTANCES AND PREPARATIONS	R20 *(Harmful by inhalation)*	Acute toxicity results ; LC_{50} inhalation rat: 2< LC_{50} < 20mg/litre per 4 hours
	R22 *(Harmful if swallowed)*	Acute toxicity results LD_{50}, rat: 200 < LD_{50} < 2000mg/kg
	R40 *(Possible risk of irreversible effects)*	Strong evidence that irreversible damage other than the effects referred to in paragraph 4 is likely to be caused by a single exposure by an appropriate route, generally in the above-mentioned dose range. In order to indicate the route of administration/exposure the following combinations should be used: R40/20, R40/21, R40/22, R40/20/21, R40/20/22, R40/21/22, R40/20/21/22.
	R42 *(May cause sensitisation by inhalation)*	If practical evidence is available which shows the substances and preparations to be capable of inducing a sensitisation reaction in humans by inhalation, at a greater frequency than would be expected from the response of a general population.
	R48 *(Danger of serious damage to health by prolong exposure)*	Serious damage (clear functional disturbance or morphological change which toxicological significance) is likely to be caused by repeated or prolonged exposure by an appropriate route.

		In order to indicate the route of administration/exposure the following combination should be used: R48/20, R48/21, R48/22, R48/20/21, R48/20/22, R48/21/22, R48/20/21/22.
CLASS	**RISK PHRASE**	**PROPERTIES**
CORROSIVE SUBSTANCES AND PREPARATIONS	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.
IRRITANT SUBSTANCES AND PREPARATIONS	R36 *(Irritating to eyes)*	If, when applied to the eye of the animal, significant ocular lesions are caused and which persist for 24 hours or more after instillation of the test material. Ocular lesions are significant if the means of the scores have any of the values: Cornea opacity equal to or greater than 2 but less than 3: iris lesion equal to or greater than 1 but not greater than 1.5: redness of the conjunctivae equal to or greater than 2.5: oedema of the conjunctivae (chemosis) equal to or greater than 2. The same shall be the case where the test have been completed using 3 animals if the lesions, on two or more animals, are equivalent to any of the above values except that for iris lesion the value should be equal to or greater than but less than 2 and for redness of conjunctivae the value should be equal to or greater than 2.5.
	R37 *(Irritating to the respiratory system)*	Substances and preparations which cause serious irritation to the respiratory system, based normally on practical observation.
	R38 *(Irritating to skin)*	If when applied to healthy intact animal skin for up to four hours, significant inflammation is caused and which persists for 24 hours or more after the end of exposure period. Inflammation is significant if the mean value of the scores is two or more for either erythema and eschar formation or oedema formation. The same shall be the case where the test has been completed using three animals, if the score for either erythema and eschar formation or oedema formation observed in two or more animals is equivalent to the value of two or more.
CLASS	**RISK PHRASE**	**PROPERTIES**
IRRITANT SUBSTANCES AND PREPARATIONS	R41 *(Risk of serious damage to eye)*	If when applied to the eye of the animal severe ocular lesions are caused and which are present 24 hours or more after instillation of the

		test material. Ocular lesions are severe if the means of the score have any of the values: cornea opacity equal to or greater than 3; iris lesion greater than 1.5. The same shall be the case where the test has been completed using three animals if these lesion, on two or more animals, have any of the values: cornea opacity equal to or greater than 3; iris lesion equal to 2. The use of R34 or R35 precludes the use of R41.
	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 person by skin contact, or on the basis of a positive response in experimental animals. In the case of the adjuvent type test method for skin sensitised detailed in the Directives or in the case of other adjuvent-type test methods, a response of at least 30% of the animals is considered positive. For any other test method a response of at least 15% of the animals is considered positive.

ADDITIONAL RISK PHRASES

R29 *(Contact with water liberates toxic gas)*	For substances and preparations which in contact with water or damp air, evolve very toxic/toxic gases in potentially dangerous amounts, e.g aluminium phosphide, phosphorus pentasulphide.
R31 *(Contact with acids liberates toxic gas)*	For substances and preparations which react with acids to evolve toxic gases in dangerous amounts e.g. sodium hypochlorite, barium polysulphide.
R32 *(Contact with acids liberates very toxic gas)*	For substances and preparations which react with acids to very toxic gases in dangerous amounts; e.g. salts of hydrogen cyanide, sodium azide.