Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

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GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS (GHS)

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FOREWORD

1. The Globally Harmonized System of Classification and Labelling of Chemicals (GHS) which is described in this document is the culmination of more than a decade of work. There were many individuals involved, from a multitude of countries, international organizations, and stakeholder organizations. Their work spanned a wide range of expertise, from toxicology to fire protection, and ultimately required extensive goodwill and the willingness to compromise, in order to achieve this system.

2. The work began with the premise that existing systems should be harmonized in order to develop a single, globally harmonized system to address classification of chemicals, labels, and safety data sheets. This was not a totally novel concept since harmonization of classification and labelling was already largely in place for physical hazards and acute toxicity in the transport sector, based on the work of the United Nations Economic and Social Council's Committee of Experts on the Transport of Dangerous Goods (UNCEDTG). Harmonization had not been achieved in the workplace or consumer sectors, however, and transport requirements in countries were often not harmonized with those of other sectors in that country.

3. The international mandate that provided the impetus for completing this work was adopted in the 1992 United Nations Conference on Environment and Development (UNCED), as reflected in Agenda 21, para.19.27

> *"A globally harmonized hazard classification and compatible labelling system, including national safety data sheets and easily understandable symbols, should be available, if feasible, by the year 2000".*

4. The work was coordinated and managed under the auspices of the Interorganization Programme for the Sound Management of Chemicals (IOMC) Coordinating Group for the Harmonization of Chemical Classification Systems (CG/HCCS). The technical focal points for completing the work were the International Labour Organization (ILO); the Organization for Economic Cooperation and Development (OECD); and the United Nations Economic and Social Council's Sub Committee of Experts on the Transport of Dangerous Goods (UNSCETDG).

5. Once completed in 2001, the work was transmitted by the IOMC to the new United Nations Economic and Social Council's Sub-Committee of Experts on the Globally Harmonized System of Classification (UNSCEGHS) established by the Council's resolution 1999/65 of 26 October 1999 as a subsidiary body of the former UNCETDG, renamed at the same occasion "Committee of Experts on the Transport of Dangerous Goods and on the Globally Harmonized System of Classification and Labelling of Chemicals" (UNCETDG/GHS). The Committee and its sub-committees work on a biennium basis and the first task of the UNSCEGHS was to make the GHS available for worldwide use and application. This document, elaborated from the original proposal by IOMC and approved by the Committee at its first session (11-13 December 2002) is intended to serve as the initial basis for global implementation of the GHS.

6. Nevertheless, the system should be dynamic, and be revised and made more efficient as experience is gained in implementation. While national or regional governments are the primary audiences for this document, it also contains sufficient context and guidance for those in industry who will ultimately be implementing the national requirements which are adopted. The UNSCEGHS is responsible for maintaining the GHS and promoting its implementation. It will provide additional guidance as needs arise, while maintaining stability in the system to encourage its adoption. Under its auspices, this document will be revised and updated to reflect national, regional and international experiences in implementing requirements into national, regional and international laws, as well as experiences of those doing the classification and labelling.

7. Bearing in mind that, in paragraph 22 (c) of its Plan of Action adopted in Johannesburg on 4 September 2002, the World Summit on Sustainable Development encouraged countries to implement the new GHS as soon as possible with a view to having the system fully operational by 2008, the Committee hopes that countries and international organizations concerned with chemical safety will adopt it in the near future. Availability of information about chemicals, their hazards, and ways to protect people, will provide the foundation for national programs for the safe management of chemicals. Widespread management of chemicals in countries around the world will lead to safer conditions for the global population and the environment, while allowing the benefits of chemical use to continue. Harmonization will also have benefits in terms of facilitating international trade, by promoting greater consistency in the national requirements for chemical hazard classification and communication that companies engaged in international trade must meet.

8. This publication has been prepared by the secretariat of the United Nations Economic Commission for Europe (UN/ECE) which provides secretariat services to the Economic and Social Council's Sub-Committee of Experts on the Classification and Labelling of Chemicals.

9. Additional information, including corrigenda to this publication, if any, may be found on the UN/ECE Transport Division web site: http://www.unece.org/trans/danger/danger.htm.

TABLE OF CONTENTS

		Page
Part 1.	**INTRODUCTION**	1
Chapter 1.1	Purpose, scope and application of the GHS	3
Chapter 1.2	Definitions and abbreviations	11
Chapter 1.3	Classification of hazardous substances and mixtures	17
Chapter 1.4	Hazard communication: Labelling	23
Chapter 1.5	Hazard communication: Safety data sheets	35
Part 2.	**PHYSICAL HAZARDS**	41
Chapter 2.1	Explosives	43
Chapter 2.2	Flammable gases	51
Chapter 2.3	Flammable aerosols	55
Chapter 2.4	Oxidizing gases	61
Chapter 2.5	Gases under pressure	65
Chapter 2.6	Flammable liquids	69
Chapter 2.7	Flammable solids	73
Chapter 2.8	Self-reactive substances	77
Chapter 2.9	Pyrophoric liquids	81
Chapter 2.10	Pyrophoric solids	83
Chapter 2.11	Self-heating substances	85
Chapter 2.12	Substances which, in contact with water, emit flammable gases	89
Chapter 2.13	Oxidizing liquids	93
Chapter 2.14	Oxidizing solids	97
Chapter 2.15	Organic peroxides	101
Chapter 2.16	Corrosive to metals	105

TABLE OF CONTENTS (cont'd)

Page

Part 3. HEALTH AND ENVIRONMENTAL HAZARDS 107

Chapter 3.1 Acute toxicity 109

Chapter 3.2 Skin corrosion/irritation 123

Chapter 3.3 Serious eye damage/eye irritation 137

Chapter 3.4 Respiratory or skin senzitisation 151

Chapter 3.5 Germ cell mutagenicity 159

Chapter 3.6 Carcinogenicity 167

Chapter 3.7 Reproductive toxicity 175

Chapter 3.8 Specific target organ systemic toxicity – Single exposure 187

Chapter 3.9 Specific target organ systemic toxicity – Repeated exposure 197

Chapter 3.10 Hazardous to the aquatic environment 209

ANNEXES 229

Annex 1 Allocation of label elements 231

Annex 2 Classification and labelling summary tables 253

Annex 3 Precautionary statements, pictograms 289

Annex 4 Consumer product labelling based on the likelihood of injury 301

Annex 5 Comprehensibility testing methodology 307

Annex 6 Examples of arrangements of the GHS label elements 323

Annex 7 An example of classification in the Globally Harmonized System 331

Annex 8 Guidance on hazards to the aquatic environment 341

Annex 9 Guidance on transformation/dissolution of metals and metal compounds in aqueous media 431

PART 1

INTRODUCTION

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CHAPTER 1.1

PURPOSE, SCOPE AND APPLICATION OF THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS (GHS)

1.1.1 Purpose

1.1.1.1 The use of chemical products to enhance and improve life is a widespread practice worldwide. But alongside the benefits of these products, there is also the potential for adverse effects to people or the environment. As a result, a number of countries or organizations have developed laws or regulations over the years that require information to be prepared and transmitted to those using chemicals, through labels or Safety Data Sheets (SDS). Given the large number of chemical products available, individual regulation of all of them is simply not possible for any entity. Provision of information gives those using chemicals the identities and hazards of these chemicals, and allows the appropriate protective measures to be implemented in the local use settings.

1.1.1.2 While these existing laws or regulations are similar in many respects, their differences are significant enough to result in different labels or SDS for the same product in different countries. Through variations in definitions of hazards, a chemical may be considered flammable in one country, but not another. Or it may be considered to cause cancer in one country, but not another. Decisions on when or how to communicate hazards on a label or SDS thus vary around the world, and companies wishing to be involved in international trade must have large staffs of experts who can follow the changes in these laws and regulations and prepare different labels and SDS. In addition, given the complexity of developing and maintaining a comprehensive system for classifying and labelling chemicals, many countries have no system at all.

1.1.1.3 Given the reality of the extensive global trade in chemicals, and the need to develop national programs to ensure their safe use, transport, and disposal, it was recognised that an internationally-harmonized approach to classification and labelling would provide the foundation for such programs. Once countries have consistent and appropriate information on the chemicals they import or produce in their own countries, the infrastructure to control chemical exposures and protect people and the environment can be established in a comprehensive manner.

1.1.1.4 Thus the reasons for setting the objective of harmonization were many. It is anticipated that, when implemented, the GHS will:

(a) enhance the protection of human health and the environment by providing an internationally comprehensible system for hazard communication;
(b) provide a recognized framework for those countries without an existing system;
(c) reduce the need for testing and evaluation of chemicals; and
(d) facilitate international trade in chemicals whose hazards have been properly assessed and identified on an international basis.

1.1.1.5 The work began with examination of existing systems, and determination of the scope of the work. While many countries had some requirements, the following systems were deemed to be the "major" existing systems and were used as the primary basis for the elaboration of the GHS:

(a) Requirements of systems in the United States of America for the workplace, consumers and pesticides;
(b) Requirements of Canada for the workplace, consumers and pesticides;
(c) European Union directives for classification and labelling of substances and preparations;
(d) The United Nations Recommendations on the Transport of Dangerous Goods.

1.1.1.6 The requirements of other countries were also examined as the work developed, but the primary task was to find ways to adopt the best aspects of these existing systems and develop a harmonized approach. This work was done based on agreed principles of harmonization that were adopted early in the process:

(a) the level of protection offered to workers, consumers, the general public and the environment should not be reduced as a result of harmonizing the classification and labelling systems;
(b) the hazard classification process refers principally to the hazards arising from the intrinsic properties of chemical elements and compounds and mixtures thereof, whether natural or synthetic[1];
(c) harmonization means establishing a common and coherent basis for chemical hazard classification and communication, from which the appropriate elements relevant to means of transport, consumer, worker and environment protection can be selected;
(d) the scope of harmonization includes both hazard classification criteria and hazard communication tools, e.g. labelling and chemical safety data sheets, taking into account especially the four existing systems identified in the ILO report[2];
(e) changes in all these systems will be required to achieve a single globally harmonized system; transitional measures should be included in the process of moving to the new system;
(f) the involvement of concerned international organizations of employers, workers, consumers, and other relevant organizations in the process of harmonization should be ensured;
(g) the comprehension of chemical hazard information, by the target audience, e.g. workers, consumers and the general public should be addressed;
(h) validated data already generated for the classification of chemicals under the existing systems should be accepted when reclassifying these chemicals under the harmonized system;
(i) a new harmonized classification system may require adaptation of existing methods for testing of chemicals;
(j) in relation to chemical hazard communication, the safety and health of workers, consumers and the public in general, as well as the protection of the environment, should be ensured while protecting confidential business information, as prescribed by the competent authorities.

1.1.2 Scope

1.1.2.1 The GHS includes the following elements:

(a) harmonized criteria for classifying substances and mixtures according to their health, environmental and physical hazards; and
(b) harmonized hazard communication elements, including requirements for labelling and safety data sheets.

1.1.2.2 This document describes the classification criteria and the hazard communication elements by type of hazard (e.g. acute toxicity; flammability). In addition, decision logics for each hazard have been developed. Some examples of classification of chemicals in the text, as well as in Annex 7, illustrate how to apply the criteria. There is also some discussion about issues that were raised during the development of the system where additional guidance was thought to be necessary to implement the system.

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1 *In some cases it is necessary also to take into account hazards arising from other properties, such as the physical state of the substance or mixture (e.g. pressure and temperature) or properties of substances produced by certain chemical reactions (e.g. flammability of gases produced by contact with water).*

2 *1992 ILO Report on the Size of the Task of Harmonizing Existing Systems of Classification and Labelling for Hazardous Chemicals.*

1.1.2.3 The scope of the GHS is based on the mandate from the 1992 United Nations Conference on Environment and Development (UNCED) for development of such a system as stated in paragraphs 26 and 27 of the Agenda 21, Chapter 19, Programme Area B, reproduced below:

> *"26. Globally harmonized hazard classification and labelling systems are not yet available to promote the safe use of chemicals, inter alia, at the workplace or in the home. Classification of chemicals can be made for different purposes and is a particularly important tool in establishing labelling systems. There is a need to develop harmonized hazard classification and labelling systems, building on ongoing work;*
>
> *27. A globally harmonized hazard classification and compatible labelling system, including material safety data sheets and easily understandable symbols, should be available, if feasible, by the year 2000."*

1.1.2.4 This mandate was later analyzed and refined in the harmonization process to identify the parameters of the GHS. As a result, the following clarification was adopted by the Interorganization Programme for the Sound Management of Chemicals (IOMC) Coordinating Group to ensure that participants were aware of the scope of the effort:

> *"The work on harmonization of hazard classification and labelling focuses on a harmonized system for all chemicals, and mixtures of chemicals. The application of the components of the system may vary by type of product or stage of the life cycle. Once a chemical is classified, the likelihood of adverse effects may be considered in deciding what informational or other steps should be taken for a given product or use setting. Pharmaceuticals, food additives, cosmetics, and pesticide residues in food will not be covered by the GHS in terms of labelling at the point of intentional intake. However, these types of chemicals would be covered where workers may be exposed, and, in transport if potential exposure warrants. The Coordinating Group for the Harmonization of Chemical Classification Systems (CG/HCCS) recognizes that further discussion will be required to address specific application issues for some product use categories which may require the use of specialized expertise."*[3]

1.1.2.5 In developing this clarification, the CG/HCCS carefully considered many different issues with regard to the possible application of the GHS. There were concerns raised about whether certain sectors or products should be exempted, for example, or about whether or not the system would be applied at all stages of the life cycle of a chemical. Three parameters were agreed in this discussion, and are critical to application of the system in a country or region. These are described below:

(a) Parameter 1:	**The GHS covers all hazardous chemicals. The mode of application of the hazard communication components of the GHS (e.g. labels, safety data sheets) may vary by product category or stage in the life cycle. Target audiences for the GHS include consumers, workers, transport workers, and emergency responders.**

(i) Existing hazard classification and labelling systems address potential exposures to all potentially hazardous chemicals in all types of use situations, including production, storage, transport, workplace use, consumer use, and presence in the environment. They are intended to protect people, facilities, and the environment. The most widely applied requirements in terms of chemicals covered are generally found in the parts of existing systems that apply to the workplace or transport. It should be noted that the term chemical is used broadly in the UNCED agreements and subsequent documents to include substances, products, mixtures, preparations, or any other terms that may be used in existing systems to denote coverage.

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[3] *IOMC Description and Further Clarification of the Anticipated Application of the Globally Harmonized System (GHS), IFCS/ISG3/98.32B.*

(ii) Since all chemicals and chemical products in commerce are made in a workplace (including consumer products), handled during shipment and transport by workers, and often used by workers, there are no complete exemptions from the scope of the GHS for any particular type of chemical or product. In some countries, for example, pharmaceuticals are currently covered by workplace and transport requirements in the manufacturing, storage, and transport stages of the life cycle. Workplace requirements may also be applied to employees involved in the administration of some drugs, or clean-up of spills and other types of potential exposures in health care settings. SDSs and training must be available for these employees under some systems. It is anticipated that the GHS would be applied to pharmaceuticals in a similar fashion.

(iii) At other stages of the life cycle for these same products, the GHS may not be applied at all. For example, at the point of intentional human intake or ingestion, or intentional application to animals, products such as human or veterinary pharmaceuticals are generally not subject to hazard labelling under existing systems. Such requirements would not normally be applied to these products as a result of the GHS. (It should be noted that the risks to subjects associated with the medical use of human or veterinary pharmaceuticals are generally addressed in package inserts and are not part of this harmonization process.) Similarly, products such as foods that may have trace amounts of food additives or pesticides in them are not currently labelled to indicate the presence or hazard of those materials. It is anticipated that application of the GHS would not require them to be labelled as such.

(b) Parameter 2:	**The mandate for development of a GHS does not include establishment of uniform test methods or promotion of further testing to address adverse health outcomes.**

(i) Tests that determine hazardous properties, which are conducted according to internationally recognized scientific principles, can be used for purposes of a hazard determination for health and environmental hazards. The GHS criteria for determining health and environmental hazards are test method neutral, allowing different approaches as long as they are scientifically sound and validated according to international procedures and criteria already referred to in existing systems for the hazard class of concern and produce mutually acceptable data. While the OECD is the lead organization for development of harmonized health hazard criteria, the GHS is not tied to the OECD Test Guidelines Program. For example, drugs are tested according to agreed criteria developed under the auspices of the World Health Organization (WHO). Data generated in accordance with these tests would be acceptable under the GHS. Criteria for physical hazards under the UNSCETDG are linked to specific test methods for hazard classes such as flammability and explosivity.

(ii) The GHS is based on currently available data. Since the harmonized classification criteria are developed on the basis of existing data, compliance with these criteria will not require retesting of chemicals for which accepted test data already exists.

(c) Parameter 3:	**In addition to animal data and valid *in vitro* testing, human experience, epidemiological data, and clinical testing provide important information that should be considered in application of the GHS.**

(i) Most of the current systems acknowledge and make use of ethically obtained human data or available human experience. Application of the GHS should not prevent the use of such data, and the GHS explicitly acknowledges the existence and use of all appropriate and relevant information concerning hazards or the likelihood of harmful effects (i.e. risk).

1.1.2.6 *Other scope limitations*

1.1.2.6.1 The GHS is not intended to harmonize risk assessment procedures or risk management decisions (such as establishment of a permissible exposure limit for employee exposure), which generally require some risk assessment in addition to hazard classification. In addition, chemical inventory requirements in various countries are not related to the GHS [4].

1.1.2.6.2 *Hazard vs. Risk*

1.1.2.6.2.1 Each hazard classification and communication system (workplace, consumer, transport) begins coverage with an assessment of the hazards posed by the chemical or chemical product involved. The degree of its capacity to harm depends on its intrinsic properties, i.e. its capacity to interfere with normal biological processes, and its capacity to burn, explode, corrode, etc. This is based primarily on a review of the scientific studies available. The concept of risk or the likelihood of harm occurring, and subsequently communication of that information, is introduced when exposure is considered in conjunction with the data regarding potential hazards. The basic approach to risk assessment is characterized by the simple formula:

Hazard × Exposure = Risk

1.1.2.6.2.2 Thus if you can minimize either hazard or exposure, you minimize the risk or likelihood of harm. Successful hazard communication alerts the user to the presence of a hazard and the need to minimize exposures and the resulting risks.

1.1.2.6.2.3 All of the systems for conveying information (workplace, consumer, transport) include both hazard and risk in some form. They vary in where and how they provide the information, and the level of detail they have regarding potential exposures. For example, exposure of the consumer to pharmaceuticals comprises a specific dose that is prescribed by the physician to address a certain condition. The exposure is intentional. Therefore, a determination has been made by a drug regulatory agency that for the consumer, an acceptable level of risk accompanies the specific dosage provided. Information that is provided to the person taking the pharmaceutical conveys the risks assessed by the drug regulatory agency rather than addressing the intrinsic hazards of the pharmaceutical or its components.

1.1.3 Application of the GHS

1.1.3.1 *Harmonization of the application of the GHS*

1.1.3.1.1 The goal of the GHS is to identify the intrinsic hazards found in chemical substances and mixtures and to convey hazard information about these hazards. The criteria for hazard classification are harmonized. Hazard statements, symbols and signal words have been standardized and harmonized and now form an integrated hazard communication system. The GHS will allow the hazard communication elements of the existing systems to converge. Competent authorities will decide how to apply the various elements of the GHS based on the needs of the competent authority and the target audience. (See also *Hazard Communication: Labelling* (Chapter 1.4, paragraph 1.4.10.5.4.2) and *Consumer Product Labelling Based on the Likelihood of Injury*, Annex 4.)

1.1.3.1.2 For transport, it is expected that application of the GHS will be similar to application of current transport requirements. Containers of dangerous goods will be marked with pictograms that address acute toxicity, physical hazards, and environmental hazards. As is true for workers in other sectors, workers in the transport sector will be trained. The elements of the GHS that address such elements as signal words and hazard statements are not expected to be adopted in the transport sector.

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[4] *IOMC Description and Further Clarification of the Anticipated Application of the Globally Harmonized System (GHS), IFCS/ISC3/98.32B.*

1.1.3.1.3 In the workplace, it is expected that all of the GHS elements will be adopted, including labels that have the harmonized core information under the GHS, and safety data sheets. It is also anticipated that this will be supplemented by employee training to help ensure effective communication.

1.1.3.1.4 For the consumer sector, it is expected that labels will be the primary focus of GHS application. These labels will include the core elements of the GHS, subject to some sector-specific considerations in certain systems. (See also *Hazard Communication: Labelling* (Chapter 1.4, paragraph 1.4.10.5.4.2) and *Consumer Product Labelling Based on the Likelihood of Injury*, Annex 4)

1.1.3.1.5 *Building block approach*

1.1.3.1.5.1 Consistent with the building block approach, countries are free to determine which of the *building blocks* will be applied in different parts of their systems. However, where a system covers something that is in the GHS, and implements the GHS, that coverage should be consistent. For example, if a system covers the carcinogenicity of a chemical, it should follow the harmonized classification scheme and the harmonized label elements.

1.1.3.1.5.2 In examining the requirements of existing systems, it was noted that coverage of hazards may vary by the perceived needs of the target audience for information. In particular, the transport sector focuses on acute health effects and physical hazards, but has not to date covered chronic effects due to the types of exposures expected to be encountered in that setting. But there may be other differences as well, with countries choosing not to cover all of the effects addressed by the GHS in each use setting.

1.1.3.1.5.3 The harmonized elements of the GHS may thus be seen as a collection of building blocks from which to form a regulatory approach. While the full range is available to everyone, and should be used if a country or organization chooses to cover a certain effect when it adopts the GHS, the full range does not have to be adopted. While physical hazards are important in the workplace and transport sectors, consumers may not need to know some of the specific physical hazards in the type of use they have for a product. As long as the hazards covered by a sector or system are covered consistently with the GHS criteria and requirements, it will be considered appropriate implementation of the GHS. Not withstanding the fact that an exporter needs to comply with importing countries'requirements for GHS implementation, it is hoped that the application of the GHS worldwide will eventually lead to a fully harmonized situation.

1.1.3.2 *Implementation and Maintenance of the GHS*

1.1.3.2.1 For the purposes of implementing the GHS, the United Nations Economic and Social Council (ECOSOC) reconfigured the UN Committee of Experts on the Transport of Dangerous Goods by resolution 1999/65 of 26 October 1999. The new Committee of Experts on the Transport of Dangerous Goods and the Globally Harmonized System of Classification and Labelling of Chemicals (UNSCETDG/GHS), maintains its Sub-Committee of Experts on the Transport of Dangerous Goods (UNSCETDG) and a new subsidiary body, the Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals (UNSCEGHS), has been created. The UNSCEGHS has the following functions:

(a) To act as custodian of the GHS, managing and giving direction to the harmonization process;
(b) To keep the GHS system up-to-date as necessary, considering the need to introduce changes, ensure its continued relevance and practical utility, and determining the need for and timing of the updating of technical criteria, working with existing bodies as appropriate;
(c) To promote understanding and use of the GHS and to encourage feedback;
(d) To make the GHS available for worldwide use and application;
(e) To make guidance available on the application of the GHS, and on the interpretation and use of technical criteria to support consistency of application; and
(f) To prepare work programmes and submit recommendations to the committee.

1.1.3.2.2 The UNSCEGHS and the UNSCETDG, both operate under the parent committee with responsibility for these two areas. The Committee is responsible for strategic issues rather than technical issues. It is not envisaged that it would review, change or revisit technical recommendations of the sub-committees. Accordingly, its main functions are:

(a) To approve the work programmes for the sub-committees in the light of available resources;
(b) To coordinate strategic and policy directions in areas of shared interests and overlap;
(c) To give formal endorsement to the recommendations of the sub-committees and provide the mechanism for channelling these to ECOSOC; and
(d) To facilitate and coordinate the smooth running of the sub-committees.

1.1.4 The GHS Document

1.1.4.1 This document describes the GHS. It contains harmonized classification criteria and hazard communication elements. In addition, guidance is included in the document to assist countries and organizations in the development of tools for implementation of the GHS. The GHS is designed to permit self-classification. The provisions for implementation of the GHS allow the uniform development of national policies, while remaining flexible enough to accommodate any special requirements that might have to be met. Furthermore, the GHS is intended to create user-friendly approach, to facilitate the work of enforcement bodies and to reduce the administrative burden.

1.1.4.2 While this document provides the primary basis for the description of the GHS, it is anticipated that technical assistance tools will be made available as well to assist and promote implementation.

