APPROVED CRITERIA FOR CLASSIFYING HAZARDOUS SUBSTANCES

[NOHSC:1008(1999)]

APRIL 1999

The National Occupational Health and Safety Commission has declared *Approved Criteria for Classifying Hazardous Substances*, 2nd Edition .

National standards declared by the National Commission under s.38(1) of the *National Occupational Health and Safety Commission Act 1985* (Cwlth) are documents which prescribe preventive action to avert occupational deaths, injuries and diseases. Most national standards deal with the elimination/reduction or management of specific workplace hazards.

The expectation of the Commonwealth Government and the National Commission is that national standards will be suitable for adoption by Commonwealth, State and Territory governments. Such action will increase uniformity in the regulation of occupational health and safety throughout Australia and contribute to the enhanced efficiency of the Australian economy.

It should be noted that National Commission documents are instruments of an advisory character, except where a law, other than *the National Occupational Health and Safety Commission Act*, or an instrument made under such a law, makes them mandatory. The application of any National Commission document in any particular State or Territory is the prerogative of that State or Territory.

National Occupational Health and Safety Commission

APPROVED CRITERIA FOR CLASSIFYING HAZARDOUS SUBSTANCES [NOHSC:1008(1999)]

APRIL 1999

National Occupational Health and Safety Commission
Sydney

ISBN 0-642-37332-9

First Edition 1994
Second Edition 1999

Foreword

The National Occupational Health and Safety Commission (NOHSC) is a tripartite body established by the Commonwealth Government to lead and coordinate national efforts to prevent or reduce the incidence and severity of occupational injury and disease by providing healthy and safe working environments. In seeking to improve Australia's occupational health and safety (OHS) performance, NOHSC works to:

- support and add value to efforts in the jurisdictions to tailor approaches to prevention improvement;
- facilitate, through strategic alliances, the development and implementation of better approaches to achieving improved prevention outcomes; and
- integrate the needs of small business into its work.

NOHSC's priorities, as endorsed by the Labour Ministers' Council (LMC) at its meeting on 27 November 1998, are:

- providing comprehensive and accurate national data, particularly to support LMC's comparative performance monitoring;
- facilitating and coordinating research efforts;
- developing and updating a nationally consistent standards framework (subject to LMC agreement);
- coordinating and disseminating information including industry specific practical guidance material; and
- developing a National OHS Improvement Strategy.

Preface

Under the National Commission's *National Model Regulations for the Control of Workplace Hazardous Substances* [NOHSC:1005(1994)][1] and the Commonwealth, State and Territory government regulations introduced in accordance with the national model regulations, manufacturers and importers of substances supplied for use at work are required to determine whether they are hazardous to health before supply. They are also required to produce labels and Material Safety Data Sheets (MSDS) for all hazardous substances, with appropriate information about the hazards of these substances.

Determining whether a substance is hazardous to health is central to a number of initiatives in the management of substances used in the workplace.

In determining whether a substance is hazardous to health or not, manufacturers and importers should first refer to the *List of Designated Hazardous Substances* [NOHSC:10005(1999)][2] (the List) published by the National Commission. The List comprises the more common hazardous substances which meet the National Commission's *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(1999)] (the Approved Criteria). If a substance is on the List, it is a hazardous substance under the *National Model Regulations for the Control of Workplace Hazardous Substances* [NOHSC:1005(1994)][1]. The List is therefore an aid to determining and classifying hazardous substances.

Where a substance is not included on the List, the manufacturer or importer will need to use the Approved Criteria to determine if it is hazardous to health. If the substance is determined to be hazardous, the Approved Criteria enable the health hazard(s) to be classified so that MSDS and labels can be more easily prepared.

The classification criteria used in this publication are the same as those used by the European Communities in their legislation for classifying dangerous substances, namely:

- EC Council Directive 67/548/EEC[3] on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances; and

- EC Council Directive 88/379/EC[4] on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous preparations.

To take into account technical progress and changes in the EC Council Directives, it is intended that the classification criteria contained in the Approved Criteria be updated from time to time.

This second edition has been updated to generally reflect the current status of EC Council Directive 67/548/EEC [as amended by EC Commission Directive 96/54/EC[5]]. Changes in this second edition include new or revised criteria relating to the classification of:

- reproductive toxicity
- corrosivity
- aspiration hazards
- sensitising effects, and
- acute oral effects - discriminating dose,

The ADG Code (*Australian Code for the Transport of Dangerous Goods by Road and Rail*) criteria for classifying corrosivity previously adopted in the first edition of this publication has been replaced in this second edition with that of EC Council Directive 67/548/EEC[3].

Furthermore, the criteria for teratogenic effects, previously adopted in the first edition, has now been replaced in this second edition with criteria for determining reproductive toxicity.

In summary then, these Approved Criteria are designed to be used by manufacturers and importers for determining whether substances are hazardous or not, and for preparing labels and MSDS. They will also be used by the National Commission in reviewing and maintaining the List.

It is not expected that employers and employees using substances in the workplace will need to apply these criteria; they would normally identify hazardous substances from the supplier's label, the MSDS or, for those substances produced in the workplace, by reference to the List.

Manufacturers and importers are expected to use the Approved Criteria in conjunction with Commonwealth, State and Territory government regulations and codes of practice introduced to regulate workplace hazardous substances.

This publication is one of six titles produced by the National Commission and released together as part of its workplace hazardous substances regulatory package. The six titles that comprise the set are:

- *National Model Regulations for the Control of Workplace Hazardous Substances* [NOHSC:1005(1994)] (which is produced under the same cover as the national code of practice);

- *National Code of Practice for the Control of Workplace Hazardous Substances* [NOHSC:2007(1994)];

- *National Code of Practice for the Preparation of Material Safety Data Sheets* [NOHSC:2011(1994)];

- *National Code of Practice for the Labelling of Workplace Substances* [NOHSC:2012(1994)];

- *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(1999)]; and

- *List of Designated Hazardous Substances* [NOHSC:10005(1999)].

These publications are supplemented by the following titles:

- *Guidance Note for the Assessment of Health Risks Arising from the Use of Hazardous Substances in the Workplace* [NOHSC:3017(1994)]; and

- *Guidance Note for the Control of Workplace Hazardous Substances in the Retail Sector* [NOHSC:3018(1994)].

As more information becomes available or practices and formats change, the National Commission maintains the regulatory package with reviews and updates of the individual titles from time to time. It is advisable to check the currency of a document prior to purchasing. Each of the above publications may be purchased separately through the Commonwealth Government Info Shops or are available on the National Occupational Health and Safety Commission website at http://www.worksafe.gov.au

Chapter 1 Introduction

1.1 The *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(1999)] are cited in the *National Model Regulations for the Control of Workplace Hazardous Substances* [NOHSC:1005(1994)][1] and provide the mandatory criteria for determining whether a substance is hazardous or not.

1.2 The Approved Criteria also provide examples showing how to apply the classification criteria to determine whether a substance is hazardous to health and for classifying the nature of the hazard(s).

Classification of Hazardous Substances - Manufacturers' and Importers' Duties.

1.3 The responsibility for determining whether a substance is hazardous and for identifying its health hazards belongs to the manufacturer or importer. If the substance or mixture cannot be classified, it cannot be supplied.

1.4 Although manufacturers and importers are responsible for determining whether substances are hazardous or not and for their classification, they do not have to carry out this work themselves. However, they should ensure that the work is carried out by a competent person.

1.5 In this context, a competent person is a person who understands the Approved Criteria and who has the skills and experience to apply the criteria to the information about the substance.

1.6 Once a manufacturer or importer determines that a substance is hazardous in accordance with the Approved Criteria and that substance does not already appear on the List, the manufacturer/importer is required to notify the National Commission of that determination. Notification of a hazardous substance shall be made to the National Commission on the approved form (see Appendix 1).

1.7 The Approved Criteria focus only on hazards to health. They do not cover physicochemical hazards - defined in the *Dangerous Goods* Code[6] - which are addressed under the relevant dangerous goods legislation of the Commonwealth, State and Territory governments. Manufacturers and importers will need to consider physicochemical hazards in addition to these criteria when producing labels and MSDS.

Definition of a hazardous substance

1.8 Under the *National Model Regulations for the Control of Workplace Hazardous Substances* [NOHSC:1005(1994)][1], a hazardous substance means a substance which:

(1) is listed on the *List of Designated Hazardous Substances* [NOHSC:10005(1999)][2]; or

(2) has been classified as a hazardous substance by the manufacturer or importer in accordance with the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(1999)].

1.9 The List contains the more common workplace hazardous substances, but is not an exhaustive list of all hazardous substances.

1.10 The List is intended primarily as an aid for determining if a substance is hazardous or not. However, if a substance is included on the List, it is a hazardous substance under hazardous substances regulations.

1.11 The List should be checked as the initial reference source to establish whether the substance or, if it is a mixture, any ingredients, are listed.

1.12 Where a substance or, in the case of mixtures, an ingredient, is not included on the List, it will be necessary to assess information about its health effects against the Approved Criteria in order to determine whether it is hazardous or not.

1.13 From such an assessment, the nature of the hazard (if any) presented by the substance can be identified and classified with the most appropriate risk phrases selected for each hazardous substance. Classification of substances is important in producing labels and MSDS as required by Commonwealth, State and Territory government regulations introduced in accordance with the *National Model Regulations for the Control of Workplace Hazardous Substances* [NOHSC:1005(1994)][1].

1.14 The national model regulations do not apply to radioactive and infectious substances or substances which are solely dangerous goods or hazardous to the environment. Therefore, the Approved Criteria do not address these hazards.

The criteria

1.15 The criteria for determining whether a substance is hazardous to health are in three parts:

Chapter 4	contains the **health effects criteria** for classifying a substance on the basis of its health effects;
Chapter 5	provides **concentration cut-off levels** for ingredients which have satisfied the health effects criteria of Chapter 4. There is a concentration cut-off level corresponding to each type of health effect and hazard category; and
Chapter 6	lists **formulae** to be used in classifying mixtures which may be hazardous due to the additive effects of ingredients which have satisfied the health effects criteria in Chapter 4, but whose concentrations do not exceed the concentration cut-off levels in Chapter 5.

1.16 Guidance on applying the criteria and concentration cut-off levels to determine whether a substance is hazardous to health is provided in Chapter 3.

1.17 ***Substances with similar health effects can produce an additive effect greater than would be suggested by their individual concentrations. Therefore, the concentration cut-off levels are designed to provide a practical level of protection and should not be used to imply that an effect cannot occur below that level.***

1.18 The health effects criteria (Chapter 4) are the same as those used by the European Communities in EC Council Directive 67/548/EC[3] [as amended by EC Commission Directive 96/54/EC[5]] for classifying substances hazardous to health.

1.19 The criteria will be revised periodically to maintain consistency with European Commission Council Directives.

1.20 Concentration cut-off levels (Chapter 5) are taken from EC Council Directive 88/379/EC[4] [as amended by EC Commission Directive 93/18/EC[7]] relating to the classification, packaging and labelling of dangerous preparations.

1.21 The risk phrases relevant to the different types of health effects (Appendix 3) are taken from EC Council Directive 67/548/EC[3] and its subsequent amendments.

Chapter 2 Definition of terms used in this document

Absorption	The process(es) by which an administered substance enters the body.
Acute toxicity	The adverse effects occurring within a given time (usually 14 days), after administration of a single dose of a substance.
Aerosol	Particles (solid and/or liquid) homogeneously dispersed in air.
Alopecia	Partial or complete lack or loss of hair.
Alveolitis	A condition of inflammation of the alveoli of the lungs. When air enters your lungs, it goes through a maze of smaller and smaller tubes until it reaches tiny sacs called alveoli. The alveoli are where the oxygen from the air enters your blood, and the carbon dioxide from your body goes into the air. Alveoli are very tiny, but you have 300,000,000 alveoli in each lung.
Aneuploidy	A condition in which a cell or organism has an abnormal total number of chromosomes and/or where numbers of individual chromosomes are not in proportion with the numbers of the other chromosomes. Hyperploidy is the presence of too many chromosomes. Hypoploidy is the presence of too few. A single set of chromosomes (which is half the full complement of genetic material), is present in the reproductive cells (egg and sperm cells) of animals and in the reproductive cells (egg and pollen cells). Human beings have 23 chromosomes in their reproductive cells (haploid) and 46 in their non-reproductive cells (diploid).
Aplasia	A condition which manifests in defective or incomplete tissue development.
Article	An item which is formed to a specific shape, surface or design during production, has an end function dependent in whole or in part on its shape or design, and which undergoes no change in chemical composition and physical state during its life cycle, including its end use except as an intrinsic aspect of that end use. Fluids and particles are not considered articles, regardless of the shape or design.

Aspiration hazards	A phrase used with respect to risk phrase R65, whereby low viscosity liquid chemicals can be dangerous to human health if they enter the lung through swallowing or vomiting.
Bradypnea	Abnormal slowness of breathing.
Can	Implies a capability or possibility, or a possibility that is available or that might occur.
Cancer	A malignant tumour which can spread to other organs of the body. As distinct from a benign tumour which cannot. (Although leukaemia and some other malignant diseases are not solid tumours, they meet other criteria for cancer and can be, and often are, included under this definition).
Carcinogen	An agent which is responsible for the formation of a cancer.
Carcinogenesis	The causing of cancer.
Chemical	Any element, compound or complex present as an entity or contained in a mixture.
Chemical Abstracts Service Registry Number (CAS Number or CAS No.)	The unique number assigned to a chemical by the Chemical Abstracts Service, Columbus, Ohio, USA.
Chemosis	Excessive oedema of the ocular conjunctiva.
Chromosome	One of the threadlike, rodlike structures in the nucleus of cell which carry the genetic information in the cell. Each species has a characteristic number of chromosomes, which in humans is 46.
Chronic toxicity	A toxic effect which occurs after repeated or prolonged exposure. Chronic effects may occur some time after exposure has ceased.
Classification	The process whereby the toxicological, physicochemical and ecotoxicological properties of a substance are identified and categorised.
Conjunctiva	The mucous membrane covering the anterior portion of the eyeball reflected upon the lids and extending to their free edges.

Corrosivity	The property of a chemical indicating its capacity to cause corrosion.
Cytogenetic	The branch of genetics devoted to study of the cellular constituents concerned with heredity, primarily the structure, function and origin of the chromosomes.
Deoxyribonucleic acid (DNA)	A large nucleic acid molecule, which contains the genetic sequence or code, found principally in the chromosomes of the nucleus of a cell. The crucial property of DNA is that it consists of two strands which are complementary joined by weak chemical bonds called hydrogen bonds. A single DNA strand is made up of four molecules called nucleotides which bind to another DNA strand via base pairs. The bases are called guanine, cytosine, adenine and thymine. Guanine pairs with cytosine and adenine with thymine. It is the specific sequence of these nucleotides which create the genetic code. Damage to the DNA may result in damage to the information carried on the DNA. This may give rise to genetic errors in the cell which may manifest in abnormal growth and metabolism of the cell.
Dermal	Relating to the skin.
Dermal Corrosion	The production of irreversible tissue damage in the skin following the application of a test substance for the duration period of 3 minutes up to 4 hours.
Distribution	The process(es) by which the absorbed substance and/or its metabolites partition within the body.
Dosage	A general term comprising of dose, its frequency and the duration of the dosing.
Dose	The amount of test substance administered. Dose is expressed as weight (grams or milligrams) or as weight of test substance per unit weight of test animal (eg. milligrams per kilogram body weight), or as constant dietary concentrations (milligrams per kilogram of food).
Discriminating dose	Used with reference to the fixed dose procedure, a discriminating dose is the highest out of four fixed dose levels (5, 50, 500 or 2000 mg/kg) which can be administered without causing compound-related mortality (including humane kills).
Dysfunction	A state of abnormal, incomplete or impaired function.
Embryotoxic	Pertaining to anything that is toxic to an embryo.

Entity	A single substance and includes discrete chemical elements, compounds and complexes which may exist as pure or technical grade or as components in a physical mixture of substances.
Epidemiological	Relating to the study of the relationships determining the frequency and distribution of disease in a human community.
Erythema	Redness or inflammation of the skin or mucous membranes.
Eschar	The slough or dry scab, for example, that forms on an area of skin that has been burned.
EuroNorm (EN)	A European Union standard that requires implementation at the national level by EU member countries.
Evident toxicity	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.
Excretion	The process(es) by which the administered substance and/or its metabolites are removed from the body.
Eye irritation	The production of changes in the eye following the application of a test substance to the anterior surface of the eye.
Fertility	The capacity to conceive or induce conception.
Fibrosis	The development of fibrous tissue in a part of an organ.
Fixed dose procedure	See Appendix 2.
Foetotoxic	Pertaining to anything that is toxic to a foetus.
Gastritis	Inflammation of the gastric mucosa.
Gavage	A procedure of feeding in which a tube passed through the nose or mouth into the stomach.
Gene	A unit of inheritable genetic material made up of a specific sequence of deoxyribonucleic acid (DNA) on a chromosome.

Genotoxin	A substance capable of causing damage to genetic material, such as DNA.
Germ cell	A sexual reproductive cell in any stage of development, from the primordial embryonic form to the mature gamete.
Granuloma	Chronic inflammatory lesion characterised by large numbers of cells of various types (macrophages, lymphocytes, fibroblasts, giant cells), some of which are involved in tissue degradation and/or tissue repair.
Hazard	An intrinsic capacity associated with an agent or process capable of causing harm.
Hazardous substance	A substance which: • is listed on the National Occupational Health and Safety Commission's List of Designated Hazardous Substances [NOHSC:10005(1999)][2]; or • has been classified as a hazardous substance by the manufacturer or importer in accordance with the National Occupational Health and Safety Commission's Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(1999)].
Health effects criteria	The basis on which a substance is evaluated with respect to its toxicological data.
Hyperplasia	The abnormal multiplication or increase in number of normal cells in normal arrangement in a tissue.
Hypersensitivity	A state of excessive and potentially damaging responsiveness to a chemical or other substance. If immunologically mediated, hypersensitivity often occurs as a result of previous exposure to the substance or closely related substance. If the hypersensitivity is of the immediate type (antibody-mediated), then the response occurs in minutes; in delayed hypersensitivity the response takes longer (about 24hr) and is mediated by primed T cells.
Hypertrophy	Enlargement or overgrowth of an organ or part due to an increase in size of constituent cells.
Hypoplasia	Incomplete development of an organ so that it fails to reach adult size.

Inanition	A condition characterised by marked weakness, extreme weight loss and a decrease in metabolism resulting from prolonged and severe insufficiency of food.
Ingredient	Any component of a substance (including impurities), in a mixture or combination.
Inhalation	Breathing in.
In vitro	Observation made in outside the living body, usually in laboratory equipment for example, test tube.
In vivo	Observation made in a living organism either in animals or humans.
Label	A set of information on a container that identifies the substance in the container identifies whether the substance is hazardous and provides basic information about the safe use and handling of the substance.
LC_{50}	Median lethal concentration. A statistically derived concentration of a substance that can be expected to cause death during exposure or within a fixed time after exposure in 50% of animals exposed for a specified time. The LC_{50} value is expressed as weight of test substance per standard volume of air (milligrams per litre).
LD_{50}	Median lethal dose. A statistically derived single dose of a substance that can be expected to cause death in 50% of dosed animals. The LD_{50} value is expressed in terms of weight of test substance per unit weight of test animal (milligrams per kilogram).
Lesion	A discontinuity of tissue or loss of function of a part of the body as a result of disease or trauma.
Material Safety Data Sheet (MSDS)	A document that describes the properties and uses of a substance, that is, identity, chemical and physical properties, health hazard information, precautions for use and safe handling information.
Maximum Tolerated Dose (MTD)	The highest dose level eliciting signs of toxicity in animals without having major effects on survival relative to the test in which it is used.
May	Indicates that a requirement is optional.