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CHAPTER 1.2

DEFINITIONS AND ABBREVIATIONS

For the purposes of the GHS:

ADR means the European Agreement concerning the International Carriage of Dangerous Goods by Road, as amended;

Aerosols means any non-refillable receptacles made of metal, glass or plastics and containing a gas compressed, liquefied or dissolved under pressure, with or without a liquid, paste or powder, and fitted with a release device allowing the contents to be ejected as solid or liquid particles in suspension in a gas, as a foam, paste or powder or in a liquid state or in a gaseous state. Aerosol includes aerosol dispensers;

Alloy means a metallic material, homogeneous on a macroscopic scale, consisting of two or more elements so combined that they cannot be readily separated by mechanical means. Alloys are considered to be mixtures for the purpose of classification under the GHS;

ASTM means the "American Society of Testing and Materials";

BCF means "bioconcentration factor";

BOD/COD means "biochemical oxygen demand/chemical oxygen demand";

CA means "competent authority";

Carcinogen means a chemical substance or a mixture of chemical substances which induce cancer or increase its incidence;

CAS means "Chemical Abstract Service";

CBI means "confidential business information";

Chemical identity means a name that will uniquely identify a chemical. This can be a name that is in accordance with the nomenclature systems of the International Union of Pure and Applied Chemistry (IUPAC) or the Chemical Abstracts Service (CAS), or a technical name;

Competent authority means any national body(ies) or authority(ies) designated or otherwise recognized as such in connection with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS);

Compressed gas means a gas which when packaged under pressure is entirely gaseous at -50 °C; including all gases with a critical temperature ≤ -50 °C;

Contact sensitizer means a substance that will induce an allergic response following skin contact. The definition for "contact sensitizer" is equivalent to "skin sensitizer";

Corrosive to metal means a substance or a mixture which by chemical action will materially damage, or even destroy, metals;

Critical temperature means the temperature above which a pure gas cannot be liquefied, regardless of the degree of compression;

Dermal Corrosion: see *skin corrosion*;

Dermal irritation: see *skin irritation*;

Dissolved gas means a gas which when packaged under pressure is dissolved in a liquid phase solvent;

EC_{50} means the effective concentration of substance that causes 50% of the maximum response;

EC Number or (ECN°) is a reference number used by the European Communities to identify dangerous substances, in particular those registered under EINECS;

ECOSOC means the Economic and Social Council of the United Nations;

EINECS means "European Inventory of Existing Commercial Chemical Substances";

ErC_{50} means EC_{50} in terms of reduction of growth rate;

EU means the "European Union";

Explosive article means an article containing one or more explosive substances;

Explosive substance means a solid or liquid substance (or mixture of substances) which is in itself capable by chemical reaction of producing gas at such a temperature and pressure and at such a speed as to cause damage to the surroundings. Pyrotechnic substances are included even when they do not evolve gases;

Eye irritation means the production of changes in the eye following the application of test substance to the anterior surface of the eye, which are fully reversible within 21 days of application;

Flammable gas means a gas having a flammable range with air at 20 °C and a standard pressure of 101.3 kPa;

Flammable liquid means a liquid having a flash point of not more than 93 °C;

Flammable solid means a solid which is readily combustible, or may cause or contribute to fire through friction;

Flash point means the lowest temperature (corrected to a standard pressure of 101.3 kPa) at which the application of an ignition source causes the vapours of a liquid to ignite under specified test conditions;

FAO means the "Food and Agriculture Organization of the United Nations";

Gas means a substance which (i) at 50 °C has a vapour pressure greater than 300 kPa; or (ii) is completely gaseous at 20 °C at a standard pressure of 101.3 kPa;

GESAMP means the "Joint Group of Experts on the Scientific Aspects of Marine Environmental Protection of IMO/FAO/UNESCO/WMO/WHO/IAEA/UN/UNEP";

GHS means the "Globally Harmonized System of Classification and Labelling of Chemicals";

Hazard category means the division of criteria within each hazard class, e.g. oral acute toxicity includes five hazard categories and flammable liquids includes four hazard categories. These categories compare hazard severity within a hazard class and should not be taken as a comparison of hazard categories more generally;

Hazard class means the nature of the physical, health or environmental hazard, e.g. flammable solid, carcinogen, oral acute toxicity;

Hazard statement means a statement assigned to a hazard class and category that describes the nature of the hazards of a hazardous product, including, where appropriate, the degree of hazard;

IAEA means the "International Atomic Energy Agency";

IARC means the "International Agency for the Research on Cancer";

ILO means the "International Labour Organization";

IMO means the "International Maritime Organization";

Initial boiling point means the temperature of a liquid at which its vapour pressure is equal to the standard pressure (101.3 kPa), i.e. the first gas bubble appears;

IOMC means the "Inter-organization Programme on the Sound Management of Chemicals";

IPCS means the "International Programme on Chemical Safety";

ISO means the "International Standards Organization";

IUPAC means the "International Union of Pure and Applied Chemistry";

Label means an appropriate group of written, printed or graphic information elements concerning a hazardous product, selected as relevant to the target sector (s), that is affixed to, printed on, or attached to the immediate container of a hazardous product, or to the outside packaging of a hazardous product;

Label element means one type of information that has been harmonized for use in a label, e.g. pictogram, signal word;

***LC_{50}* (50% lethal concentration)** means the concentration of a chemical in air or of a chemical in water which causes the death of 50% (one half) of a group of test animals;

LD_{50} means the amount of a chemical, given all at once, which causes the death of 50% (one half) of a group of test animals;

$L(E)C_{50}$ means LC_{50} or EC_{50};

Liquefied gas means a gas which when packaged under pressure, is partially liquid at temperatures above -50 °C. A distinction is made between:

(i) High pressure liquefied gas: a gas with a critical temperature between -50 °C and +65 °C; and
(ii) Low pressure liquefied gas: a gas with a critical temperature above +65 °C;

Liquid means a substance or mixture which at 50 °C has a vapour pressure of not more than 300 kPa (3 bar), which is not completely gaseous at 20 °C and at a standard pressure of 101.3 kPa, and which has a melting point or initial melting point of 20 °C or less at a standard pressure of 101.3 kPa. A viscous substance or mixture for which a specific melting point cannot be determined shall be subjected to the ASTM D 4359-90 test; or to the test for determining fluidity (penetrometer test) prescribed in section 2.3.4 of Annex A of the European Agreement concerning the International Carriage of Dangerous Goods by Road (ADR);

MARPOL means the "International Convention for the Prevention of Pollution from Ships";

Mixture means a mixture or a solution composed of two or more substances in which they do not react;

Mutagen means an agent giving rise to an increased occurrence of mutations in populations of cells and /or organisms;

Mutation means a permanent change in the amount or structure of the genetic material in a cell;

NGO means "non-governmental organization";

NOEC means the "no observed effect concentration";

OECD means the "Organization for Economic Cooperation and Development";

Organic peroxide means a liquid or solid organic substance which contains the bivalent -0-0- structure and may be considered a derivative of hydrogen peroxide, where one or both of the hydrogen atoms have been replaced by organic radicals. The term also includes organic peroxide formulations (mixtures);

Oxidizing gas means any gas which may, generally by providing oxygen, cause or contribute to the combustion of other material more than air does;

Oxidizing liquid means a liquid which, while in itself not necessarily combustible, may, generally by yielding oxygen, cause, or contribute to, the combustion of other material;

Oxidizing solid means a solid which, while in itself not necessarily combustible, may, generally by yielding oxygen, cause, or contribute to, the combustion of other material;

QSAR means "quantitative structure-activity relationships";

Pictogram means a graphical composition that may include a symbol plus other graphic elements, such as a border, background pattern or colour that is intended to convey specific information;

Precautionary statement means a phrase (and/or pictogram) that describes recommended measures that should be taken to minimize or prevent adverse effects resulting from exposure to a hazardous product, or improper storage or handling of a hazardous product;

Product identifier means the name or number used for a hazardous product on a label or in the SDS. It provides a unique means by which the product user can identify the substance or mixture within the particular use setting e.g. transport, consumer or workplace;

Pyrophoric liquid means a liquid which, even in small quantities, is liable of igniting within five minutes after coming into contact with air;

Pyrophoric solid means a solid which, even in small quantities, is liable of igniting within five minutes after coming into contact with air;

Pyrotechnic article means an article containing one or more pyrotechnic substances;

Pyrotechnic substance means a substance or mixture of substances designed to produce an effect by heat, light, sound, gas or smoke or a combination of these as the result of non-detonative self-sustaining exothermic chemical reactions;

Readily combustible solid means powdered, granular, or pasty substance or mixture which is dangerous if it can be easily ignited by brief contact with an ignition source, such as a burning match, and if the flame spreads rapidly;

Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria means the latest revised edition of the United Nations publication bearing this title, and any published amendment thereto;

Recommendations on the Transport of Dangerous Goods, Model Regulations means the latest revised edition of the United Nations publication bearing this title, and any published amendment thereto;

Refrigerated liquefied gas means a gas which when packaged is made partially liquid because of its low temperature;

Respiratory sensitizer means a substance that induces hypersensitivity of the airways following inhalation of the substance;

RID means The Regulations concerning the International Carriage of Dangerous Goods by Rail [Annex 1 to Appendix B (Uniform Rules concerning the Contract for International Carriage of Goods by Rail) (CIM) of COTIF (Convention concerning international carriage by rail)], as amended;

SAR means "Structure Activity Relationship";

SDS means "Safety Data Sheet";

Self-Accelerating Decomposition Temperature (SADT) means the lowest temperature at which self-accelerating decomposition may occur with substance as packaged;

Self-heating substance means a solid or liquid substance, other than a pyrophoric substance, which, by reaction with air and without energy supply, is liable to self-heat; this substance differs from a pyrophoric substance in that it will ignite only when in large amounts (kilograms) and after long periods of time (hours or days);

Self-reactive substance means a thermally unstable liquid or solid substance liable to undergo a strongly exothermic decomposition even without participation of oxygen (air). This definition excludes substances or mixtures classified under the GHS as explosive, organic peroxides or as oxidizing;

Serious eye damage means the production of tissue damage in the eye, or serious physical decay of vision, following application of a test substance to the anterior surface of the eye, which is not fully reversible within 21 days of application;

Signal word means a word used to indicate the relative level of severity of hazard and alert the reader to a potential hazard on the label. The GHS uses 'Danger' and 'Warning' as signal words;

Skin corrosion means the production of irreversible damage to the skin following the application of a test substance for up to 4 hours;

Skin irritation means the production of reversible damage to the skin following the application of a test substance for up to 4 hours;

Skin sensitizer means a substance that will induce an allergic response following skin contact. The definition for "skin sensitizer" is equivalent to "contact sensitizer";

Solid means a substance or mixture which does not meet the definitions of liquid or gas;

SPR means "Structure Property Relationship";

Substance means chemical elements and their compounds in the natural state or obtained by any production process, including any additive necessary to preserve the stability of the product and any impurities deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition;

Substance which, in contact with water, emits flammable gases means a solid or liquid substance or mixture which, by interaction with water, is liable to become spontaneously flammable or to give off flammable gases in dangerous quantities;

Supplemental label element means any additional non-harmonized type of information supplied on the container of a hazardous product that is not required or specified under the GHS. In some cases this information may be required by other competent authorities or it may be additional information provided at the discretion of the manufacturer/distributor;

Symbol means a graphical element intended to succinctly convey information;

Technical name means a name that is generally used in commerce, regulations and codes to identify a substance or mixture, other than the IUPAC or CAS name, and that is recognized by the scientific community. Examples of technical names include those used for complex mixtures (e.g., petroleum fractions or natural products), pesticides (e.g., ISO or ANSI systems), dyestuffs (Colour Index system) and minerals;

UNCED means the "United Nations Conference on Environment and Development";

UNCETDG/GHS means the "United Nations Committee of Experts on the Transport of Dangerous Goods and on the Globally Harmonized System of Classification and Labelling of Chemicals";

UN means the "United Nations";

UNEP means the "United Nations Environment Programme";

UNESCO means the "United Nations Educational, Scientific and Cultural Organization";

UNITAR means the "United Nations Institute for Training and Research";

UNSCEGHS means the "United Nations Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals";

UNSCETDG means the "United Nations Sub-Committee of Experts on the Transport of Dangerous Goods";

WHO means the "World Health Organization";

WMO means the "World Meteorological Organization".

CHAPTER 1.3

CLASSIFICATION OF HAZARDOUS SUBSTANCES AND MIXTURES

1.3.1 Introduction

Development of the GHS began with the work on classification criteria by the OECD Task Force on Harmonization of Classification and Labelling (Task Force on HCL) for health and environmental hazards, and by the UNCETDG/ILO Working Group for Physical Hazards.

1.3.1.1 *Health and Environmental Hazard Classes: OECD Task Force on Harmonization of Classification and Labelling (OECD Task Force on HCL)*

1.3.1.1.1 The work of the OECD Task Force on HCL was generally of three related kinds:

(a) Comparison of the major classification systems, identification of similar or identical elements and, for the elements which were dissimilar, development of a consensus on a compromise;

(b) Examination of the scientific basis for the criteria which define the hazard class of concern (e.g. acute toxicity, carcinogenicity), gaining expert consensus on the test methods, data interpretation and level of concern, and then seeking consensus on the criteria. For some hazard classes, the existing schemes had no criteria and the relevant criteria were developed by the Task Force;

(c) Where there was a decision-tree approach (e.g. irritation) or where there were dependent criteria in the classification scheme (acute aquatic toxicity), development of consensus on the process or the scheme for using the criteria.

1.3.1.1.2 The OECD Task Force on HCL proceeded stepwise in developing its harmonized classification criteria. For each hazard class the following steps were undertaken:

(a) Step 1: A thorough analysis of existing classification systems, including the scientific basis for the system and its criteria, its rationale and an explanation of how it is used. Step 1 documents were prepared and amended as required after discussion by the OECD Task Force on HCL for the following hazard classes: Eye Irritation/Serious Eye Damage, Skin Irritation/Corrosion, Sensitising Substances, Germ Cell Mutagenicity, Reproductive Toxicity, Specific Target Organ/Systemic Toxicity, and Chemical Mixtures;

(b) Step 2: A proposal for a harmonized classification system and criteria for each hazard class and category was developed. A Step 2 document was prepared and amended as required after discussion by the OECD Task Force on HCL;

(c) Step 3:

(i) OECD Task Force on HCL reached consensus on the revised Step 2 proposal;

or

(ii) If attempts at consensus building failed, the OECD Task Force on HCL identified specific "non-consensus" items as alternatives in a revised Step 2 proposal for further discussion and resolution.

(d) Step 4: Final proposals were submitted to the OECD Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology for approval and subsequently to the IOMC CG-HCCS for incorporation into the GHS.

1.3.1.2 *UNCETDG/ILO Working Group on Physical Hazards*

The UNCETDG/ILO Working Group for Physical Hazards used a similar process to the OECD Task Force on HCL. The work involved a comparison of the major classification systems, identification of similar or identical elements, and for the elements which were dissimilar, development of a consensus on a compromise. For physical hazards, however, the transport definitions, test methods and classification criteria were used as a basis for the work since they were already substantially harmonized. The work proceeded through examination of the scientific basis for the criteria, gaining consensus on the test methods, data interpretation and on the criteria. For most hazard classes, the existing schemes were already in place and being used by the transport sector. On this basis, a portion of the work focused on ensuring that workplace, environment and consumer safety issues were adequately addressed.

1.3.2 General considerations on the GHS

1.3.2.1 *Scope of the System*

1.3.2.1.1 The GHS applies to pure chemical substances, their dilute solutions and to mixtures of chemical substances. "Articles" as defined in the Hazard Communication Standard (29 CFR 1910.1200) of the US Occupational Safety and Health Administration, or by similar definition, are outside the scope of the system.

1.3.2.1.2 One objective of the GHS is for it to be simple and transparent with a clear distinction between classes and categories in order to allow for "self classification" as far as possible. For many hazard classes the criteria are semi-quantitative or qualitative and expert judgement is required to interpret the data for classification purposes. Furthermore, for some hazard classes (e.g. eye irritation, explosives or self-reactive substances) a decision tree approach is provided to enhance ease of use.

1.3.2.2 *Concept of "Classification"*

1.3.2.2.1 The GHS uses the term "hazard classification" to indicate that only the intrinsic hazardous properties of substances or mixtures are considered.

1.3.2.2.2 Hazard classification incorporates only 3 steps, i.e.:

(a) identification of relevant data regarding the hazards of a substance or mixture;
(b) subsequent review of those data to ascertain the hazards associated with the substance or mixture; and
(c) a decision on whether the substance or mixture will be classified as a hazardous substance or mixture and the degree of hazard, where appropriate, by comparison of the data with agreed hazard classification criteria.

1.3.2.2.3 As noted in IOMC Description and Further Clarification of the Anticipated Application of the GHS text in the *Purpose, Scope and Application* (Chapter 1.1, paragraph 1.1.2.4), it is recognised that once a chemical is classified, the likelihood of adverse effects may be considered in deciding what informational or other steps should be taken for a given product or use setting.

1.3.2.3 *Classification criteria*

The classification criteria for substances and mixtures are presented in Parts 2 and 3 of this document, each of which is for a specific hazard class or a group of closely related hazard classes. The recommended process of classification of mixtures is based on the following sequence:

(a) Where test data are available for the complete mixture, the classification of the mixture will always be based on that data;
(b) Where test data are not available for the mixture itself, then bridging principles included and explained in each specific chapter should be considered to see whether they permit classification of the mixture;

In addition, for the health and environmental classes,

(c) If (i) test data are not available for the mixture itself, and (ii) the available information is not sufficient to allow application of the above mentioned bridging principles, then the agreed method(s) described in each chapter for estimating the hazards based on the information known will be applied to classify the mixture.

1.3.2.4 ***Available data, test methods and test data quality***

1.3.2.4.1 The GHS itself does not include requirements for testing substances or mixtures. Therefore, there is no requirement under the GHS to generate test data for any hazard class. It is recognised that some parts of regulatory systems do require data to be generated (e.g. pesticides), but these requirements are not related specifically to the GHS. The criteria established for classifying a mixture will allow the use of available data for the mixture itself and /or similar mixtures and /or data for ingredients of the mixture.

1.3.2.4.2 The classification of a chemical substance or mixture depends both on the criteria and on the reliability of the test methods underpinning the criteria. In some cases the classification is determined by a pass or fail of a specific test, (e.g. the ready biodegradation test for substances or ingredients of mixtures), while in other cases, interpretations are made from dose/response curves and observations during testing. In all cases, the test conditions need to be standardised so that the results are reproducible with a given chemical substance and the standardised test yields "valid" data for defining the hazard class of concern. In this context, validation is the process by which the reliability and the relevance of a procedure are established for a particular purpose.

1.3.2.4.3 Tests that determine hazardous properties, which are conducted according to internationally recognised scientific principles, can be used for purposes of a hazard determination for health and environmental hazards. The GHS criteria for determining health and environmental hazards are test method neutral, allowing different approaches as long as they are scientifically sound and validated according to international procedures and criteria already referred to in existing systems for the hazard of concern and produce mutually acceptable data. Test methods for determining physical hazards are generally more clear-cut, and are specified in the GHS.

1.3.2.4.4 *Previously classified chemicals*

One of the general principles established by the IOMC-CG-HCCS states that test data already generated for the classification of chemicals under the existing systems should be accepted when classifying these chemicals under the harmonized system thereby avoiding duplicative testing and the unnecessary use of test animals. This policy has important implications in those cases where the criteria in the GHS are different from those in an existing system. In some cases, it may be difficult to determine the quality of existing data from older studies. In such cases, expert judgement will be needed.

1.3.2.4.5 *Substances / Mixtures posing special problems*

The effect of a substance or mixture on biological and environmental systems is influenced, among other factors, by the physico chemical properties of the substance or mixture and/or ingredients of the mixture and the way in which ingredient substances are biologically available. Some groups of substances may present special problems in this respect, for example, some polymers and metals. A substance or mixture need not be classified when it can be shown by conclusive experimental data from internationally acceptable test methods that the substance or mixture is not biologically available. Similarly, bioavailability data on ingredients of a mixture should be used where appropriate in conjunction with the harmonized classification criteria when classifying mixtures.

1.3.2.4.6 *Animal welfare*

The welfare of experimental animals is a concern. This ethical concern includes not only the alleviation of stress and suffering but also, in some countries, the use and consumption of test animals. Where possible and appropriate, tests and experiments that do not require the use of live animals are preferred to those using sentient live experimental animals. To that end, for certain hazards (skin irritation/corrosion and eye irritation/serious eye damage) testing schemes starting with non-animal observations/measurements are included as part of the classification system. For other hazards, such as acute toxicity, alternative animal tests, using fewer animals or causing less suffering are internationally accepted and should be preferred to the conventional LD_{50} test.

1.3.2.4.7 *Evidence from humans*

For classification purposes, reliable epidemiological data and experience on the effects of chemicals on humans (e.g. occupational data, data from accident databases) should be taken into account in the evaluation of human health hazards of a chemical. Testing on humans solely for hazard identification purposes is generally not acceptable.

1.3.2.4.8 *Expert judgement*

The approach to classifying mixtures includes the application of expert judgement in a number of areas in order to ensure existing information can be used for as many mixtures as possible to provide protection for human health and the environment. Expert judgement may also be required in interpreting data for hazard classification of substances, especially where weight of evidence determinations are needed.

1.3.2.4.9 *Weight of evidence*

1.3.2.4.9.1 For some hazard classes, classification results directly when the data satisfy the criteria. For others, classification of a substance or a mixture is made on the basis of the total weight of evidence. This means that all available information bearing on the determination of toxicity is considered together, including the results of valid *in vitro* tests, relevant animal data, and human experience such as epidemiological and clinical studies and well-documented case reports and observations.

1.3.2.4.9.2 The quality and consistency of the data are important. Evaluation of substances or mixtures related to the material being classified should be included, as should site of action and mechanism or mode of action study results. Both positive and negative results are assembled together in a single weight of evidence determination.

1.3.2.4.9.3 Positive effects which are consistent with the criteria for classification in each chapter, whether seen in humans or animals, will normally justify classification. Where evidence is available from both sources and there is a conflict between the findings, the quality and reliability of the evidence from both sources must be assessed in order to resolve the question of classification. Generally, data of good quality and reliability in humans will have precedence over other data. However, even well-designed and conducted epidemiological studies may lack sufficient numbers of subjects to detect relatively rare but still significant effects, or to assess potentially confounding factors. Positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of the robustness and quality of both the human and animal data relative to the expected frequency of occurrence of effects and the impact of potentially confounding factors.

1.3.2.4.9.4 Route of exposure, mechanistic information and metabolism studies are pertinent to determining the relevance of an effect in humans. When such information raises doubt about relevance in humans, a lower classification may be warranted. When it is clear that the mechanism or mode of action is not relevant to humans, the substance or mixture should not be classified.

1.3.2.4.9.5 Both positive and negative results are assembled together in the weight of evidence determination. However, a single positive study performed according to good scientific principles and with statistically and biologically significant positive results may justify classification.

1.3.3 Specific considerations for the classification of mixtures

1.3.3.1 *Definitions*

1.3.3.1.1 In order to ensure a full understanding of the provisions for classifying mixtures, definitions of certain terms are required. These definitions are for the purpose of evaluating or determining the hazards of a product for classification and labelling, and are not intended to be applied in other situations such as inventory reporting. The intent of the definitions as drawn is to ensure that (a) all products within the scope of the Globally Harmonized System are evaluated to determine their hazards, and are subsequently classified according to the GHS criteria as appropriate; and (b) the evaluation is based on the actual product involved, i.e. on a stable product. If a reaction occurs during manufacture and a new product results, a new hazard evaluation and classification must take place to apply the GHS to the new product.

1.3.3.1.2 Working definitions have been accepted for the following terms: substance, mixture, alloy (see Chapter 1.2 for other Definitions and Abbreviations used in the GHS).

Substance: Chemical elements and their compounds in the natural state or obtained by any production process, including any additive necessary to preserve the stability of the product and any impurities deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition.

Mixture: Mixtures or solutions composed of two or more substances in which they do not react.

Alloy: An alloy is a metallic material, homogeneous on a macroscopic scale, consisting of two or more elements so combined that they cannot be readily separated by mechanical means. Alloys are considered to be mixtures for the purpose of classification under the GHS.

1.3.3.1.3 These definitions should be used to maintain consistency when classifying substances and mixtures in the GHS. Note also that where impurities, additives or individual constituents of a substance or mixture have been identified and are themselves classified, they should be taken into account during classification if they exceed the cut-off value/concentration limit for a given hazard class.

1.3.3.1.4 It is recognised, as a practical matter, that some substances may react slowly with atmospheric gases, e.g. oxygen, carbon dioxide, water vapour, to form different substances; or they may react very slowly with other ingredient substances of a mixture to form different substances; or they may self-polymerise to form oligomers or polymers. However, the concentrations of different substances produced by such reactions are typically considered to be sufficiently low that they do not affect the hazard classification of the mixture.

1.3.3.2 *Use of cut-off values/concentration limits*

1.3.3.2.1 When classifying an untested mixture based on the hazards of its ingredients, generic cut-off values or concentration limits for the classified ingredients of the mixture are used for several hazard classes in the GHS. While the adopted cut-off values/concentration limits adequately identify the hazard for most mixtures, there may be some that contain hazardous ingredients at lower concentrations than the harmonized cut-off value/concentration limit that still pose an identifiable hazard. There may also be cases where the harmonized cut-off value/concentration limit is considerably lower than could be expected on the basis of an established non-hazardous level for an ingredient.

1.3.3.2.2 Normally, the generic cut-off values/concentration limits adopted in the GHS should be applied uniformly in all jurisdictions and for all sectors. However, if the classifier has information that the hazard of an ingredient will be evident below the generic cut-off values/concentration limits, the mixture containing that ingredient should be classified accordingly.

1.3.3.2.3 On occasion, conclusive data may show that the hazard of an ingredient will not be evident when present at a level above the generic GHS cut-off values/concentration limit(s). In these cases the mixture could be classified according to those data. The data should exclude the possibility that the ingredient would behave in the mixture in a manner that would increase the hazard over that of the pure substance. Furthermore, the mixture should not contain ingredients that would affect that determination.

1.3.3.2.4 Adequate documentation supporting the use of any values other than the generic cut-off values/ concentration limits should be retained and made available for review on request.

1.3.3.3 *Synergistic or antagonistic effects*

When performing an assessment in accordance with the GHS requirements, the evaluator must take into account all available information about the potential occurrence of synergistic effects among the ingredients of the mixture. Lowering classification of a mixture to a less hazardous category on the basis of antagonistic effects may be done only if the determination is supported by sufficient data.

CHAPTER 1.4

HAZARD COMMUNICATION: LABELLING

1.4.1 Objectives, scope and application

1.4.1.1 One of the objectives of the work on the Globally Harmonized System (GHS) has been the development of a harmonized hazard communication system, including labelling, safety data sheets and easily understandable symbols, based on the classification criteria developed for the GHS. This work was carried out under the auspices of the ILO, by the ILO Working Group on Hazard Communication using the same 3-step procedure outlined for the harmonization of classification in *Classification of Hazardous Substances and Mixtures* (Chapter 1.3, paragraph 1.3.1.1.2).

1.4.1.2 The harmonized system for hazard communication includes the appropriate labelling tools to convey information about each of the hazard classes and categories in the GHS. The use of symbols, signal words or hazard statements other than those which have been assigned to each of the GHS hazard classes and categories would be contrary to harmonization.

1.4.1.3 The ILO Working Group considered the application of the General Principles described in the IOMC CG/HCCS Terms of Reference[1] as they apply to hazard communication and recognised that there will be circumstances where the demands and rationale of systems may warrant some flexibility in whether to incorporate certain hazard classes and categories for certain target audiences.

1.4.1.4 For example, the scope of the UN Recommendations on the Transport of Dangerous Goods, Model Regulations, encompasses only the most severe hazard categories of the acute toxicity hazard class. This system would not label substances or mixtures falling within the scope of the less severe hazard categories (e.g. those falling within the oral range > 300mg/kg). However, should the scope of that system be amended to incorporate substances and mixtures falling in these less severe hazard categories, they should be labelled with the appropriate GHS labelling tools. The use of different cut-off values to determine which products are labelled in a hazard category would be contrary to harmonization.

1.4.1.5 It is recognised that the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations* provide label information primarily in a graphic form because of the needs of the target audiences. Therefore the UN Sub-Committee of Experts on the Transport of Dangerous Goods may choose not to include signal words and hazard statements as part of the information provided on the label under the Model Regulations.

1.4.2 Terminology

1.4.2.1 A description of common terms and definitions related to hazard communication is included in Chapter 1.2: Definitions and Abbreviations.

1.4.3 Target audiences

1.4.3.1 The needs of the target audiences that will be the primary end-users of the harmonized hazard communication scheme have been identified. Particular attention was given to a discussion of the manner in which these target audiences will receive and use the information conveyed about hazardous chemicals. Factors discussed include the potential use of products, availability of information other than the label and the availability of training.

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[1] *IOMC, Coordinating Group for the Harmonization of Chemical Classification Systems, Revised Terms of Reference and Work Programme (IOMC/HCS/95 – 14 January 1996).*

1.4.3.2 It was recognized that it is difficult to completely separate the needs of different target audiences. For example, both workers and emergency responders use labels in storage facilities, and products such as paints and solvents are used both by consumers and in workplaces. In addition, pesticides can be used in consumer settings (e.g. lawn and garden products) and workplaces (e.g. pesticides used to treat seed in seed treatment plants). That said, there are certain characteristics which are particular to the different target audiences. The following paragraphs in this section consider the target audiences and the type of information they need.