Metabolism	The process(es) by which the administered substances are structurally changed in the body either by enzymatic or non-enzymatic reactions.
Mixture	A physical combination of chemicals resulting from the deliberate mixing of those chemicals or from a chemical reaction.
Mutagen	An agent capable of producing a mutation.
Mutagenesis	The process of producing a mutation.
Mutagenic	Able to produce a mutation.
Mutation	A change in the genetic material of cells.
Myocardium	The muscular structure of the heart.
Necrosis	Changes which are indicative of cell death.
Neoplasm	Any abnormal growth of new tissue, benign or malignant.
Nephrosis	A syndrome caused by a primary non-inflammatory degeneration of the renal tubules.
NOAEL	The abbreviation for no observed adverse effect level. The highest dose or exposure level where no adverse treatment-related findings are observed.
Ocular	Of the eye or affecting the eye.
Oedema (edema)	Excessive accumulation of fluid in the tissue spaces of the body due to increase transudation of the fluid from the capillaries.
Oogenesis	The process of the formation of the female reproductive cells.
Oral	Ingested or administered via the mouth.
Particulate	Pertaining to a minute discrete particle or fragment of a substance or material.
Perinatal	Pertaining to or occurring in the period shortly before and after birth.
Phenotype	The visible form of an organism, as contrasted with its genetic character (genotype). In different environments the same genotype may produce different phenotypes.

Point mutation	A point mutation is a mutation that cause the replacement of a single base pair with another. This result is the misreading of the correct nucleotide as another. (see DNA)
Postnatal	Occurring after birth, with reference to the newborn.
Progeny	Offspring or descendants.
Repeated dose/ Sub chronic toxicity	The adverse effects occurring in experimental animals as a result of repeated daily dosing with, or exposure to, a chemical for a short part of their expected life-span.
Reproductive hazard	An agent capable of causing abnormalities in a developing foetus, that is, causing birth defects.
Resorption	The process of breaking down and absorbing already formed tissues and structures in an organism. Early resorption of the developing foetus is thought to be caused by errors in development which may result from chemical damage to the foetus.
Rhinitis	A inflammation of the mucous membranes of the nose, runny nose.
Risk	The likelihood that a substance will cause harm in the circumstances of its use.
Sensitisation	To become sensitive/allergic to the effects of minute quantities of a substance.
Should	Indicates a recommendation.
Sister chromatid exchange	A technique used for monitoring DNA damage in a pair of chromosomes during one of the phases of cell division. Undamaged segments are exchanged for damaged segments between homologous duplex DNA molecules.
Skin irritation	The production of inflammatory changes in the skin following the application of a test substance.
Somatic cells	Cells of the body other than germ cells.
Spermatogenesis	The process of formation of spermatozoa.

Substance	Any natural or artificial entity, composite material, mixture or formulation, other than an article.
Teratogen	An agent capable of causing abnormalities in a developing foetus, that is, causing birth defects.
Toxicity	The capacity of an agent to produce damage to an organism. This usually refers to functional (systemic) damage but may be developmental in respect of tissue and skeleton in the case of the embryo. The damage may be permanent or transient.
Toxicokinetics	The study of the absorption, distribution, metabolism and excretion of test substances.
Tumour	A swelling or enlargement or an abnormal mass of tissue in which the growth of cells is uncontrolled. A tumour can be either benign (not malignant) or malignant (cancerous). A tumour is also called a 'neoplasm'.
Unscheduled DNA synthesis (UDS)	Unscheduled DNA synthesis (UDS) refers to DNA synthesis occurring outside of the usual replication phase of the cell cycle when chromosomes are duplicated. UDS in animal cells in vitro measures the repair of DNA damage induced by variety of agents including chemicals, radiation and viruses.
Urticaria	A vascular reaction of the skin characterised by the formation of evanescent whitish, pink or red elevations or weals, with itching, stinging or burning.

Chapter 3 How to apply the criteria

3.1 This chapter gives guidance on how to use the health effects criteria given in Chapter 4 to determine whether a substance is hazardous. If the substance is a mixture, then the criteria in Chapter 5 and Chapter 6 should also be used. See also the flow chart at the end of this chapter.

3.2 The guidance given in this chapter is to be used when the substance is not already on the List.

3.3 The criteria in this publication are applicable to all substances including gaseous substances.

3.4 Classifying the substance will involve finding and putting together all the available information on the substance and assessing this information against the criteria. This process will identify the health hazards of the substances and appropriate risk phrases to be used.

3.5 The method of applying the criteria to determine whether a substance is hazardous to health will depend on:

- whether the substance is an ingredient in a mixture; and
- whether the mixture has been tested as a whole for its health effects.

3.6 Information on health effects for a substance can be obtained from a number of different sources, for example:

- scientific reference works and literature;
- practical experience, for example, the health effects of the substance on exposed persons;
- the results of experimental animal testing;
- information required by international rules on the transport of dangerous goods and notification of hazardous substances; and
- existing classifications for substances which have similar structural relationships.

See Appendix 1 for further suggestions on information resources.

3.7 It is not intended that additional animal testing will need to be carried out.

3.8 The classification of substances should include consideration of all the toxicological properties covered in Chapter 4.

3.9 Some substances do not pose a hazard to human health by ingestion, inhalation or contact with the skin in the form in which they are supplied, for example, certain polymers. In these cases, the available information may show that they may be determined not to be hazardous.

3.10 If evidence is available to show that in practice the toxic effect of a substance on humans is, or is likely to be, different from that suggested by the results of animal testing, then the substance should be classified according to its toxicity in humans.

3.11 If only some information is available for the substance, then the health effects criteria and other suitable information should be applied as far as possible to classify the substance. For assistance in classification matters which may be difficult or contentious, the relevant Commonwealth, State or Territory government authority should be consulted for assistance.

3.12 The classification for a substance may need to be revised periodically as new information about that substance becomes available.

For substances not in mixtures

3.13 To determine whether a substance is hazardous and to determine its classification, a comparison should be made of the health effects data for the substance with the health effects criteria in Chapter 4. All the health effects of the substance should be considered.

3.14 For example, a substance with acute lethal effects and an oral LD_{50} of 20mg/kg would be determined to be hazardous and categorised as Very Toxic. If it also causes significant inflammation of the skin, then the substance would be categorised as Very Toxic and Irritant. The most appropriate risk phrases can then be identified for the substance, for example, R28 and R38.

For ingredients in mixtures

Mixtures tested as a whole

3.15 If a mixture has been tested for its health effects as a whole, then it can be classified by applying the health effects criteria in Chapter 4. The most appropriate risk phrases can then be assigned to the mixture.

Mixtures not tested as a whole

3.16 If the mixture has not been tested as a whole, then the health effects data of each ingredient in the mixture will need to be considered separately against the health effects criteria in Chapter 4.

3.17 The classification of the mixture is dependent on the:

- health effects data or other information available for each of the ingredients; and
- concentration of each ingredient in the mixture.

3.18 In the case of ingredients which are on the List, the information from the List - including concentration cut-off levels and risk phrases - can be used in the classification of the mixture.

3.19 In the case of ingredients which are not on the List, each ingredient should be considered separately as a pure substance to determine its health effects.

3.20 Once all the ingredients in a mixture have been classified, the mixture as a whole can be classified.

3.21 The mixture is a hazardous substance if any of the ingredients of the mixture meets any of the health effects criteria in Chapter 4, and the ingredient is present in the mixture at a concentration that exceeds the concentration cut-off level for the relevant health effect given in Chapter 5.

3.22 By use of the concentration cut-off levels, the mixture can be classified overall and the appropriate risk phrases selected. For example, if an ingredient, classified as Toxic by virtue of its acute lethal effects, is present in a mixture at a concentration of 15% by weight, then the mixture would only be classified as Harmful (Table 1, Chapter 5).

3.23 Note: Identified impurities, additives or individual constituents should be taken into account if their concentration is greater than or equal to the cut-off levels specified in Chapter 5, that is:

- 0.1% for liquid or solid substances which are classified as:

  Very Toxic,
  Toxic,
  Carcinogenic (category 1 or 2),
  Mutagenic (category 1 or 2) or
  Toxic to Reproduction (category 1 or 2);

- 1% for liquid or solid substances which are classified as:

  Harmful,
  Corrosive,
  Irritant,
  Sensitising,
  Carcinogenic (category 3),
  Mutagenic (category 3),
  Toxic to Reproduction (category 3); or
  unless lower values have been specified in the List[2].

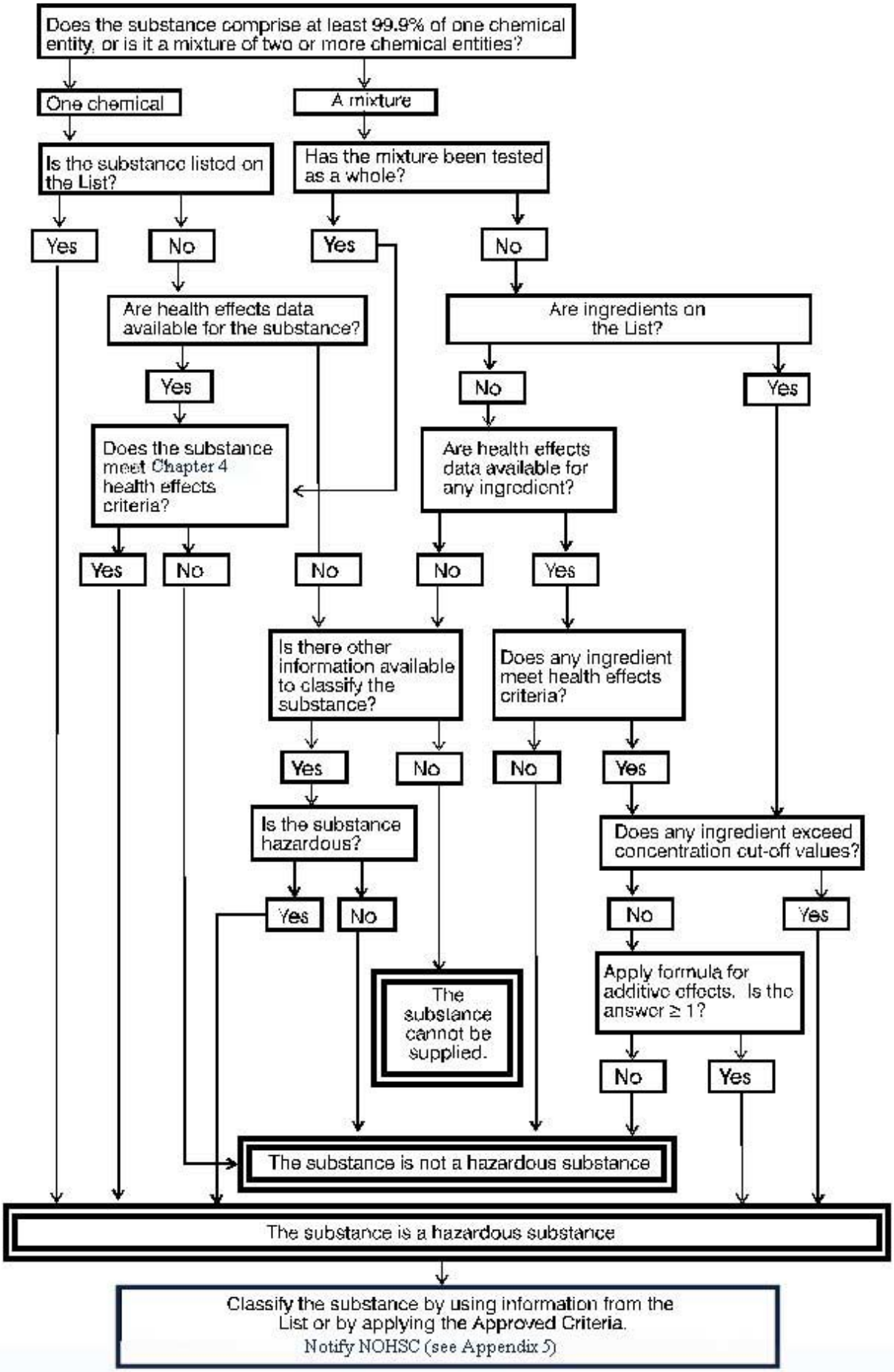
Interaction of substances

3.24 A mixture containing ingredients, classified as hazardous on the basis of acute lethal effects, corrosivity or irritancy, present at concentrations below the relevant concentration cut-off levels, may still need to be classified as a hazardous substance. This can be determined by applying the formulae in Chapter 6. These formulae are used for the classification of mixtures containing ingredients with similar and additive health effects at concentrations below the cut-off levels.

3.25 An additive effect is when the combined toxic effect of the chemical is equal to the sum of each individual agent, that is, 3+2=5. For example, two organophosphate insecticides which both act as cholinesterase enzyme inhibitors, will give rise to an additive toxic effect.

3.26 Occasionally the combined effect of multiple exposure is greater than the sum of the effects from the individual components. Synergism occurs when both chemicals have an individual effect but the combined effect is more than additive. Potentiation occurs when only one chemical is individually effective but the second inactive chemical enhances the first. Subtractive effects are also possible.

Process of determining whether a substance is hazardous



Chapter 4 Health Effects Criteria

RISK PHRASES: For a list of relevant risk phrases see the end of this chapter.

INTRODUCTION

4.1 The criteria in this chapter are those used by the European Communities in EC Council Directive 67/548/EC[3] for classifying dangerous substances based on their hazards to health. These criteria take into account both short and long term health effects, and are applicable to both pure substances and mixtures.

4.2 Health effects criteria are to be applied to:

- substances which are not listed on the *List of Designated Hazardous Substances* [NOHSC:10005(1999)][2];
- mixtures tested as a whole; and
- ingredients of mixtures which have not been tested as a whole.

4.3 The process of classification results in assigning the substance to a hazard category, that is, **Very Toxic, Toxic, Harmful, Corrosive** or **Irritant.** Risk phrases are identified directly from the classification process as there is a risk phrase corresponding to each classification criteria.

4.4 For the purposes of classification, health effects are subdivided into:

- acute lethal effects (R20-28);
- non-lethal irreversible effects after a single exposure (R39, R40);
- severe effects after repeated or prolonged exposure (R48);
- cumulative effects (R33);
- corrosive effects (R34, R35);
- irritant effects (R36, R37, R38, R41, R65);
- sensitising effects (R42, R43);
- carcinogenic effects (R40, R45, R49);
- mutagenic effects (R40, R46); and
- reproductive effects (R60-64).

A substance may have more than one health effect.

Criteria for classification and choice of risk phrases for ingredients and mixtures

4.5 For acute toxicity (lethal and irreversible effects after a single exposure), the criteria in paragraphs 4.10 to 4.21 and 4.24 to 4.30 are to be used.

4.6 For subacute, subchronic or chronic toxicity the criteria in paragraphs 4.10 to 4.36.3 and 4.22 to 4.23 are to be used.

4.7 For corrosive and irritant effects the criteria in paragraphs 4.38 to 4.54 are to be used.

4.8 For sensitising effects the criteria in paragraphs 4.55 to 4.75 are to be used.

4.9 For specific effects on health (carcinogenicity, mutagenicity and reproductive toxicity) the criteria in paragraphs 4.76 to 4.133 are to be used.

ACUTE TOXICITY

VERY TOXIC (T^+)

4.10 A substance is determined to be hazardous and classified as Very Toxic (T^+) and assigned one of the following risk phrases in accordance with the criteria given below.

R26 VERY TOXIC BY INHALATION

4.11 Acute toxicity results:

- LC_{50} inhalation, rat, for aerosols or particulates:

  ≤ 0.25 mg/l over 4hrs,

- LC_{50} inhalation, rat, for gases and vapours:

  ≤ 0.5 mg/l over 4hrs.

R27 VERY TOXIC IN CONTACT WITH SKIN

4.12 Acute toxicity results:

- LD_{50} dermal, rat or rabbit: ≤ 50 mg/kg.

R28 VERY TOXIC IF SWALLOWED

4.13 Acute toxicity results:

- LD_{50} oral, rat ≤ 25 mg/kg,
- less than 100 % survival at 5 mg/kg oral, rat, by the fixed dose procedure.

R39 DANGER OF VERY SERIOUS IRREVERSIBLE EFFECTS

4.14 Strong evidence that irreversible damage, other than the effects referred to in Paragraphs 4.76 to 4.131 (ie, carcinogenicity, mutagenicity and reproductive effects), is likely to be caused by a single exposure in the dose ranges used for classification as being very toxic (T^+) by different routes, that is:

- Inhalation LC_{50} rat, for aerosols or particulates:

  ≤ 0.25 mg/l over 4hrs,
- Inhalation LC_{50} rat, for gases and vapours:

  ≤ 0.5 mg/l over 4hrs,
- Dermal LD_{50} rat or rabbit: ≤ 50 mg/kg.,
- Oral LD_{50} rat ≤ 25 mg/kg.

4.15 In order to indicate the route of administration/exposure one of the following combination risk phrases should be used:

- R39/26, R39/27, R39/28.
- R39/26/27, R39/26/28, R39/27/28.
- R39/26/27/28.

TOXIC (T)

4.16 A substance is determined to be hazardous and classified as Toxic (T) and assigned one or more of the following risk phrase in accordance with the criteria given below.

R23 TOXIC BY INHALATION

4.17 Acute toxicity results:

- LC_{50} inhalation, rat, for aerosols or particulates:

  $0.25 < LC_{50} \leq 1$ mg/l over 4hrs,

- LC_{50} inhalation, rat, for gases and vapours:

  $0.5 < LC_{50} \leq 2$ mg/l over 4hrs.

R24 TOXIC IN CONTACT WITH SKIN

4.18 Acute toxicity results:

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

R25 TOXIC IF SWALLOWED

4.19 Acute toxicity results:

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

R39 DANGER OF VERY SERIOUS IRREVERSIBLE EFFECTS

4.20 Strong evidence that irreversible damage other than the effects referred to in Paragraphs 4.76 to 4.131 (ie, carcinogenicity, mutagenicity and reproductive effects), is likely to be caused by a **single exposure** by an appropriate route. Substances are classified at least as Toxic (T) when these effects are observed at acutely toxic dose levels, that is:

- Inhalation LC_{50} rat, for aerosols or particulates:

  $0.25 < LC_{50} \leq 1$ mg/l over 4hrs,

- Inhalation LC_{50} rat, for gases and vapours:

  $0.5 < LC_{50} \leq 2$ mg/l over 4hrs,

- Dermal LD_{50} rat or rabbit: $50 < LD_{50} \leq 400$ mg/kg.,
- Oral LD_{50} rat: $25 < LD_{50} \leq 200$ mg/kg.

4.21 In order to indicate the route of administration/exposure one of the following combination risk phrases should be used:

- R39/23, R39/24, R39/25.
- R39/23/24, R39/23/25, R39/24/25.
- R39/23/24/25.

R48 DANGER OF SERIOUS DAMAGE TO HEALTH BY PROLONGED EXPOSURE (*Not Acute*)

4.22 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 are classified at least as Toxic (T) when these effects are observed at the following dose ranges:

- Inhalation, rat ≤ 0.025 mg/l, 6h/day,
- Oral, rat ≤ 5 mg/kg (bodyweight)/day,
- Dermal, rat or rabbit ≤ 10 mg/kg (bodyweight)/day.

4.23 In order to indicate the route of administration/exposure one of the following combination risk phrases should be used:

- R48/23, R48/24, R48/25.
- R48/23/24, R48/23/25, R48/24/25.
- R48/23/24/25.

HARMFUL (Xn)

4.24 A substance is determined to be hazardous and classified as Harmful (Xn) and assigned one or more of the following risk phrases in accordance with the criteria given below.

R20 HARMFUL BY INHALATION

4.25 Acute toxicity results:

- LC_{50} inhalation, rat, for aerosols or particulates:
  $1 < LC_{50} \leq 5$ mg/l over 4hrs,
- LC_{50} inhalation, rat, for gases or vapours:
  $2 < LC_{50} \leq 20$ mg/l over 4hrs.

R65 HARMFUL: MAY CAUSE LUNG DAMAGE IF SWALLOWED

4.26 Liquid substances and preparations presenting an aspiration hazard in humans because of their low viscosity:

a) For substances containing aliphatic, alicyclic and aromatic hydrocarbons in a total concentration equal to or greater than 10% and having either:

- a flow time of less than 30 sec. in a 3 mm ISO (International Standards Organisation) cup according to ISO 2431; or
- a kinematic viscosity measured by a calibrated glass capillary viscometer in accordance with ISO 3104/3105 of less than 7×10^{-6} m^2/sec at 40^oC; or
- a kinematic viscosity derived from measurements of rotational viscometery in accordance with ISO 3219 of less than 7×10^{-6} m^2/sec at 40^oC.