1.4.3.3 *Workplace*: Employers and workers need to know the hazards specific to the chemicals used and or handled in the workplace, as well as information about the specific protective measures required to avoid the adverse effects that might be caused by those hazards. In the case of storage of chemicals, potential hazards are minimised by the containment (packaging) of the chemical, but in the case of an accident, workers and emergency responders need to know what mitigation measures are appropriate. Here they may require information which can be read at a distance. The label, however, is not the sole source of this information, which is also available through the SDS and workplace risk management system. The latter should also provide for training in hazard identification and prevention. The nature of training provided and the accuracy, comprehensibility and completeness of the information provided on the SDS may vary. However, compared to consumers for example, workers can develop a more in depth understanding of symbols and other types of information.

1.4.3.4 *Consumers:* The label in most cases is likely to be the sole source of information readily available to the consumer. The label, therefore, will need to be sufficiently detailed and relevant to the use of the product. There are considerable philosophical differences on the approach to providing information to consumers. Labelling based on the likelihood of injury (i.e. risk communication) is considered to be an effective approach in this respect by some consumer labelling systems, whilst others take account of the 'right to know' principle in providing information to consumers which is solely based on the product's hazards. Consumer education is more difficult and less efficient than education for other audiences. Providing sufficient information to consumers in the simplest and most easily understandable terms presents a considerable challenge. The issue of comprehensibility is of particular importance for this target audience, since consumers may rely solely on label information.

1.4.3.5 *Emergency responders*: Emergency responders need information on a range of levels. To facilitate immediate responses, they need accurate, detailed and sufficiently clear information. This applies in the event of an accident during transportation, in storage facilities or at workplaces. Fire fighters and those first at the scene of an accident for example, need information that can be distinguished and interpreted at a distance. Such personnel are highly trained in the use of graphical and coded information. However, emergency responders also require more detailed information about hazards and response techniques, which they obtain from a range of sources. The information needs of medical personnel responsible for treating the victims of an accident or emergency may differ from those of fire fighters.

1.4.3.6 *Transport*: The UN Recommendations on the Transport of Dangerous Goods, Model Regulations, cater for a wide range of target audiences although transport workers and emergency responders are the principal ones. Others include employers, those who offer or accept dangerous goods for transport or load or unload packages of dangerous goods into or from transport vehicles, or freight containers. All need information concerning general safe practices that are appropriate for all transport situations. For example, a driver will have to know what has to be done in case of an accident irrespective of the substance transported: (e.g. report the accident to authorities, keep the shipping documents in a given place, etc.) Drivers may only require limited information concerning specific hazards, unless they also load and unload packages or fill tanks, etc. Workers who might come into direct contact with dangerous goods, for example on board ships, require more detailed information.

1.4.4 Comprehensibility

1.4.4.1 Comprehensibility of the information provided has been one of the most important issues addressed in the development of the hazard communication system (see Annex 5 on Comprehensibility Testing Methodology). The aim of the harmonized system is to present the information in a manner that the intended audience can easily understand. The GHS identifies some guiding principles to assist this process:

(a) Information should be conveyed in more than one way;
(b) The comprehensibility of the components of the system should take account of existing studies and literature as well as any evidence gained from testing;
(c) The phrases used to indicate degree (severity) of hazard should be consistent across different hazard types.

1.4.4.2 The latter point was subject to some debate concerning the comparison of severity between long-term effects such as carcinogenicity and physical hazards such as flammability. Whilst it might not be possible to directly compare physical hazards to health hazards, it may be possible to provide target audiences with a means of putting the degree of hazard into context and therefore convey the same degree of concern about the hazard.

1.4.4.3 *Comprehensibility testing methodology*

A preliminary review of the literature undertaken by the University of Maryland indicated that common principles related to comprehensibility could be applied to the development of the harmonized hazard communication scheme. The University of Cape Town developed these into a comprehensive testing methodology to assess the comprehensibility of the hazard communication system (see Annex 5). In addition to testing individual label components, this methodology considers the comprehensibility of label components in combination. This was considered particularly important to assess the comprehensibility of warning messages for consumers where there is less reliance on training to aid understandability. The testing methodology also includes a means of assessing SDS comprehensibility. A summary description of this methodology is provided in Annex 5.

1.4.5 Translation

Options for the use of textual information present an additional challenge for comprehensibility. Clearly words and phrases need to retain their comprehensibility when translated, whilst conveying the same meaning. The IPCS Chemical Safety Card Programme has gained experience of this in translating standard phrases in a wide variety of languages. The EU also has experience of translating terms to ensure the same message is conveyed in multiple languages e.g. hazard, risk etc. Similar experience has been gained in North America where the North American Emergency Response Guidebook, which uses key phrases, is available in a number of languages.

1.4.6 Standardization

1.4.6.1 To fulfil the goal of having as many countries as possible adopt the system, much of the GHS is based on standardised approaches to make it easier for companies to comply with and for countries to implement the system. Standardisation can be applied to certain label elements – symbols, signal words, statements of hazard, precautionary statements – and to label format and colour and to SDS format.

1.4.6.2 *Application of standardization in the harmonized system*

For labels, the hazard symbols, signal words and hazard statements have all been standardised and assigned to each of the hazard categories. These standardised elements should not be subject to variation, and should appear on the GHS label as indicated in the Chapters for each hazard class in this document. For safety data sheets, the chapter *Hazard Communication: Safety Data Sheets* (Chapter 1.5) provides a standardised format for the presentation of information. Whilst precautionary information was considered for standardisation, there was insufficient time to develop detailed proposals. However, there are examples of

precautionary statements and pictograms in Annex 3 and it remains a goal to develop them into fully standardised label elements.

1.4.6.3 *Use of non-standardized or supplemental information*

1.4.6.3.1 There are many other label elements which may appear on a label which have not been standardised in the harmonized system. Some of these clearly need to be included on the label, for example precautionary statements. Competent authorities may require additional information, or suppliers may choose to add supplementary information on their own initiative. In order to ensure that the use of non-standardised information does not lead to unnecessarily wide variation in information or undermine GHS information, the use of supplementary information should be limited to the following circumstances:

(a) the supplementary information provides further detail and does not contradict or cast doubt on the validity of the standardised hazard information; or
(b) the supplementary information provides information about hazards not yet incorporated into the GHS.

In either instance, the supplementary information should not lower standards of protection.

1.4.6.3.2 The labeller should have the option of providing supplementary information related to the hazard, such as physical state or route of exposure, with the hazard statement rather than in the supplementary information section on the label, see also paragraph 1.4.10.5.4.1.

1.4.7 Updating information

1.4.7.1 All systems should specify a means of responding in an appropriate and timely manner to new information and updating labels and SDS information accordingly. The following are examples of how this could be achieved.

1.4.7.2 *General guidance on updating of information*

1.4.7.2.1 Suppliers should respond to "new and significant" information they receive about a chemical hazard by updating the label and safety data sheet for that chemical. New and significant information is any information that changes the GHS classification of the substance or mixture and leads to a resulting change in the information provided on the label or any information concerning the chemical and appropriate control measures that may affect the SDS. This could include, for example, new information on the potential adverse chronic health effects of exposure as a result of recently published documentation or test results, even if a change in classification may not yet be triggered.

1.4.7.2.2 Updating should be carried out promptly on receipt of the information that necessitates the revision. The competent authority may choose to specify a time limit within which the information should be revised. This applies only to labels and SDS for products that are not subject to an approval mechanism such as pesticides. In pesticide labelling systems, where the label is part of the product approval mechanism, suppliers cannot update the supply label on their own initiative. However when the products are subject to the transport of dangerous goods requirements, the label used should be updated on receipt of the new information, as above.

1.4.7.2.3 Suppliers should also periodically review the information on which the label and safety data sheet for a substance or mixture is based, even if no new and significant information has been provided to them in respect of that substance or mixture. This will require e.g. a search of chemical hazard databases for new information. The competent authority may choose to specify a time (typically 3 – 5 years) from the date of original preparation, within which suppliers should review the labels and SDS information.

1.4.8 Confidential business information

1.4.8.1 Systems adopting the GHS should consider what provisions may be appropriate for the protection of confidential business information (CBI). Such provisions should not compromise the health and safety of workers or consumers, or the protection of the environment. As with other parts of the GHS, the rules of the importing country should apply with respect to CBI claims for imported substances and mixtures.

1.4.8.2 Where a system chooses to provide for protection of confidential business information, competent authorities should establish appropriate mechanisms, in accordance with national law and practice, and consider:

(a) whether the inclusion of certain chemicals or classes of chemicals in the arrangements is appropriate to the needs of the system;

(b) what definition of "confidential business information" should apply, taking account of factors such as the accessibility of the information by competitors, intellectual property rights and the potential harm disclosure would cause to the employer or supplier's business; and

(c) appropriate procedures for the disclosure of confidential business information, where necessary to protect the health and safety of workers or consumers, or to protect the environment, and measures to prevent further disclosure.

1.4.8.3 Specific provisions for the protection of confidential business information may differ among systems in accordance with national law and practice. However, they should be consistent with the following general principles:

(a) For information otherwise required on labels or safety data sheets, CBI claims should be limited to the names of chemicals, and their concentrations in mixtures. All other information should be disclosed on the label and/or safety data sheet, as required;

(b) Where CBI has been withheld, the label or chemical safety data sheet should so indicate;

(c) CBI should be disclosed to the competent authority upon request. The competent authority should protect the confidentiality of the information in accordance with applicable law and practice;

(d) Where a medical professional determines that a medical emergency exists due to exposure to a hazardous chemical or a chemical mixture, mechanisms should be in place to ensure timely disclosure by the supplier or employer or competent authority of any specific confidential information necessary for treatment. The medical professional should maintain the confidentiality of the information;

(e) For non-emergency situations, the supplier or employer should ensure disclosure of confidential information to a safety or health professional providing medical or other safety and health services to exposed workers or consumers, and to workers or workers' representatives. Persons requesting the information should provide specific reasons for the disclosure, and should agree to use the information only for the purpose of consumer or worker protection, and to otherwise maintain its confidentiality;

(f) Where non-disclosure of CBI is challenged, the competent authority should address such challenges or provide for an alternative process for challenges. The supplier or employer should be responsible for supporting the assertion that the withheld information qualifies for CBI protection.

1.4.9 Training

Training users of hazard information is an integral part of hazard communication. Systems should identify the appropriate education and training for GHS target audiences who are required to interpret label and/or SDS information and to take appropriate action in response to chemical hazards. Training requirements should be appropriate for and commensurate with the nature of the work or exposure. Key target audiences for training include workers, emergency responders, and those involved in the preparation of labels, SDS and hazard communication strategies as part of risk management systems. Others involved in the transport and supply of hazardous chemicals also require training to varying degrees. In addition, systems should consider strategies required for educating consumers in interpreting label information on products that they use.

1.4.10 Labelling procedures

1.4.10.1 *Scope*

The following sections describe the procedures for preparing labels in the GHS, comprising the following:

(a) Allocation of label elements;
(b) Reproduction of the symbol;
(c) Reproduction of the hazard pictogram;
(d) Signal words;
(e) Hazard statements;
(f) Precautionary statements and pictograms;
(g) Product and supplier identification;
(h) Multiple hazards and precedence of information;
(i) Arrangements for presenting the GHS label elements;
(j) Special labelling arrangements.

1.4.10.2 *Label elements*

The tables in the individual Chapters for each hazard class detail the label elements (symbol, signal word, hazard statement) that have been assigned to each of the hazard categories of the GHS. Hazard categories reflect the harmonized classification criteria. A summary of the allocation of label elements is provided in Annex 1. Special arrangements to take into account the information needs of different target audiences are further described in paragraph 1.4.10.5.4.

1.4.10.3 *Reproduction of the symbol*

The following hazard symbols are the standard symbols which should be used in the GHS. With the exception of the new symbol which will be used for certain health hazards, the exclamation mark and the fish and tree, they are part of the standard symbol set used in the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations*.

Flame	Flame over circle	Exploding bomb
Corrosion	Gas cylinder	Skull and crossbones
Exclamation mark	Environment	Health Hazard

1.4.10.4 *Pictograms and reproduction of the hazard pictograms*

1.4.10.4.1 A pictogram means a graphical composition that includes a symbol plus other graphic elements, such as a border, background pattern or colour that is intended to convey specific information.

1.4.10.4.2 *Shape and colour*

1.4.10.4.2.1 All hazard pictograms used in the GHS should be in the shape of a square set at a point.

1.4.10.4.2.2 For transport, the pictograms (*commonly referred to as labels in transport regulations*) prescribed by the UN Model Regulations on the Transport of Dangerous Goods should be used. The UN Model Regulations prescribe transport pictogram specifications including colour, symbols, size, background contrast, additional safety information (e.g. hazard class) and general format. Transport pictograms are required to have minimum dimensions of 100 mm by 100 mm, with some exceptions for allowing smaller pictograms for very small packagings and for gas cylinders. Transport pictograms include the symbol in the upper half of the label. The UN Model Regulations require that transport pictograms be printed or affixed to a packaging on a background of contrasting colour. An example showing a typical label for a flammable liquid hazard according to the UN Model Regulations is provided below:

Pictogram for flammable liquid in the UN Model Regulations (Symbol: Flame: Black or White; Background: red; Figure 3 in bottom corner; minimum dimensions 100 mm × 100 mm.)

1.4.10.4.2.3 Pictograms prescribed by the GHS but not the UN Recommendations on the Transport of Dangerous Goods, Model Regulations, should have a black symbol on a white background with a red frame sufficiently wide to be clearly visible. However, when such a pictogram appears on a label for a package which will not be exported, the competent authority may choose to give suppliers and employers discretion to use a black border. In addition, competent authorities may allow the use of UN Recommendations on the Transport of Dangerous Goods, Model Regulations pictograms in other use settings where the package is not covered by the Model Regulations. An example of a GHS pictogram used for a skin irritant is provided below.

Pictogram for skin irritant

1.4.10.5 *Allocation of label elements*

1.4.10.5.1 *Information required for packages covered by the UN Model Regulations on the Transport of Dangerous Goods*

Where a UN Model Regulations on the Transport of Dangerous Goods pictogram appears on a label, a GHS pictogram for the same hazard should not appear. The GHS pictograms not required for the transport of dangerous goods should not be displayed on freight containers, road vehicles or railway wagons/tanks.

1.4.10.5.2 *Information required on a GHS label*

(a) Signal words

A signal word means a word used to indicate the relative level of severity of hazard and alert the reader to a potential hazard on the label. The signal words used in the GHS are "Danger" and "Warning". "Danger" is used for the more severe hazard categories (i.e. in the main for hazard categories 1 and 2), while "Warning" is used for the less severe. The tables in the individual Chapters for each hazard class detail the signal words that have been assigned to each of the hazard categories of the GHS.

(b) Hazard statements

A hazard statement means a phrase assigned to a hazard class and category that describes the nature of the hazards of a hazardous product, including, where appropriate, the degree of hazard. The tables of label elements in the individual Chapters for each hazard class detail the hazard statements that have been assigned to each of the hazard categories of the GHS.

(c) Precautionary statements and pictograms

A precautionary statement means a phrase (and/or pictogram) that describes recommended measures that should be taken to minimise or prevent adverse effects resulting from exposure to a hazardous product, or improper storage or handling of a hazardous product. The GHS label should include appropriate precautionary information, the choice of which is with the labeller or the competent authority. Annex 3 contains examples of precautionary statements, which can be used, and also examples of precautionary pictograms, which can be used where allowed by the competent authority.

(d) Product identifier

(i) A product identifier should be used on a GHS label and it should match the product identifier used on the SDS. Where a substance or mixture is covered by the UN Model Regulations on the Transport of Dangerous Goods, the UN proper shipping name should also be used on the package;

(ii) The label for a substance should include the chemical identity of the substance. For mixtures or alloys, the label should include the chemical identities of all ingredients or alloying elements that contribute to acute toxicity, skin corrosion or serious eye damage, germ cell mutagenicity, carcinogenicity, reproductive toxicity, skin or respiratory sensitisation, or Target Organ Systemic Toxicity (TOST), when these hazards appear on the label. Alternatively, the competent authority may require the inclusion of all ingredients or alloying elements that contribute to the hazard of the mixture or alloy;

(iii) Where a substance or mixture is supplied exclusively for workplace use, the competent authority may choose to give suppliers discretion to include chemical identities on the SDS, in lieu of including them on labels;

(iv) The competent authority rules for CBI take priority over the rules for product identification. This means that where an ingredient would normally be included on the label, if it meets the competent authority criteria for CBI, its identity does not have to be included on the label.

(e) Supplier identification

The name, address and telephone number of the manufacturer or supplier of the substance or mixture should be provided on the label.

1.4.10.5.3 *Multiple hazards and precedence of hazard information*

The following arrangements apply where a substance or mixture presents more than one GHS hazard. It is without prejudice to the building block principle described in the *Purpose, Scope and Application* (Chapter 1.1). Therefore where a system does not provide information on the label for a particular hazard, the application of the arrangements should be modified accordingly.

1.4.10.5.3.1 Precedence for the allocation of symbols

For substances and mixtures covered by the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations*, the precedence of symbols for physical hazards should follow the rules of the UN Model Regulations. In workplace situations, the competent authority may require all symbols for physical hazards to be used. For health hazards the following principles of precedence apply:

(a) if the skull and crossbones applies, the exclamation mark should not appear;

(b) if the corrosive symbol applies, the exclamation mark should not appear where it is used for skin or eye irritation;

(c) if the new health hazard symbol appears for respiratory sensitisation, the exclamation mark should not appear where it is used for skin sensitisation or for skin or eye irritation.

1.4.10.5.3.2 Precedence for allocation of signal words

If the signal word 'Danger' applies, the signal word 'Warning' should not appear.

1.4.10.5.3.3 Precedence for allocation of hazard statements

All assigned hazard statements should appear on the label. The competent authority may choose to specify the order in which they appear.

1.4.10.5.4 *Arrangements for presenting the GHS label elements*

1.4.10.5.4.1 Location of GHS information on the label

The GHS hazard pictograms, signal word and hazard statements should be located together on the label. The competent authority may choose to provide a specified layout for the presentation of these and for the presentation of precautionary information, or allow supplier discretion. Specific guidance and examples are provided in the Chapters on individual hazard classes.

There have been some concerns about how the label elements should appear on different packagings. Specific examples are provided in Annex 6.

1.4.10.5.4.2 Supplemental information

The competent authority has the discretion to allow the use of supplemental information subject to the parameters outlined in 1.4.6.3. The competent authority may choose to specify where this information should appear on the label or allow supplier discretion. In either approach, the placement of supplemental information should not impede identification of GHS information.

1.4.10.5.4.3 Use of colour outside pictograms

In addition to its use in pictograms, colour can be used on other areas of the label to implement special labelling requirements such as the use of the pesticide bands in the FAO Labelling Guide, for signal words and hazard statements or as background to them, or as otherwise provided for by the competent authority.

1.4.10.5.5 *Special labelling arrangements*

The competent authority may choose to allow communication of certain hazard information for carcinogens, reproductive toxicity and target organ systemic toxicity repeat exposure on the label and on the SDS, or through the SDS alone (see specific chapters for details of relevant cut-offs for these classes).

Similarly, for metals and alloys, the competent authority may choose to allow communication of the hazard information through the SDS alone when they are supplied in the massive, non-dispersible, form.

1.4.10.5.5.1 Workplace labelling

Products falling within the scope of the GHS will carry the GHS label at the point where they are supplied to the workplace, and that label should be maintained on the supplied container in the workplace. The GHS label or label elements should also be used for workplace containers. However, the competent authority can allow employers to use alternative means of giving workers the same information in a different written or displayed format when such a format is more appropriate to the workplace and communicates the information as effectively as the GHS label. For example, label information could be displayed in the work area, rather than on the individual containers.

Alternative means of providing workers with the information contained in GHS labels are needed usually where hazardous chemicals are transferred from an original supplier container into a workplace container or system, or where chemicals are produced in a workplace but are not packaged in containers intended for sale or supply. Chemicals that are produced in a workplace may be contained or stored in many different ways such as: small samples collected for testing or analysis, piping systems including valves, process or reaction vessels, ore cars, conveyer systems or free-standing bulk storage of solids. In batch manufacturing processes, one mixing vessel may be used to contain a number of different chemical mixtures.

In many situations, it is impractical to produce a complete GHS label and attach it to the container, due, for example, to container size limitations or lack of access to a process container. Some examples of workplace situations where chemicals may be transferred from supplier containers include: containers for laboratory testing or analysis, storage vessels, piping or process reaction systems or temporary containers where the chemical will be used by one worker within a short timeframe. Decanted chemicals intended for immediate use could be labelled with the main components and directly refer the user to the supplier label information and SDS.

All such systems should ensure that there is clear hazard communication. Workers should be trained to understand the specific communication methods used in a workplace. Examples of alternative methods include: use of product identifiers together with GHS symbols and other pictograms to describe precautionary measures; use of process flow charts for complex systems to identify chemicals contained in pipes and vessels with links to the appropriate SDS; use of displays with GHS symbols, colour and signal words in piping systems and processing equipment; use of permanent placarding for fixed piping; use of batch tickets or recipes for labelling batch mixing vessels and use of piping bands with hazard symbols and product identifiers.

1.4.10.5.5.2 Consumer product labelling based on the likelihood of injury

All systems should use the GHS classification criteria based on hazard, however competent authorities may authorize consumer labelling systems providing information based on the likelihood of harm (risk-based labelling). In the latter case the competent authority would establish procedures for determining the potential exposure and risk for the use of the product. Labels based on this approach provide targeted information on identified risks but may not include certain information on chronic health effects (e.g. Target Organ Systemic Toxicity (TOST)) following repeated exposure, reproductive toxicity and carcinogenicity), that would appear on a label based on hazard alone. A general explanation of the broad principles of risk-based labelling is contained in Annex 4.

1.4.10.5.5.3 Tactile warnings

If tactile warnings are used, the technical specifications should conform with ISO standard 11683 (1997 edition) relating to tactile warnings of danger.

CHAPTER 1.5

HAZARD COMMUNICATION: SAFETY DATA SHEETS (SDS)

1.5.1 The role of the Safety Data Sheet (SDS) in the Harmonized System

1.5.1.1 The SDS should provide comprehensive information about a chemical substance or mixture for use in workplace chemical control regulatory frameworks. Both employers and workers use it as a source of information about hazards, including environmental hazards, and to obtain advice on safety precautions. The information acts as a reference source for the management of hazardous chemicals in the workplace. The SDS is product related and, usually, is not able to provide specific information that is relevant for any given workplace where the product may finally be used, although where products have specialised end uses the SDS information may be more workplace-specific. The information therefore enables the employer (i) to develop an active programme of worker protection measures, including training, which is specific to the individual workplace and (ii) to consider any measures which may be necessary to protect the environment.

1.5.1.2 In addition, the SDS provides an important source of information for other target audiences in the GHS. So certain elements of information may be used by those involved with the transport of dangerous goods, emergency responders (including poison centres), those involved in the professional use of pesticides and consumers. However, these audiences receive additional information from a variety of other sources such as the UN Recommendations on the Transport of Dangerous Goods, Model Regulations document and package inserts for consumers and will continue to do so. The introduction of a harmonized labelling system therefore, is not intended to affect the primary use of the SDS which is for workplace users.

1.5.2 Criteria for determining whether an SDS should be produced

An SDS should be produced for all substances and mixtures which meet the harmonized criteria for physical, health or environmental hazards under the GHS and for all mixtures which contain substances that meet the criteria for carcinogenic, toxic to reproduction or target organ systemic toxicity in concentrations exceeding the cut-off limits for SDS specified by the criteria for mixtures (see paragraph1.5.3.1). The competent authority may choose also to require SDSs for mixtures not meeting the criteria for classification as hazardous but which contain hazardous substances in certain concentrations (see paragraph1.5.3.1).

1.5.3 General guidance for compiling a Safety Data Sheet

1.5.3.1 *Cut-off values/concentration limits*

1.5.3.1.1 An SDS should be provided based on the generic cut-off values/concentration limits indicated in Table 1.5.1:

Table 1.5.1: Cut-off values/Concentration limits for each *health and environmental* hazard class

Hazard Class	Cut-off value/Concentration Limit
Acute Toxicity	≥ 1.0%
Skin Corrosion/Irritation	≥ 1.0%
Serious damage to eyes/eye irritation	≥ 1.0%
Respiratory/Skin Sensitization	≥ 1.0%
Mutagenicity: Category 1	≥ 0.1%
Mutagenicity: Category 2	≥ 1.0%
Carcinogenicity	≥ 0.1%
Reproductive Toxicity	≥ 0.1%
Target Organ Systemic Toxicity (Single Exposure)	≥ 1.0%
Target Organ Systemic Toxicity (Repeat Exposure)	≥ 1.0%
Hazardous to the Aquatic Environment	≥ 1.0%

1.5.3.1.2 As noted in the *Classification of Hazardous Substances and Mixtures* (see 1.3.3.2), there may be some cases when the available hazard data may justify classification on the basis of other cut-off values/concentration limits than the generic ones specified in the health and environment hazard class chapters (Chapters 3.2 to 3.10). When such specific cut-off values are used for classification, they should also apply to the obligation to compile an SDS.

1.5.3.1.3 Some competent authorities (CA) may require SDSs to be compiled for mixtures which are not classified for acute toxicity or aquatic toxicity as a result of application of the additivity formula, but which contain acutely toxic substances or substances toxic to the aquatic environment in concentrations equal to or greater than 1 %.[4]

1.5.3.1.4 In accordance with the building block principle, some competent authorities may choose not to regulate certain categories within a hazard class. In such situations, there would be no obligation to compile an SDS.

1.5.3.1.5 Once it is clear that an SDS is required for a substance or a mixture then the information required to be included in the SDS should in all cases be provided in accordance with GHS requirements.

[4] *The cut-off values for classification of mixtures are normally specified by concentrations expressed as % of the component substance. In some cases, for example acute toxicity (human health), the cut-off values are expressed as acute toxicity values (ATE). The classification of a mixture is determined by additivity calculation based on acute toxicity values (see Chapter 3.1) and concentrations of component substances. Similarly acute aquatic toxicity classification may be calculated on the basis of acute aquatic toxicity values (See Chapter 3.10) and where appropriate, corrosion/irritation by adding up concentrations of individual substances (See Chapters 3.2 and 3.3). Component substances are taken into consideration for application of the formula when the concentration is equal to or greater than 1 %. Some competent authorities (CA) may use this cut-off as a basis of obligation to compile a SDS.*

1.5.3.2 *SDS format*

1.5.3.2.1 The information in the SDS should be presented using the following 16 headings in the order given below.

1. Identification
2. Hazard(s) identification
3. Composition/information on ingredients
4. First-aid measures
5. Fire-fighting measures
6. Accidental release measures
7. Handling and storage
8. Exposure controls/personal protection
9. Physical and chemical properties
10. Stability and reactivity
11. Toxicological information
12. Ecological information
13. Disposal considerations
14. Transport information
15. Regulatory information
16. Other information.

1.5.3.3 *SDS content*

1.5.3.3.1 The SDS should provide a clear description of the data used to identify the hazards. The minimum information in Table 1.5.2 should be included, where applicable and available, on the SDS under the relevant headings[5]. If specific information is not applicable or not available under a particular subheading, the SDS should clearly state this. Additional information may be required by competent authorities.

1.5.3.3.2 Some subheadings relate to information that is national or regional in nature, for example "EC number" and "occupational exposure limits". Suppliers or employers should include information under such SDS subheadings that is appropriate and relevant to the countries or regions for which the SDS is intended and into which the product is being supplied.

1.5.3.3.3 There are a number of internationally-recognised standards that provide guidance in the preparation of an SDS, including the ILO Standard under the Recommendation 177 on Safety in the Use of Chemicals at Work, the International Standard 11014 of the International Standard Organization (ISO), the European Union Safety Data Sheet Directive 91/155/EEC and the American National Standard Institute (ANSI) standard Z 400.1. Further guidance on preparation of an SDS may be developed by the GHS Subcommittee, based on the work of these organizations.

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[5] *Where "applicable" means where the information is applicable to the specific product covered by the SDS. Where "available" means where the information is available to the supplier or other entity that is preparing the SDS.*

Table 1.5.2 Minimum information for an SDS

1.	**Identification of the substance or mixture and of the supplier**	• GHS product identifier. • Other means of identification. • Recommended use of the chemical and restrictions on use. • Supplier's details (including name, address, phone number etc). • Emergency phone number.
2.	**Hazards identification**	• GHS classification of the substance/mixture and any national or regional information. • GHS label elements, including precautionary statements. (Hazard symbols may be provided as a graphical reproduction of the symbols in black and white or the name of the symbol e.g. flame, skull and crossbones.) • Other hazards which do not result in classification (e.g. dust explosion hazard) or are not covered by the GHS.
3.	**Composition/information on ingredients**	**Substance** • Chemical identity. • Common name, synonyms, etc. • CAS number, EC number, etc. • Impurities and stabilizing additives which are themselves classified and which contribute to the classification of the substance. Mixture • The chemical identity and concentration or concentration ranges of all ingredients which are hazardous within the meaning of the GHS and are present above their cut-off levels. ***NOTE**: For information on ingredients, the competent authority rules for CBI take priority over the rules for product identification.*
4.	**First aid measures**	• Description of necessary measures, subdivided according to the different routes of exposure, i.e. inhalation, skin and eye contact and ingestion. • Most important symptoms/effects, acute and delayed. • Indication of immediate medical attention and special treatment needed, if necessary.
5.	**Fire-fighting measures**	• Suitable (and unsuitable) extinguishing media. • Specific hazards arising from the chemical (e.g. nature of any hazardous combustion products). • Special protective equipment and precautions for fire-fighters.
6.	**Accidental release measures**	• Personal precautions, protective equipment and emergency procedures. • Environmental precautions. • Methods and materials for containment and cleaning up
7.	**Handling and storage**	• Precautions for safe handling. • Conditions for safe storage, including any incompatibilities.

8.	**Exposure controls/personal protection.**	• Control parameters e.g. occupational exposure limit values or biological limit values. • Appropriate engineering controls. • Individual protection measures, such as personal protective equipment.
9.	**Physical and chemical properties**	• Appearance (physical state, colour etc). • Odour. • Odour threshold. • PH. • Melting point/freezing point. • Initial boiling point and boiling range. • Flash point. • Evaporation rate. • Flammability (solid, gas). • Upper/lower flammability or explosive limits. • Vapour pressure. • Vapour density. • Relative density. • Solubility(ies). • Partition coefficient: n-octanol/water. • Auto-ignition temperature. • Decomposition temperature.
10.	**Stability and reactivity**	• Chemical stability. • Possibility of hazardous reactions. • Conditions to avoid (e.g. static discharge, shock or vibration). • Incompatible materials. • Hazardous decomposition products.
11.	**Toxicological information**	Concise but complete and comprehensible description of the various toxicological (health) effects and the available data used to identify those effects, including: • information on the likely routes of exposure (inhalation, ingestion, skin and eye contact); • Symptoms related to the physical, chemical and toxicological characteristics; • Delayed and immediate effects and also chronic effects from short- and long-term exposure; • Numerical measures of toxicity (such as acute toxicity estimates).
12.	**Ecological information**	• Ecotoxicity (aquatic and terrestrial, where available). • Persistence and degradability. • Bioaccumulative potential. • Mobility in soil. • Other adverse effects.
13.	**Disposal considerations**	• Description of waste residues and information on their safe handling and methods of disposal, including the disposal of any contaminated packaging.

14.	**Transport information**	• UN number. • UN Proper shipping name. • Transport Hazard class(es). • Packing group, if applicable. • Marine pollutant (Yes/No). • Special precautions which a user needs to be aware of or needs to comply with in connection with transport or conveyance either within or outside their premises.
15.	**Regulatory information**	• Safety, health and environmental regulations specific for the product in question.
16.	**Other information including information on preparation and revision of the SDS**	

PART 2

PHYSICAL HAZARDS

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CHAPTER 2.1

EXPLOSIVES

2.1.1 Definitions and general considerations

2.1.1.1 An explosive substance (or mixture) is a solid or liquid substance (or mixture of substances) which is in itself capable by chemical reaction of producing gas at such a temperature and pressure and at such a speed as to cause damage to the surroundings. Pyrotechnic substances are included even when they do not evolve gases.

A pyrotechnic substance (or mixture) is a substance or mixture of substances designed to produce an effect by heat, light, sound, gas or smoke or a combination of these as the result of non-detonative self-sustaining exothermic chemical reactions.

An explosive article is an article containing one or more explosive substances or mixtures.

A pyrotechnic article is an article containing one or more pyrotechnic substances or mixtures.

2.1.1.2 The class of explosives comprises:

(a) Explosive substances and mixtures;

(b) Explosive articles, except devices containing explosive substances or mixtures in such quantity or of such a character that their inadvertent or accidental ignition or initiation shali not cause any effect external to the device either by projection, fire, smoke, heat or loud noise; and

(c) Substances, mixtures and articles not mentioned under (a) and (b) above which are manufactured with the view to producing a practical, explosive or pyrotechnic effect.

2.1.2 Classification criteria

2.1.2.1 Substances, mixtures and articles of this class are assigned to one of the following six divisions depending on the type of hazard they present:

(a) Division 1.1 Substances, mixtures and articles which have a mass explosion hazard (a mass explosion is one which affects almost the entire load virtually instantaneously);

(b) Division 1.2 Substances, mixtures and articles which have a projection hazard but not a mass explosion hazard;

(c) Division 1.3 Substances, mixtures and articles which have a fire hazard and either a minor blast hazard or a minor projection hazard or both, but not a mass explosion hazard:

(i) combustion of which gives rise to considerable radiant heat; or
(ii) which burn one after another, producing minor blast or projection effects or both;

(d) Division 1.4 Substances, mixtures and articles which present no significant hazard: substances, mixtures and articles which present only a small hazard in the event of ignition or initiation. The effects are largely confined to the

package and no projection of fragments of appreciable size or range is to be expected. An external fire shall not cause virtually instantaneous explosion of almost the entire contents of the package;

(e) Division 1.5 Very insensitive substances or mixtures which have a mass explosion hazard: substances and mixtures which have a mass explosion hazard but are so insensitive that there is very little probability of initiation or of transition from burning to detonation under normal conditions;

(f) Division 1.6 Extremely insensitive articles which do not have a mass explosion hazard: articles which contain only extremely insensitive detonating substances or mixtures and which demonstrate a negligible probability of accidental initiation or propagation.

2.1.2.2 Explosives are classified in one of the six divisions above based on Test Series 2 to 8 in Part I of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria* according to the following table:

Table 2.1.1: Criteria for explosives

Category	Criteria
Unstable [a] explosives or explosives of Division 1.1 to 1.6	For explosives of Divisions 1.1 to 1.6, the following are the core set of tests that need to be performed: Explosibility: according to UN Test series 2 (Section 12 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*). Intentional explosives [b] are not subject to UN Test series 2. Sensitiveness: according to UN Test series 3 (Section 13 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*). Thermal stability: according to UN Test 3(c) (Sub-section 13.6.1 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*). Further tests are necessary to allocate the correct Division.

[a] *Unstable explosives are those which are thermally unstable and/or too sensitive for normal handling and use. Special precautions are necessary.*

[b] *This comprises substances, mixtures and articles which are manufactured with a view to producing a practical, explosive or pyrotechnic effect.*

NOTE 1: *Explosive substances or mixtures in packaged form and articles may be classified under divisions 1.1 to 1.6 and, for some regulatory purposes, are further subdivided into compatibility groups A to S to distinguish technical requirements (see UN Recommendations on the Transport of Dangerous Goods, Model Regulations, Chapter 2.1).*

NOTE 2: *Some explosive substances and mixtures are wetted with water or alcohols or diluted with other substances to suppress their explosives properties. They may be treated differently from explosive substances and mixtures (as desensitised explosives) for some regulatory purposes (e.g. transport).*

NOTE 3: *For classification tests on solid substances or mixtures, the tests should be performed on the substance or mixture as presented. If for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance or mixture must also be tested in the new form.*

2.1.3 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 2.1.2: Label elements for explosives

	Division 1.1	Division 1.2	Division 1.3	Division 1.4	Division 1.5	Division 1.6
Symbol	Exploding bomb	Exploding bomb	Exploding bomb	1.4 on orange background [a]	1.5 on orange background [a]	1.6 on orange background [a]
Signal word	Danger	Danger	Danger	Warning	Warning	No signal word
Hazard statement	Explosive; mass explosion hazard	Explosive; severe projection hazard	Explosive; fire, blast or projection hazard.	Fire or projection hazard	May explode in fire	No hazard statement

[a] *Applies to substances, mixtures and articles subject to some regulatory purposes (e.g. transport).*

2.1.4 Decision logic and guidance

The decision logic and guidance, which follow, are not part of the harmonized classification system, but have been provided here as additional guidance. It is strongly recommended that the person responsible for classification studies the criteria before and during use of the decision logic.

2.1.4.1 *Decision logic*

The classification of substances, mixtures and articles in the class of explosives and further allocation to a division is a very complex, three step procedure. Reference to Part I *of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* is necessary. The first step is to ascertain whether the substance or mixture has explosive effects (Test Series 1). The second step is the acceptance procedure (Test Series 2 to 4) and the third step is the assignment to a hazard division (Test Series 5 to 7). The assessment whether a candidate for "ammonium nitrate emulsion or suspension or gel, intermediate for blasting explosives (ANE)" is insensitive enough for inclusion in Division 5.1 is answered by test Series 8 tests. The classification procedure is according to the following decision logic (see Figures 2.1.1 to 2.1.3).

Figure 2.1.1: Overall scheme of the procedure for classifying a substance, mixture or article in the class of explosives (Class 1)

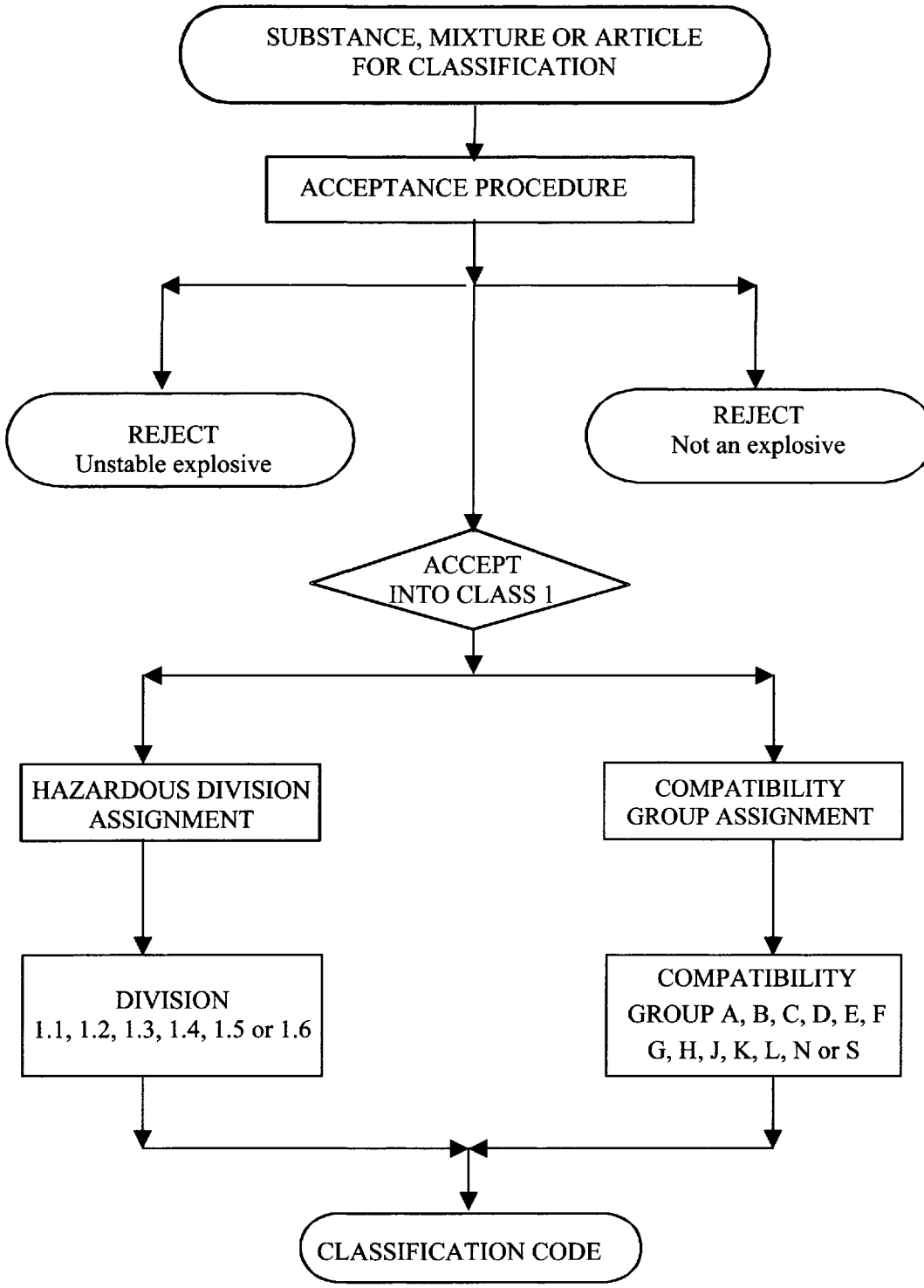
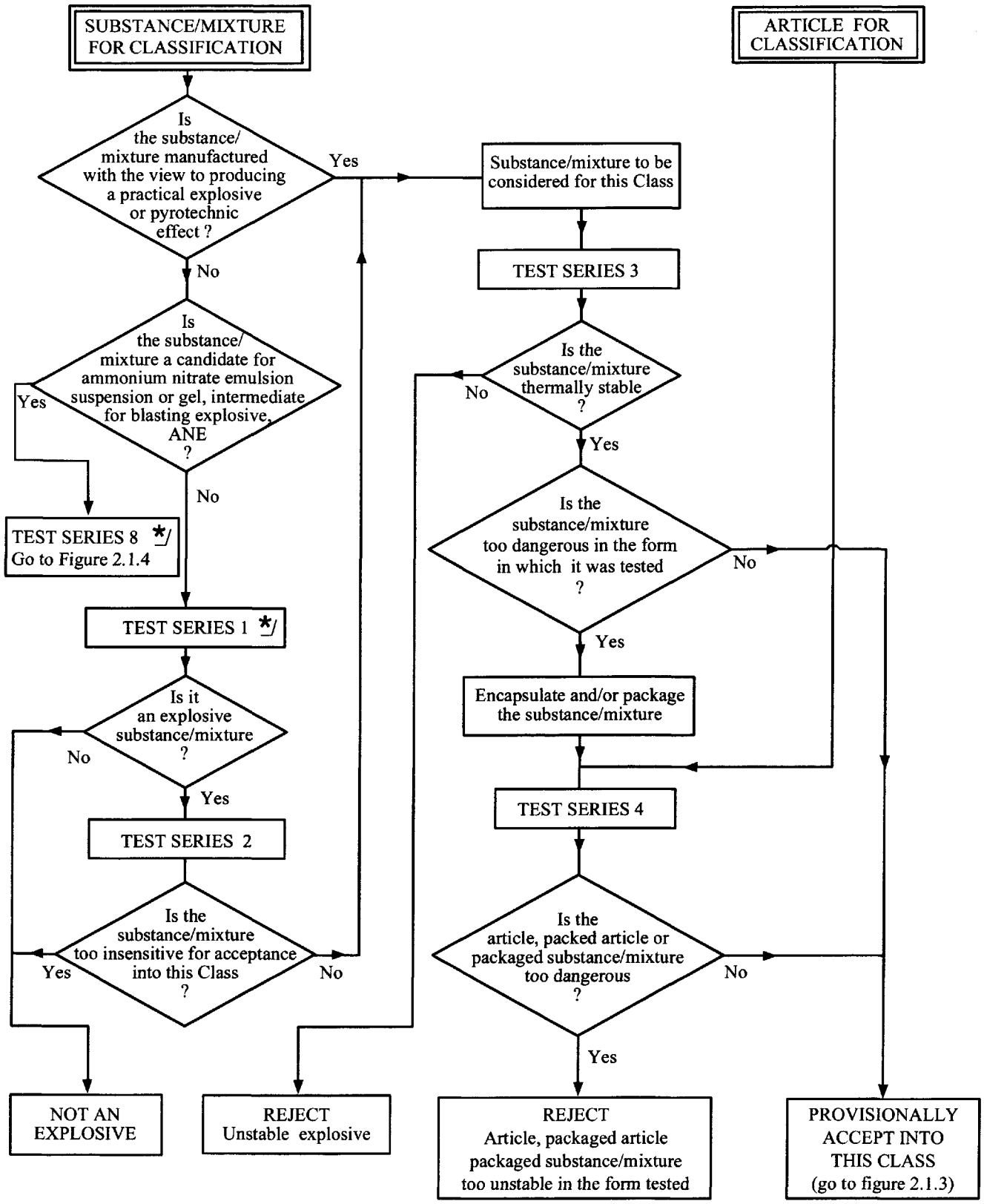


Figure 2.1.2: Procedure for provisional acceptance of a substance, mixture or article in the class of explosives (Class 1)



*/ For classification purposes, start with test series 2.

Figure 2.1.3: Procedure for assignment to a division of Class 1

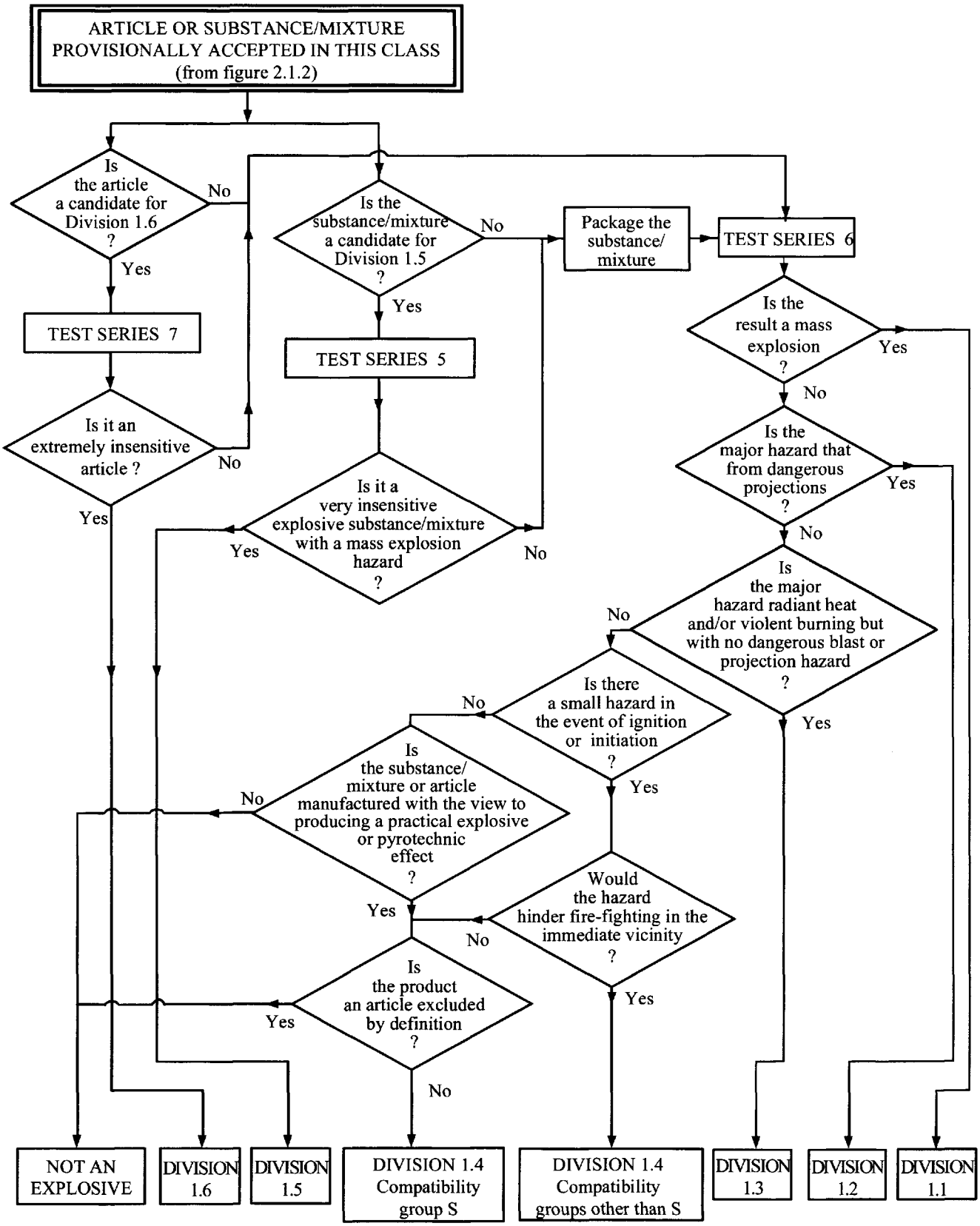
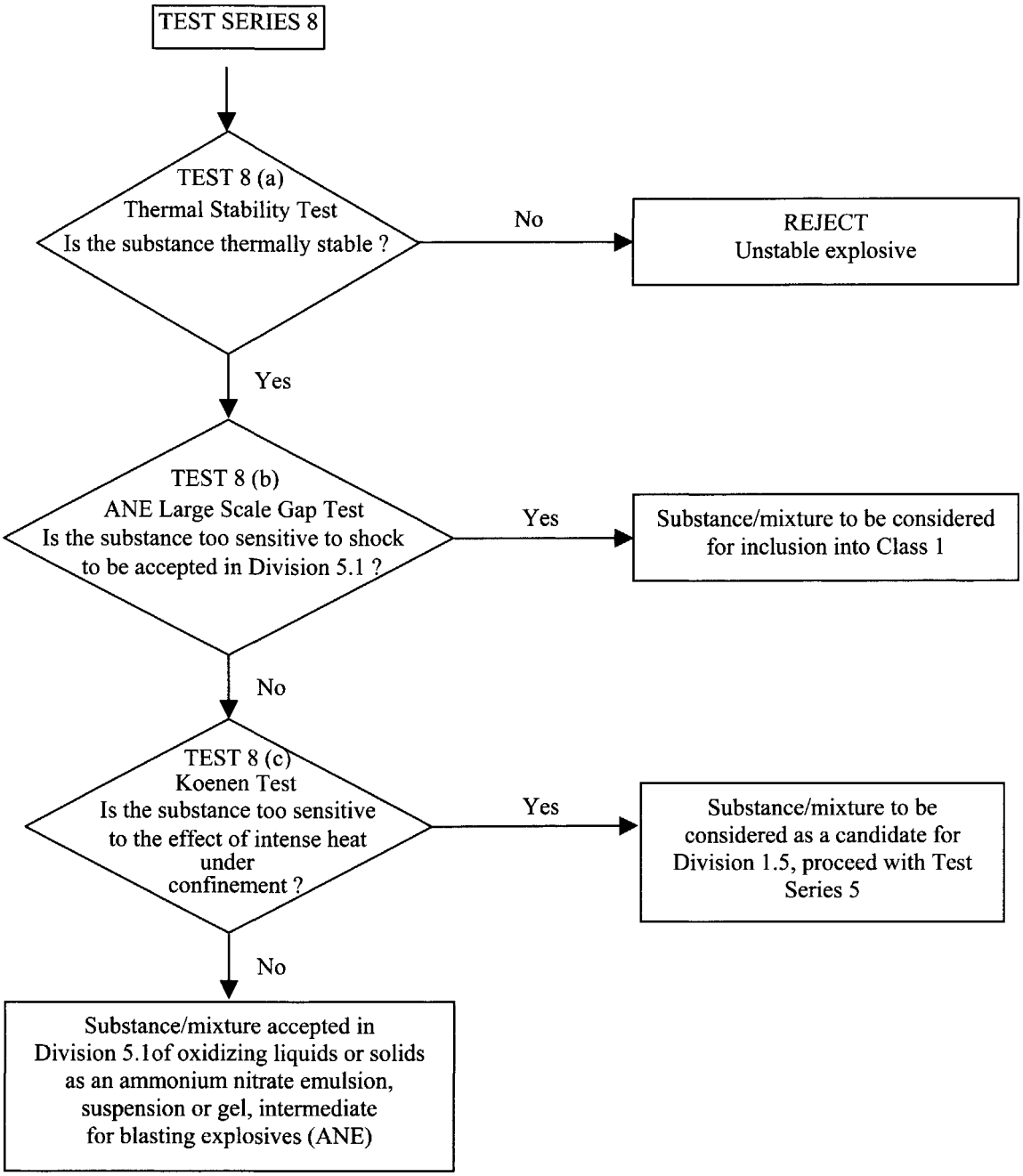


Figure 2.1.4: Procedure for provisional acceptance of a substance, mixture or article in oxidizing liquids or solids as ANE



2.1.4.2 *Guidance*

2.1.4.2.1 Explosive properties are associated with the presence of certain chemical groups in a molecule which can react to produce very rapid increases in temperature or pressure. The screening procedure is aimed at identifying the presence of such reactive groups and the potential for rapid energy release. If the screening procedure identifies the substance or mixture to be a potential explosive, the acceptance procedure (see section 10.3 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*) has to be performed.