[Please note these standards may be viewed at the Worksafe Australia and Australian Standards Organisation libraries in Sydney].

Note that substances meeting these criteria need not be classified if they have a mean surface tension greater than 33mN/m (or 25 dynes/cm) at 25^oC as measured by the du Nouy tensiometer or by the test methods shown in Appendix 6.

b) For substances and preparations, based on practical experience in humans.

Comments regarding volatile substances (see 4.37)

R21 HARMFUL IN CONTACT WITH SKIN

4.27 Acute toxicity results:

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

R22 HARMFUL IF SWALLOWED

4.28 Acute toxicity results:

- LD_{50} per oral, rat $200 \leq LD_{50} < 2000$ mg/kg.,
- discriminating dose, oral, rat, 50 mg/kg: 100 % survival but evident toxicity,
- less than 100% survival at 500 mg/kg, rat oral by the fixed dose procedure. (Refer to the evaluation table in Appendix 2).

R40 POSSIBLE RISK OF IRREVERSIBLE EFFECTS

4.29 Strong evidence that irreversible damage, other than the effects referred to in paragraphs 4.76 to 4.131 (ie. carcinogenicity, mutagenicity and reproductive effects), is likely to be caused by a single exposure by an appropriate route. Substances are classified at least as Harmful (Xn) when these effects are observed at acutely toxic dose levels, that is:

- Inhalation, LC_{50} rat, for aerosols or particulates: $1 < LC_{50} \leq 5$ mg/l over 4hrs,
- Inhalation, LC_{50} rat, for gases or vapours: $2 < LC_{50} \leq 20$ mg/l over 4hrs,
- Dermal, LD_{50} rat or rabbit: $400 < LD_{50} \leq 2000$ mg/kg.,
- Oral, LD_{50} rat $200 \leq LD_{50} < 2000$ mg/kg.

4.30 In order to indicate route of administration/exposure one of the following combination risk phrases should be used:

- R40/20, R40/21, R40/22.
- R40/20/21, R40/20/22, R40/21/22.
- R40/20/21/22.

R48 DANGER OF SERIOUS DAMAGE TO HEALTH BY PROLONGED EXPOSURE

4.31 Serious damage (clear functional disturbance or morphological changes which have toxicological significance) is likely to be caused by repeated or prolonged exposure by an appropriate route. Substances are classified at least as Harmful (Xn) when these effects are observed at the following dose ranges:

- Inhalation, rat ≤ 0.25 mg/l, 6h/day,
- Oral, rat ≤ 50 mg/kg (bodyweight)/day,
- Dermal, rat or rabbit ≤ 100 mg/kg (bodyweight)/day.

4.32 These guide values can apply directly when severe lesions have been observed in a subchronic (90 days) toxicity test. As a guideline, when interpreting the results of a sub-acute (28 days) toxicity test these figures should be increased at least 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.

4.33 In order to indicate the route of administration/exposure one of the following combination risk phrases should be used:

- R48/20, R48/21, R48/22.
- R48/20/21, R48/20/22, R48/21/22.
- R48/20/21/22.

EXPLANATORY NOTES REGARDING THE USE OF R48

4.34 Use of this risk phrase refers to the specific range of biological effects within the terms described below. For application of this risk phrase serious damage to health is 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 change 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.

4.35 When assessing whether there is evidence for these types of effects reference should be made to the following guidelines:

4.36.1 Evidence indicating that R48 should be applied:

- substance-related deaths,
- major functional changes in the central or peripheral nervous systems, including sight, hearing and the sense of smell, assessed by clinical observations or other appropriate methods (for example, electrophysiology),
- major functional changes in other organ systems (for example, the lung),
- 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,
- severe organ damage noted on microscopic examination following autopsy, including,
- widespread or severe necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity (for example, liver),
- severe morphological changes that are potentially reversible but are clear evidence of marked organ dysfunction (for example, severe fatty change in the liver, severe acute tubular nephrosis in the kidney, ulcerative gastritis),
- evidence of appreciable cell death in vital organs incapable of regeneration (for example, fibrosis of the myocardium or dying back of a nerve) or in stem cell populations (for example, aplasia or hypoplasia of the bone marrow).

4.36.2 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.

4.36.3 Evidence indicating that R48 should not be applied.

The use of this risk phrase is restricted to ‘serious damage to health by prolonged exposure’. A number of substance-related effects may be observed in both humans and animals that would not justify the use of R48. These effects are relevant when attempting to determine a no-effect level for a chemical substance. Examples of well documented changes which would not normally justify classification with R48, irrespective of their statistical significance, include:

- clinical observations or changes in bodyweight gain, food consumption or water intake, which may have some toxicological importance but which do not, by themselves, indicate 'serious damage',
- small changes in clinical biochemistry, haematology or urinalysis parameters which are of doubtful or minimal toxicological importance,
- changes in organ weights with no evidence of organ dysfunction,
- adaptive responses (for example, 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',
- where a species-specific mechanism of toxicity (for example, specific metabolic pathways) has been demonstrated, that is, the effect is not relevant to humans.

EXPLANATORY NOTES REGARDING VERY VOLATILE SUBSTANCES

4.37 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 acute lethality (Paragraphs 4.24 to 4.33). However, due to their high volatility and where there is appropriate evidence that such substances may present a risk in normal handling and use, then classification as Harmful (Xn) on a case-by-case basis, with the assignment of risk phrases R20, R21, R22 may be necessary. Such substances may already appear on the List[(2)] with specific concentration cut-off levels. For example, a very volatile substance such as nitromethane [CAS No. 75-52-5] is classified on the List[(2)] as Harmful, R22 at and above 12.5% rather than 25% which is normally specified for R22. Very volatile substances will need to be considered and classified appropriately.

CORROSIVE (C)

4.38 A substance is considered to be Corrosive (C) if, when applied to healthy intact animal skin, it produces full thickness destruction of skin tissue on at least one animal during the test[1] for skin irritation or if the results can be predicted, for example from strongly acid or alkaline reactions (demonstrated pH of 2 or less or 11.5 or greater. Alkaline or acidic reserves should also be taken into account).

4.39 Classification can be based on the results of validated *in vitro* tests.

4.40 A substance is determined to be hazardous and classified as Corrosive (C) and assigned either risk phrase R34 or R35 in accordance with the criteria given below.

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.

[1] A test conducted in accordance with a method analogous to OECD method TG 404[8].

IRRITANT (Xi)

4.41 A substance is determined to be hazardous and classified as Irritant (Xi) if it causes:

- inflammation of the skin;
- eye irritation;
- serious eye effects; or
- irritation to the respiratory system.

4.42 One or more of the following risk phrases are assigned in accordance with the criteria given.

Inflammation of the skin

R38 IRRITATING TO SKIN

4.43 Organic peroxides, except where evidence to the contrary is available.

4.44 Substances which cause significant inflammation of the skin, based on practical observation in humans.

4.45 Substances which cause significant inflammation of the skin which persists for at least 24 hours after an exposure period of up to four hours determined on the rabbit according to a test method analogous to OECD TG 404[8].

Inflammation of the skin is significant if:

- the mean value of the scores for either erythema and eschar formation or oedema formation, calculated over all the animals tested, is 2 or more, or
- in the case where the test has been completed using three animals, either erythema and eschar formation or oedema formation equivalent to a mean value of 2 or more calculated for each animal separately has been observed in two or more animals.

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

Inflammation of the skin is also significant if it persists in at least two animals at the end of the observation time. Particular effects, for example, hyperplasia, scaling, discolouration, fissures, scabs and alopecia should be taken into account.

Irritation due to the defatting properties of a substance

4.46 When test results or practical experience show irritation in accordance with the above criteria, risk phrases should be used. However, safety-phrases should be used when there are reasons to suspect that the defatting properties of the substance may cause irritation in humans even though the above criteria are not met, or if an inappropriate test has been used. A list of suitable safety phrases is provided at Appendix 3.

Ocular lesions

R36 IRRITATING TO EYES

4.47 Organic peroxides except where evidence to the contrary is available.

4.48 Substances which cause significant ocular lesions, based on practical experience in humans.

4.49 Substances which, when applied to the eye of the animal, cause significant ocular lesions which occur within 72 hours after exposure and which persist for at least 24 hours.

Ocular lesions are considered significant when the results of tests carried out in accordance with a method analogous to OECD test TG 405[8] correspond to any of the following values:

- cornea opacity equal to or greater than 2 but less than 3,
- iris lesion equal to or greater than 1 but not greater than 1.5,
- redness of the conjunctivae equal to or greater than 2.5,

- oedema of the conjunctivae (chemosis) equal to or greater than 2,

or, in the case where three animals are used in the test, the mean values, on two or more animals, are equivalent to any of the following:

- cornea opacity equal to or greater than 2 but less than 3,
- iris lesion equal to or greater than 1 but less than 2,
- redness of the conjunctivae equal to or greater than 2.5,
- oedema of the conjunctivae (chemosis): equal to or greater than 2.

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

R41 RISK OF SERIOUS DAMAGE TO EYES

4.50 Substances which cause severe ocular lesions, based on practical experience in humans.

4.51 Substances which, when applied to the eye of the animal cause severe ocular lesions which occur within 72 hours after exposure and which persist for at least 24 hours.

Ocular lesions are severe when the results of the standard eye irritation test correspond to any of the following values:

- cornea opacity equal to or greater than 3,
- iris lesion greater than 1.5.

In the case where three animals are used in the test, the mean values, on two or more animals, are equivalent to any of the following:

- cornea opacity equal to or greater than 3,
- iris lesion equal to 2.

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

- ocular lesions are also severe when they are still present at the end of the observation time,
- ocular lesions are also severe if the substance causes irreversible coloration of the eyes.

4.52 NB: When an ingredient or mixture 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. However, in the case of mixtures, when calculating the sum of quotients by the formulae in Chapter 6 (Paragraphs 6.11 and 6.13) substances classified as corrosive should be considered as if R41 had been assigned.

Respiratory system irritation

R37 IRRITATING TO RESPIRATORY SYSTEMS

4.53 Substances which cause serious irritation to the respiratory system based on:

- practical observation in humans,
- positive results from appropriate animal tests.

EXPLANATORY NOTES REGARDING THE USE OF R37

4.54 In interpreting practical observations in humans, care should be taken to distinguish between effects which lead to classification with R48 (see also paragraph 4.35) from those leading to classification with R37. Conditions normally leading to classification with R37 are reversible and usually limited to the upper airways. Positive results from appropriate animal tests may include data obtained in a general toxicity test, including histopathological data from the respiratory system. Data from the measurement of experimental bradypnea may also be used to assess airway irritation.

SENSITISATION (Xn)

4.55 Substances are determined to be hazardous and classified as Harmful (Xn) and assigned one or more of the following risk phrases in accordance with the criteria given below.

Sensitisation by inhalation

R42 MAY CAUSE SENSITISATION BY INHALATION

4.56 If there is evidence that the substance or preparation can induce specific respiratory hypersensitivity.

4.57 Where there are positive results from appropriate animal tests.

4.58 If the substance is an isocyanate, unless there is evidence that the substance does not cause respiratory hypersensitivity.

EXPLANATORY NOTES REGARDING THE USE OF R42

Human Evidence

4.59 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.

4.60 When considering the evidence from human exposure, it is necessary for a decision on classification to take into account in addition to the evidence from the cases:

- the size of the population exposed,
- the extent of exposure.

4.61 The evidence referred to above could be:

- clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include:
- a chemical structure related to substances known to cause respiratory hypersensitivity,
- *in vivo* immunological test (for example, skin prick test),
- *in vitro* immunological test (for example, serological analysis),
- studies that may indicate other specific but non-immunological mechanisms of action, for example, repeated low-level irritation, pharmacologically mediated effects,
- data from a positive bronchial challenge test with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.

4.62 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.

4.63 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.

4.64 Substances that elicit symptoms of asthma by irritation only in people with bronchial hyper-reactivity should not be assigned R42.

Animal Studies

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

- IgE measurements (e.g. in mice),
- specific pulmonary responses in guinea pigs.

SENSITISATION BY SKIN CONTACT

R43 MAY CAUSE SENSITISATION BY SKIN CONTACT

4.66 If practical experience shows that the substances are capable of inducing sensitisation by skin contact in a substantial number of persons.

4.67 Where there are positive results from an appropriate animal test.

EXPLANATORY NOTES REGARDING THE USE OF R43

Human Evidence

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

- Positive data from appropriate patch testing, normally in more than one dermatological clinic, or
- Epidemiological studies showing allergic contact dermatitis caused by the substance. Situations in which a high proportion of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small, or
- Positive data from experimental studies in humans (see also Paragraph 3.10).

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

- Isolated episodes of allergic contact dermatitis, or
- Epidemiological studies where chance, bias or confounders have not been ruled out fully with reasonable confidence.

4.70 Supportive evidence may include:

- data from animal tests performed according to existing guidelines, with a result that does not meet the criteria given in the section on animal studies but is sufficiently close to the limit to be considered significant, or

- data from non-standard methods, or
- appropriate structure-active relationships.

Animal Studies

4.71 Positive results from appropriate animal tests are:

- In the case of adjuvant type test methods for skin sensitisation a response of at least 30% of the animals is considered as positive. For any other test method a response of at least 15% of the animals is considered positive.

IMMUNOLOGICAL CONTACT URTICARIA

4.72 Some substances 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 safety phrases, usually S24 and S36/37. See Appendix 3 for definitions of these safety phrases.

4.73 For substances which produce signs of immunological contact urticaria which do not fulfil the criteria for R42, consideration should be given to classification with R43.

4.74 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).

4.75 Note that if the indication of hazard Harmful (Xn) is assigned, the indication of hazard Irritant (Xi) is optional.

CARCINOGENIC SUBSTANCES

4.76 Substances are determined to be hazardous due to carcinogenic effects if they fall into one of the following categories:

Category 1 Substances known to be carcinogenic to humans.

Category 2 Substances which should be regarded as if they are carcinogenic to humans.

Category 3 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.

EXPLANATORY NOTES REGARDING THE CATEGORISATION OF CARCINOGENIC SUBSTANCES

4.77 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.

CATEGORY 1

4.78 Substances are determined to be hazardous and classified as

Toxic (T) and assigned risk phrase R45 or R49 in accordance with the criteria given below.

R45 MAY CAUSE CANCER

R49 MAY CAUSE CANCER BY INHALATION[2]

4.79 A substance is included in Category 1 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 any of the following:

[2] For substances which present a carcinogenic risk only when inhaled, for example, dust, vapour or fumes (and where other routes of exposure, for example, by swallowing or in contact with the skin do not present any carcinogenic risk) the specific risk phrase R49 should be used.

- 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.

CATEGORY 2

4.80 Substances are determined to be hazardous and classified as Toxic (T) and assigned risk phrase R45 or R49 in accordance with the criteria given below.

R45 MAY CAUSE CANCER

R49 MAY CAUSE CANCER BY INHALATION[2]

4.81 A substance is included in Category 2 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.

4.82 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.

4.83 Human data providing suspicions of carcinogenic potential may warrant a Category 2 classification irrespective of the nature of any animal data. Increased confidence in the credibility of a

[2] For substances which present a carcinogenic risk only when inhaled, for example, dust, vapour or fumes (and where other routes of exposure, for example, by swallowing or in contact with the skin do not present any carcinogenic risk) the specific risk phrase R49 should be used.

causal relationship would be provided by evidence of carcinogenicity in animals and/or of genotoxic potential in short term screening tests.

CATEGORY 3

4.84 Substances are determined to be hazardous and classified as Harmful (Xn) and assigned risk phrase R40 in accordance with the criteria given below.

R40 POSSIBLE RISK OF IRREVERSIBLE EFFECTS

4.85 A substance is included in Category 3 if there is some evidence from appropriate animal studies that human exposure can result in the development of cancer, but this evidence is insufficient to place the substance in Category 2.

Category 3 actually comprises 2 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 they raise concern for humans. This classification is provisional; further experiments are necessary before a final decision can be made.

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

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

- appearance of tumours, especially at high dose levels, only in particular organs of certain species known to be susceptible to a high spontaneous tumour formation,
- appearance of tumours, only at the site of application, in very sensitive test systems (eg intraperitoneal, or subcutaneous application of certain locally active compounds), 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 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),
- existence of a species-specific mechanism of tumour formation (eg by specific metabolic pathways) irrelevant for humans.

NO CARCINOGEN CLASSIFICATION

4.87 For a distinction between Category 3 and no classification arguments are relevant which exclude a concern for humans:

- a substance should not be classified in any of the categories if the mechanism(s) of experimental tumour formation is/are clearly identified, with good evidence that such mechanism(s) cannot be extrapolated to humans for each tumour,
- if the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories,
- particular attention should be paid to cases where the only available tumour data are the occurrence of neoplasms at sites and in strains where they are well known to occur spontaneously with a high incidence.

MUTAGENIC SUBSTANCES

4.88 Substances are determined to be hazardous due to mutagenic effects if they fall into one of 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.
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.

EXPLANATORY NOTES REGARDING THE CATEGORISATION OF MUTAGENIC SUBSTANCES

4.89 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 DNA, 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.

4.90 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.

4.91 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

4.92 Substances are determined to be hazardous and classified as

Toxic (T) and assigned risk phrase R46 in accordance with the criteria given below.

R46 MAY CAUSE HERITABLE GENETIC DAMAGE

4.93 A substance is included in Category 1 if there is sufficient evidence to establish a causal relationship between human exposure to a substance and heritable genetic damage.

4.94 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

4.95 Substances are determined to be hazardous and classified as Toxic (T) and assigned risk phrase R46 in accordance with the criteria given below.

R46 MAY CAUSE HERITABLE GENETIC DAMAGE

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

4.97 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.

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

(a) *in vivo* germ cell mutagenicity assays:

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

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

(b) *in vivo* assays showing relevant interaction with germ cells (usually DNA):

- assays for chromosomal abnormalities, as detected by cytogenetic analysis, including aneuploidy caused by malsegregation of chromosomes,
- test for sister chromatid exchanges (SCEs),
- test for unscheduled DNA synthesis (UDS),
- assay of (covalent) binding of mutagen to germ cell DNA,
- assaying other kinds of DNA damage.

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

(c) *in vivo* assays showing mutagenic effects in somatic cells of mammals (see sub section 4.98(a)), in combination with toxicokinetic methods, or other methodologies capable of demonstrating that the compound or a relevant metabolite reaches the germ cells.

For paragraphs 4.98(b) and 4.98 (c), positive results from host-mediated assays or the demonstration of unequivocal effects in *in vitro* assays can be considered as supporting evidence.

CATEGORY 3

4.99 Substances are determined to be hazardous and classified as Harmful (Xn) and assigned risk phrase R40 in accordance with the criteria given below.

R40 POSSIBLE RISK OF IRREVERSIBLE EFFECTS

4.100 A substance is included in Category 3 if there is evidence from appropriate mutagenicity studies, of concern that human exposure can result in the development of heritable genetic damage, but that this evidence is insufficient to place the substance in Category 2.

4.101 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.

4.102 For effects in somatic cells *in vivo* at present the following methods are appropriate:

(a) *in vivo* somatic cell mutagenicity assays:

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

(b) *in vivo* somatic cell DNA interaction assays:

- test for SCEs in somatic cells,
- test for UDS in somatic cells,
- assay for the (covalent) binding of mutagen to somatic cell DNA,
- assay for DNA damage,for example,by alkaline elution, in somatic cells.

4.103 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, for example, 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 TO REPRODUCTION

4.104 Substances are determined to be hazardous due to reproductive effects if they fall into one of two categories covering Effects on Fertility and Developmental Toxicity:

EFFECTS ON FERTILITY

Category 1 Substances known to impair fertility in humans.

Category 2 Substances which should be regarded as if they impair fertility in humans.

Category 3 Substances which cause concern for human fertility.

DEVELOPMENTAL TOXICITY

Category 1 Substances known to cause developmental toxicity in humans.

Category 2 Substances which should be regarded as if they cause developmental toxicity to humans.

Category 3 Substances which cause concern for humans owing to possible developmental toxic effects.

EXPLANATORY NOTES REGARDING THE CATEGORISATION OF SUBSTANCES TOXIC TO REPRODUCTION

4.105 Reproductive toxicity includes impairment of male and female reproductive functions or capacity and the induction of non-inheritable harmful effects on the progeny.