***NOTE**: Neither a Series 1 type (a) propagation of detonation test nor a Series 2 type (a) test of sensitivity to detonative shock is required if the exothermic decomposition energy of organic materials is less than 800 J/g.*

2.1.4.2.2 A substance or mixture is not classified as explosive if:

(a) There are no chemical groups associated with explosive properties present in the molecule. Examples of groups which may indicate explosive properties are given in Table A6.1 in Appendix 6 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*; or

(b) The substance contains chemical groups associated with explosive properties which include oxygen and the calculated oxygen balance is less than -200.

The oxygen balance is calculated for the chemical reaction:

$C_xH_yO_z + [x + (y/4)-(z/2)]. O_2 \rightarrow x. CO_2 + (y/2). H_2O$

using the formula:

oxygen balance = -1600.[2.x +(y/2) -z]/molecular weight;

(c) When the organic substance or a homogenous mixture of organic substances contain chemical groups associated with explosive properties but the exothermic decomposition energy is less than 500 J/g and the onset of exothermic decomposition is below 500 °C. (The temperature limit is to prevent the procedure being applied to a large number of organic materials which are not explosive but which will decompose slowly above 500 °C to release more than 500 J/g.) The exothermic decomposition energy may be determined using a suitable calorimetric technique; or

(d) For mixtures of inorganic oxidizing substances with organic material(s), the concentration of the inorganic oxidizing substance is:

less than 15 %, by mass, if the oxidizing substance is assigned to category 1 or 2;
less than 30 %, by mass, if the oxidizing substance is assigned to category 3.

2.1.4.2.3 In the case of mixtures containing any known explosives, the acceptance procedure has to be performed.

CHAPTER 2.2

FLAMMABLE GASES

2.2.1 Definition

A flammable gas is a gas having a flammable range with air at 20 °C and a standard pressure of 101.3 kPa.

2.2.2 Classification criteria

A flammable gas is classified in one of the two categories for this class according to the following table:

Table 2.2.1: Criteria for flammable gases

Category	Criteria
1	Gases, which at 20 °C and a standard pressure of 101.3 kPa: (a) are ignitable when in a mixture of 13% or less by volume in air; or (b) have a flammable range with air of at least 12 percentage points regardless of the lower flammable limit.
2	Gases, other than those of category 1, which, at 20 °C and a standard pressure of 101.3 kPa, have a flammable range while mixed in air.

NOTE 1: Ammonia and methyl bromide may be regarded as special cases for some regulatory purposes.

NOTE 2: For the classification of aerosols, see Chapter 2.3.

2.2.3 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 2.2.2: Label elements for flammable gases

	Category 1	Category 2
Symbol	Flame	*No symbol used*
Signal word	Danger	Warning
Hazard statement	Extremely flammable gas	Flammable gas

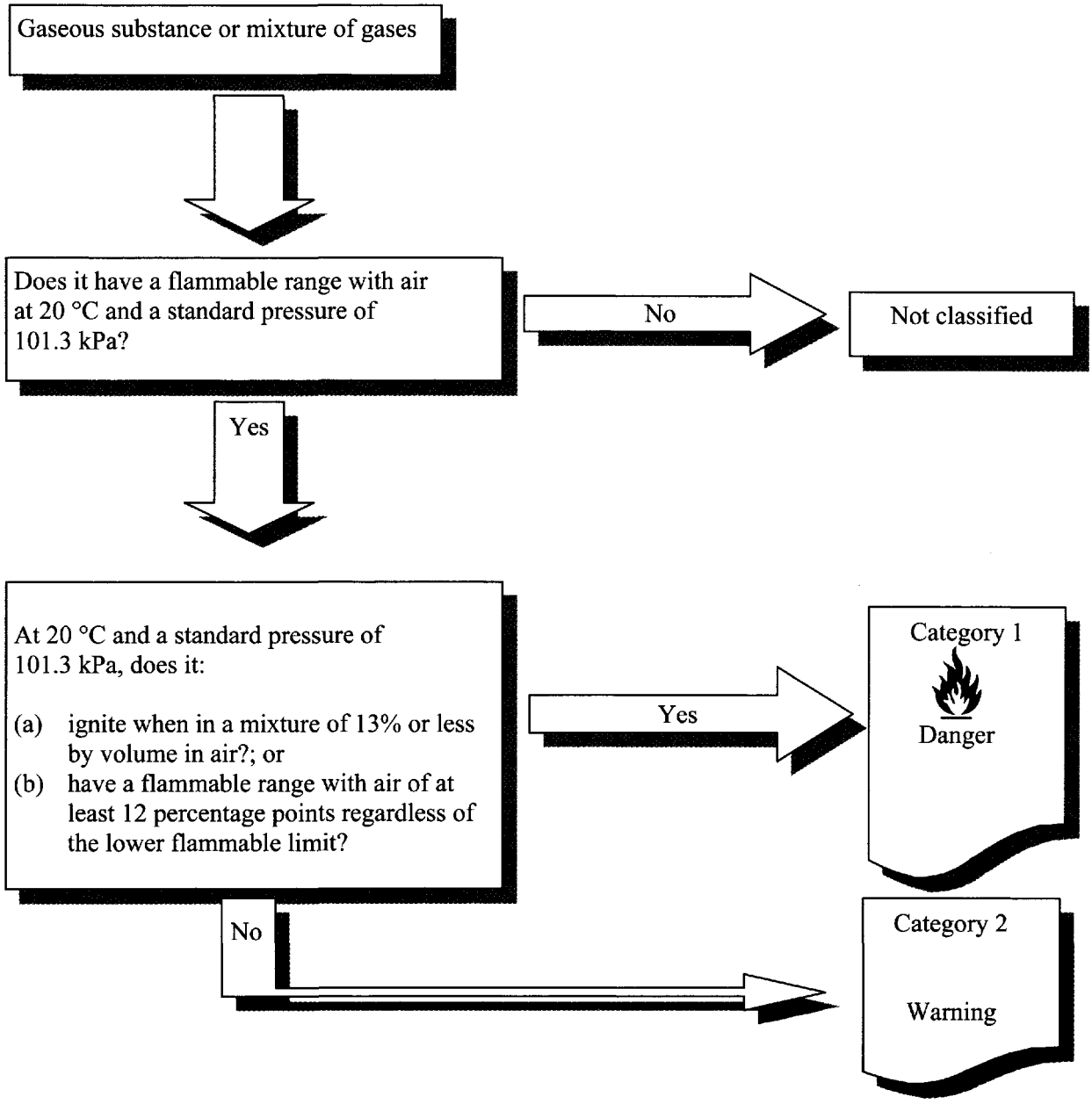
2.2.4 Decision logic and guidance

The decision logic and guidance, which follow, are not part of the harmonized classification system, but have been provided here as additional guidance. It is strongly recommended that the person responsible for classification studies the criteria before and during use of the decision logic.

2.2.4.1 *Decision logic*

To classify a flammable gas, data on its flammability are required. The classification is according to the following decision logic.

Decision logic 2.2 for flammable gases



2.2.4.2 ***Guidance***

Flammability should be determined by tests or by calculation in accordance with methods adopted by ISO (see ISO 10156:1996 Gases and gas mixtures – Determination of fire potential and oxidizing ability for the selection of cylinder valve outlets). Where insufficient data are available to use these methods, tests by a comparable method recognized by the competent authority may be used.

2.2.5 Example: Classification of a flammable gas mixture by calculation according to ISO 10156:1996

Formula

$$\sum_{i}^{n} \frac{V_i\%}{T_{ci}}$$

Where:

$V_i\%$ is the equivalent flammable gas content
T_{ci} is the maximum concentration of a flammable gas in nitrogen at which the mixture is still not flammable in air
i is the first gas in the mixture
n is the n^{th} gas in the mixture
Ki is the equivalency factor for an inert gas versus nitrogen

Where a gas mixture contains an inert diluent other than nitrogen, the volume of this diluent is adjusted to the equivalent volume of nitrogen using the equivalency factor for the inert gas (K_i).

Criterion:

$$\sum_{i}^{n} \frac{V_i\%}{T_{ci}} \geq 1$$

Gas mixture

For the purpose of this example the following is the gas mixture to be used

$$2\%\ (H_2) + 6\%(CH_4) + 27\%(Ar) + 65\%(He)$$

Calculation

1. Ascertain the equivalency factors (Ki) for the inert gases versus nitrogen

   Ki (Ar) = 0.5
   Ki (He) = 0.5

2. Calculate the equivalent mixture with nitrogen as balance gas using the Ki figures for the inert gases.
   $2\%(H_2) + 6\%(CH_4) + [27\%x0.5 + 65\%x0.5](N_2) = 2\%(H_2) + 6\%(CH_4) + 46\%(N_2) = 54\%$

3. Adjust the sum of the contents to 100%
   $\frac{100}{54} \times [2\%(H_2) + 6\%(CH_4) + 46\%(N_2)] = 3.7\%(H_2) + 11.1\%(CH_4) + 85.2\%(N_2)$

4. Ascertain the Tci coefficients for the flammable gases

   Tci H_2 = 5.7%
   Tci CH_4 = 14.3%

5. Calculate the flammability of the equivalent mixture using the formula

$$\sum_{i}^{n} \frac{V_i\%}{T_{ci}} = \frac{3.7}{5.7} + \frac{11.1}{14.3} = 1.42$$

$1.42 > 1$,

Therefore the mixture is flammable in air.

CHAPTER 2.3

FLAMMABLE AEROSOLS

2.3.1 Definition

Aerosols, this means aerosol dispensers, are any non-refillable receptacles made of metal, glass or plastics and containing a gas compressed, liquefied or dissolved under pressure, with or without a liquid, paste or powder, and fitted with a release device allowing the contents to be ejected as solid or liquid particles in suspension in a gas, as a foam, paste or powder or in a liquid state or in a gaseous state.

2.3.2 Classification criteria

2.3.2.1 Aerosols should be considered for classification as flammable if they contain any component which is classified as flammable according to the GHS criteria, i.e.:

flammable liquids (see Chapter 2.6);

flammable gases (see Chapter 2.2);

flammable solids (see Chapter 2.7).

NOTE: Flammable components do not cover pyrophoric, self-heating or water-reactive substances because such components are never used as aerosol contents.

2.3.2.2 A flammable aerosol is classified in one of the two categories for this Class on the basis of its components, of its chemical heat of combustion and, if applicable, of the results of the foam test (for foam aerosols) and of the ignition distance test and enclosed space test (for spray aerosols). See decision logic in 2.3.4.1.

2.3.3 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

	Category 1	**Category 2**
Symbol	Flame	Flame
Signal word	Danger	Warning
Hazard statement	Extremely flammable aerosol	Flammable aerosol

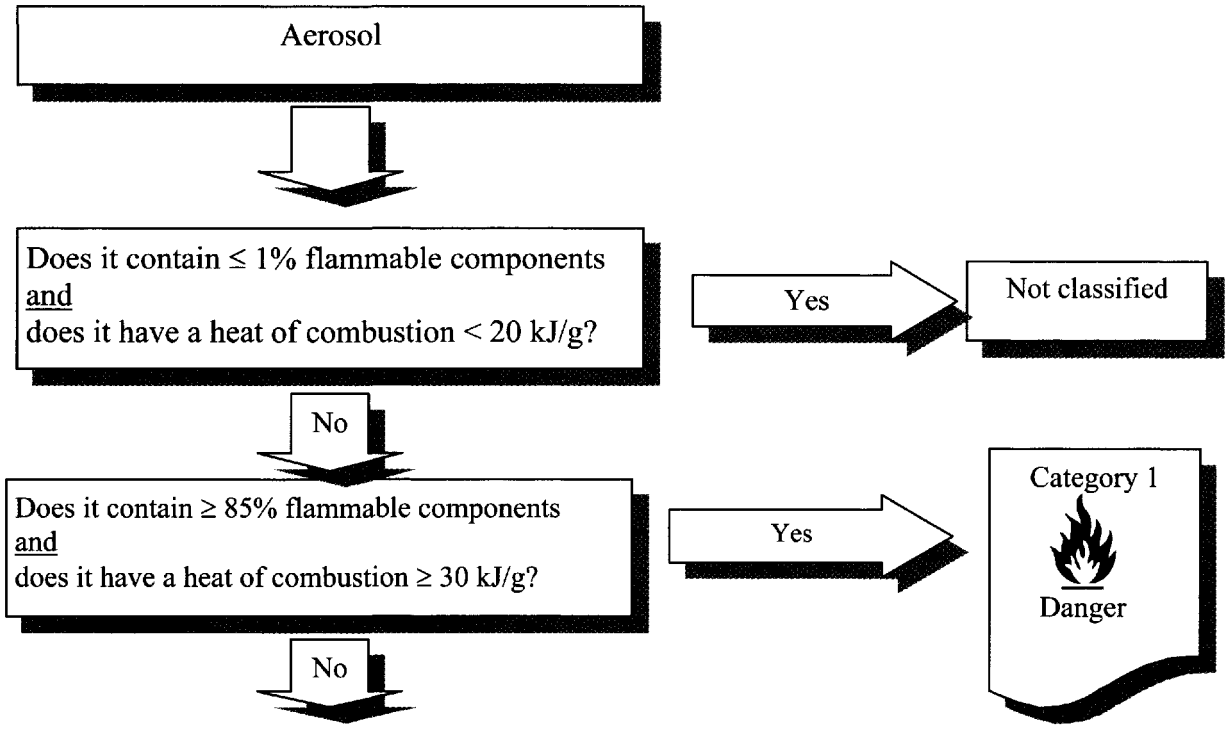
2.3.4 Decision logic and guidance

The decision logic and guidance, which follow, are not part of the harmonized classification system, but have been provided here as additional guidance. It is strongly recommended that the person responsible for classification studies the criteria before and during use of the decision logic

2.3.4.1 *Decision logic*

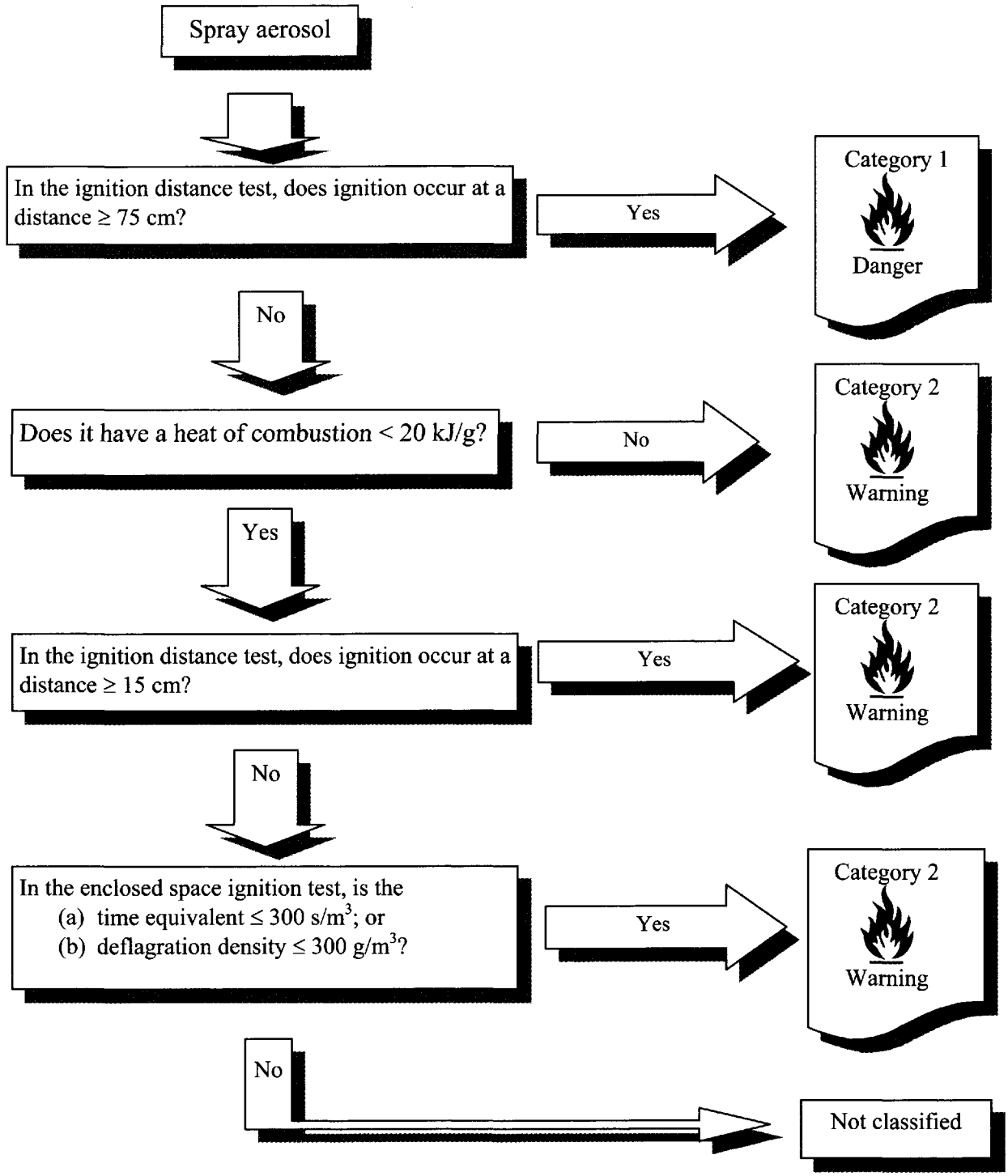
To classify a flammable aerosol, data on its flammable components, on its chemical heat of combustion and, if applicable, the results of the foam test (for foam aerosols) and of the ignition distance test and enclosed space test (for spray aerosols) are required. Classification should be made according to the following decision logics.

Decision logic 2.3 (a) for flammable aerosols

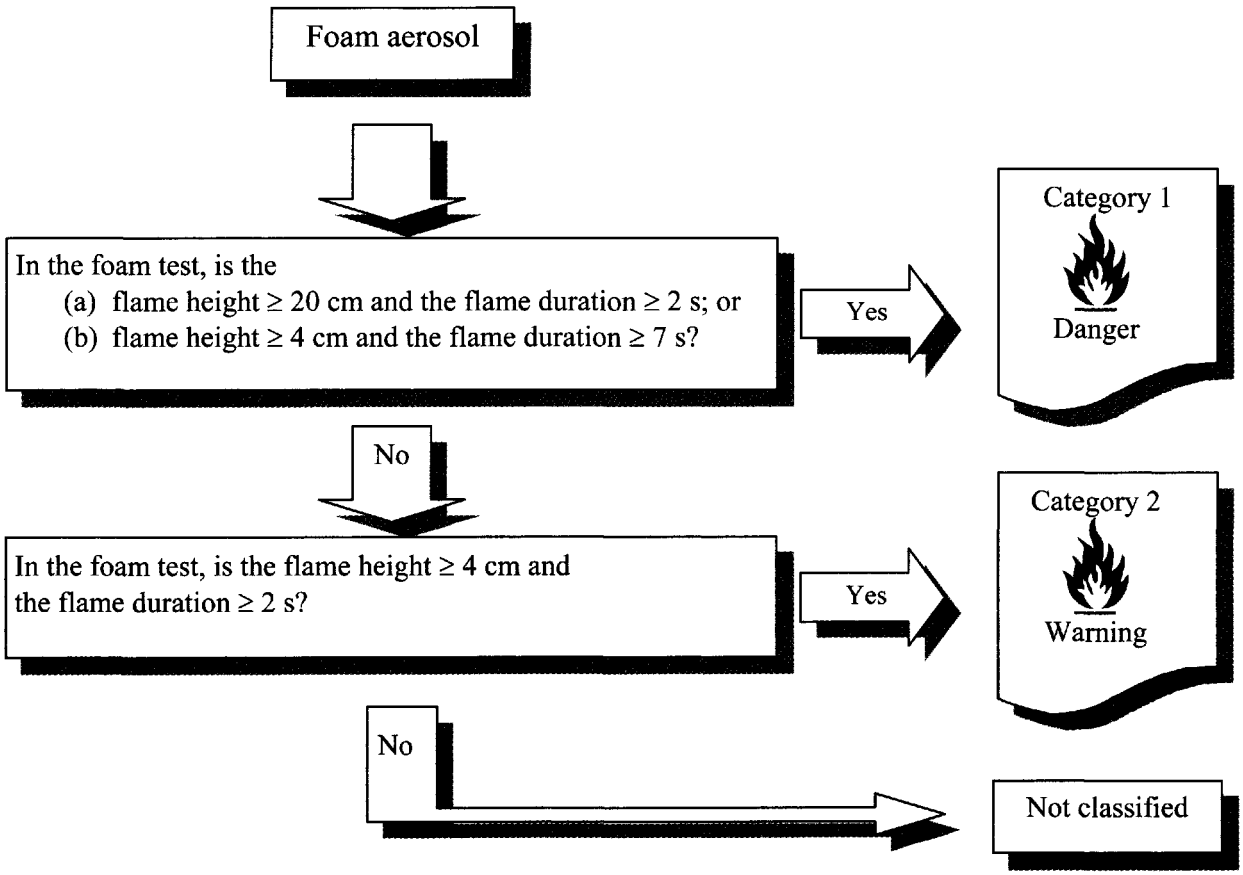


For spray aerosols, go to decision logic 2.3. (b)
For foam aerosols, go to decision logic 2.3. (c)

Decision logic 2.3 (b) for spray aerosols



Decision logic 2.3 (c) for foam aerosols



2.3.4.2 *Guidance*

2.3.4.2.1 The chemical heat of combustion (ΔHc), in kilojoules per gram (kJ/g), is the product of the theoretical heat of combustion (ΔHcomb), and a combustion efficiency, usually less than 1.0 (a typical combustion efficiency is 0.95 or 95%.).

For a composite aerosol formulation, the chemical heat of combustion is the summation of the weighted heats of combustion for the individual components, as follows:

$$\Delta H_{c\ (product)} = \sum_{i}^{n} [\ w_i\% \times \Delta H_{c(i)}]$$

where:

ΔH_c = chemical heat of combustion (kJ/g)
$w_i\%$ = mass fraction of component i in the product
$\Delta H_{c(i)}$ = specific heat of combustion (kJ/g)of component i in the product.

The chemical heats of combustion can be found in literature, calculated or determined by tests (see ASTM D 240, ISO/FDIS 13943:1999 (E/F) 86.1 to 86.3 and NFPA 30B).

2.3.4.2.2 See sub-sections 31.4, 31.5, and 31.6 of the *of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* for Ignition Distance Test, Enclosed Space Ignition Test and Aerosol Foam Flammability Test.

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CHAPTER 2.4

OXIDIZING GASES

2.4.1 Definition

An oxidizing gas is any gas which may, generally by providing oxygen, cause or contribute to the combustion of other material more than air does.

2.4.2 Classification criteria

An oxidizing gas is classified in a single category for this class according to the following table:

Table 2.4.1: Criteria for oxidizing gases

Category	Criteria
1	Any gas which may, generally by providing oxygen, cause or contribute to the combustion of other material more than air does.

NOTE: *Artificial air containing up to 23.5% vol % oxygen may be regarded as not oxidizing for some regulatory purposes (e.g. transport).*

2.4.3 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

	Category 1
Symbol	Flame over circle
Signal word	Danger
Hazard statement	May cause or intensify fire; oxidizer

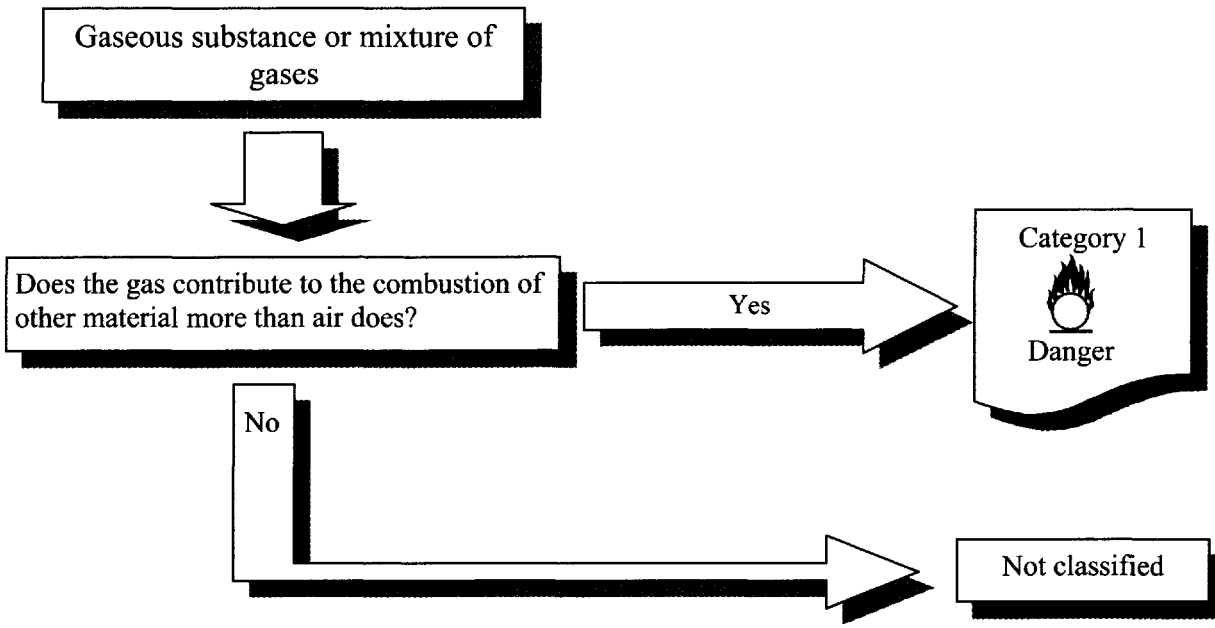
2.4.4 Decision logic and guidance

The decision logic and guidance, which follow, are not part of the harmonized classification system, but have been provided here as additional guidance. It is strongly recommended that the person responsible for classification studies the criteria before and during use of the decision logic.

2.4.4.1 *Decision logic*

To classify an oxidizing gas tests or calculation methods as described in ISO 10156:1996 Gases and gas mixtures – Determination of fire potential and oxidizing ability for the selection of cylinder valve outlet - should be performed.

Decision logic 2.4 for oxidizing gases



2.4.4.2 ***Example of the classification of an oxidizing gas mixture by calculation according to ISO-10156***

Formula

$$\sum_{i}^{n} Vi\% \times Ci$$

Where:

$V_i\%$	is the volume percentage of a gas
C_i	is the coefficient of oxygen equivalency
i	is the first gas in the mixture
n	is the n^{th} gas in the mixture

***NOTE**: Balance gas is not taken into consideration.*

Criterion:

$$\sum_{i}^{n} Vi\% \times Ci \geq 21$$

Gas mixture

For the purpose of this example the following is the gas mixture to be used

$$9\%(O_2) + 16\%(N_2O) + 75\%(N_2)$$

Calculation

1. Ascertain the coefficient of oxygen equivalency (Ci) for the oxidizing gases in the mixture

Ci (N_2O)	= 0.6 (nitrous oxide)
Ci (O)	= 1 (oxygen)
Ci (all other oxidizing gases)	= 40

2. Calculate if the gas mixture is oxidizing using the coefficient of oxygen equivalency figures for the oxidizing gases

$$9\%(O_2) + 16\%(N_2O) + 75\%(N_2) = (9 \times 1) + (16 \times 0.6)$$

$$18.6 < 21$$

Therefore the mixture is considered less oxidizing than air.

If the gas mixture had been 0.6 % F_2 in Nitrogen, the equivalent calculation would have been

$$0.6\%(F_2) + 99.4\%(N_2)$$

The coefficient of oxygen equivalency (Ci) for F_2 = 40

$$40 \times 0.6 = 24 > 21.$$

Therefore the mixture is considered more oxidizing than air.

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CHAPTER 2.5

GASES UNDER PRESSURE

2.5.1 Definition

Gases under pressure are gases which are contained in a receptacle at a pressure not less than 280 kPa at 20 °C or as a refrigerated liquid.

They comprise compressed gases; liquefied gases; dissolved gases; refrigerated liquefied gases.

2.5.2 Classification criteria

Gases are classified, according to their physical state when packaged, in one of four groups in the following table:

Table 2.5.1: Criteria for gases under pressure

Group	Criteria
Compressed gas	A gas which when packaged under pressure is entirely gaseous at -50 °C; including all gases with a critical temperature ≤ -50 °C.
Liquefied gas	A gas which when packaged under pressure, is partially liquid at temperatures above -50 °C. A distinction is made between: (a) High pressure liquefied gas: a gas with a critical temperature between -50°C and +65°C; and (b) Low pressure liquefied gas: a gas with a critical temperature above +65°C.
Refrigerated liquefied gas	A gas which when packaged is made partially liquid because of its low temperature.
Dissolved gas	A gas which when packaged under pressure is dissolved in a liquid phase solvent.

The critical temperature is the temperature above which a pure gas cannot be liquefied, regardless of the degree of compression.

2.5.3 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 2.5.2: Label elements for gases under pressure

	Compressed gas	Liquefied gas	Refrigerated liquefied gas	Dissolved gas
Symbol	Gas cylinder	Gas cylinder	Gas cylinder	Gas cylinder
Signal word	Warning	Warning	Warning	Warning
Hazard statement	Contains gas under pressure; may explode if heated	Contains gas under pressure; may explode if heated	Contains refrigerated gas; may cause cryogenic burns or injury	Contains gas under pressure; may explode if heated

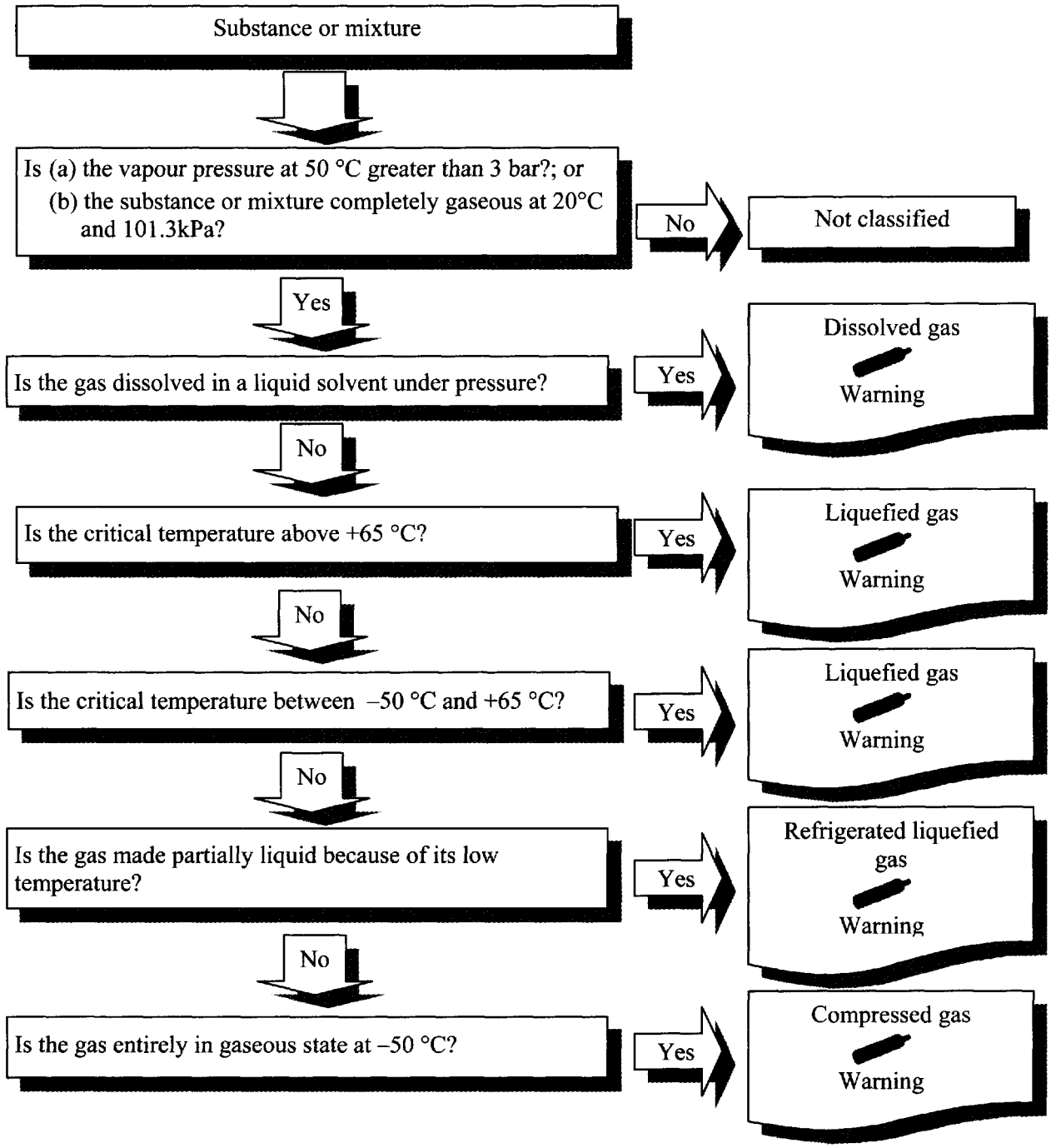
2.5.4 Decision logic and guidance

The decision logic and guidance, which follow, are not part of the harmonized classification system, but have been provided here as additional guidance. It is strongly recommended that the person responsible for classification studies the criteria before and during use of the decision logic.

2.5.4.1 *Decision logic*

Classification can be made according to the following decision logic.

Decision logic 2.5 for gases under pressure



2.5.4.2 *Guidance*

For this group of gases, the following information is required to be known:

- The vapour pressure at 50 °C;
- The physical state at 20 °C at standard ambient pressure;
- The critical temperature.

In order to classify a gas, the above data are needed. Data can be found in literature, calculated or determined by testing. Most pure gases are already classified in the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations*. Most one off mixtures require additional calculations that can be very complex.

CHAPTER 2.6

FLAMMABLE LIQUIDS

2.6.1 Definition

A flammable liquid means a liquid having a flash point of not more than 93 °C.

2.6.2 Classification criteria

A flammable liquid is classified in one of the four categories for this class according to the following table:

Table 2.6.1: Criteria for flammable liquids

Category	Criteria
1	Flash point < 23 °C and initial boiling point ≤ 35 °C
2	Flash point < 23 °C and initial boiling point > 35 °C
3	Flash point ≥ 23 °C and ≤ 60 °C
4	Flash point > 60 °C and ≤ 93 °C

NOTE 1: *Gas oils, diesel and light heating oils in the flash point range of 55 °C to 75 °C may be regarded as a special group for some regulatory purposes.*

NOTE 2: *Liquids with a flash point of more than 35 °C may be regarded as non-flammable liquids for some regulatory purposes (e.g. transport) if negative results have been obtained in the sustained combustibility test L.2 of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria.*

NOTE 3: *Viscous flammable liquids such as paints, enamels, lacquers, varnishes, adhesives and polishes may be regarded as a special group for some regulatory purposes (e.g. transport). The classification or the decision to consider these liquids as non-flammable may be determined by the pertinent regulation or competent authority.*

2.6.3 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 2.6.2: Label elements for flammable liquids

	Category 1	Category 2	Category 3	Category 4
Symbol	Flame	Flame	Flame	**No symbol used**
Signal word	Danger	Danger	Warning	Warning
Hazard statement	Extremely flammable liquid and vapour	Highly flammable liquid and vapour	Flammable liquid and vapour	Combustible liquid

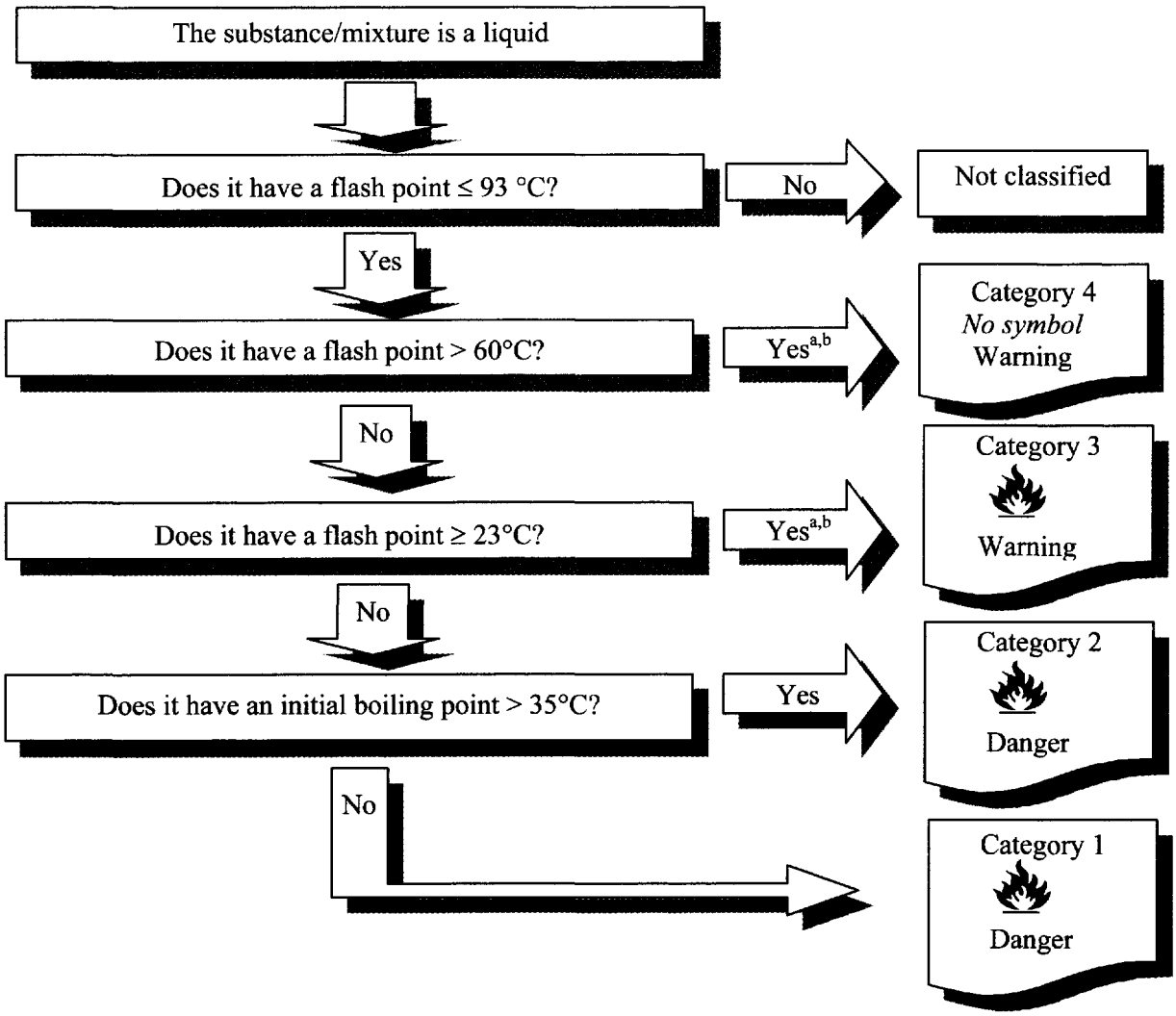
2.6.4 Decision logic and guidance

The decision logic and guidance, which follow, are not part of the harmonized classification system, but have been provided here as additional guidance. It is strongly recommended that the person responsible for classification studies the criteria before and during use of the decision logic.

2.6.4.1 *Decision logic*

Once flash point and initial boiling point are known, the classification of the substance or mixture and the relevant harmonized label information can be obtained with the following decision tree:

Decision logic 2.6 for flammable liquids



[a] *Gas oils, diesel and light heating oils in the flash point range of 55 °C to 75 °C may be regarded as a special group for some regulatory purposes as these hydrocarbons mixtures have varying flash point in that range. Thus classification in category 3 or 4 of these products may be determined by the pertinent regulation or competent authority.*

[b] *Liquids with a flash point of more than 35 °C may be regarded as non-flammable liquids for some regulatory purposes (e.g. transport) if negative results have been obtained in the sustained combustibility test L.2 of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria.*

2.6.4.2 *Guidance*

2.6.4.2.1 In order to classify a flammable liquid, data on its flash point and initial boiling point are needed. Data can be determined by testing, found in literature or calculated.

2.6.4.2.2 In the case of mixtures[1] containing known flammable liquids in defined concentrations, although they may contain non-volatile components e.g. polymers, additives, the flash point need not be determined experimentally if the calculated flash point of the mixture, using the method given in 2.6.4.2.3 below, is at least 5 °C greater than the relevant classification criterion and provided that

(a) The composition of the mixture is accurately known (if the material has a specified range of composition, the composition with the lowest calculated flash point should be selected for assessment);

(b) The flash point (closed cup as given in 2.6.4.2.5 below) of each component is known (an appropriate correlation has to be applied when these data are extrapolated to other temperatures than test conditions);

(c) The activity coefficient is known for each component as present in the mixture including the temperature dependence;

(d) The liquid phase is homogeneous.

2.6.4.2.3 A suitable method is described in Gmehling and Rasmussen (Ind. Eng. Chem. Fundament, 21, 186, (1982)). For a mixture containing non-volatile components, e.g. polymers or additives, the flash point is calculated from the volatile components. It is considered that a non-volatile component only slightly decreases the partial pressure of the solvents and the calculated flash point is only slightly below the measured value.

2.6.4.2.4 If data are not available, the flash point and the initial boiling point shall be determined through testing. The flash point shall be determined by closed-cup test method. Open-cup tests are acceptable only in special cases.

2.6.4.2.5 The following is a list of documents describing methods for determining the flash point of flammable liquids:

International standards:

ISO 1516
ISO 1523
ISO 3679
ISO 3680

National standards:

American Society for Testing Materials, 1916 Race Street, Philadelphia, Penna 19103:
ASTM D 3828-93, Standard Test Methods for Flash Point by Small Scale Closed Tester
ASTM D 56-93, Standard Test Method for Flash Point by Tag Closed Tester
ASTM D 3278-96, Standard Test Methods for Flash Point of Liquids by Setaflash Closed-Cup Apparatus
ASTM D 0093-96, Standard Test Methods for Flash Point by Pensky-Martens Closed Cup Tester

[1] *Screening procedures are well established for ideal mixture of solvents, i.e. mainly hydrocarbures.*

Association française de normalisation, AFNOR, Tour Europe, 92049 Paris La Défense:
French Standard NF M 07 - 019
French Standards NF M 07 - 011 / NF T 30 - 050 / NF T 66 - 009
French Standard NF M 07 - 036

British Standards Institution, Linford Wood, Milton Keynes, MK14 6LE:
British Standard BS EN 22719
British Standard BS 2000 Part 170

Deutscher Normenausschuss:
Standard DIN 51755 (flash points below 65 °C)
Standard DIN 51758 (flash points 65 °C to 165 °C)
Standard DIN 53213 (for varnishes, lacquers and similar viscous liquids with flash points below 65 °C)

State Committee of the Council of Ministers for Standardization, 113813, GSP, Moscow, M-49 Leninsky Prospect, 9:
GOST 12.1.044-84

CHAPTER 2.7

FLAMMABLE SOLIDS

2.7.1 Definitions

A flammable solid is a solid which is readily combustible, or may cause or contribute to fire through friction.

Readily combustible solids are powdered, granular, or pasty substances which are dangerous if they can be easily ignited by brief contact with an ignition source, such as a burning match, and if the flame spreads rapidly.

2.7.2 Classification criteria

2.7.2.1 Powdered, granular or pasty substances or mixtures shall be classified as readily combustible solids when the time of burning of one or more of the test runs, performed in accordance with the test method described in the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*, Part III, sub-section 33.2.1, is less than 45 seconds or the rate of burning is more than 2.2 mm/s.

2.7.2.2 Powders of metals or metal alloys shall be classified as flammable solids when they can be ignited and the reaction spreads over the whole length of the sample in 10 minutes or less.

2.7.2.3 Solids which may cause fire through friction shall be classified in this class by analogy with existing entries (e.g. matches) until definitive criteria are established.

2.7.2.4 A flammable solid is classified in one of the two categories for this class using Method N.1 as described in 33.2.1 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* according to the following table:

Table 2.7.1: Criteria for flammable solids

Category	Criteria
1	Burning rate test: Substances or mixtures other than metal powders: (a) wetted zone does not stop fire and (b) burning time < 45 seconds or burning rate > 2.2 mm/second Metal powders: - burning time ≤ 5 minutes
2	Burning rate test: Substances or mixtures other than metal powders: (a) wetted zone stops the fire for at least 4 minutes and (b) burning time < 45 seconds or burning rate > 2.2 mm/second Metal powders: - burning time > 5 minutes and ≤ 10 minutes

NOTE: *For classification tests on solid substances or mixtures, the tests should be performed on the substance or mixture as presented. If for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance must also be tested in the new form.*

2.7.3 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 2.7.2: Label elements for flammable solids

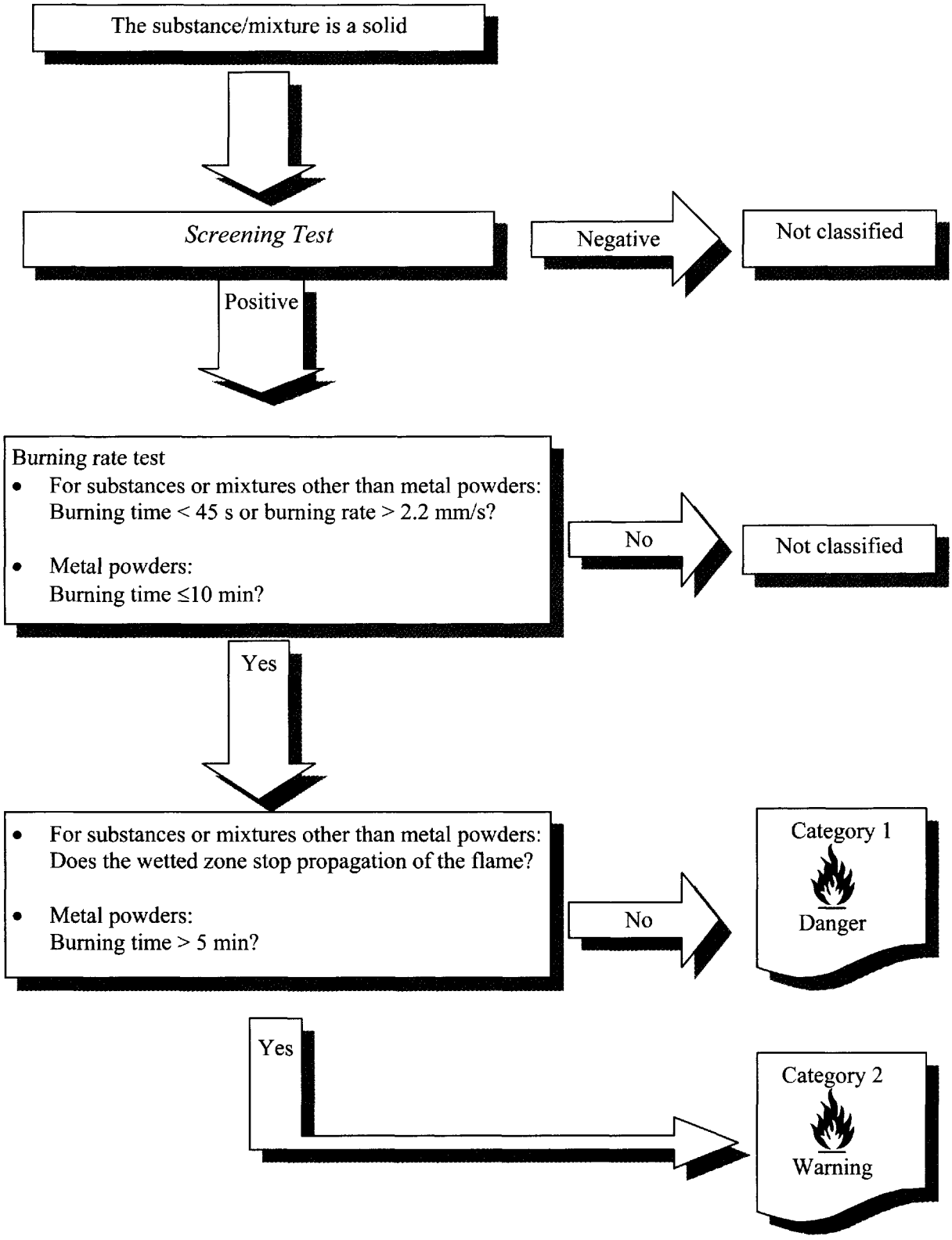
	Category 1	**Category 2**
Symbol	Flame	Flame
Signal word	Danger	Warning
Hazard statement	Flammable solid	Flammable solid

2.7.4 Decision logic

The decision logic, which follows, is not part of the harmonized classification system, but has been provided here as additional guidance. It is strongly recommended that the person responsible for classification studies the criteria before and during use of the decision logic.

To classify a flammable solid, the test method N.1 as described in 33.2.1 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria* should be performed. The procedure consists of two tests: a preliminary screening test and a burning rate test. Classification is according to the following decision tree.

Decision logic 2.7 for flammable solids



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CHAPTER 2.8

SELF-REACTIVE SUBSTANCES

2.8.1 Definitions

2.8.1.1 Self-reactive substances or mixtures are thermally unstable liquid or solid substances or mixtures liable to undergo a strongly exothermic decomposition even without participation of oxygen (air). This definition excludes substances and mixtures classified under the GHS as explosives, organic peroxides or as oxidizing.

2.8.1.2 A self-reactive substance or mixture is regarded as possessing explosive properties when in laboratory testing the formulation is liable to detonate, to deflagrate rapidly or to show a violent effect when heated under confinement.

2.8.2 Classification criteria

2.8.2.1 Any self-reactive substance or mixture should be considered for classification in this class unless:

(a) They are explosives, according to the GHS criteria of Chapter 2.1;

(b) They are oxidizing liquids or solids, according to the GHS criteria of Chapters 2.13 or 2.14;

(c) They are organic peroxides, according to the GHS criteria of Chapter 2.15;

(d) Their heat of decomposition is less than 300 J/g; or

(e) Their self-accelerating decomposition temperature (SADT) is greater than 75 °C for a 50 kg package.

2.8.2.2 Self-reactive substances and mixtures are classified in one of the seven categories of "types A to G" for this class, according to the following principles:

(a) Any self-reactive substance or mixture which can detonate or deflagrate rapidly, as packaged, will be defined as **self-reactive substance TYPE A**;

(b) Any self-reactive substance or mixture possessing explosive properties and which, as packaged, neither detonates nor deflagrates rapidly, but is liable to undergo a thermal explosion in that package will be defined as **self-reactive substance TYPE B**;

(c) Any self-reactive substance or mixture possessing explosive properties when the substance or mixture as packaged cannot detonate or deflagrate rapidly or undergo a thermal explosion will be defined as **self-reactive substance TYPE C**;

(d) Any self-reactive substance or mixture which in laboratory testing:
   (i) detonates partially, does not deflagrate rapidly and shows no violent effect when heated under confinement; or
   (ii) does not detonate at all, deflagrates slowly and shows no violent effect when heated under confinement; or
   (iii) does not detonate or deflagrate at all and shows a medium effect when heated under confinement;

   will be defined as **self-reactive substance TYPE D**;

(e) Any self-reactive substance or mixture which, in laboratory testing, neither detonates nor deflagrates at all and shows low or no effect when heated under confinement will be defined as **self-reactive substance TYPE E**;

(f) Any self-reactive substance or mixture which, in laboratory testing, neither detonates in the cavitated state nor deflagrates at all and shows only a low or no effect when heated under confinement as well as low or no explosive power will be defined as **self-reactive substance TYPE F**;

(g) Any self-reactive substance or mixture which, in laboratory testing, neither detonates in the cavitated state nor deflagrates at all and shows no effect when heated under confinement nor any explosive power, provided that it is thermally stable (self-accelerating decomposition temperature is 60 °C to 75 °C for a 50 kg package), and, for liquid mixtures, a diluent having a boiling point not less than 150 °C is used for desensitisation will be defined as **self-reactive substance TYPE G**. If the mixture is not thermally stable or a diluent having a boiling point less than 150 °C is used for desensitisation, the mixture shall be defined as **self-reactive substance TYPE F**.