4.106 Classification of substances as toxic to reproduction is intended to be used for substances which have an intrinsic or specific property to produce such toxic effects. Substances should not be classified as toxic to reproduction where such effects are solely produced as a non-specific secondary consequence of other toxic effects. Chemicals of most concern are those which are toxic to reproduction at exposure levels which do not produce other signs of toxicity.

4.107 The placing of a substance 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.

4.108 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.

4.109 If a dose level of at least 1000 mg/kg orally produces no evidence of effects toxic to reproduction, studies at other dose levels may not be considered necessary. If data are available from studies carried out with doses higher than the above limit dose, this data should be evaluated together with other relevant data. Under normal circumstances it is considered that effects seen only at

doses in excess of the limit dose would not necessarily lead to classification as 'Toxic to Reproduction'.

EFFECTS ON FERTILITY

4.110 Effects on 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.

CATEGORY 1

4.111 Substances are determined to be hazardous and classified as Toxic (T) and assigned risk phrase R60 in accordance with the criteria given below.

R60 MAY IMPAIR FERTILITY

4.112 A substance is included in Category 1 if there is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility.

CATEGORY 2

4.113 Substances are determined to be hazardous and classified as Toxic (T) and assigned risk phrase R60 in accordance with the criteria given below.

R60 MAY IMPAIR FERTILITY

4.114 A substance is included in Category 2 if there is sufficient evidence to provide a strong presumption that human exposure to the substance may result in impaired fertility on the basis of:

- clear evidence in animal studies of impaired fertility in the absence of toxic effects, or, evidence of impaired fertility occurring at around the same dose levels as other toxic

effects but which is not a secondary non-specific consequence of the other toxic effects,

- other relevant information.

4.115 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.

4.116 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 in order to interpret whether any adverse effect such as alteration in pattern of hormonal release would be likely to occur in humans.

CATEGORY 3

4.117 Substances are determined to be hazardous and classified as Harmful (Xn) and assigned risk phrase R62 in accordance with the criteria given below.

R62 POSSIBLE RISK OF IMPAIRED FERTILITY

4.118 A substance is included in Category 3 generally on the basis of:

- results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of impaired fertility in the absence of toxic effects, or evidence of impaired fertility 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,

- other relevant information.

DEVELOPMENTAL EFFECTS

4.119 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 embryotoxic/foetotoxic effects such as reduced body weight, growth and developmental retardation, organ toxicity, death, abortion,* structural defects (reproductive effects), functional defects, peripostnatal defects, and impaired postnatal mental or physical development up to and including normal pubertal development. (*including resorptions)

CATEGORY 1

4.120 Substances are determined to be hazardous and classified as Toxic (T) and assigned risk phrase R61 in accordance with the criteria given below.

R61 MAY CAUSE HARM TO THE UNBORN CHILD

4.121 A substance is included in Category 1 if 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

4.122 Substances are determined to be hazardous and classified as Toxic (T) and assigned risk phrase R61 in accordance with the criteria given below.

R61 MAY CAUSE HARM TO THE UNBORN CHILD

4.123 A substance is included in Category 2 if there is sufficient evidence to provide a strong presumption that human exposure to the substance may result in developmental toxicity, generally on the basis of:

- clear results in appropriate animal studies where effects have been observed in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary nonspecific consequence of the other toxic effects,

- other relevant information.

4.124 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 should be interpreted with caution and on their own would not normally lead to classification.

CATEGORY 3

4.125 Substances are determined to be hazardous and classified as Harmful (Xn) and assigned risk phrase R63 in accordance with the criteria given below.

R63 POSSIBLE RISK OF HARM TO THE UNBORN CHILD

4.126 A substance is included in Category 3 generally on the basis of:

- results in appropriate animal studies which provide sufficient , evidence to cause a strong suspicion of developmental toxicity in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in Category 2,
- other relevant information.

4.127 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.

FOR A DISTINCTION BETWEEN CATEGORY 3 AND NO CLASSIFICATION - DEVELOPMENTAL TOXICITY

4.128 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 ON LACTATION (Xn)

R64 MAY CAUSE HARM TO BREAST FED BABIES

4.129 Substances which are determined to cause effects on reproduction and which also cause concern due to their effects on lactation should in addition be assigned with R64 (see also Paragraph 4.137)

4.130 For the purpose of classification, toxic effects on offspring resulting only from exposure via the breast milk, or toxic effects resulting from direct exposure of children will not be regarded as Toxic to Reproduction, unless such effects result in impaired development of the offspring.

4.131 Substances which are not classified as Toxic to Reproduction but which cause concern due to toxicity when transferred to the baby during the period of lactation should be classified as

Harmful (Xn) and assigned R64 (see also Paragraph 4.137). This risk phrase may also be appropriate for substances which affect the quantity or quality of the milk.

4.132 R64 would normally be assigned on the basis of, for example:

- toxicokinetic studies that would indicate the likelihood that the substance would be present in potentially toxic levels in breast milk; and/or
- on the basis of results of one or more generation studies in animals which indicate the presence of adverse effects on the offspring due to transfer in the milk; and/or
- on the basis of evidence in humans indicating a risk to babies during the lactational period.

4.133 Substances which are known to accumulate in the body and which subsequently may be released into milk during lactation may be labelled with R33 (danger of cumulative effects) and R64 if the guidance in Paragraph 4.130 is met.

OTHER TOXICOLOGICAL PROPERTIES

4.134 Irrespective of whether other classification criteria are met the following risk phrases should be applied where specific hazards arise.

R29 CONTACT WITH WATER LIBERATES TOXIC GAS

4.135 For substances which in contact with water or damp air, evolve very toxic/ toxic gases in potentially hazardous amounts, for example, aluminium phosphide, phosphorus pentasulphide.

R31 CONTACT WITH ACIDS LIBERATES TOXIC GAS

4.136 For substances which react with acids to evolve toxic gases in hazardous amounts, for example, sodium hypochlorite, barium polysulphide.

R32 CONTACT WITH ACIDS LIBERATES VERY TOXIC GAS

4.137 For substances which react with acids to evolve very toxic gases in hazardous amounts; for example, salts of hydrogen cyanide, sodium azide.

R33 DANGER OF CUMULATIVE EFFECTS

4.138 For substances 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

4.139 For substances 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 risk phrase (and in some cases R33) see also Paragraph 4.130.

Relevant Risk Phrases:

The following risk phrases are concerned with health effects criteria and their application in the classification process is described in this chapter.

R20 **Harmful by inhalation.**

R21 **Harmful in contact with skin.**

R22 **Harmful if swallowed.**

R23 **Toxic by inhalation.**

R24 **Toxic in contact with skin.**

R25 **Toxic if swallowed.**

R26 **Very toxic by inhalation.**

R27 **Very toxic in contact with skin.**

R28 **Very toxic if swallowed.**

R29 **Contact with water liberates toxic gas.**

R30 Does not apply. Not health effect. See complete list**.**

R31 **Contact with acids liberates toxic gas.**

R32 **Contact with acids liberates very toxic gas.**

R33 **Danger of cumulative effects.**

R34 **Causes burns.**

R35 **Causes severe burns.**

R36 **Irritating to eyes.**

R37 **Irritating to respiratory system.**

R38 **Irritating to skin.**

R39 **Danger of very serious irreversible effects.**

R40 **Possible risk of irreversible effects.**

Relevant Risk Phrases: (continued)

R41 **Risk of serious damage to eyes.**

R42 **May cause sensitisation by inhalation.**

R43 **May cause sensitisation by skin contact.**

R44 Does not apply. Not health effect. See complete list**.**

R45 **May cause cancer.**

R46 **May cause heritable genetic damage.**

R48 **Danger of serious damage to health by prolonged exposure.**

R49 **May cause cancer by inhalation.**

R60 **May impair fertility.**

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

R62 **Possible risk of impaired fertility.**

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

R64 **May cause harm to breastfed babies.**

R65 **Harmful: May cause lung damage if swallowed.**

Chapter 5 Concentration cut-off levels

5.1 Concentration cut-off levels are used to determine whether or not a mixture is hazardous on the basis of its ingredients, and to classify the mixture on the basis of its health effects. The concentration cut-off levels are designed to provide a practical level of protection and information provision, but should not be used to imply that an effect cannot occur below that level.

5.2 Mixtures are hazardous if any ingredient meets any of the health effects criteria of Chapter 4 and is present at a concentration above the minimum concentration cut-off level for that ingredient as shown in Tables 1 to 15 (see also Paragraphs 3.17-3.23).

5.3 For the purposes of classification, health effects are subdivided into:

- acute lethal effects (R20-28);
- non-lethal irreversible effects after a single exposure (R39, R40);
- severe effects after repeated or prolonged exposure (R48);
- cumulative effects (R33);
- corrosive effects (R34, R35);
- irritant effects (R36, R37, R38, R41);
- sensitising effects (R42, R43);
- carcinogenic effects (R40, R45, R49);
- mutagenic effects (R40, R46); and
- reproductive effects (R60-64).

A substance may have more than one health effect.

5.4 Unless a mixture has been tested and hence classified as a whole, the mixture is assessed by consideration of the health effects of each ingredient in the mixture, and classified according to the concentrations of each hazardous ingredient in the mixture.

5.5 Tables 1 to 15 are provided for determining whether an ingredient in a mixture exceeds its concentration cut-off level and, if so, the hazard classification of the mixture. For example, a mixture which contains an ingredient hazardous to health on the basis of its acute lethal effects may be classified as Very Toxic, Toxic or Harmful depending on its concentration (see Table 1).

5.6 Tables are provided for both solid and liquid mixtures and for gaseous mixtures. For solid and liquid mixtures, concentrations are expressed on a weight/weight (w/w) basis; for gaseous mixtures, concentrations are on a volume/volume (v/v) basis.

5.7 To read the tables:

- identify the ingredient classification in the left-hand vertical column of the table, titled 'Classification of the Ingredient';
- compare the concentration of the ingredient in the mixture with the concentration cut-off levels listed in the table (horizontal column) for the ingredient classification; and
- determine the mixture classification by reading the column heading for the concentration range matching the ingredient concentration in the mixture.

5.8 The hazardous ingredients of mixtures have risk phrases which are based on their health effects. Use of the tables in this chapter enables appropriate risk phrases to be selected for mixtures, for example, a mixture with 15% of an ingredient classified as Toxic on the basis of its health effects is classified as Harmful, with risk phrases of R20, R21 or R22 (see Table 1).

Appropriate risk phrases for substances which are hazardous on the basis of their health effects are listed in Appendix 3.

5.9 In some instances, the hazard classification of a mixture may be different to the hazard classifications of the individual ingredients. For example, a mixture containing a Corrosive ingredient (risk phrase R35) at 3% w/w will be classified as Irritant (risk phrases R36 or R38) (see Table 7).

5.10 Tables 1 to 15 have been adapted from EC Council Directive 88/379/EC[4] as amended by EC Council Directive 93/18/EC[7].

ACUTE LETHAL EFFECTS

Table 1 Solid and liquid mixtures (includes aerosols and particulates)

INGREDIENT - CLASSIFICATION (*start*) ↓	MIXTURE – CLASSIFICATION (*result*)		
	Very Toxic (T^+) (R26, R27, R28)	Toxic (T) (R23, R24, R25)	Harmful (Xn) (R20, R21, R22)
Very Toxic (T^+) CUT-OFFS (R26, R27, R28) →	≥7%	1%≤conc<7%	0.1%≤conc<1%
Toxic (T) CUT-OFFS (R23, R24, R25) →		≥25%	3%≤conc<25%
Harmful (Xn) CUT-OFFS (R20, R21, R22) →			≥25%

Concentrations are in % w/w.

Table 2 Gas and Vapour Mixtures

INGREDIENT - CLASSIFICATION (*start*) ↓	MIXTURE – CLASSIFICATION (*result*)		
	Very Toxic (T^+) (R26, R27, R28)	Toxic (T) (R23, R24, R25)	Harmful (Xn) (R20, R21, R22)
Very Toxic (T^+) CUT-OFFS (R26, R27, R28) →	≥1%	0.2%≤conc<1%	0.02%≤conc<0.2%
Toxic (T) CUT-OFFS (R23, R24, R25) →		≥5%	0.5%≤conc<5%
Harmful (Xn) CUT-OFFS (R20, R21, R22) →			≥5%

Concentrations are in % v/v.

NON-LETHAL IRREVERSIBLE EFFECTS AFTER A SINGLE EXPOSURE

Table 3 Solid and liquid mixtures

INGREDIENT - CLASSIFICATION (*start*)- ⬇	**MIXTURE – CLASSIFICATION** (*result*)		
	Very Toxic (T^+) (R39*[1])	**Toxic (T) (R39*[2])**	**Harmful (Xn) (R40*[3])**
Very Toxic (T^+) CUT-OFFS (R39/Route of exposure) ➔	**≥10%**	**1%≤conc<10%**	**0.1%≤conc<1%**
Toxic (T) CUT-OFFS (R39/Route of exposure) ➔		**≥10%**	**1%≤conc<10%**
Harmful (Xn) CUT-OFFS (R40/Route of exposure) ➔			**≥10%**

Concentrations are in % w/w.

*To indicate the route of administration/exposure one of the combination risk phrases listed below should be used.

Very Toxic (T^+)[1]
R39/26, R39/27, R39/28,
R39/26/27, R39/26/28, R39/27/28
R39/26/27/28

Toxic (T)[2]
R39/23, R39/24, R39/25
R39/23/24, R39/23/25, R39/24/25
R39/23/24/25

Harmful (Xn)[3]
R40/20, R40/21, R40/22
R40/20/21, R40/20/22, R40/21/22
R40/20/21/22

Table 4 Gaseous mixtures

INGREDIENT - CLASSIFICATION (*start*)- ⬇	MIXTURE – CLASSIFICATION (*result*)		
	Very Toxic (T^+) (R39*[1])	**Toxic (T) (R39*[2])**	**Harmful (Xn) (R40*[3])**
Very Toxic (T^+) CUT-OFFS (R39/Route of exposure) ➔	**≥1%**	**0.2%≤conc<1%**	**0.02%≤conc<0.2%**
Toxic (T) CUT-OFFS (R39/Route of exposure) ➔		**≥5%**	**0.5%≤conc<5%**
Harmful (Xn) CUT-OFFS (R40/Route of exposure) ➔			**>5%**

Concentrations are in % v/v.

*To indicate the route of administration/exposure one of the combination risk phrases listed below should be used.

Very Toxic (T^+)[1]
R39/26, R39/27, R39/28,
R39/26/27, R39/26/28, R39/27/28
R39/26/27/28

Toxic (T)[2]
R39/23, R39/24, R39/25
R39/23/24, R39/23/25, R39/24/25
R39/23/24/25

Harmful (Xn)[3]
R40/20, R40/21, R40/22
R40/20/21, R40/20/22, R40/21/22
R40/20/21/22

SEVERE EFFECTS AFTER REPEATED OR PROLONGED EXPOSURE

Table 5 Solid and liquid mixtures

INGREDIENT - CLASSIFICATION (*start*)- ⬇	**MIXTURE – CLASSIFICATION** (*result*)	
	Toxic (T) (R48*[1])	**Harmful (Xn) (R48*[2])**
Toxic (T) CUT-OFFS (R48/Route of exposure) ➔	**≥10%**	**1%≤conc<10%**
Harmful (Xn) CUT-OFFS (R48/Route of exposure) ➔		**≥10%**

Concentrations are in % w/w.

*To indicate the route of administration/exposure one of the combination risk phrases listed below should be used.

Toxic (T)[1]	**Harmful (Xn)**[2]
R48/23, R48/24, R48/25	R48/20, R48/21, R48/22
R48/23/24, R48/23/25, R48/24/25	R48/20/21, R48/20/22, R48/21/22
R48/23/24/25	R48/20/21/22

Table 6 Gaseous mixtures

INGREDIENT - CLASSIFICATION (*start*)- ⬇	**MIXTURE – CLASSIFICATION** (*result*)	
	Toxic (T) (R48*[1])	**Harmful (Xn) (R48*[2])**
Toxic (T) CUT-OFFS (R48/Route of exposure) ➔	**≥5%**	**0.5%≤conc<5%**
Harmful (Xn) CUT-OFFS (R48/Route of exposure) ➔		**≥5%**

Concentrations are in % v/v.

*To indicate the route of administration/exposure one of the combination risk phrases listed below should be used.

Toxic (T)[1]	**Harmful (Xn)**[2]
R48/23, R48/24, R48/25	R48/20, R48/21, R48/22
R48/23/24, R48/23/25, R48/24/25	R48/20/21, R48/20/22, R48/21/22
R48/23/24/25	R48/20/21/22

CORROSIVE AND IRRITANT EFFECTS

Table 7 Solid and liquid mixtures

INGREDIENT-CLASSIFICATION (*start*)- ⬇	**MIXTURE – CLASSIFICATION** (*result*)			
	Corrosive (C) (R35)	**Corrosive (C) (R34)**	**Irritant (Xi) (R41)** (serious eye damage)	**Irritant (Xi) (R36, R37, R38)**
Corrosive (C) CUT-OFFS (R35) ➔	**≥10%**	**5%≤conc<10%**	*	**1%≤conc<5% R36, R38**
Corrosive (C) CUT-OFFS (R34) ➔		**≥10%**	*	**5%≤conc<10% R36, R38**
Irritant (Xi) CUT-OFFS (R41) ➔ (serious eye damage)			**≥10%**	**5%≤conc≤10% R36**
Irritant CUT-OFFS (R36, R37, R38) ➔				**≥20% R36, R37, R38**

Concentrations are in w/w%

* Corrosive ingredients assigned risk phrases R35 or R34 should be considered as assigned risk phrase R41 that is, capable of causing serious eye damage. Consequently, if the mixture contains corrosive substances with R35 or R34 below the concentration cut off levels for a classification of the mixture as corrosive, such ingredients can contribute to a classification of the mixture as irritant (R41) or irritant (R36). Therefore, when the formulae for classifying mixtures at Paragraphs 6.11 and 6.13 of Chapter 6 are applied the following concentration cut-off levels should be used:

Formula at 6.11: The concentration cut off levels to be used for LXi.R41 in the formula are:	Formula at 6.13: The concentration cut off levels to be used for LXi.R36 in the formula are:
10% for ingredients Xi.R41 10% for ingredients C.R34 5% for ingredients C.R35	20% for ingredients Xi.R36 5% for ingredients Xi.R41 5% for ingredients C.R34 1% for ingredients C.R35

Table 8 Gaseous mixtures

INGREDIENT-CLASSIFICATION (*start*)- ⬇	**MIXTURE – CLASSIFICATION** (*result*)			
	Corrosive (C) (R35)	**Corrosive (C) (R34)**	**Irritant (Xi) (R41)** (serious eye damage)	**Irritant (Xi) (R36, R37, R38)**
Corrosive (C) CUT-OFFS (R35) ➔	**≥1%**	**0.2%≤conc<1 %**	*****	**0.02%≤conc<0.2 % R37**
Corrosive (C) CUT-OFFS (R34) ➔		**≥5%**	*****	**0.5%≤conc<5% R37**
Irritant (Xi) CUT-OFFS (R41) ➔ (serious eye damage)			**≥5%**	**0.5%≤conc<5% R36**
Irritant (Xi) CUT-OFFS (R36, R37, R38) ➔				**≥5% R36, R37, R38**

Concentrations are in v/v%

* Corrosive ingredients assigned risk phrases R35 or R34 should be considered as assigned risk phrase 41 (ie, capable of causing serious eye damage). Consequently, if the mixture contains corrosive ingredients with R35 or R34 below the concentration cut-off level for a classification of the mixture as corrosive, such ingredients can contribute to a classification of the mixture as irritant (R41) or irritant (R36). Therefore when the formulae for classifying mixtures at Paragraphs 6.11 and 6.13 of Chapter 6 are applied the following concentration cut off levels should be used:

Formula at 6.11: The concentration cut-off levels to be used for LXi R4 in the formula are:	Formula at 6.13: The concentration cut-off levels to be used for LXi R36 in the formula are:
5% for the ingredients Xi R41 2% for the ingredients C R34 0.2% for the ingredients C R35	5% for the ingredients Xi R36 0.5% for the ingredients Xi R41 0.5% for the ingredients C R34 0.02% for the ingredients C R35

SENSITISING EFFECTS

Table 9 Solid and liquid mixtures

INGREDIENT-CLASSIFICATION (*start*)- ⬇	**MIXTURE – CLASSIFICATION** (*result*)	
	Harmful (Xn) (R42)	**Irritant (Xi) (R43)**
Respiratory Sensitising CUT-OFFS (R42) ➔	**≥1%**	
Skin Sensitising CUT-OFFS R43 ➔		**≥1%**
Skin and Respiratory Sensitising CUT-OFFS R42/43 ➔	**≥1% R42/43**	

Concentrations are in % w/w.