***NOTE 1**: Type G has no hazard communication elements assigned but should be considered for properties belonging to other hazard classes.*

***NOTE 2:** Types A to G may not be necessary for all systems.*

2.8.3 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 2.8.1: Label elements for self-reactive substances and mixtures

	Type A	Type B	Type C and D	Type E and F	Type G [a]
Symbol	Exploding bomb	Exploding bomb and flame	Flame	Flame	There are no label elements allocated to this hazard category
Signal word	Danger	Danger	Danger	Warning	
Hazard statement	Heating may cause an explosion	Heating may cause a fire or explosion	Heating may cause a fire	Heating may cause a fire	

[a] *Type G has no hazard communication elements assigned but should be considered for properties belonging to other hazard classes.*

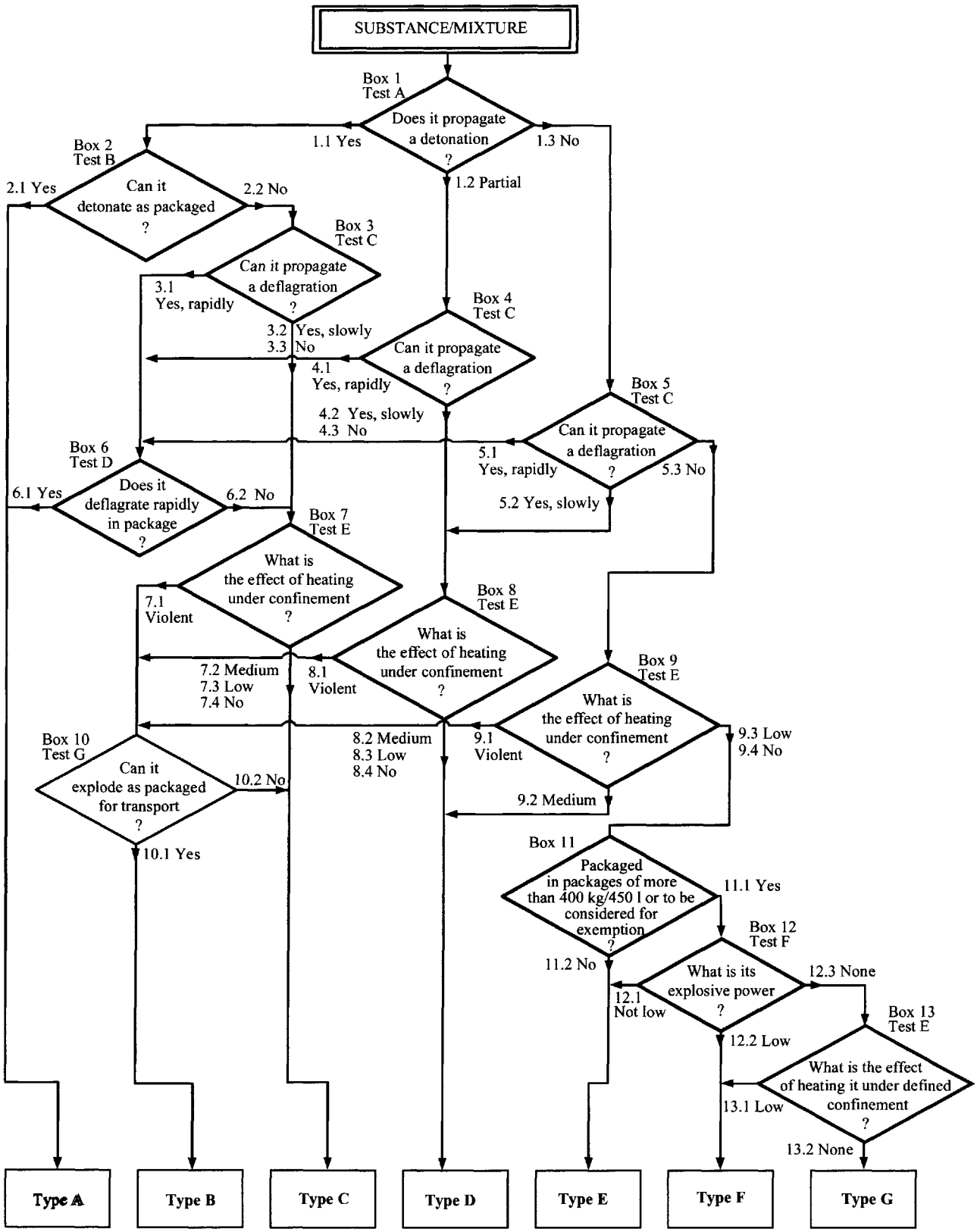
2.8.4 Decision logic and guidance

The decision logic and guidance, which follow, are not part of the harmonized classification system, but have been provided here as additional guidance. It is strongly recommended that the person responsible for classification studies the criteria before and during use of the decision logic.

2.8.4.1 *Decision logic*

To classify a self-reactive substance or mixture test series A to H as described in Part II of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria* should be performed. Classification is according to the following decision logic.

Decision logic 2.8 for self-reactive substances and mixtures



The properties of self-reactive substances or mixtures which are decisive for their classification should be determined experimentally. Test methods with pertinent evaluation criteria are given in the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria, Part II (test series A to H).

2.8.4.2 ***Guidance***

The classification procedures for self-reactive substances and mixtures need not be applied if:

(a) There are no chemical groups present in the molecule associated with explosive or self-reactive properties; examples of such groups are given in Tables A6.1 and A6.2 in the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*, Appendix 6; or

(b) For a single organic substance or a homogeneous mixture of organic substances, the estimated SADT is greater than 75 °C or the exothermic decomposition energy is less than 300J/g. The onset temperature and decomposition energy may be estimated using a suitable calorimetric technique (see 20.3.3.3 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*).

CHAPTER 2.9

PYROPHORIC LIQUIDS

2.9.1 Definition

A pyrophoric liquid is a liquid which, even in small quantities, is liable to ignite within five minutes after coming into contact with air.

2.9.2 Classification criteria

A pyrophoric liquid is classified in a single category for this class using test N.3 in 33.3.1.5 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* according to the following table:

Table 2.9.1: Criteria for pyrophoric liquids

Category	Criteria
1	The liquid ignites within 5 min when added to an inert carrier and exposed to air, or it ignites or chars a filter paper on contact with air within 5 min.

2.9.3 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 2.9.2: Label elements for pyrophoric liquids

	Category 1
Symbol	Flame
Signal word	Danger
Hazard statement	Catches fire spontaneously if exposed to air

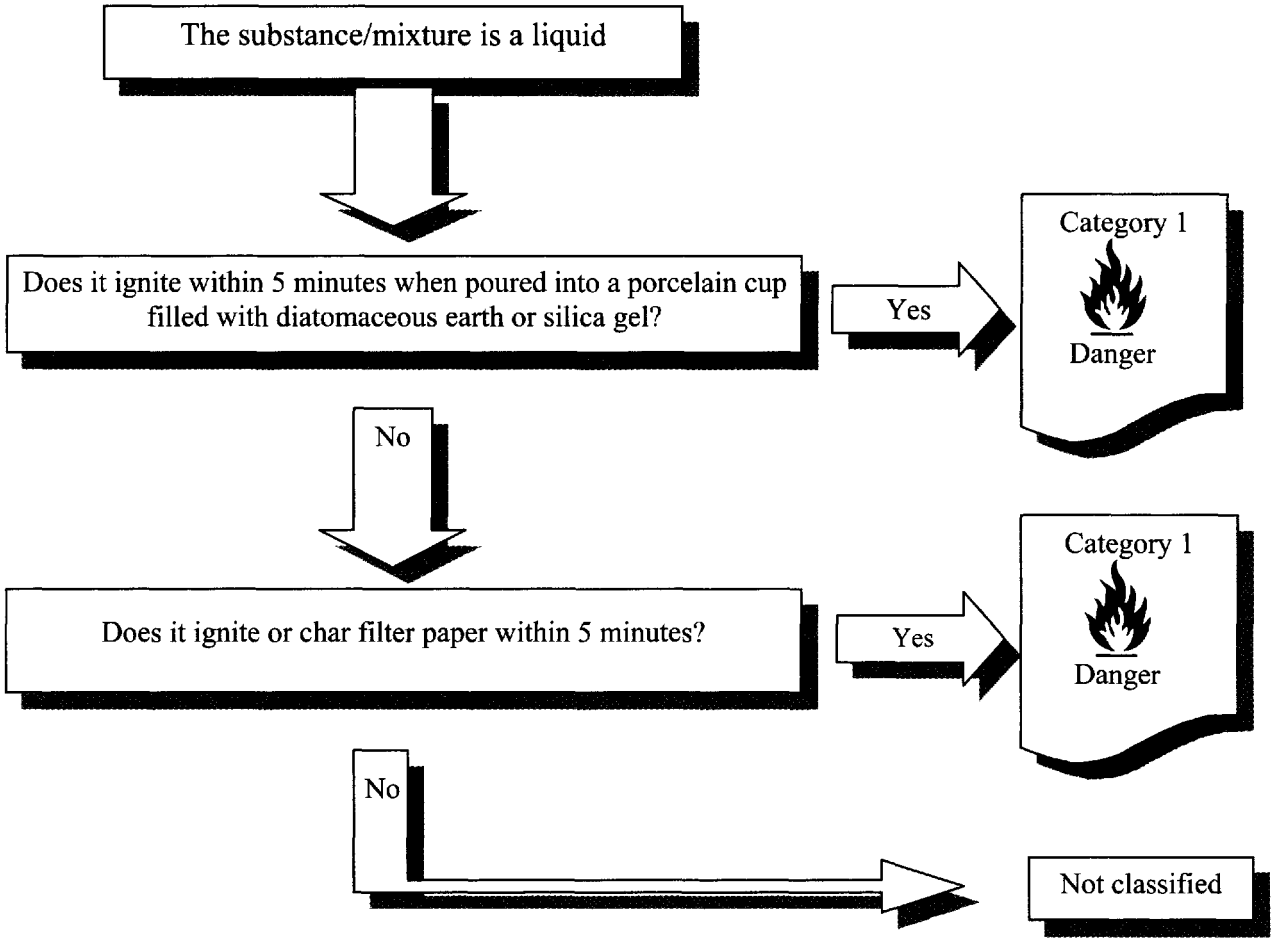
2.9.4 Decision logic and guidance

The decision logic and guidance, which follow, are not part of the harmonized classification system, but have been provided here as additional guidance. It is strongly recommended that the person responsible for classification studies the criteria before and during use of the decision logic.

2.9.4.1 *Decision logic*

To classify a pyrophoric liquid, the test method N.3 as described in 33.3.1.5 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria* should be performed. The procedure consists of two steps. Classification is according to the following decision logic.

Decision logic 2.9 for pyrophoric liquids



2.9.4.2 *Guidance*

The classification procedure for pyrophoric liquids need not be applied when experience in production or handling shows that the substance or mixture does not ignite spontaneously on coming into contact with air at normal temperatures (i.e. the substance is known to be stable at room temperature for prolonged periods of time (days)).

CHAPTER 2.10

PYROPHORIC SOLIDS

2.10.1 Definition

A pyrophoric solid is a solid which, even in small quantities, is liable to ignite within five minutes after coming into contact with air.

2.10.2 Classification criteria

A pyrophoric solid is classified in a single category for this class using test N.2 in 33.3.1.4 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria* according to the following table:

Table 2.10.1: Criteria for pyrophoric solids

Category	Criteria
1	The solid ignites within 5 minutes of coming into contact with air.

NOTE: *For classification tests on solid substances or mixtures, the tests should be performed on the substance or mixture as presented. If for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance or mixture must also be tested in the new form.*

2.10.3 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 2.10.2: Label elements for pyrophoric solids

	Category 1
Symbol	Flame
Signal word	Danger
Hazard statement	Catches fire spontaneously if exposed to air

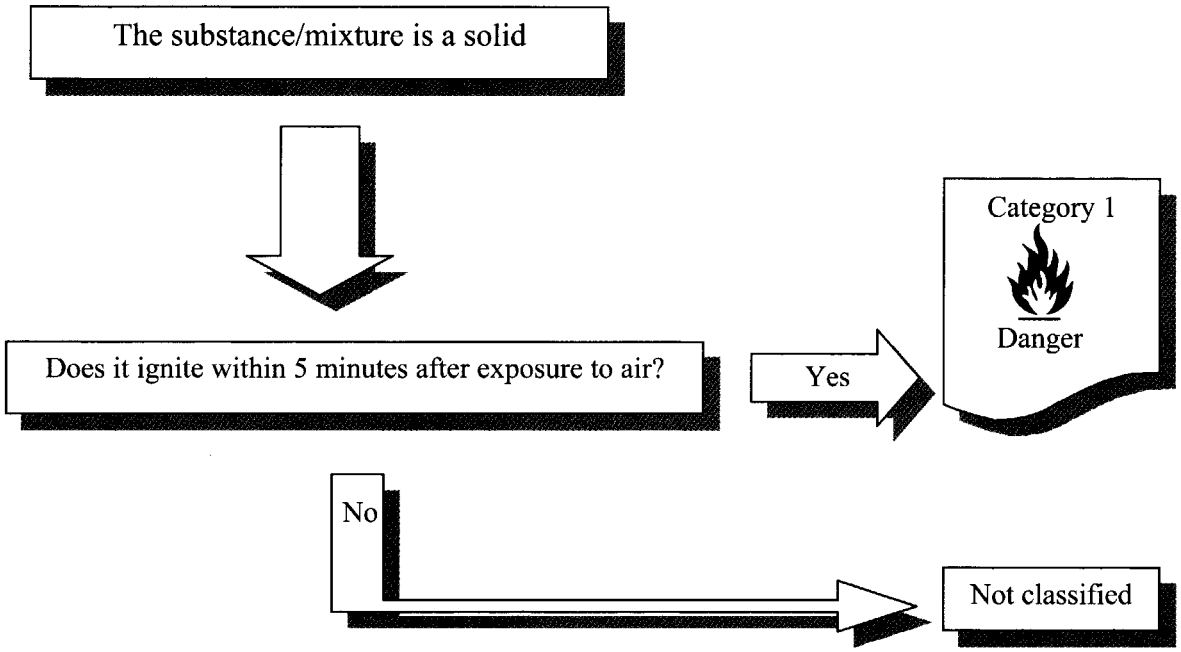
2.10.4 Decision logic and guidance

The decision logic and guidance, which follow, are not part of the harmonized classification system, but have been provided here as additional guidance. It is strongly recommended that the person responsible for classification studies the criteria before and during use of the decision logic.

2.10.4.1 *Decision logic*

To classify a pyrophoric solid, the test method n.2 as described in 33.3.1.4 of *the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria* should be performed. Classification is according to the following decision logic.

Decision logic 2.10 for pyrophoric solids



2.10.4.2 *Guidance*

The classification procedure for pyrophoric solids need not be applied when experience in production or handling shows that the substance or mixture does not ignite spontaneously on coming into contact with air at normal temperatures (i.e. the substance or mixture is known to be stable at room temperature for prolonged periods of time (days)).

CHAPTER 2.11

SELF-HEATING SUBSTANCES

2.11.1 Definition

A self-heating substance or mixture is a solid substance or mixture, other than a pyrophoric liquid or solid, which, by reaction with air and without energy supply, is liable to self-heat; this substance or mixture differs from a pyrophoric liquid or solid in that it will ignite only when in large amounts (kilograms) and after long periods of time (hours or days).

NOTE: *Self-heating of substances or mixtures, leading to spontaneous combustion, is caused by reaction of the substance or mixture with oxygen (in the air) and the heat developed not being conducted away rapidly enough to the surroundings. Spontaneous combustion occurs when the rate of heat production exceeds the rate of heat loss and the auto-ignition temperature is reached.*

2.11.2 Classification criteria

2.11.2.1 A substance or mixture shall be classified as a self-heating substance of this class, if in tests performed in accordance with the test method given in the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*, Part III, sub-section 33.3.1.6:

(a) A positive result is obtained using a 25 mm cube sample at 140 °C;

(b) A positive result is obtained in a test using a 100 mm sample cube at 140 °C and a negative result is obtained in a test using a 100 mm cube sample at 120 °C and the substance or mixture is to be packed in packages with a volume of more than 3 m^3;

(c) A positive result is obtained in a test using a 100 mm sample cube at 140 °C and a negative result is obtained in a test using a 100 mm cube sample at 100 °C and the substance or mixture is to be packed in packages with a volume of more than 450 litres;

(d) A positive result is obtained in a test using a 100 mm sample cube at 140 °C and a positive result is obtained using a 100 mm cube sample at 100 °C.

2.11.2.2 A self-heating substance or mixture is classified in one of the two categories for this class if, in test performed in accordance with test method N. 4 in 33.3.1.6 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*, the result meets the criteria shown in Table 2.11.1.

Table 2.11.1: Criteria for self-heating substances and mixtures

Category	Criteria
1	A positive result is obtained in a test using a 25 mm sample cube at 140 °C
2	(a) A positive result is obtained in a test using a 100 mm sample cube at 140 °C and a negative result is obtained in a test using a 25 mm cube sample at 140 °C and the substance or mixture is to be packed in packages with a volume of more than 3 m^3; or (b) A positive result is obtained in a test using a 100 mm sample cube at 140 °C and a negative result is obtained in a test using a 25 mm cube sample at 140 °C, a positive result is obtained in a test using a 100 mm cube sample at 120 °C and the substance or mixture is to be packed in packages with a volume of more than 450 litres; or (c) A positive result is obtained in a test using a 100 mm sample cube at 140 °C and a negative result is obtained in a test using a 25 mm cube sample at 140 °C and a positive result is obtained in a test using a 100 mm cube sample at 100 °C.

NOTE 1: For classification tests on solid substances or mixtures, the tests should be performed on the substance or mixture as presented. If for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance or mixture must also be tested in the new form.

NOTE 2: The criteria are based on the self-ignition temperature of charcoal, which is 50°C for a sample cube of 27m^3. Substances and mixtures with a temperature of spontaneous combustion higher than 50°C for a volume of 27m^3 should not be assigned to this hazard class. Substances and mixtures with a spontaneous ignition temperature higher than 50°C for a volume of 450 litres should not be assigned to hazard category 1 of this hazard class.

2.11.3 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 2.11.2: Label elements for self-heating substances and mixtures

	Category 1	Category 2
Symbol	Flame	Flame
Signal word	Danger	Warning
Hazard statement	Self-heating; may catch fire	Self-heating in large quantities; may catch fire

2.11.4 Decision logic and guidance

The decision logic and guidance, which follow, are not part of the harmonized classification system, but have been provided here as additional guidance. It is strongly recommended that the person responsible for classification studies the criteria before and during use of the decision logic.

2.11.4.1 *Decision logic*

To classify a self-heating substance, test method N.4, as described in 33.3.1.6 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*, should be performed. Classification is according to decision logic 2.11.

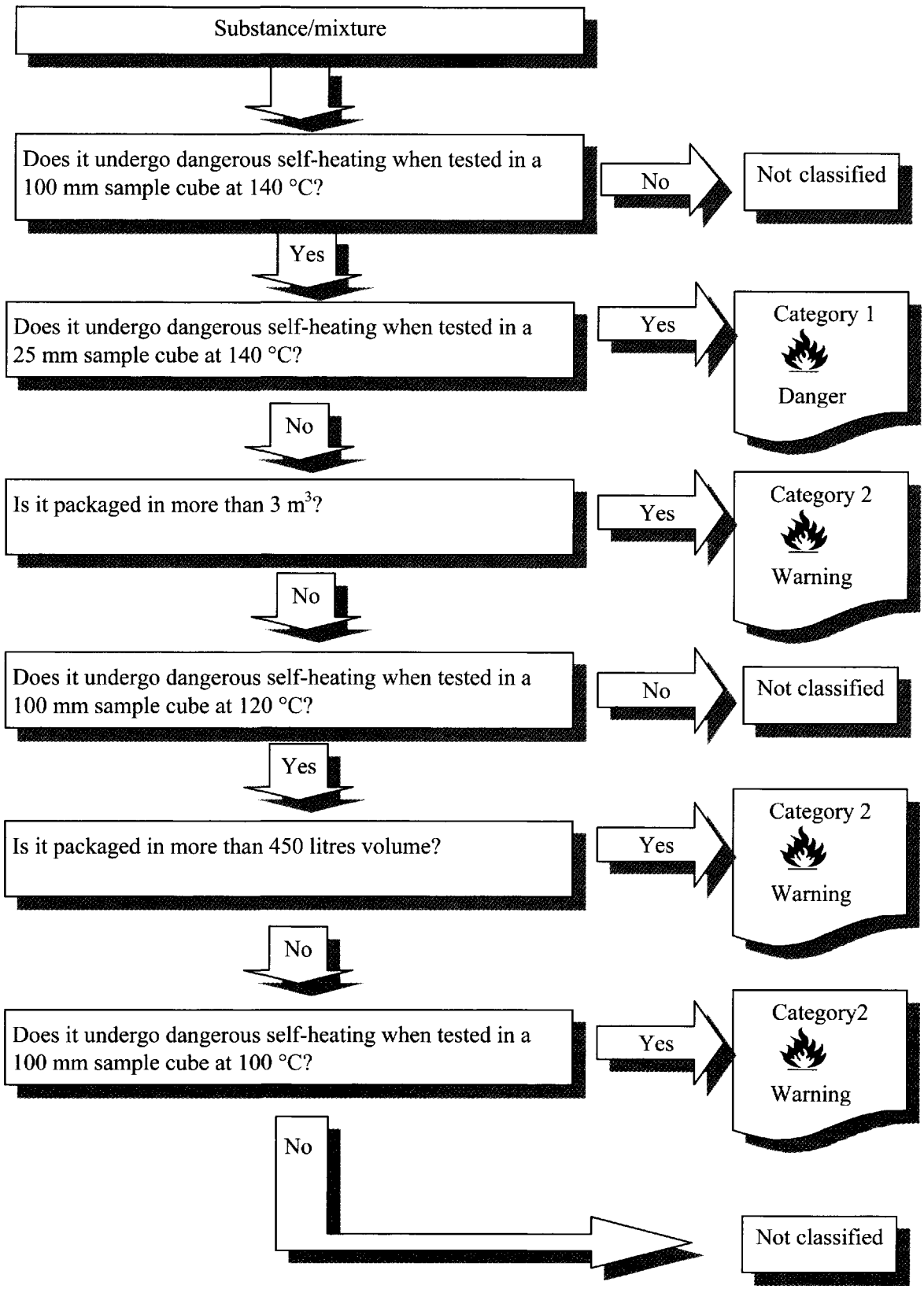
2.11.4.2 *Guidance*

The classification procedure for self-heating substances need not be applied if the results of a screening test can be adequately correlated with the classification test and an appropriate safety margin is applied. Examples of screening tests are:

(a) The Grewer Oven test (VDI guideline 2263, part 1, 1990, Test methods for the Determination of the Safety Characteristics of Dusts) with an onset temperature 80 K above the reference temperature for a volume of 1 l;

(b) The Bulk Powder Screening Test (Gibson, N. Harper, D. J. Rogers, R. Evaluation of the fire and explosion risks in drying powders, Plant Operations Progress, 4 (3), 181 - 189, 1985) with an onset temperature 60 K above the reference temperature for a volume of 1 l.

Decision logic 2.11 for self-heating substances



CHAPTER 2.12

SUBSTANCES WHICH, IN CONTACT WITH WATER, EMIT FLAMMABLE GASES

2.12.1 Definition

Substances or mixtures which, in contact with water, emit flammable gases are solid or liquid substances or mixtures which, by interaction with water, are liable to become spontaneously flammable or to give off flammable gases in dangerous quantities.

2.12.2 Classification criteria

A substance or mixture which, in contact with water, emit flammable gases is classified in one of the three categories for this class, using test N.5 in 33.4.1.4 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*, according to the following table:

Table 2.12.1: Criteria for substances and mixtures which, in contact with water, emit flammable gases

Category	Criteria
1	Any substance or mixture which reacts vigorously with water at ambient temperatures and demonstrates generally a tendency for the gas produced to ignite spontaneously, or which reacts readily with water at ambient temperatures such that the rate of evolution of flammable gas is equal to or greater than 10 litres per kilogram of substance over any one minute.
2	Any substance or mixture which reacts readily with water at ambient temperatures such that the maximum rate of evolution of flammable gas is equal to or greater than 20 litres per kilogram of substance per hour, and which does not meet the criteria for category 1.
3	Any substance or mixture which reacts slowly with water at ambient temperatures such that the maximum rate of evolution of flammable gas is equal to or greater than 1 litre per kilogram of substance per hour, and which does not meet the criteria for categories 1 and 2.

NOTE 1: *A substance or mixture is classified as a substance which, in contact with water, emits flammable gases if spontaneous ignition takes place in any step of the test procedure.*

NOTE 2: *For classification tests on solid substances or mixtures, the tests should be performed on the substance or mixture as presented. If for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance or mixture must also be tested in the new form.*

2.12.3 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 2.12.2: Label elements for substances and mixtures, which in contact with water, emit flammable gases

	Category 1	Category 2	Category 3
Symbol	Flame	Flame	Flame
Signal word	Danger	Danger	Warning
Hazard statement	In contact with water releases flammable gases which may ignite spontaneously	In contact with water releases flammable gases	In contact with water releases flammable gases

2.12.4 Decision logic and guidance

The decision logic and guidance, which follow, are not part of the harmonized classification system, but have been provided here as additional guidance. It is strongly recommended that the person responsible for classification studies the criteria before and during use of the decision logic.

2.12.4.1 *Decision logic*

To classify a substance or mixture which, in contact with water emits flammable gases, test N.5 as described in 33.4.1.4 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* should be performed. Classification is according to decision logic 2.12.

2.12.4.2 *Guidance*

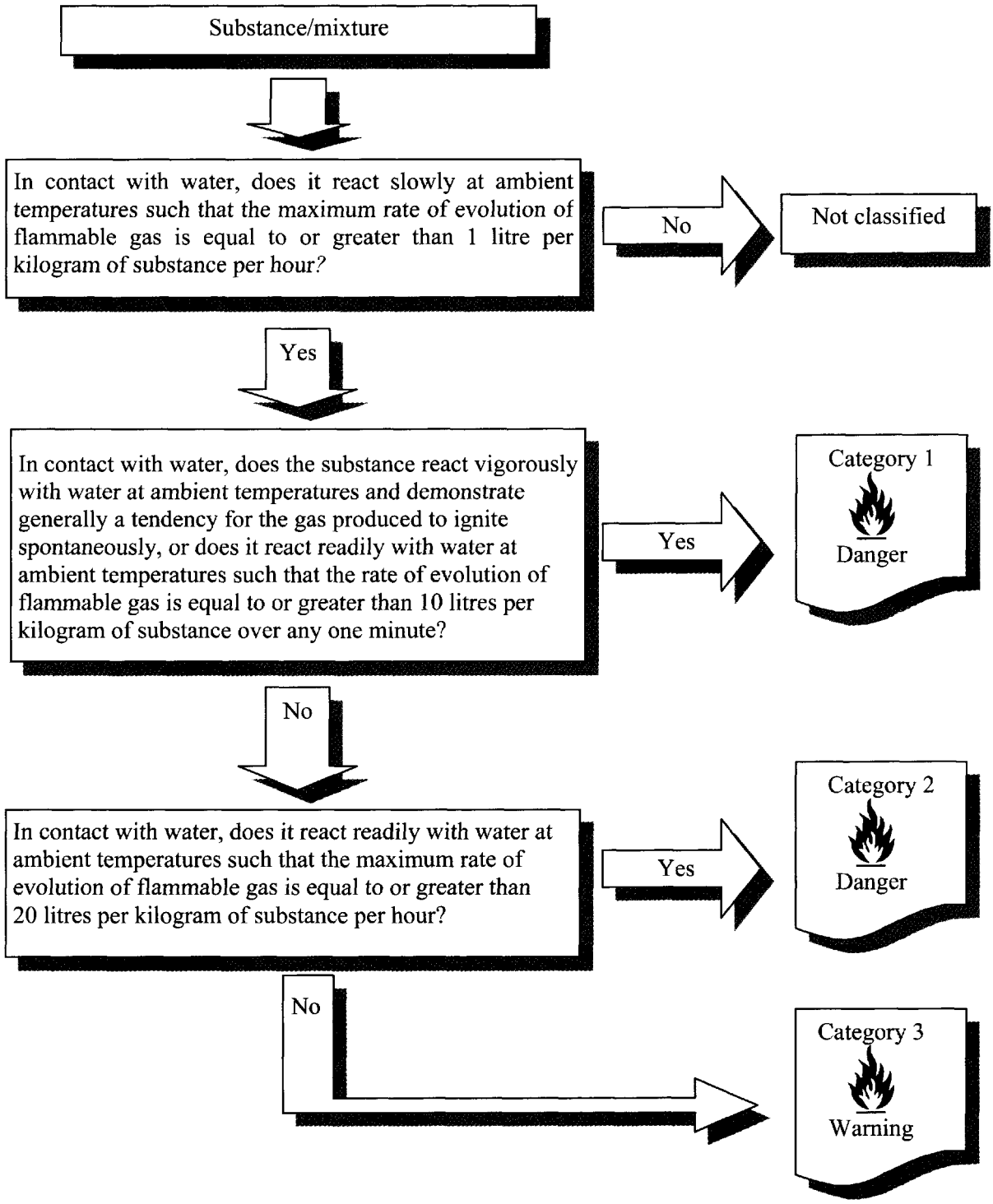
The classification procedure for this class need not be applied if:

(a) The chemical structure of the substance or mixture does not contain metals or metalloids;

(b) Experience in production or handling shows that the substance or mixture does not react with water, e.g. the substance is manufactured with water or washed with water; or

(c) The substance or mixture is known to be soluble in water to form a stable mixture.