Table 10 Gaseous mixtures

INGREDIENT-CLASSIFICATION (*start*)- ⬇	**MIXTURE – CLASSIFICATION** (*result*)
	Harmful (Xn)
Respiratory Sensitising CUT-OFFS (R42) ➔	**≥0.2% (R42)**
Skin and Respiratory Sensitising CUT-OFFS R42/43 ➔	**≥0.2% R42/43**

Concentrations are in % v/v.

CARCINOGENIC EFFECTS

Table 11 Solid, liquid and gaseous mixtures

INGREDIENT-CLASSIFICATION (*start*)- ↓	**MIXTURE – CLASSIFICATION** (*result*)	
	Toxic (T) (R45 or R49)	**Harmful (Xn) (R40)**
Category 1 CUT-OFFS R45 or R49 →	**≥0.1%**	
Category 2 CUT-OFFS R45 or R49 →	**≥0.1%**	
Category 3 CUT-OFFS R40 →		**≥1%**

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

The risk phrase R49 is used for substances which present a carcinogenic risk only when inhaled, for example, as dust, vapour or fumes, and for which other routes of exposure, such as ingestion or skin contact, do not present any carcinogenic risk.

MUTAGENIC EFFECTS

Table 12 Solid, liquid and gaseous mixtures

INGREDIENT-CLASSIFICATION (*start*)- ↓	**MIXTURE – CLASSIFICATION** (*result*)	
	Toxic (T) (R46)	**Harmful (Xn) (R40)**
Category 1 CUT-OFFS R46 →	**≥0.1%**	
Category 2 CUT-OFFS R46 →	**≥0.1%**	
Category 3 CUT-OFFS R40 →		**≥1%**

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

TOXIC EFFECTS FOR REPRODUCTION

Effects on Fertility

Table 13A Solid and liquid mixtures

INGREDIENT-CLASSIFICATION (*start*)- ↓	MIXTURE – CLASSIFICATION (*result*)	
	Toxic (T) (R60)	Harmful (Xn) (R62)
Category 1 CUT-OFFS R60 →	≥0.5%	
Category 2 CUT-OFFS R60 →	≥0.5%	
Category 3 CUT-OFFS R62 →		≥5.0%

Concentrations are in % w/w.

Table 13B Gaseous mixtures

INGREDIENT-CLASSIFICATION (*start*)- ↓	MIXTURE – CLASSIFICATION (*result*)	
	Toxic (T) (R60)	Harmful (Xn) (R62)
Category 1 CUT-OFFS R60 →	≥0.2%	
Category 2 CUT-OFFS R60 →	≥0.2%	
Category 3 CUT-OFFS R62 →		≥1.0%

Concentrations are in % v/v.

TOXIC EFFECTS FOR REPRODUCTION

Developmental Toxicity

Table 14A Solid and liquid mixtures

INGREDIENT-CLASSIFICATION (*start*)- ↓	**MIXTURE – CLASSIFICATION** (*result*)	
	Toxic (T) (R61)	**Harmful (Xn) (R63)**
Category 1 CUT-OFFS R61 ➔	**≥0.5%**	
Category 2 CUT-OFFS R61 ➔	**≥0.5%**	
Category 3 CUT-OFFS R63 ➔		**≥5.0%**

Concentrations are in % w/w.

Table 14B Gaseous mixtures

INGREDIENT-CLASSIFICATION (*start*)- ↓	**MIXTURE – CLASSIFICATION** (*result*)	
	Toxic (T) (R61)	**Harmful (Xn) (R63)**
Category 1 CUT-OFFS R61 ➔	**≥0.2%**	
Category 2 CUT-OFFS R61 ➔	**≥0.2%**	
Category 3 CUT-OFFS R63 ➔		**≥1.0%**

Concentrations are in % v/v.

OTHER TOXICOLOGICAL EFFECTS

Table 15 Solid, liquid and gaseous mixtures

INGREDIENT- **CLASSIFICATION** (*start*)**-** ↓	**MIXTURE –** **CLASSIFICATION** (*result*) **Harmful (Xn)**
CUT-OFFS **R33** →	**≥1%** **R33**
CUT-OFFS **R64** →	**≥1%** **R64**
CUT-OFFS **R65** →	**≥10.0%** **R65**

Concentrations are in % w/w.

Chapter 6 Classification of mixtures where ingredients do not exceed the concentration cut-off levels

6.1 For mixtures containing more than one hazardous substance in individual concentrations below the relevant concentration cut-off levels, formulae are provided to determine if the mixture is a hazardous substance, and to classify the substance so that the proper risk phrases can be assigned.

6.2 The formulae are applicable only for substances with either acute lethal, corrosive or irritant effects. The concentration cut-off levels from Chapter 5 are used in the formulae.

6.3 These formulae provide a safeguard, as substances with similar health effects can produce an additive effect greater than would be suggested by their individual concentrations.

6.4 For calculating the additive effects of hazardous ingredients in mixtures (at concentrations below their concentration cut-off levels) in order to determine the hazard classification of the mixture, the following procedure is used:

- Identify the ingredient classification in the first column of the appropriate table in Chapter 5.
- Compare the concentration of the ingredient in the mixture with the concentration cut-off levels in the table for the ingredient classification.
- Check to see if two or more ingredients are classified with acute lethal, corrosive or irritant effects.
- For each type of health effect (that is, acute lethal, corrosive or irritant effects) use the formulae listed below to classify the mixture, beginning with the most severe classification for each health effect. For example, determine whether the mixture is Very Toxic (T^+) before determining whether it is Toxic.
- For each denominator in the equation, select the concentration cut-off level for the ingredient which is appropriate for the mixture classification. For example, in the case of a Very Toxic (T^+) ingredient, the

concentration cut-off level (Table 1) is 7% for a Very Toxic (T^+) mixture, 1% for a Toxic mixture and 0.1% for a Harmful mixture.

- Where a concentration range is indicated in Chapter 5, use the lowest concentration cut-off level as the denominator in the equation, for example, use 3% if the range shown in Table 1 is 3% $\leq$ conc < 25%.

Acute lethal effects

EXPLANATORY NOTES REGARDING APPLICATION OF FORMULAE

6.5 Lethality resulting from different routes of exposure is considered to be additive for the purpose of applying the following formulae. The appropriate combination risk phrases is then assigned to the mixture.

Very Toxic (T^+) mixtures (R26, R27, R28)

6.6 Mixtures containing more than one Very Toxic (T^+) ingredient are classified as Very Toxic (R26, R27, R28) if:

$$\sum\left(\frac{P_T{}^+}{L_T{}^+}\right) \geq 1$$

where,

P_{T+} is the percentage by weight or by volume of each Very Toxic (R26, R27, R28) ingredient in the mixture.

L_{T+} is the Very Toxic (T^+) concentration cut-off level specified for each Very Toxic (R26, R27, R28) ingredient expressed as a percentage by weight or by volume.

Toxic (T) mixtures (R23, R24, R25)

6.7 Mixtures containing more than one Very Toxic (T^+) or Toxic (T) ingredient are classified as Toxic (R23, R24, R25) if:

$$\sum\left(\frac{P_T^+}{L_T}+\frac{P_T}{L_T}\right)\geq 1$$

where,

P_{T+} is the percentage by weight or by volume of each Very Toxic (R26, R27, R28) ingredient in the mixture.

P_T is the percentage by weight or by volume of each Toxic (R23, R24, R25) ingredient in the mixture.

L_T is the Toxic (T) concentration cut-off level specified for each Very Toxic (R26, R27, R28) or Toxic (R23, R24, R25) ingredient expressed as a percentage by weight or by volume.

Harmful (Xn) mixtures (R20, R21, R22)

6.8 Mixtures containing more than one Very Toxic (T^+), Toxic (T) or Harmful (Xn) ingredient are classified as Harmful (R20, R21, R22) if:

$$\sum\left(\frac{P_T^+}{L_{Xn}}+\frac{P_T}{L_{Xn}}+\frac{P_{Xn}}{L_{Xn}}\right)\geq 1$$

where,

P_{T+} is the percentage by weight or by volume of each Very Toxic (R26, R27, R28) ingredient in the mixture.

P_T is the percentage by weight or by volume of each Toxic (R23, R24, R25) ingredient in the mixture.

P_{Xn} is the percentage by weight or by volume of each Harmful (R20, R21, R22) ingredient in the mixture.

L_{Xn} is the Harmful (Xn) concentration cut-off level specified for each Very Toxic (R26, R27, R28), Toxic (R23, R24, R25) or Harmful (R20, R21, R22) ingredient expressed as a percentage by weight or by volume.

Corrosive (C) effects (R34, R35)

Corrosive mixtures (R35)

6.9 Mixtures containing more than one Corrosive (R35) ingredient are classified as Corrosive (R35) if:

$$\sum\left(\frac{P_{C.R35}}{L_{C.R35}}\right)\geq 1$$

where,

$P_{C.R35}$ is the percentage by weight or by volume of each Corrosive (R35) ingredient in the mixture.

$L_{C.R35}$ is the Corrosive (R35) concentration cut-off level specified for each Corrosive ingredient with risk phrase R35 expressed as a percentage by weight or by volume.

Corrosive mixtures (R34)

6.10 Mixtures containing more than one Corrosive (R34) ingredient are classified as Corrosive (R34) if:

$$\sum\left(\frac{P_{C.R35}}{L_{C.R34}}+\frac{P_{C.R34}}{L_{C.R34}}\right)\geq 1$$

where,

$P_{C.R35}$ is the percentage by weight or by volume of each Corrosive ingredient with risk phrase R35 in the mixture.

$P_{C.R34}$ is the percentage by weight or by volume of each Corrosive ingredient with risk phrase R34 in the mixture.

$L_{C.R34}$ is the Corrosive (R34) concentration cut-off level specified for each Corrosive ingredient with risk phrase R34 expressed as a percentage by weight or by volume.

Irritant (Xi) effects (R36, R37, R38, R41)

EXPLANATORY NOTES REGARDING APPLICATION OF FORMULAE

6.11 Corrosive ingredients assigned risk phrases R35 or R34 are considered capable of causing serious eye damage and/or skin irritation. Consequently, these ingredients can contribute to the overall Irritant (R41/R38) classification of the mixture. Refer to Tables 7 & 8 of Chapter 5 for the relevant concentration cut-off levels for R35 and R34 ingredients.

Irritant mixtures with risk of serious eye damage (R41)

6.12 Mixtures containing more than one Corrosive or Irritant (Xi) ingredient with risk phrase R41 assigned are classified as Irritant (R41) if:

$$\sum\left(\frac{P_{Xi.R41}}{L_{Xi.R41}}\right)\geq 1$$

where,

$P_{Xi.R41}$ is the percentage by weight or by volume of each irritant ingredient with risk phrase R41 in the mixture.

$L_{Xi.R41}$ is the Irritant (Xi R41) concentration cut-off level for specified irritant ingredient which is assigned risk phrase R41 expressed as a percentage by weight.

Skin Irritant mixtures (R38)

6.13 Mixtures containing more than one corrosive or Irritant (Xi) ingredient with risk phrase R38 assigned are classified as Irritants (R38) if:

$$\sum\left(\frac{P_{C.R35}}{L_{Xi.R38}}+\frac{P_{C.R34}}{L_{Xi.R38}}+\frac{P_{Xi.R38}}{L_{Xi.R38}}\right)\geq 1$$

where,

$P_{C.R35}$ is the percentage by weight or by volume of each Corrosive ingredient with risk phrase R35 in the mixture.

$P_{C.R34}$ is the percentage by weight or by volume of each Corrosive ingredient with risk phrase R34 in the mixture.

$P_{Xi.R38}$ is the percentage by weight or by volume of each Irritant ingredient with risk phrase R38 in the mixture.

$L_{Xi.R38}$ is the Irritant (Xi) concentration cut-off level specified for each Corrosive ingredient assigned with risk phrase R35 or R34 or Irritant ingredient with risk phrase R38 expressed as a percentage by weight or by volume.

Eye Irritant mixtures (R36)

6.14 Mixtures containing more than one eye irritant R36 (Xi) ingredient with risk phrases R35, R34, R41 or R36 assigned are classified as Irritants (R36) if:

$$\sum\left(\frac{P_{Xi.R41}}{L_{Xi.R36}}+\frac{P_{Xi.R36}}{L_{Xi.R36}}\right)\geq 1$$

where,

$P_{Xi.R41}$ is the percentage by weight of each corrosive ingredient with risk phrase R35, R34 or R41 in the mixture.

$P_{Xi.R36}$ is the percentage by weight or by volume of each corrosive ingredient with risk phrases R36 in the mixture.

$L_{Xi.R36}$ is the Irritant (Xi) concentration cut-off level specified for each Corrosive ingredient with risk phrase R35, R34 or R41 or Irritant ingredient with risk phrase R36 expressed as a percentage by weight.

Respiratory Irritant mixtures (R37)

6.15 Mixtures containing more than one Irritant (Xi) ingredient with risk phrase R37 assigned are classified as Irritants (R37) if:

$$\sum\left(\frac{P_{Xi.R37}}{L_{Xi.R37}}\right)\geq 1$$

where,

$P_{Xi.R37}$ is the percentage by weight or by volume of each Irritant ingredient with risk phrase R37 in the mixture.

$L_{Xi\cdot R37}$ is the Irritant (Xi) concentration cut-off level specified for each Irritant ingredient with risk phrase R37 expressed as a percentage by weight or by volume.

APPENDIX 1

INFORMATION SOURCES

Although not an exhaustive listing, the following information sources described in this appendix may be useful in the process of collating and interpreting data on the health effects of a substance.

BOOKS, MONOGRAPHS AND OTHER PUBLICATIONS

A1.1 International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, International Agency for Research on Cancer, Lyon, France. (Web site: http://www.iarc.fr)

These monographs are critical reviews of the literature on chemicals, industrial processes and industries associated with human cancer by the various IARC Working Groups.

A1.2 International Agency for Research on Cancer, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 7 (IARC Monographs, Volumes 1 to 42), International Agency for Research on Cancer, Lyon, France, 1987.

The supplement summarises the data reviewed in the IARC Monographs, Volumes 1 to 42, and provides a cumulative index.

A1.3 International Agency for Research on Cancer, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 6 (Genetic and Related Effects: An Updating of Selected IARC Monographs, Volumes 1 to 42), International Agency for Research on Cancer, Lyon, France, l987.

This is a tabulation of the published literature on the genotoxic effects of 200 IARC evaluated chemicals and agents.

A1.4 International Programme on Chemical Safety, Environmental Health Criteria, World Health Organisation, Geneva, Switzerland.

These criteria are reviews of environmental and toxicological literature on chemicals and physical agents published as a joint venture of the United Nations Environment Programme, the International Labour Organisation and the World Health Organisation.

A1.5 Klaasen, C.D., Amdur, M.O. and Doull, J., Casarett and Doull's Toxicology: The Basic Science of Poisons, McGraw Hill Companies, Inc, New York, USA, 1995.

This is a text book covering theoretical aspects of toxicology including concepts and mechanisms.

A1.6 Schardein, J.L., Chemically Induced Birth Defects, Marcel Dekker, New York, USA, 1993.

This is a valuable reference text on chemicals and their interaction with the processes of development and growth.

A1.7 Shepard, T.H., Catalogue of Teratogenic Agents, 7th Edition, Johns Hopkins University Press, Baltimore, USA, 1992.

This is a comprehensive listing of teratogens, as abstracted from the published literature.

A1.8 Australian Occupational Health and Safety Index.

This service provides access to over 20,000 documents on a wide range of occupational health and safety topics. Material is drawn from both overseas and Australian sources, including the National Occupational Health and Safety Commission and Standards Australia. Entire documents are included.

Available from IHS Australia Pty Ltd:

Freecall: 1800 252 633
email: ihs@ihs.com.au
Web site: http://www.ihs.com.au

SYDNEY	MELBOURNE	BRISBANE
244 Beecroft Road	666 Chapel Street	42 Mary Pleasant Drive
Epping. NSW. 2121	South Yarra. VIC. 3141	Birkdale. QLD. 4159
Ph: 02 9876 5333	Ph: 03 9826 6099	Ph: 0418 190 336
Fax: 02 9876 2299	Fax: 03 9826 6886	Fax: 07 3822 4006

A1.9 The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC).

ECETOC publishes a range of reports varying in scope from those on specific chemicals (eg the Joint Assessment of Commodity Chemicals reports (JACC)) to those dealing with the fundamental principles underlying the various branches of science in toxicology and ecotoxicology (eg. Monographs and Technical Reports). ECETOC publications are produced by Task Forces composed of appropriate experts drawn from member companies and other organisations.

The European Centre for Ecotoxicology and Toxicology of Chemicals
Avenue E, Van Nieuwenhuyse, 4-B6
B-1160 Brussels, Belgium.

A small collection of ECETOC publications are held in the Worksafe Australia library. See paragraph A2.61 for library contact details.

COMPUTER DATABASES

A1.10 There are two principal types of computer databases available:

(a) Factual - a listing of information on the properties of a chemical. For example, RTECS and HSDB; and

(b) Bibliographic - a list of references in the scientific literature, usually with abstracts or summaries. For example, TOXLINE, CISDOC, HSELINE, MEDLINE and NIOSHTIC.

A1.11 Factual databases have the advantage of allowing immediate access to information, for example, specific physical properties of a chemical or toxicity values. Retrieving information by searching a bibliographic database is more time consuming as it involves obtaining copies of the articles from books and journals. However, it should be noted that reference to articles in the scientific literature will generally provide more current information in a greater amount of detail.

A1.12 Searching databases containing chemical information demands a knowledge and experience of the different search techniques. Searching by inexperienced users may yield results which are not a true representation of the information available. Advice from an experienced user should be sought before commencing a search.

A1.13 Databases are available either by online access or on a CD-ROM. Some databases, such as RTECS, are available from a number of different database suppliers as well as on several CD-ROM products. Online database suppliers provide access to hundreds of databases and very powerful search engines. Account holders are charged for what they use, usually on a monthly basis. This method of searching can prove expensive for the inexperienced or untrained user.

A1.14 There are an increasing number of CD-ROM products containing one or a package of several databases which are purchased via annual subscription and updated during the year. For the frequent user this may prove more cost effective as once the subscription fees are paid no charge is made for access.

A1.15 There are currently over 300 databases worldwide providing occupational health and safety information. Some of the more widely used databases providing information on chemicals are described below. In parenthesis after each description is a list of database suppliers and/or CD-ROM products which provide access to each particular database. At the end of this appendix is a list of database suppliers and CD-ROMs, with contact details.

Factual Databases

A1.16 CCRIS - Chemical Carcinogenesis Research Information System. CCRIS contains scientifically evaluated data derived from carcinogenicity, mutagenicity, tumour promotion, and tumour inhibition studies on over 2500 chemicals.
(CIS, TOXNET)

A1.17 CHEMINFO - produced by the Canadian Centre for Occupational Health and Safety (CCOHS), Cheminfo contains property information, exposure limit values, NFPA hazard assessments and toxicity data.
(CCINFO)

A1.18 CHEMLIST - The Regulated Chemicals Listing contains identifying and US regulatory information for chemical substances listed on the US EPA Toxic Substances Control Act Inventory or subject to regulation under TSCA; the Australian Inventory of Chemical Substances (AICS); the Canadian Domestic Substances List (DSL) and Non-Domestic Substances List (NDSL); the Korean Existing Chemicals List (ECL), the European Inventory of Existing Commercial Chemicals Substances (EINECS) and the European List of Notified Chemical Substances (ELINCS), and the Japanese Chemical Inventory (ECN). (STN).

A1.19 CHEMSAFE - contains evaluated safety characteristics of flammable substances. More than 40 properties, such as flash points, explosion limits, minimum ignition energy and autoignition temperature are provided. Sources include technical laws, collections of safety parameters and accident prevention regulations. Chemsafe is produced in Germany and provides information in English and German.
(STN)

A1.20 CHEMTOX - provides a collection of environmental, health and safety data for chemical substances regulated or which are candidates for regulation in the US. The database contains identifying information, physical and chemical properties, US regulatory information, toxicity data, and emergency and disposal guidelines for 6,000 chemicals.
(Dialog Corp -Dialog)

A1.21 CHRIS - Chemical Hazard Response Information System from the US Coast Dept of Transportation (CoastGuard) contains information to assist with emergency response, accident response, accident prevention and safety procedure design, and transportation of chemicals.
(CIS, Chembank, TOMES Plus)

A1.22 GENE-TOX - contains mutagenicity data on over 3,000 chemicals assembled from expert review of the open scientific literature.
(TOXNET)

A1.23 HAZARDTEXT - provides information to assist with the management of hazardous chemical incidents such as spills or leaks - toxicity, fire and explosion data, chemical reactivity, personal protective equipment and disposal guidelines. A good source of information on personal protective equipment.
(TOMES Plus)

A1.24 HSDB - Hazardous Substances Databank from the US National Library of Medicine's TOXNET system, provides information on properties, manufacture and use, toxicity, safety and handling, environmental fate and standards and regulations for over 4,500 chemicals.
(STN, TOXNET, Chembank, CCINFO, TOMES Plus)

A1.25 IRIS - Integrated Risk Information System, sponsored by the US EPA, provides EPA health risk and regulatory information on over 600 chemicals. Carcinogenic (eg unit risks) and non-carcinogenic (eg reference doses) risk assessment data is provided for the oral and inhalation routes of exposure.
(TOXNET, CIS, TOMES Plus)

A1.26 NATIONAL CHEMICAL INVENTORIES - includes identifying data (chemical names, synonyms and trade names, and if available molecular formulae and structure diagrams) for over 175,000 substances taken from the following national inventories: Australian Inventory of Chemical Substances (AICS), United States (TSCA); Canada (DSL, NDSL); The European Communities (EINECS/ELINCS); Japan (ECN) and Korea (ECL).
(STN)

A1.27 REGISTRY FILE - contains over 15 million unique chemical substance records identified by the Chemical Abstracts Service (CAS). Records contain identifying information such as CAS Registry numbers, CA index names, commonly used synonyms and some trade names, polymer class terms, molecular formula and structure diagrams. The Registry file is unique to STN and the locator field indicates which other files (indexed by CAS numbers) on the STN system contain information on the chemical - thus it will indicate whether there is a record for the chemical in RTECS, HSDB, Chemlist, Medline, Toxline, Toxlit etc. (STN)

A1.28 REPROTEXT - is produced by Micromedex and provides information on the acute and chronic clinical effects of chemicals and physical agents. Each chemical has a dual hazard rating, one for general toxicity and one for reproductive hazard.
(TOMES Plus)

A1.29 RTECS - Registry of Toxic Effects of Chemical Substances is produced by the US National Institute for Occupational Safety and Health (NIOSH). RTECS provides data for over 130,000 chemicals including identifying information such as CAS number, chemical names and synonyms. Toxicity data include acute and chronic animal tests data, human data, skin and eye irritation data, Threshold Limit Values, IARC determinations, *in vitro* toxicity test data, US National Toxicology Programme (NTP) and TSCA Inventory data. RTECS provides the original reference for each value given.
(STN, TOXNET, CIS, CCINFO, Chembank, TOMES Plus.)

A1.30 TERIS - Teratogen Information System provides information on the teratogenic effects of chemicals and is produced by the University of Washington.
(TOMES Plus)

Bibliographic Databases

A1.31 CANCERLIT - Produced by the US National Library of Medicine, Cancerlit covers all areas of the international literature on cancer. It covers material on carcinogens and mutagens.
(Dialog Corp - Dialog and DataStar; Ovid; STN, also available as a CD-ROM from Silverplatter)

A1.32 CHEMICAL ABSTRACTS - This huge database (over 13 million records) is produced by the Chemical Abstracts Service and covers worldwide literature in all areas of chemistry, biochemistry and chemical engineering from 1967 to the present. It indexes over 9,000 journals as well as patents, conference papers, technical reports, books and theses. Chemical Abstracts is available from several online suppliers but only STN contains the abstracts.
(STN, Dialog Corp.-Dialog and DataStar, Questel-Orbit)

A1.33 CISDOC - is produced by the International Labour Organisation and indexes worldwide literature in OH&S. CIS abstracts information on the toxicology of industrial chemicals, chemical hazards and industrial hygiene. It is a source of European regulatory information as it indexes OH&S information from the Official Journal of the European Communities and EC Directives.
(Questel-Orbit, CCINFO, OSHROM)

A1.34 CSNB - Chemical Safety Newsbase, indexes sources such as journals, books, conference papers, legislation and press releases in areas relating to fire and explosions, storage and transport, toxicity and waste removal of chemicals. It is produced by the Royal Society of Chemistry.
(Dialog Corp.-Datastar, Questel-Orbit, STN)

A1.35 EMBASE - is equivalent to the printed Excerpta Medica and covers worldwide literature in the biomedical and pharmaceutical fields, including biological science, biochemistry, environmental science, toxicology and pharmacology. It indexes more than 3,500 journals as well as monographs, conference proceedings, dissertations and reports.
(Dialog Corp.- Dialog and DataStar; Ovid, STN)

A1.36 ENVIRONMENTAL CHEMICALS HEALTH AND SAFETY - is produced by the Royal Society of Chemistry. It does not index the toxicological literature as comprehensively as does Toxline but has good coverage of regulatory information and chemical industry literature on industrial chemicals.
(Dialog Corp.)

A1.37 HSELINE - is produced by the UK Health and Safety Executive and covers all areas of health and safety at work. It is a good source for UK and European regulatory information.
(Dialog Corp - Datastar, Questel-Orbit, OSHROM)

A1.38 KOSMET - Indexes world literature related to cosmetics and perfumes, with an emphasis on scientific and technical aspects.
(Dialog Corp. -Datastar)

A1.39 MEDLINE - Produced by the US National Library of Medicine. Medline covers all areas of medicine and contains over 8.4 million references from 1966 to the present. Medline indexes over 3,700 international health and medical journals and is the online equivalent of the printed *Index Medicus, Index to Dental Literature* and *International Nursing Index*. The Medline database is available free via the US National Library of Medicine's website: http://www.nlm.nih.gov
(STN, Dialog Corp.- Dialog and DataStar; OVID, also available as a CD-ROM from Silverplatter)

A1.40 NAPRALERT - The Natural Products Alert database contains bibliographic and factual data on natural products and covers pharmacological, biological activity and chemistry of plant, microbial and animal extracts. The database indexes journals, books, patents, conference papers, government reports and newsletters.
(STN)

A1.41 **NIOSHTIC** - is produced by the US National Institute for Occupational Safety and Health and indexes both US and international literature in all areas of OH&S including toxicology, hazardous wastes and industrial hygiene. It covers a broad range of literature in toxicology and includes references to both animal and human studies. NIOSHTIC contains some references dating back to the early twentieth century.
(Dialog Corp -Dialog, CCINFO, OSHROM.)

A1.42 **TOXLINE** - Produced by the US National Library of Medicine. Toxline indexes the literature on pharmacological, biochemical, physiological and toxicological effects of chemicals. Toxline consists of 16 different files, including TSCATS and indexes journals, patents, government reports, criteria documents and meeting reports as well as the IARC (International Agency for Research on Cancer) Monographs and the WHO/ILO/UN sponsored Environmental Health Criteria.
(STN, Dialog and DataStar TOXNET, Questel-Orbit, also Silverplatter, CCINFO)

A1.43 **TOXLIT** - Produced by the US National Library of Medicine with data supplied by CAS, Toxlit has the same scope as Toxline but is derived from portions of the Chemical Abstracts database.
(STN, TOXNET)

A1.44 **TSCATS** - (Toxic Substances Control Act Test Submissions) enables users to identify unpublished health and safety studies submitted to the US EPA under various sections of the US Toxic Substances Control Act. TSCATS is updated quarterly and provides access to over 50,000 test submissions on over 6,500 chemicals substances.
(TSCATS is available as a subfile on Toxline and as a separate database on the CIS system. The latter allows online ordering of the fulltext of the test submissions)

Online Database Suppliers

A1.45 Accessing online databases usually involves opening an account with a database supplier or vendor. Charges are based on a combination of amount of time online, and/or search terms entered and/or number of records or amount of information downloaded and will vary according to which database is searched and which supplier is used to access it. Traditionally, searching these online systems required a knowledge of the systems' commands and this way of searching is still quicker and provides the experienced searcher with more control. Increasingly, database suppliers are providing access via user friendly interfaces on the Internet. Account holders usually receive a set of database descriptions, a manual of commands and a newsletter on new databases, enhancements to databases and searching tips. For the systems below with an Australian representative training is provided periodically throughout the year.

A1.46 **CIS** - (Chemical Information Systems) provides online access to a series of databases containing information on specific chemical substances, including toxicological and carcinogenic research data, hazardous materials handling information, chemical/physical property information, regulatory information, spectroscopic data, and pharmaceutical data. CIS does not have an Australian representative, however, they can be contacted directly at:

Chemical Information System. Oxford Molecular Group, Inc.
810 Gleneagles Court,
Ste. 300, Townson,
MD 21286 USA
Ph: 410 321 8440, Fax: 1 410 296 0712
.

(CIS provides access to CCRIS, CHRIS, IRIS, RTECS, TSCATS, and other more specific databases).

A1.47 The Dialog Corporation - provides access to over 400 databases in all areas of science and technology, business and company information and social sciences and humanities through its two systems DIALOG and Datastar. Contact:

The Dialog Corporation
5/50 Margaret Street
Sydney. 2000
Ph: 02 9299 6767, Fax: 02 9299 6769
Freecall: 1800 654 525
email: mark_ostryn@maid.com
Web site. http://www.dialog.com

(Chemical Abstracts, Medline, NIOSHTIC, HSELINE, Cancerlit, KOSMET, and Toxline.)

A1.48 Ovid Technologies - provides access to over 80 Databases via a common user interface online or in stand-alone or network configurations at your site. Databases are concentrated mainly in medical and health sciences but include some databases in the areas of business, science and social science and humanities. Contact:

Ovid Technologies
Suite 1702, Level 17
25 Bligh Street
SYDNEY NSW 2000
Ph: 02 9231 5599, Fax: 02 9231 5086
Freecall: 1800 22 6474.
Email: ovid@unilinc.edu.au.

(Cancerlit, Embase, Chemical Abstracts, Medline.)

A1.49 Questel-Orbit Inc. - provides online access to some 200 databases concentrated in the areas of business, science and engineering and patents through its two database systems Questel and Orbit. Questel-Orbit is represented in Australia and can be contacted at:

Questel-Orbit
PO Box 1883
NORTH SYDNEY NSW 2059
Ph: 02 9929 8775, Fax: 02 9922 5611
Freecall: 1800 658 898,
Email: aine@harkers.com.au
Web site: http://www.harkers.com.au

(Chemical Abstracts, CISDOC, HSEline, NIOSHTIC, CSNB, Medline)

A1.50 **STN** - (Scientific and Technical Network) is a joint operation by CAS (Chemical Abstracts Service), a division of the American Chemical Society in the US; FIZ Karlsruhe in Europe and JICST (The Japan Information Center of Science and Technology) in Japan. The STN system provides access to some 200 databases in all areas of science and technology. STN is represented in Australia by:

Dr Damon Ridley
School of Chemistry, F11
University of Sydney
SYDNEY NSW 2006
Ph: 02 9351 2180, Fax: 02 9351 6650
Email: dridley@chem.usyd.edu.au.
Web site - http://www.cas.org.

(Registry File, Chemical Abstracts, Chemlist, HSDB, RTECS, Chemsafe, CSNB, Medline, Napralert, Cancerlit, Toxline, and Toxlit.)

A1.51 on **TOXNET**, contact:

Specialized Information Services
National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894
Ph: 1 301 496 6531, Fax: 1 301 480 3537
email: toxmail@tox.nlm.nih.gov
Web site: http://www.nlm.nih.gov.

(CCRIS, DART, EMICBACK, ETICBACK, GENE-TOX, HSDB, IRIS, RTECS and TRI)

CD-ROM Products

A1.52 Some CD-ROM products (such as TOMES Plus) bring together several databases on the one disc, others (such as TOXLINE) are published as separate databases, while others are subsets of much larger and more general databases. Examples of the latter are Poltox II which is a subset of Embase, and Physicians' Silverplatter: Occupational and Environmental Medicine which is a subset of Medline.

A1.53 CCINFO is a numbered series of CD-ROM products published by CCOHS (Canadian Centre of Occupational Health and Safety). Discs available in the series include: MSDS (contains over 100,000 material safety datasheets prepared by over 550 US or Canadian chemical suppliers or manufacturers); CHEMSource (including Cheminfo, CESARS, CHRIS) ; NIOSHTIC; RTECS, HSDB and Toxline. CCINFO discs can be obtained directly from

CCOHS
250 Main Street East
Hamilton, Ontario,
L8N 1H6.
TEL: 905 570 8094, FAX: 905 572 2206
EMAIL: custserv@ccohs.ca.
Web site: http://www.ccohs.ca

A1.54 **CHEM-BANK** contains the five fulltext databases; RTECS, HSDB, OHMTADS, CHRIS and IRIS.

OSHROM contains the three bibliographic databases HSELine, CISDOC and NIOSHTIC and a fourth MHIDAS which summarises major hazardous incidents involving chemicals.

Physicians' Silverplatter: Occupational and Environmental Medicine is a subset of the huge Medline database in the areas of occupational diseases and accidents, environmental safety and protective measures and toxicology.

POLTOX II (Pollution and Toxicology Abstracts) is a subset of the large Embase database.

TOXLINE is produced by the US National Library of Medicine Toxline indexes the literature on the pharmacological, biochemical, physiological and toxicological effects of chemicals. Toxline is made up of 16 different sub-files, including TSCATS' Toxline indexes journals, patents, government reports, criteria documents, meeting reports and research projects as well as the IARC (International Agency for Research on Cancer) Monographs and the WHO/ILO/UN sponsored Environmental Health Criteria.

The above 5 CD-ROM products are all published by Silverplatter and available in Australia from:

GEAC Global Information
35 Miles Street
SOUTHBANK VICTORIA 3006.
Ph: 03 9257 7600, Fax: 03 9257 7689.
Email: global@geac.com.au
Web site: http://www.geac.com.au/global

A1.55 ENVIRONMENTAL CHEMICALS HEALTH AND SAFETY - is produced by the Royal Society of Chemistry and published on a single CD-ROM by The Dialog Corporation and is available from:

The Dialog Corporation
5/50 Margaret Street
Sydney. 2000
Ph: 02 9299 6767, Fax: 02 9299 6769
Freecall: 1800 654 525
email: mark_ostryn@maid.com
Web site. http://www.dialog.com

A1.56 TOMES Plus is produced by the US company Micromedex Inc. It contains (on a single CD-ROM) the following fulltext databases: Meditext, Hazardtext, Saratext, Reprorisk, Reprotext, RTECS, HSDB, IRIS, OHM/TADS, CHRIS, DOT Emergency Response Guides. TOMES Plus is available in Australia from:

IHS Australia Pty Ltd (see **A1.8** of this appendix)

Libraries and Information Centres

A1.57 Many of the larger research libraries (such as state and university libraries) hold some of the CD-ROM products listed above and provide access to the public for free or for a nominal sum. In addition, some libraries provide a fee-based search service and will conduct searches on online databases and/or CD-ROM databases specific to the information need of the client.

A1.58 The National Occupational Health and Safety Commission Library (Worksafe Australia Library) has access to all the databases listed above (either on CD-ROM or online) as well as an excellent collection of reference books, monographs and journals in the area of toxicology, hazardous substances and regulation of chemicals. The Library offers a number of services to make these resources available to Australian industry. For a minimal fee clients can search a selection of CD-ROM products including TOMES Plus, Toxline, CCINFO - Chemsource and MSDS, OSHROM, Physicians Silverplatter: Occupational & Environmental Medicine and Environmental Chemistry Health and Safety. Inexperienced clients receive assistance in their search. Appointments can be made by contacting the Library.

A1.59 Search Service - The Library's experienced searching-staff conduct a search tailored to your needs using CD-ROMs, online databases and printed sources. This is a fee based service. Contact the External Services Librarian for a quote Ph: 02 9577 9255.

A1.60 Associate Membership - is available to all Australian residents and entitles the member to borrow books and videos (these can be sent to any part of Australia), unlimited use of the CD-ROMs, delivery of copies of articles and two free searches done by our experienced staff. Contact the External Services Librarian.

A1.61 WORKSAFE AUSTRALIA LIBRARY
National Occupational Health and Safety Commission
92 Parramatta Road
CAMPERDOWN, NSW. 2050
Ph: 02 9577 9253, Fax: 02 9577 9201

Opening Hours: 8:30 to 17:00 (Mon-Friday).8.30 to 20:00 on Thursdays, from March to November.

INTERNET RESOURCES

Note:

Internet resources, in particular address details, are subject to change. This short list is provided as a starting point for a few direct resources with many links to other internet sites with chemical safety resources. Wherever possible, to hopefully provide relatively stable sources, large organisations or government agencies have been selected. However other addresses of a more specific or temporary nature may prove useful. Wherever possible in reference to other source material in the previous sections of this information resource list, (eg see databases), internet addresses have been included and may provide links or occasionally access to free material. This list was current as of January 1998.

A1.62 http://www.indiana.edu/~cheminfo/

CHEMINFO is a list of links to chemical resources on the internet. CHEMINFO is a good starting place for any search for chemical information which is organised into subject areas including MSDS sources and guides to chemical safety or toxicology information.

A subset of CHEMINFO with a slightly different format is found at:
http://www.indiana.edu/~cheminfo/cisindex.html
This is the Index to Selected Internet Resources for Chemistry (SIRCh). Also a good place to start. It is arranged alphabetically rather than by subject area.

A1.63 http://www.chem.uky.edu/resources/msds.html

There are many MSDS sites on the internet. This collection of links from the University of Kentucky seems well maintained and gives good background material for the MSDS beginner.

A1.64 http://chemfinder.camsoft.com

For those interested in chemical identification Cambridge Soft provide a useful search tool online, Chem Finder. The company also provides ChemDraw, a useful structural drawing program. Demonstration versions of this product may be downloaded from this site by following links.

A1.65 http://www.cdc.gov/niosh/homepage.html

NIOSH, the National Institute for Occupational Safety and Health of the USA maintains a series of links and some databases for chemical safety information searching. This is a good site to catch up on conferences and current topics of worker safety in general in the United States.

A1.66 http://www.who.ch/programmes/pcs/pcs_act.htm

The International Programme on Chemical Safety or IPCS established in 1980, is a joint program of three cooperating organisations, ILO, UNEP and WHO, implementing activities related to chemical safety. It is provided as another useful starting place with many links and some of their own resources. The best address for one of their resources is maintained by NIOSH at the following address

A1.67 http://www.cdc.gov/niosh/ipcs/ipcs0000.html

The International Chemical Safety Cards (ICSCs), a product of IPCS, are a series of records of chemicals, alphabetically arranged, listing their properties and hazard information.

A1.68 http://www.arcade.uiowa.edu/hardin-www/md-tox.html

The *Hardin Meta Directory - Toxicology* is one of the best sites for toxicology resources. It is short, quick to load and refers to excellent toxicology sites.

A1.69 http://www.rtk.net

RTK NET, or the Right To Know network, provides free access to numerous databases, text files, and conferences on the environment, housing, and sustainable development. This reference is the often not directly related to chemical safety but if your interests are environmental with respect to chemicals, it should prove useful.

A1.70 Chemical Information Discussion List

If you have an email address, keep up with discussions about chemical information or ask questions yourself, using the chemical information discussion list. You can join this group by sending the message:

"**sub CHMINF-L your name listserv@listserv.indiana.edu**"
(your name = your email address)

APPENDIX 2

Acute Toxicity - Notes on the Fixed Dose Procedure

A2.1 The fixed dose procedure is conducted in two stages - a preliminary sighting study and a main study. In a preliminary sighting study, the effects of various doses administered orally by gavage to single animals of one sex are investigated in a sequential manner. The sighting study yields information on the dose-toxicity relationship, including an estimate of the minimum lethal dose. In the main study, the substance is administered orally by gavage to groups of five male and five female animals at one of the pre-set dose levels (5, 50, 500 or 2,000 mg/kg). The dose used is derived from the sighting study and is that which is likely to produce evident toxicity but no deaths.

A2.2 The discriminating dose is the dose which causes evident toxicity but not mortality and should be one of the four dosage levels specified: 5, 50, 500 or 2000 mg per kg per body weight. The concept “evident toxicity” is used to designate toxic effects, after exposure to the substance tested, which are so severe that exposure to the next highest fixed dose would probably lead to mortality. The results of testing at a particular dose may be either:

- less than 100% survival,
- 100% survival, but evident toxicity,
- 100% survival, but no evident toxicity.

EVALUATION AND INTERPRETATION

DOSE	RESULTS	INTERPRETATION
5 mg/kg	Less than 100% survival	Compounds which are VERY TOXIC
	100% survival; but evident toxicity	Compounds which are TOXIC
	100% survival; no evident toxicity	See results at 50 mg/kg.
50 mg/kg	Less than 100% survival	Compounds which may be TOXIC or VERY TOXIC. See results at 5 mg/kg.
	100% survival; but evident toxicity	Compounds which are HARMFUL.
	100% survival; no evident toxicity	See results at 500 mg/kg.
500 mg/kg	Less than 100% survival	Compounds which may be TOXIC or HARMFUL. See results at 50 mg/kg.
	100% survival, but evident toxicity	Compounds considered as having no significant acute toxicity.
	100% survival; no evident toxicity	See results at 2,000 mg/kg
2000 mg/kg	Less than 100% survival	See results at 500mg/kg
	100% survival; with or without evident toxicity	Compounds which do not have significant acute toxicity.

APPENDIX 3

Risk and Safety Phrases

RISK PHRASES

The following risk phrases and combination risk phrases are those adopted by the European Communities in EC Council Directive 67/548/EC[3] to describe health effects and they apply to Australia

R20	Harmful by inhalation.
R21	Harmful in contact with skin.
R22	Harmful if swallowed.
R23	Toxic by inhalation.
R24	Toxic in contact with skin.
R25	Toxic if swallowed.
R26	Very toxic by inhalation.
R27	Very toxic in contact with skin.
R28	Very toxic if swallowed.
R29	Contact with water liberates toxic gas.
R31	Contact with acids liberates toxic gas.
R32	Contact with acids liberates very toxic gas.
R33	Danger of cumulative effects.
R34	Causes burns.
R35	Causes severe burns.
R36	Irritating to eyes.
R37	Irritating to respiratory system.
R38	Irritating to skin.
R39	Danger of very serious irreversible effects.
R40	Possible risks of irreversible effects.
R41	Risk of serious damage to eyes.
R42	May cause sensitisation by inhalation.
R43	May cause sensitisation by skin contact.
R45	May cause cancer.
R46	May cause heritable genetic damage.

R48	Danger of serious damage to health by prolonged exposure.
R49	May cause cancer by inhalation.
R60	May impair fertility
R61	May cause harm to the unborn child.
R62	Possible risk of impaired fertility.
R63	Possible risk of harm to the unborn child.
R64	May cause harm to breastfed babies.
R65	Harmful: May cause lung damage if swallowed.
R20/21	Harmful by inhalation and in contact with skin.
R20/22	Harmful by inhalation and if swallowed.
R20/21/22	Harmful by inhalation, in contact with skin and if swallowed.
R21/22	Harmful in contact with skin and if swallowed.
R23/24	Toxic by inhalation and in contact with skin.
R23/25	Toxic by inhalation and if swallowed.
R23/24/25	Toxic by inhalation, in contact with skin and if swallowed.
R24/25	Toxic in contact with skin and if swallowed.
R26/27	Very toxic by inhalation and in contact with skin.
R26/28	Very toxic by inhalation and if swallowed.
R26/27/28	Very toxic by inhalation, in contact with skin and if swallowed.
R27/28	Very toxic in contact with skin and if swallowed.
R36/37	Irritating to eyes and respiratory system.
R36/38	Irritating to eyes and skin.
R36/37/38	Irritating to eyes, respiratory system and skin.
R37/38	Irritating to respiratory system and skin.
R39/23	Toxic: danger of very serious irreversible effects through inhalation.
R39/24	Toxic: danger of very serious irreversible effects in contact with skin.
R39/25	Toxic: danger of very serious irreversible effects if swallowed.
R39/23/24	Toxic: danger of very serious irreversible effects through inhalation and in contact with skin.
R39/23/25	Toxic: danger of very serious irreversible effects through inhalation and if swallowed.
R39/24/25	Toxic: danger of very serious irreversible effects in contact with skin and if swallowed.
R39/23/24/25	Toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed.

R39/26	Very toxic: danger of very serious irreversible effects through inhalation.
R39/27	Very toxic: danger of very serious irreversible effects in contact with skin.
R39/28	Very toxic: danger of very serious irreversible effects if swallowed.
R39/26/27	Very toxic: danger of very serious irreversible effects through inhalation and in contact with skin.
R39/26/28	Very toxic: danger of very serious irreversible effects through inhalation and if swallowed.
R39/27/28	Very toxic: danger of very serious irreversible effects in contact with skin and if swallowed.
R39/26/27/28	Very toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed.
R40/20	Harmful: possible risk of irreversible effects through inhalation.
R40/21	Harmful: possible risk of irreversible effects in contact with skin.
R40/22	Harmful: possible risk of irreversible effects if swallowed.
R40/20/21	Harmful: possible risk of irreversible effects through inhalation and in contact with skin.
R40/20/22	Harmful: possible risk of irreversible effects through inhalation and if swallowed.
R40/21/22	Harmful: possible risk of irreversible effects in contact with skin and if swallowed.
R40/20/21/22	Harmful: possible risk of irreversible effects through inhalation, in contact with skin and if swallowed.
R42/43	May cause sensitisation by inhalation and skin contact.
R48/20	Harmful: danger of serious damage to health by prolonged exposure through inhalation.
R48/21	Harmful: danger of serious damage to health by prolonged exposure in contact with skin.
R48/22	Harmful: danger of serious damage to health by prolonged exposure if swallowed.
R48/20/21	Harmful: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin.
R48/20/22	Harmful: danger of serious damage to health by prolonged exposure through inhalation and if swallowed.
R48/21/22	Harmful: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed.
R48/20/21/22	Harmful: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed.
R48/23	Toxic: danger of serious damage to health by prolonged exposure through inhalation.
R48/24	Toxic: danger of serious damage to health by prolonged exposure in contact with skin.

R48/25	Toxic: danger of serious damage to health by prolonged exposure if swallowed.
R48/23/24	Toxic: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin.
R48/23/25	Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed.
R48/24/25	Toxic: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed.
R48/23/24/25	Toxic: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed.

SAFETY PHRASES

Suggested safety phrases for substances classified as either 'Irritating due to the defatting properties of the skin' (see Paragraph 4.46) or substances that cause 'Immunological contact urticaria' (see Paragraph 4.72).

S24	Avoid contact with skin.
S28	After contact with skin, wash immediately with plenty of .... (material to be specified by the manufacturer).
S36	Wear suitable protective clothing.
S37	Wear suitable gloves.
S36/37	Wear suitable protective clothing and gloves.

APPENDIX 4

Examples of applying the criteria to classify a hazardous substance

Example 1 - A substance containing 0.5% w/w Parathion

A4.1 The data show that Parathion is Very Toxic on the basis of its acute lethal effects (risk phrase R27/R28).

A4.2 Therefore, Parathion meets the health effects criteria of Chapter 4. The concentration cut-off levels of Chapter 5 should now be applied.

A4.3 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 R21/22 the most appropriate risk phrase.

Example 2 - A substance containing 7% w/w Acetyl chloride

A4.4 The data show that Acetyl chloride is Corrosive (risk phrase R34).

A4.5 Therefore, Acetyl chloride meets the health effects criteria of Chapter 4. The concentration cut-off levels of Chapter 5 should now be applied.

A4.6 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 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 3a,4,7,7a-Tetrahydro-4,7-methanoindene and 30% w/w Amyl alcohol

A4.7 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 Chapter 4. If the mixture has not been tested as a whole, the availability of health effects data on the ingredients (3a,4,7,7a-Tetrahydro-4,7-methanoindene and Amyl alcohol) needs to be considered.

A4.8 The data available for 3a,4,7,7a-Tetrahydro-4,7-methanoindene and Amyl alcohol show that:

- 3a,4,7,7a-Tetrahydro-4,7-methanoindene is Harmful by inhalation or if swallowed on the basis of its acute lethal effects (risk phrases R20, R22) and is an Irritant (risk phrase R36/37/38); and

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

A4.9 Therefore, both 3a,4,7,7a-Tetrahydro-4,7-methanoindene and Amyl alcohol meet the health effects criteria of Chapter 4. The concentration cut-off levels of Chapter 5 should now be applied.

A4.10 According to Table 1, a mixture containing a Harmful substance (risk phrases R20, R22) at a concentration above 25% w/w is a hazardous substance. The mixture is classified as Harmful, with risk phrases R20, R22 considered appropriate for the mixture.

A4.11 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.

A4.12 Therefore, according to the health effects criteria of Chapter 4 and the concentration cut-off levels of Chapter 5, a 70% 3a,4,7,7a-Tetrahydro-4,7-methanoindene and 30% Amyl alcohol mixture is a hazardous substance and the mixture is classified as Harmful and Irritant, with R20, R22 and R36/37/38 the most appropriate risk phrases.

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

A4.13 The data show that 3,3-Dichlorobenzidine is:

- a Category 2 Carcinogen (R45);
- Harmful by skin contact on the basis of its acute lethal effects (R21); and
- a skin sensitiser (R43).

A4.14 Therefore, 3,3-Dichlorobenzidine meets the health effects criteria of Chapter 4. The concentration cut-off levels of Chapter 5 should now be applied.

A4.15 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.

A4.16 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.

A4.17 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 1,2,4-Trimethylbenzene and 2% w/w 2,4,6-Trinitrophenol;

A4.18 The data show that:

- Methyl mercaptan is Harmful by inhalation on the basis of its acute lethal effects (risk phrase R20);
- 1,2,4-Trimethylbenzene is Harmful (Xn) by inhalation on the basis of its acute lethal effects (risk phrase R20) and is Harmful (Xi) on the basis of its irritant effects (R36/37/38); and
- 2,4,6-Trinitrophenol is Toxic if swallowed, by inhalation or by contact with the skin on the basis of its acute lethal effects (risk phrase R23/24/25).

A4.19 Therefore, each of the three ingredients in the mixture meets the health effects criteria of Chapter 4. The concentration cut-off levels of Chapter 5 should now be applied.

A4.20 According to Table 1, a mixture with less than 25% w/w of a Harmful ingredient is not classified as a 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. 1,2,4-Trimethylbenzene is present at 20% which in Table 7 (Chapter 5) is at the cut-off for classification as an irritant by virtue of R36/37/38 and therefore should be classified as Harmful (Xi) with R36/37/38. Since all the other hazardous ingredients in the mixture are in concentrations below their respective cut-off levels and they have similar health effects, the formulae of Chapter 6 should be used to determine whether the mixture overall is a hazardous substance.

A4.21 Assuming that the three ingredients have additive health effects, the appropriate formulae in Chapter 6 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, the mixture is not classified as Toxic as the only toxic ingredient (2,4,6-Trinitrophenol) is present at a concentration below 25% w/w, the sum is less than 1, that is:

$$\frac{P_T}{L_T} = \frac{2}{25} \text{ (Toxic cut-off for T ingredient)}$$

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 Paragraph 6.8 can be applied.

$$\sum\left(\frac{P_T^+}{L_{Xn}} + \frac{P_T}{L_{Xn}} + \frac{P_{Xn}}{L_{Xn}}\right) \geq 1$$

where,

P_{T+} = the percentage by weight of each Very Toxic (R26, R27, R28) ingredient in the mixture

P_T = the percentage by weight of each Toxic (R23, R24, R25) ingredient in the mixture.

P_{Xn} = the percentage by weight of each Harmful (R20, R21, R22) ingredient in the mixture.

L_{Xn} = the concentration cut-off level specified for each Very Toxic (R26, R27, R28), Toxic (R23, R24, R25) or Harmful (R20, R21, R22) ingredient expressed as a percentage by weight.

- There are no Very Toxic ingredients, so there is no PT^+ that is:

$$\frac{P_{T+}}{L_{Xn}} = \frac{0}{0.1} \text{ (Toxic cut-off for } T^+ \text{ ingredient)}$$

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

$$\frac{P_T}{L_{Xn}} = \frac{2}{3} \text{ (Toxic cut-off for T ingredient)}$$

- Methyl mercaptan and 1,2,4-Trimethylbenzene are both Harmful ingredients, so:

$$\frac{P_{Xn}}{L_{Xn}} = \frac{10}{25} + \frac{20}{25} = \frac{30}{25}$$ (Harmful cut-off for Xn ingredient)

- Applying the formula:

$$\sum\left(\frac{P_T^+}{L_{Xn}} + \frac{P_T}{L_{Xn}} + \frac{P_{Xn}}{L_{Xn}}\right) \geq 1$$

$$\Sigma = \frac{(0}{(0.1} + \frac{2}{3} + \frac{30)}{25)} = 1.9, \text{ which is} > 1$$

- Therefore, the mixture is a hazardous substance and is classified as Harmful with R20 the most appropriate risk phrase.

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

A4.22 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).

A4.23 Therefore, each of the two ingredients in the mixture meets the health effects criteria of Chapter 4. The concentration cut-off levels in Chapter 5 should now be applied.

A4.24 According to Table 1, a mixture containing less than 25% w/w of a Harmful ingredient is 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.

A4.25 As the health effects for each ingredient are different, they are not additive, so it is not necessary to apply the formulae in Chapter 6. The mixture is therefore not a hazardous substance.

Example 7 - A substance containing 5.7% w/w Lead azide

A4.26 The data show that Lead azide is:

- a Category 1-Toxic for Reproduction (development) substance (R 61),
- a Category 3-Harmful for Reproduction (fertility) substance (R62),
- Harmful by inhalation and if swallowed on the basis of its acute lethal effects (R20/22); and
- Accumulation in the human body is likely (R33).

A4.27 Therefore, Lead azide meets the health effects criteria of Chapter 4. The concentration cut-off levels of Chapter 5 should now be applied.

A4.28 According to Table 14A a mixture containing 0.5% w/w or more of a category 1-Toxic for reproduction substance is to be classified as Toxic, with risk phrase R61 to be assigned to the mixture.

A4.29 According to Table 13A a mixture containing 5% w/w or more of a Category 3-Toxic for Reproduction substance, is to be assigned with risk phrase R62. The hazard category 'Harmful' is redundant and not assigned, as the 'Toxic' hazard category from above, which is valid at concentrations of 0.5% w/w and above, takes precedence.

A4.30 According to Table 1 a mixture containing less than 25% w/w or more of a Harmful substance is not classified as a hazardous substance on the basis of its acute lethal effects.

A4.31 According to Table 15 a mixture containing a substance at a concentration of 1% or more, and this substance is likely to accumulate in the body, then the risk phrase R33 should be assigned to the mixture.

A4.32 Therefore, according to the health effects criteria of Chapter 4 and the concentration cut-off levels of Chapter 5 a 5.7% Lead azide mixture is a hazardous substance and is classified as Toxic with risk phrases R61, R62, and R33.

Example 8 - A substance containing 2.5% w/w Aqueous Ammonia solution, 0.4% w/w Sodium hydroxide and 2.4% w/w Bis(3-(trimethoxysilyl)propyl) amine;

NOTE: This example includes three different members of the corrosive/irritant hazard family of chemicals. It is chosen because corrosivity/irritancy is a very common basis for hazard classification, particularly in cleaning agents.

A4.33 Information, current in 1998 and to be included in the 1999 List of Designated Hazardous Substances, shows the following classification and cut-off information.

	CLASSIFICATION	CUT-OFFS
Ammonia solution	C; R34	Conc&10%: C; R34 &5%Conc<10%: Xi; R36/37/38
Sodium hydroxide	C; R35	Conc&5%: C; R35 &2%Conc<5%: C; R34 &0.5%Conc<2%: Xi; R36/38
Bis(3-(trimethoxysilyl) propyl)amine	Xi; R41	Conc&10%: Xi; R41 &5%Conc<10%: Xi; R36

A4.34 The data show that:

- Ammonia solution is corrosive causing burns (risk phrase R34);
- Sodium hydroxide is corrosive causing severe burns (risk phrase R35); and
- Bis(3-(trimethoxysilyl)propyl)amine causes serious damage to eyes(risk phrase R41).

A4.35 Therefore, each of the three ingredients in the mixture meets the health effects criteria of Chapter 4. The concentration cut-off levels of Chapter 5 should now be applied.

A4.36 According to Table 7, a mixture with less than 5% w/w of a Corrosive (Ammonia, R34) ingredient is not classified as a hazardous substance (Irritant) on the basis of its corrosive effects. Similarly, a mixture with less than 5% w/w of an ingredient with a risk of serious damage to eyes (Bis(3-(trimethoxysilyl)propyl)amine) is not classified as a hazardous substance on the basis of its irritant effects. Finally a mixture with less than 0.5% Sodium hydroxide with a risk of corrosivity (Sodium hydroxide) is not classified as a hazardous substance on the basis of its corrosive effects. **Note that Sodium hydroxide has been**

assigned specific cut-offs in the Designated List of Hazardous Substances and these must be applied, not the generic cut-offs in Table 7. 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 Chapter 6 should be used to determine whether the mixture overall is a hazardous substance.

A4.37 Assuming that the three ingredients have additive health effects, the appropriate formulae in Chapter 6 can be applied.

Note: Classification begins with the most hazardous classification in the family and proceeds to the next hazardous classification if classification is not satisfied at any level.

Step 1 Normally the concentration cut-off levels for the most hazardous substance in a mixture are taken from the appropriate Table(s) in Chapter 5. For a Corrosive/Irritant mixture. this is Table 7. However since Sodium hydroxide has specific cut-offs these values are applied from the List of Designated Hazardous Substances, for corrosive and irritant effects. For R35 corrosive, causes severe burns, the cut-off for Sodium hydroxide is 5% w/w. No others apply.

Step 2 for R34 Corrosive, causes burns, the cut-offs are 2% for Sodium hydroxide and 10% for Ammonia solution.

$$\sum\left(\frac{P_{C.R35}}{L_{C.R34}} + \frac{P_{C.R34}}{L_{C.R34}}\right) \geq 1$$

$=0.4/2.0 + 2.5/10 \quad = 0.45 < 1$

since the value of 1 is not met or exceeded the substance is not classified as hazardous in terms of R34.

where,

$P_{C.R35}$ = the percentage by weight of each ingredient in the mixture which cause serious burns (R35)

$P_{C.R34}$ = the percentage by weight of each ingredient in the mixture which cause burns

$L_{C.R34}$ = the concentration cut-off level specified for each ingredient in terms of causing burns, (R34)

Step 3 Consider the concentration cut-off levels for an R41 mixture (causing serious eye damage) in Table 7, that is:

- for Sodium hydroxide 2.0 % w/w;
- for a R34 ingredient, 10% w/w; and
- for a R41 ingredient, 10% w/w.
- Therefore, the formula for an irritant mixture with serious damage to eyes in Paragraph 6.12 can be applied.

$$\sum \left(\frac{P_{Xi.R41}}{L_{Xi.R41}} \right) \geq 1$$

$=0.4/2.0 + 2.5/10 + 2.4/10 = 0.69 < 1$

since the value of 1 is not met or exceeded, the substance is not classified as hazardous in terms of R41.

Please note that mixtures classified with the risk phrases R35, R34 are automatically assigned serious damage to eyes risk phrases when present at a higher concentration than their R34 cut-off.

$P_{Xi.R41}$ = the percentage by weight of each ingredient in the mixture which cause serious damage to eyes

$L_{Xi.R41}$ = the concentration cut-off level specified for each ingredient in terms of serious damage to eyes, (R41)

Step 4 Consider the concentration cut-off levels for an irritant mixture with risk phrase R36 (eye irritation) assigned as in Table 7, that is:

- for Sodium hydroxide 0.5 % w/w;
- for a R34 ingredient, 5% w/w; and
- for a R41 ingredient, 5% w/w.
- Therefore, the formula for an irritant mixture with R36 in Paragraph 6.14 can be applied.

$$\sum \left(\frac{P_{Xi.R41}}{L_{Xi.R36}} + \frac{P_{Xi.R36}}{L_{Xi.R36}} \right) \geq 1$$

where,

$P_{Xi.R41}$ is the percentage by weight of each corrosive ingredient with risk phrase R35,R34 or R41 in the mixture.

$P_{Xi.R36}$ is the percentage by weight or by volume of each corrosive ingredient with risk phrases R36 in the mixture.

$L_{Xi.R36}$ is the Irritant (Xi) concentration cut-off level specified for each Corrosive ingredient with risk phrase R35, R34 or R41 or Irritant ingredient with risk phrase R36 expressed as a percentage by weight.

=0.4/0.5 + 2.5/5 + 2.4/5 =1.78 > 1

since the value of 1 is exceeded, the substance is classified as hazardous ie an eye irritant with the risk phrase R36.

Step 5 consider the concentration cut-off levels for this irritant mixture with risk phrase R38 (skin irritant) assigned as in Table 7, that is:

- for Sodium hydroxide 0.5 % w/w;
- for Ammonia, 5% w/w; and

Therefore, the formula for the irritant mixture with R38 in Paragraph 6.13 can be applied.

$$\sum\left(\frac{P_{C.R35}}{L_{Xi.R38}}+\frac{P_{C.R34}}{L_{Xi.R38}}+\frac{P_{Xi.R38}}{L_{Xi.R38}}\right)\geq 1$$

where,

$P_{C.R35}$ is the percentage by weight of each Corrosive ingredient with risk phrase R35 in the mixture.

$P_{C.R34}$ is the percentage by weight or by volume of each Corrosive ingredient with risk phrase R34 in the mixture.

$P_{Xi.R38}$ is the percentage by weight or by volume of each Irritant ingredient with risk phrase R38 in the mixture.

$L_{Xi.R38}$ is the Irritant (Xi) concentration cut-off level specified for each Corrosive ingredient assigned with risk phrase R35 or R34 or Irritant ingredient with risk phrase R38 expressed as a percentage by weight.

=0.4/0.5 + 2.5/5 =1.3 > 1

since the value of 1 is exceeded, the substance is classified as hazardous ie a skin irritant with the risk phrase R38.

Overall Classification Harmful R36, R38 (see steps 4,5)

APPENDIX 5

NOTIFICATION OF HAZARDOUS SUBSTANCES

Hazardous substances regulations have been implemented by State, Territory and Commonwealth governments in accordance with the National Occupational Health and Safety Commission's *National Model Regulations for the Control of Workplace Hazardous Substances.* The *Model Regulations* require manufacturers or importers to determine if a substance to be used in the workplace is a hazardous substance.

If the substance meets the National Occupational Health and Safety Commission's *Approved Criteria for Classifying Hazardous Substances* and that hazardous substance is not already included in the National Commission's *List of Designated Hazardous Substances* [NOHSC:10005(1999)], and provided the substance is not a composite material, mixture or formulation, then the manufacturer or importer has a duty to notify the National Commission of that determination.

This Notification Form is provided for manufacturers/importers to advise the National Commission of their determination of a hazardous substance and the associated hazard classification assigned for that substance. In order for the National Commission to keep an accurate and complete register of all notifications the notifier is required to complete this Notification Form.

The information contained in this form is not regarded as confidential

Completed forms should be forwarded to:

Manager
Hazardous Substances Unit
National Occupational Health and Safety Commission
GPO Box 58
Sydney NSW 2001
Fax: (02) 9577 9204

All notifications received will be acknowledged by National Commission staff

NOTIFIER'S DETAILS

Date:

Company name:

ACN:

Contact name and position:

Address:

Phone number:

Facsimile number:

Email address:

Tick which is applicable: Manufacturer [ ] Supplier [ ]

SUBSTANCE IDENTIFICATION

Chemical name:

Synonyms:

Product or Trade names:

Chemical Abstract Services Registry (CAS) Number:

If a CAS number is not available, please supply:

Molecular Formula:

AND

Structural Formula:

PROPOSED CLASSIFICATION

Risk Phrase(s):_____

Safety Phrase(s):_____

Note(s): _____
Concentration cut-offs:

Xn **Harmful**	**T** **Toxic**	**T+** **Very Toxic**	**Xi** **Irritant**	**C** **Corrosive**

Please state how this classification determination was reached:

_____

_____

_____

APPENDIX 6

Surface Tension Test Methods

Method

A6.1 The methods described are based on the OECD test guideline (1). The fundamental principles are given in reference (2).

Introduction

A6.2 The described methods are to be applied to the measurement of the surface tension of aqueous solutions.

It is useful to have preliminary information on the water solubility, the structure, the hydrolysis properties and the critical concentration for micelle formation of the substance before performing these tests.

The following methods are applicable to most chemical substances, without any restriction in respect to their degree of purity.

The measurement of the surface tension by the ring tensiometer method is restricted to aqueous solutions with a dynamic viscosity of less than approximately 200 mpa.s.

Definitions and units The free surface enthalpy per unit of surface area is referred to as surface tension.

A6.3 The surface tension is given as:

N/m (SI unit) or

mN/m (SI sub-unit)

1 N/m = 10^3 Dynes/cm

1 mN/m = dyne/cm in the obsolete cgs system

Reference substances

A6.4 Reference substances do not need to be employed in all cases when investigating a new substance. This shall primarily serve to calibrate the method from time to time and to offer a chance to compare results when another method is applied.

Reference substances which cover a wide range of surface tensions are given in references 1 and 2.

Principle of the methods

A6.5 The methods are based on the measurement of the maximum force which it is necessary to exert vertically, on a stirrup or a ring in contact with the surface of the liquid being examined placed in a measuring cup, in order to separate it from this surface, or on a plate, with an edge in contact with the surface, in order to draw up the film that has formed.

Substances which are soluble in water at least at a concentration of 1 mg/l are tested in aqueous solution at a single concentration.

Quality criteria

A6.6 These methods are capable of greater precision than is likely to be required for environmental assessment.

Description of the methods

Plate method

A6.7 See ISO-304 and NF T 73-060 (surface active agents - determination of surface tension by drawing up liquid films).

Stirrup method

A6.8 See ISO 304 and NF T 73-060 (surface active agents - determination of surface tension by drawing up liquid films).

Ring method

A6.9 See ISO 304 and NF T 73-060 (surface active agents - determination of surface tension by drawing up liquid films).

OECD harmonized ring method

Apparatus

A6.10 Commercially available tensiometers are adequate for this measurement. They consist of the following elements:

- Mobile sample table
- Force measuring system
- Measuring body (ring)
- Measurement vessel.

Mobile sample table

A6.11 The mobile sample table is used as a support for the temperature-controlled measurement vessel holding the liquid to be tested. Together with the force measuring system, it is mounted on a stand.

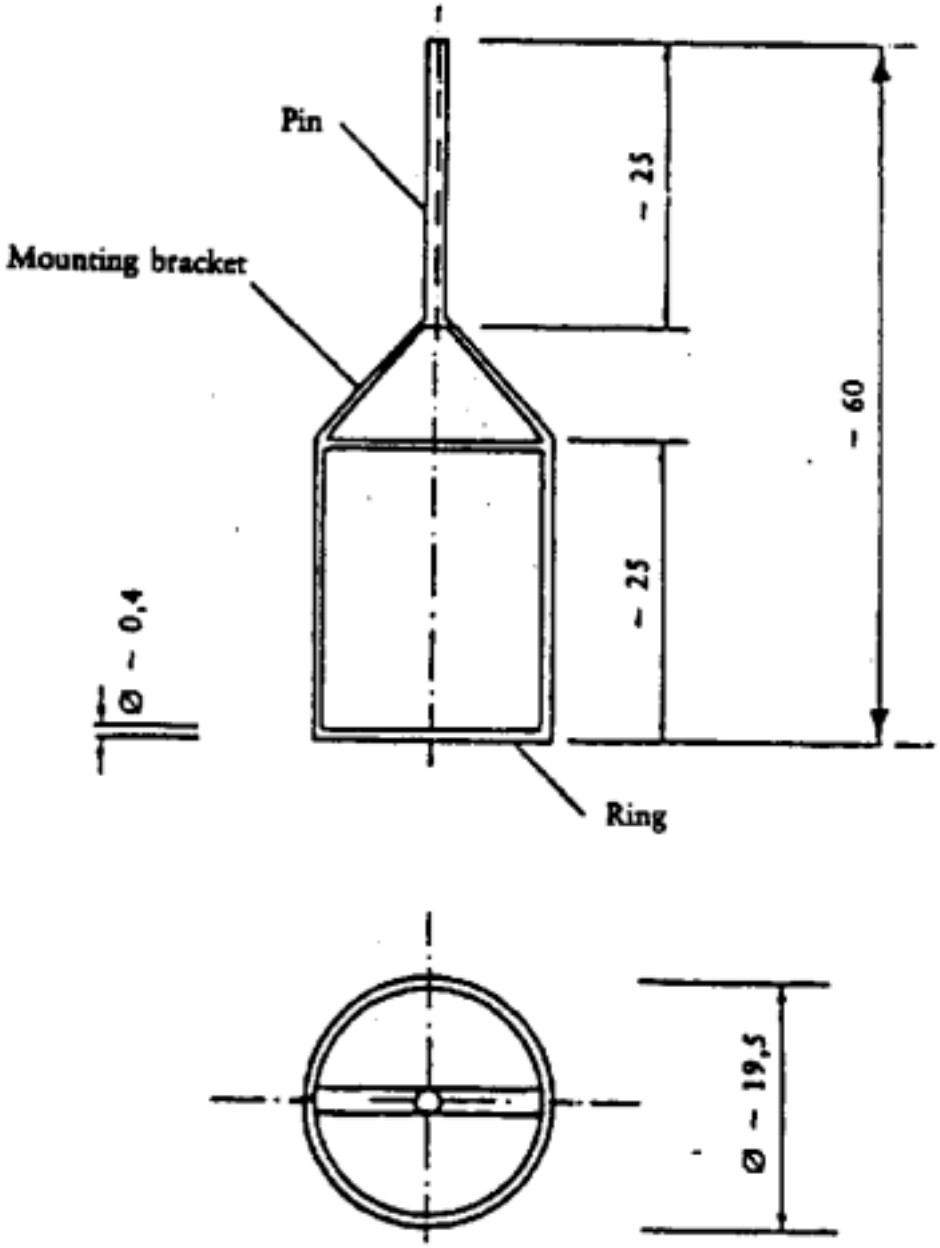
Force measuring system

A6.12 The force measuring system (see figure) is located above the sample table. The error of the force measurement shall not exceed $\pm 10^{-6}$ N, corresponding to an error limit of ± 0.1 mg in a mass measurement. In most cases, the measuring scale of commercially available tensiometers is calibrated in mN/m so that the surface tension can be read directly in mN/m with an accuracy of 0.1 mN/m.

Measuring body (ring)

A6.13 The ring is usually made of a platinum-iridium wire of about 0.4 mm thickness and a mean circumference of 60 mm. The wire ring is suspended horizontally from a metal pin and a wire mounting bracket to establish the connection to the force measuring system (see figure).

Figure
Measuring body
(All dimensions expressed in millimetres)



Measurement vessel

A6.14 The measurement vessel holding the test solution to be measured shall be a temperature-controlled glass vessel. It shall be designed so that during the measurement the temperature of the test solution liquid and the gas phase above its surface remains constant and that the sample cannot evaporate. Cylindrical glass

vessels having an inside diameter of not less than 45 mm are acceptable.

Preparation of the apparatus

Cleaning

A6.15 Glass vessels shall be cleaned carefully. If necessary they shall be washed with hot chromo-sulphuric acid and subsequently with syrupy phosphoric acid (83 to 98 % by weight of H_3PO_4), thoroughly rinsed in tap water and finally washed with double-distilled water until a neutral reaction is obtained and subsequently dried or rinsed with part of the sample liquid to be measured.

The ring shall first be rinsed thoroughly in water to remove any substances which are soluble in water, briefly immersed in chromo-sulphuric acid, washed in double-distilled water until a neutral reaction is obtained and finally heated briefly above a methanol flame.

Note:

Contamination by substances which are not dissolved or destroyed by chromo-sulphuric acid or phosphoric acid, such as silicones, shall be removed by means of a suitable organic solvent.

Calibration of the apparatus

A6.16 The verification of the apparatus consists of verifying the zero point and adjusting it so that the indication of the instrument allows reliable determination in mN/m.

Mounting

A6.17 The apparatus shall be levelled, for instance by means of a spirit level on the tensiometer base, by adjusting the levelling screws in the base.

Zero point adjustment

A6.18 After mounting the ring on the apparatus and prior to immersion in the liquid, the tensiometer indication shall be adjusted to zero and the ring checked for parallelism to the liquid surface. For this purpose, the liquid surface can be used as a mirror.

Calibrations

A6.19 The actual test calibration can be accomplished by means of either of two procedures:

(a) using a mass: procedure using riders of known mass between 0.1 and 1.0 g placed on the ring. The calibration factor a (ìa), by which all the instrument readings must be multiplied, shall be determined according to equation (1):

$$ìa = (\tau r / \tau a)$$

Where:

$\tau r = [mg / 2b]$ (mN/m)

m = mass of the rider (g)

g = gravity acceleration (981 $cm.s^{-2}$ at sea level)

b = mean circumference of the ring (cm)

τa = reading of the tensiometer after placing the rider on the ring (mN/m).

(b) using water: procedure using pure water whose surface tension at, for instance, 23 °C is equal to 72.3 mN/m. This procedure is accomplished faster than the weight calibration but there is always the danger that the surface tension of the water is falsified by traces of contamination by surfactants.

The calibration factor b (ìb), by which all the instrument indications shall be multiplied, shall be determined in accordance with the equation (2):

$$ìb = (\tau o / \tau g)$$

Where:

τo = value cited in the literature for the surface tension of water (mN/m)

τg = measured value of the surface tension of the water (mN/m)

both at the same temperature.

Preparation of samples

A6.20 Aqueous solutions shall be prepared of the substances to be tested, using the required concentrations in water, and shall not contain any non-dissolved substances.

The solution must be maintained at a constant temperature (± 0.5 °C). Since the surface tension of a solution in the measurement vessel alters over a period of time, several measurements shall be made at various times and a curve plotted showing surface tension as a function of time. When no further change occurs, a state of equilibrium has been reached.

Dust and gaseous contamination by other substances interfere with the measurement. The work shall therefore be carried out under a protective cover.

Test conditions

A6.21 The measurement shall be made at approximately 20 °C and shall be controlled to within ± 0.5 °C.

Performance of test

A6.22 The solutions to be measured shall be fixed into the carefully cleaned measuring vessel, taking care to avoid foaming, and subsequently the measuring vessel shall be placed onto the table of the test apparatus. The table-top with measuring vessel shall be raised until the ring is immersed below the surface of the solution to be measured. Subsequently, the table-top shall be lowered gradually and evenly (at a rate of approximately 0.5 cm/min) to detach the ring from the surface until the maximum force has been reached. The liquid layer attached to the ring must not separate from the ring. After completing the measurements, the ring shall be immersed below the surface again and the measurements repeated until a constant surface tension value is reached. The time from transferring the solution in the measurement vessel shall be recorded for each determination. Readings shall be taken at the maximum force required to detach the ring from the liquid surface.

Data

A6.23 In order to calculate the surface tension, the value read in mn/m on the apparatus shall be first multiplied by the calibration factor ìa or ìb (depending on the calibration procedure used). This will yield a value which applies only approximately and therefore requires correction.

Harkins and Jordan (4) have empirically determined correction factors for surface-tension values measured by the ring method which are dependent on ring dimensions, the density of the liquid and its surface tension.

Since it is laborious to determine the correction factor for each individual measurement from the Harkins and Jordan tables, in order to calculate the surface tension for aqueous solutions the simplified procedure of reading the corrected surface-tension values directly from table may be used (interpolation shall be used for readings ranging between the tabular values).

Table: Correction of the measured surface tension
(Only for aqueous solutions, p = 1g/cm^3)
R = 9.55 mm (average ring radius), r = 0.185 mm (ring wire radius)

Experimental Value (mN/m)	Corrected Value (mN/m)	
	Weight calibration	Water calibration
20	16.9	18.1
22	19.7	20.1
24	20.6	22.1
26	22.4	24.1
28	24.3	26.1
30	26.2	28.1
32	28.1	30.1
34	29.9	32.1
36	31.8	34.1
38	33.7	36.1
40	35.6	38.2
42	37.6	40.3
44	39.5	42.3
46	41.4	44.4
48	43.4	46.5
50	45.3	48.6
52	47.3	50.7
54	49.3	52.8
56	51.2	54.9
58	53.2	57.0
60	55.2	59.1
62	57.2	61.3
64	59.2	63.4
66	61.2	65.5
68	63.2	67.7
70	65.2	69.9
72	67.1	72.0
74	69.2	
76	71.2	
78	73.2	

This table has been compiled on the basis of the Harkins-Jordan correction and is similar to that in the DIN standard (din 53914) for water and aqueous solutions (density p = 1 g/cm^3) and is for a commercially available ring having the dimensions r = 9.55 mm (mean ring radius) and r = 0.185 mm (ring wire radius). The table provides corrected values for surface-tension measurements taken after calibration with weights or calibration with water.

Alternatively, without the preceding calibration, the surface tension can be calculated according to the following formula:

$t = [f \times F / 4\pi R]$

Where:

F = the force measured on the dynamometer at the breakpoint of the film

R = the radius of the ring

f = the correction factor (1)

Reporting

Test report

A6.24 The test report shall, if possible, include the following information:

- Method used
- Type of water or solution used
- Precise specification of the substance (identity and impurities)
- Measurement results: surface tension (reading) stating both the individual readings and their arithmetic mean as well as the corrected mean (taking into consideration the equipment factor and the correction table)
- Concentration of the solution
- Test temperature
- Age of solution used; in particular the time between preparation and measurement of the solution
- Description of time dependence of surface tension after transferring the solution to the measurement vessel
- All information and remarks relevant for the interpretation of results have to be reported, especially with regard to impurities and physical state of the substance.

Interpretation of results

A6.25 Considering the distilled water has a surface tension of 72.75 mN/m at 20 °C, substances showing a surface tension lower than 60 mN/m under the conditions of this method should be regarded as being surface-active materials.

References

A6.26 (1) OECD, Paris, 1981, test guideline 115, Decision of the Council c (81) 30 final.

(2) R. Weissberger ed.: Technique of Organic Chemistry, Physical Methods of Organic Chemistry, 3rd ed., Interscience Publ., New York, 1959, Vol. I, Part I, Chapter XIV

(3) Pure Appl. Chem., 1976, vol. 48, 511.

(4) Harkins, W. D., Jordan, H. F., J. Amer. Chem. Soc., 1930, vol. 52, p. 1751.

Referenced documents

1. National Occupational Health and Safety Commission, 'National Model Regulations for the Control of Workplace Hazardous Substances [NOHSC:1005(1994)]', in *Control of Workplace Hazardous Substances: National Model Regulations and National Code of Practice,* AGPS, Canberra, 1994.

2. National Occupational Health and Safety Commission, *List of Designated Hazardous Substances* [NOHSC:10005(1999)], NOHSC, Sydney, 1999.

3. EC Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances, *Official Journal of the European Communities,* No. L196 (16 August 1967).

4. EC Council Directive 88/379/EC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous preparations, *Official Journal of the European Communities,* No. L187 (16 July 1988).

5. EC Council Directive 96/54/EC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances, *Official Journal of the European Communities,* No. L248 (30 September 1996).

6. Federal Office of Road Safety, *Australian Dangerous Goods Code* 6th Edition, Vol 1, Attachment 1, Road Transport Reform (Dangerous Goods) Regulations, AusInfo, Canberra, 1998.

7. EC Council Directive 93/18/EC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous preparations, *Official Journal of the European Communities,* No. L104 (30 April 1993).

8. Organisation for Economic Cooperation and Development (OECD), *Guidelines for the Testing of Chemicals,* Organisation for Economic Cooperation and Development, Paris, 1992

.