Decision logic 2.12 for substances and mixtures which, in contact with water, emit flammable gases



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CHAPTER 2.13

OXIDIZING LIQUIDS

2.13.1 Definition

An oxidizing liquid is a liquid which, while in itself not necessarily combustible, may, generally by yielding oxygen, cause, or contribute to, the combustion of other material.

2.13.2 Classification criteria

An oxidizing liquid is classified in one of the three categories for this class using test O.2 in 34.4.2 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* according to the following table:

Table 2.13.1: Criteria for oxidizing liquids

Category	Criteria
1	Any substance or mixture which, in the 1:1 mixture, by mass, of substance (or mixture) and cellulose tested, spontaneously ignites; or the mean pressure rise time of a 1:1 mixture, by mass, of substance and cellulose is less than that of a 1:1 mixture, by mass, of 50% perchloric acid and cellulose
2	Any substance or mixture which, in the 1:1 mixture, by mass, of substance (or mixture) and cellulose tested, exhibits a mean pressure rise time less than or equal to the mean pressure rise time of a 1:1 mixture, by mass, of 40% aqueous sodium chlorate solution and cellulose; and the criteria for category 1 are not met
3	Any substance or mixture which, in the 1:1 mixture, by mass, of substance (or mixture) and cellulose tested, exhibits a mean pressure rise time less than or equal to the mean pressure rise time of a 1:1 mixture, by mass, of 65% aqueous nitric acid and cellulose; and the criteria for category 1 and 2 are not met

2.13.3 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 2.13.2: Label elements for oxidizing liquids

	Category 1	Category 2	Category 3
Symbol	Flame over circle	Flame over circle	Flame over circle
Signal word	Danger	Danger	Warning
Hazard statement	May cause fire or explosion; strong oxidizer	May intensify fire; oxidizer	May intensify fire; oxidizer

2.13.4 Decision logic and guidance

The decision logic and guidance, which follow, are not part of the harmonized classification system, but have been provided here as additional guidance. It is strongly recommended that the person responsible for classification studies the criteria before and during use of the decision logic.

2.13.4.1 *Decision logic*

To classify an oxidizing liquid test method O.2 as described in 34.4.2 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria* should be performed. Classification is according to decision logic 2.13.

2.13.4.2 *Guidance*

2.13.4.2.1 Experience in the handling and use of substances or mixtures which shows them to be oxidizing is an important additional factor in considering classification in this class. In the event of divergence between tests results and known experience, judgement based on known experience should take precedence over test results.

2.13.4.2.2 In some cases, substances or mixtures may generate a pressure rise (too high or too low), caused by chemical reactions not characterising the oxidizing properties of the substance or mixture. In these cases, it may be necessary to repeat the test described in 34.4.2 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria* with an inert substance, e.g. diatomite (kieselguhr), in place of the cellulose in order to clarify the nature of the reaction.

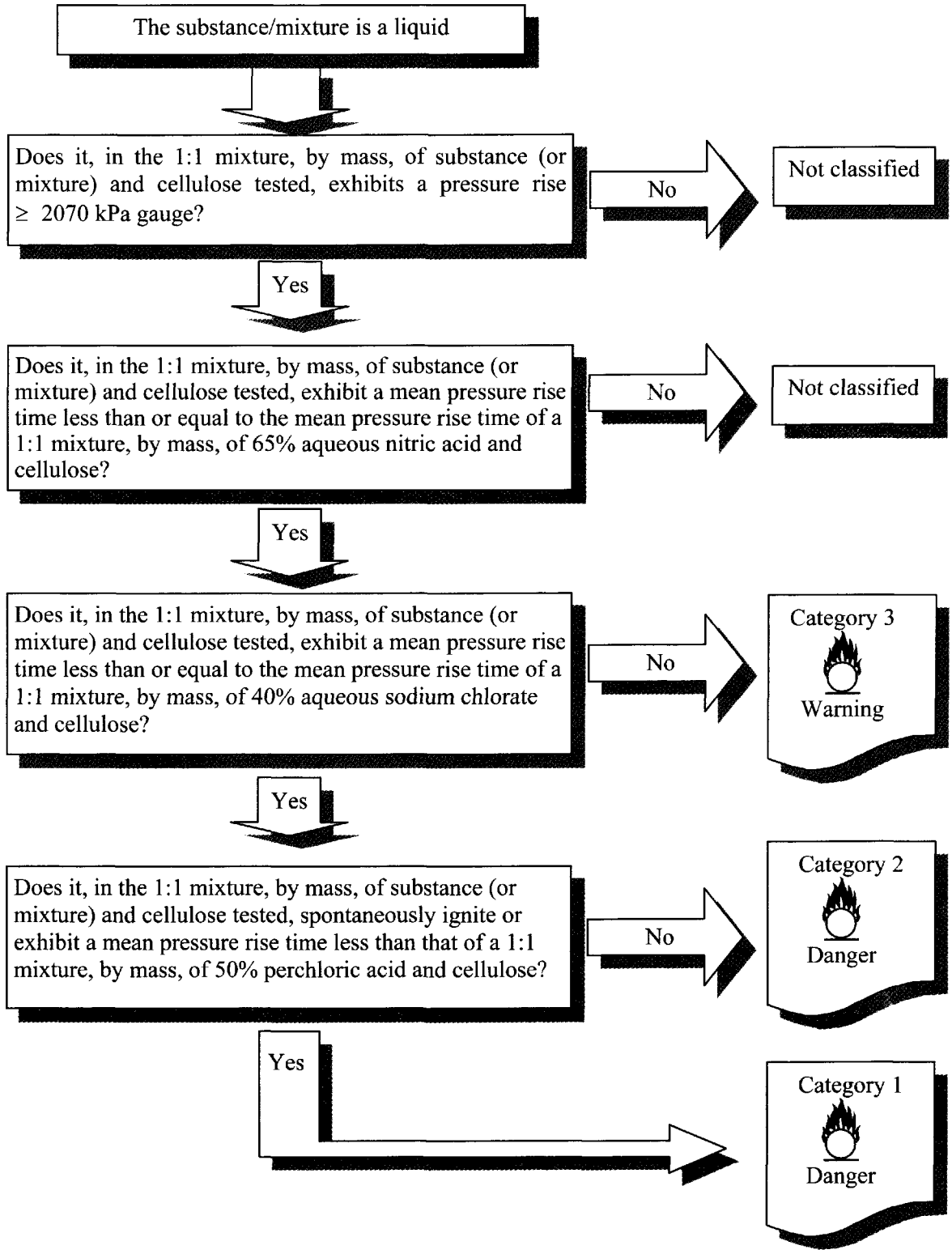
2.13.4.2.3 For organic substances or mixtures the classification procedure for this class need not be applied if:

(a) The substance or mixture does not contain oxygen, fluorine or chlorine; or

(b) The substance or mixture contains oxygen, fluorine or chlorine and these elements are chemically bonded only to carbon or hydrogen.

2.13.4.2.4 For inorganic substances or mixtures, the classification procedure for this class need not be applied if they do not contain oxygen or halogen atoms.

Decision logic 2.13 for oxidizing liquids



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CHAPTER 2.14

OXIDIZING SOLIDS

2.14.1 Definition

An oxidizing solid is a solid which, while in itself is not necessarily combustible, may, generally by yielding oxygen, cause, or contribute to, the combustion of other material.

2.14.2 Classification criteria

An oxidizing solid is classified in one of the three categories for this class using test O.1 in 34.4.1 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* according to the following table:

Table 2.14.1: Criteria for oxidizing solids

Category	Criteria
1	Any substance or mixture which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning time less than the mean burning time of a 3:2 mixture, by mass, of potassium bromate and cellulose.
2	Any substance or mixture which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning time equal to or less than the mean burning time of a 2:3 mixture (by mass) of potassium bromate and cellulose and the criteria for category 1 are not met.
3	Any substance or mixture which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning time equal to or less than the mean burning time of a 3:7 mixture (by mass) of potassium bromate and cellulose and the criteria for categories 1 and 2 are not met.

NOTE: *For classification tests on solid substances or mixtures, the tests should be performed on the substance or mixture as presented. If for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance or mixture must also be tested in the new form.*

2.14.3 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 2.14.2: Label elements for oxidizing solids

	Category 1	Category 2	Category 3
Symbol	Flame over circle	Flame over circle	Flame over circle
Signal word	Danger	Danger	Warning
Hazard statement	May cause fire or explosion; strong oxidizer	May intensify fire; oxidizer	May intensify fire; oxidizer

2.14.4 Decision logic and guidance

The decision logic and guidance, which follow, are not part of the harmonized classification system, but have been provided here as additional guidance. It is strongly recommended that the person responsible for classification studies the criteria before and during use of the decision logic.

2.14.4.1 *Decision logic*

To classify an oxidizing solid test method O.1 as described in 34.4.1 of *the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* should be performed. Classification is according to decision logic 2.14.

2.14.4.2 *Guidance*

2.14.4.2.1 Experience in the handling and use of substances or mixtures which shows them to be oxidizing is an important additional factor in considering classification in this class. In the event of divergence between tests results and known experience, judgement based on known experience should take precedence over test results.

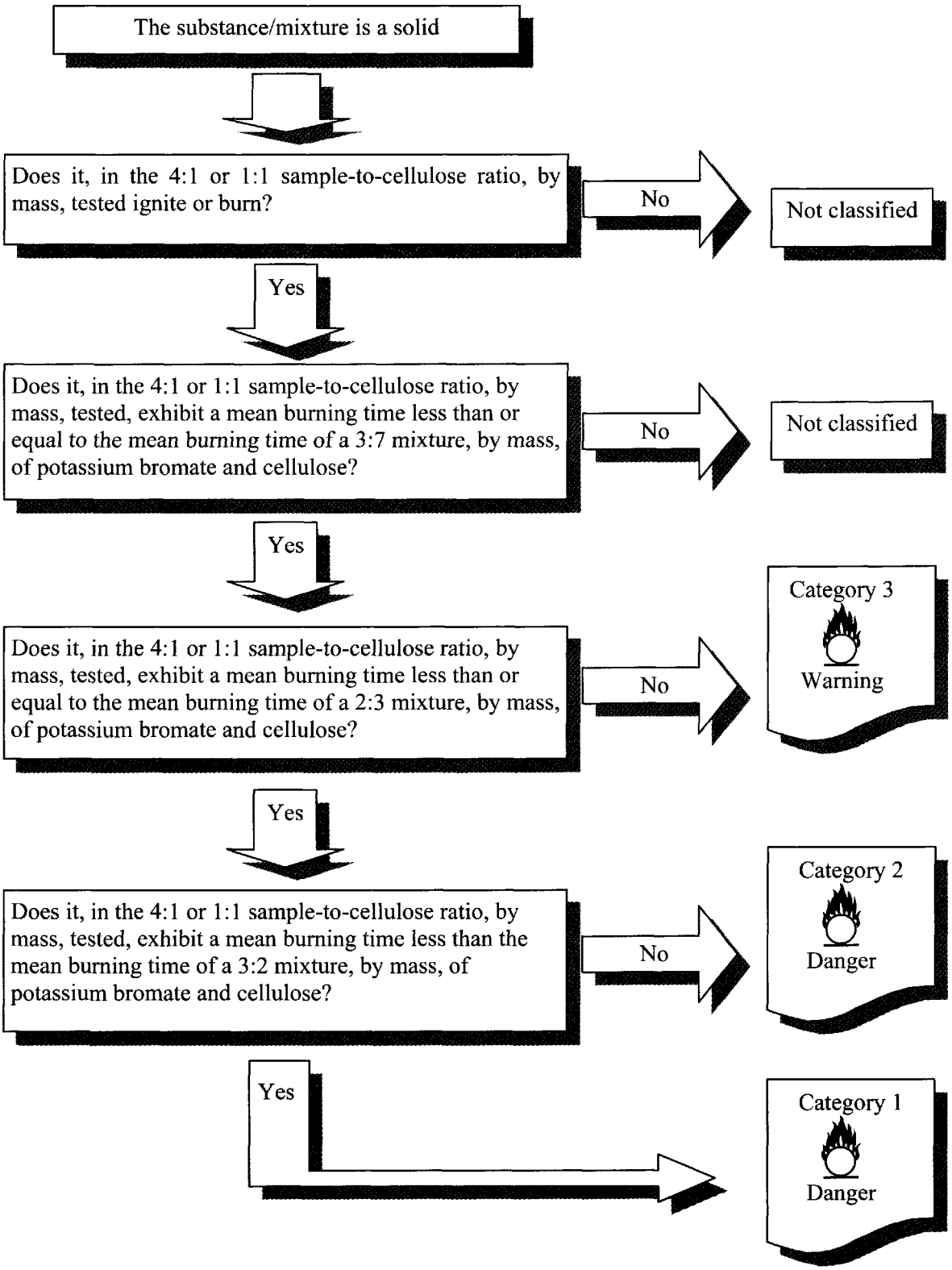
2.14.4.2.2 The classification procedure for this class need not be applied to organic substances or mixtures if:

(a) The substance or mixture does not contain oxygen, fluorine or chlorine; or

(b) The substance or mixture contains oxygen, fluorine or chlorine and these elements are chemically bonded only to carbon or hydrogen.

2.14.4.2.3 The classification procedure for this class need not be applied to inorganic substances or mixtures if they do not contain oxygen or halogen atoms.

Decision logic 2.14 for oxidizing solids



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CHAPTER 2.15

ORGANIC PEROXIDES

2.15.1 Definition

2.15.1.1 Organic peroxides are liquid or solid organic substances which contain the bivalent -0-0- structure and may be considered derivatives of hydrogen peroxide, where one or both of the hydrogen atoms have been replaced by organic radicals. The term also includes organic peroxide formulations (mixtures). Organic peroxides are thermally unstable substances or mixtures, which may undergo exothermic self-accelerating decomposition. In addition, they may have one or more of the following properties:

(a) be liable to explosive decomposition;
(b) burn rapidly;
(c) be sensitive to impact or friction;
(d) react dangerously with other substances.

2.15.1.2 An organic peroxide is regarded as possessing explosive properties when in laboratory testing the formulation is liable to detonate, to deflagrate rapidly or to show a violent effect when heated under confinement.

2.15.2 Classification criteria

2.15.2.1 Any organic peroxide shall be considered for classification in this class, unless it contains:

(a) Not more than 1.0% available oxygen from the organic peroxides when containing not more than 1.0% hydrogen peroxide; or

(b) Not more than 0.5% available oxygen from the organic peroxides when containing more than 1.0% but not more than 7.0% hydrogen peroxide.

NOTE: *The available oxygen content (%) of an organic peroxide mixture is given by the formula:*

$$16 \times \sum_{i}^{n} \left(\frac{n_i \times c_i}{m_i} \right)$$

where: n_i = *number of peroxygen groups per molecule of organic peroxide i;*
c_i = *concentration (mass %) of organic peroxide i;*
m_i = *molecular mass of organic peroxide i.*

2.15.2.2 Organic peroxides are classified in one of the seven categories of "Types A to G" for this class, according to the following principles:

(a) Any organic peroxide which, as packaged, can detonate or deflagrate rapidly will be defined as organic peroxide TYPE A;

(b) Any organic peroxide possessing explosive properties and which, as packaged, neither detonates nor deflagrates rapidly, but is liable to undergo a thermal explosion in that package will be defined as **organic peroxide TYPE B**;

(c) Any organic peroxide possessing explosive properties when the substance or mixture as packaged cannot detonate or deflagrate rapidly or undergo a thermal explosion will be defined as **organic peroxide TYPE C**;

(d) Any organic peroxide which in laboratory testing:

(i) detonates partially, does not deflagrate rapidly and shows no violent effect when heated under confinement; or

(ii) does not detonate at all, deflagrates slowly and shows no violent effect when heated under confinement; or

(iii) does not detonate or deflagrate at all and shows a medium effect when heated under confinement;

will be defined as **organic peroxide TYPE D**;

(e) Any organic peroxide which, in laboratory testing, neither detonates nor deflagrates at all and shows low or no effect when heated under confinement will be defined as **organic peroxide TYPE E**;

(f) Any organic peroxide which, in laboratory testing, neither detonates in the cavitated state nor deflagrates at all and shows only a low or no effect when heated under confinement as well as low or no explosive power will be defined as **organic peroxide TYPE F**;

(g) Any organic peroxide which, in laboratory testing, neither detonates in the cavitated state nor deflagrates at all and shows no effect when heated under confinement nor any explosive power, provided that it is thermally stable (self-accelerating decomposition temperature is 60°C or higher for a 50 kg package), and, for liquid mixtures, a diluent having a boiling point of not less than 150 °C is used for desensitisation, will be defined as **organic peroxide TYPE G**. If the organic peroxide is not thermally stable or a diluent having a boiling point less than 150 °C is used for desensitization, it shall be defined as **organic peroxide TYPE F**.

***NOTE 1**: Type G has no hazard communication elements assigned but should be considered for properties belonging to other hazard classes.*

***NOTE 2:** Types A to G may not be necessary for all systems.*

2.15.3 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 2.15.1: Label elements for organic peroxides

	Type A	Type B	Type C and D	Type E and F	Type G [a]
Symbol	Exploding bomb	Exploding bomb and flame over circle	Flame over circle	Flame over circle	*There are no label elements allocated to this hazard category.*
Signal word	Danger	Danger	Danger	Warning	
Hazard statement	Heating may cause an explosion	Heating may cause a fire or explosion	Heating may cause a fire	Heating may cause a fire	

[a] *Type G has no hazard communication elements assigned but should be considered for properties belonging to other hazard classes.*

2.15.4 Decision logic and guidance

The decision logic and guidance, which follow, are not part of the harmonized classification system, but have been provided here as additional guidance. It is strongly recommended that the person responsible for classification studies the criteria before and during use of the decision logic.

2.15.4.1 *Decision logic*

To classify an organic peroxide test series A to H as described in Part II of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* should be performed. Classification is according to decision logic 2.15.

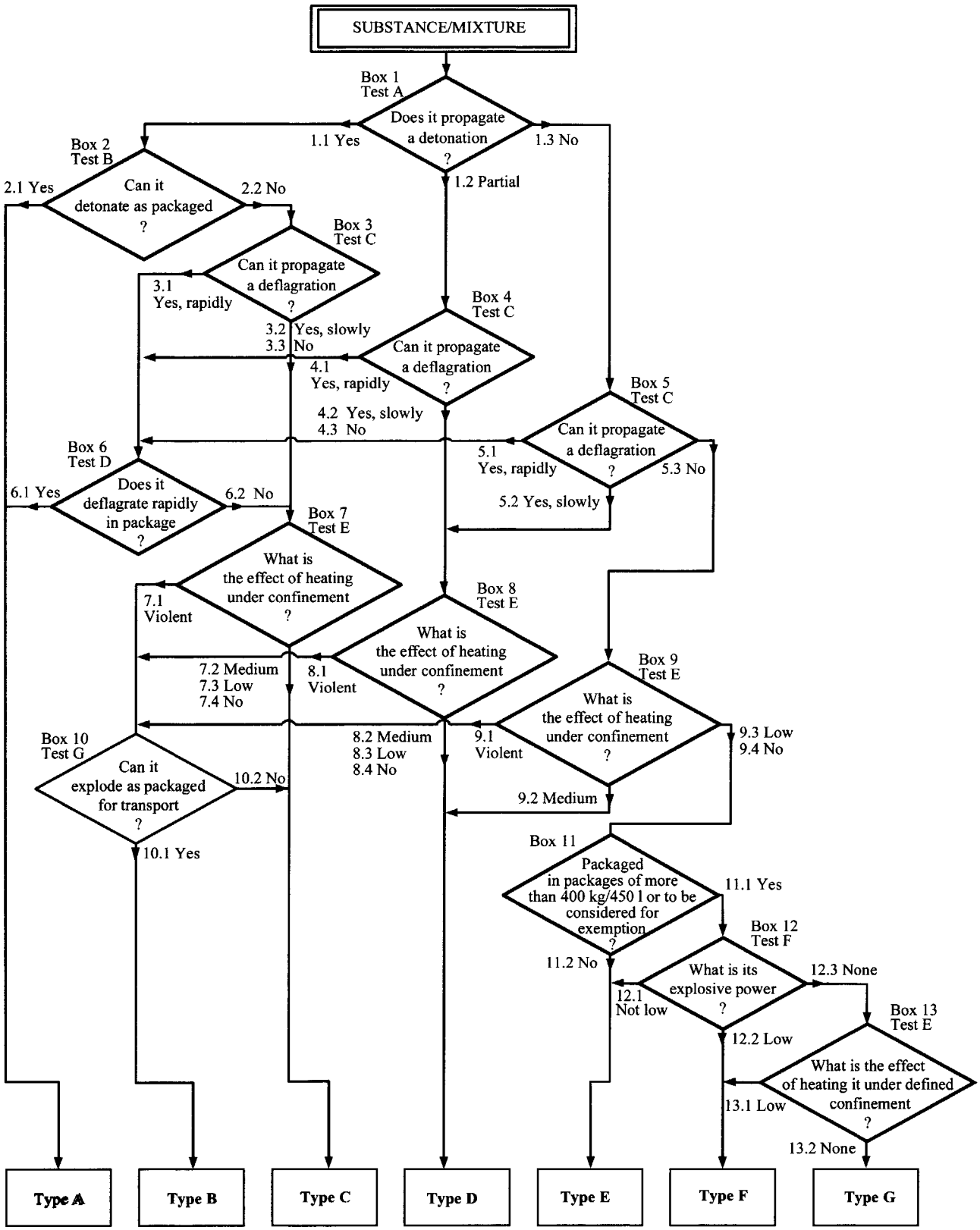
2.15.4.2 *Guidance*

2.15.4.2.1 Organic peroxides are classified by definition based on their chemical structure and on the available oxygen and hydrogen peroxide contents of the mixture (see 2.15.2.1).

2.15.4.2.2 The properties of organic peroxides which are decisive for their classification should be determined experimentally. Test methods with pertinent evaluation criteria are given in the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*, Part II (test series A to H).

2.15.4.2.3 Mixtures of organic peroxides may be classified as the same type of organic peroxide as that of the most dangerous component. However, as two stable components can form a thermally less stable mixture, the self-accelerating decomposition temperature (SADT) of the mixture shall be determined.

Decision logic 2.15 for organic peroxides



CHAPTER 2.16

CORROSIVE TO METALS

2.16.1 Definition

A substance or a mixture that is corrosive to metal is a substance or a mixture which by chemical action will materially damage, or even destroy, metals.

2.16.2 Classification criteria

A substance or a mixture which is corrosive to metal is classified in a single category for this class, using the test in part III, section 37, para.37.4 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of tests and Criteria*, according to the following table

Table 2.16.1: Criteria for substances and mixtures corrosive to metal

Category	Criteria
1	Corrosion rate on steel or aluminium surfaces exceeding 6.25 mm per year at a test temperature of 55 °C.

2.16.3 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 2.16.2: Label elements for substances and mixtures corrosive to metals

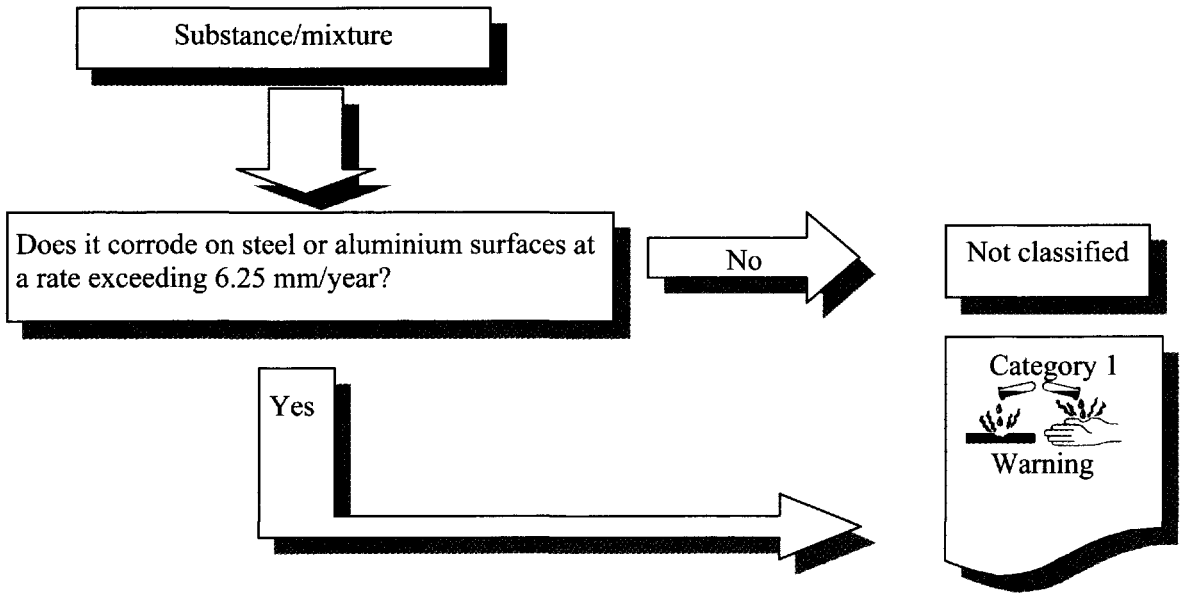
	Category 1
Symbol	Corrosive
Signal word	Warning
Hazard statement	May be corrosive to metals

2.16.4 Decision logic and guidance

The decision logic and guidance, which follow, are not part of the harmonized classification system but have been provided here as additional guidance. It is strongly recommended that the person responsible for classification studies the criteria before and during use of the decision logic.

2.16.4.1 *Decision logic*

Decision Logic 2.16 for substances and mixtures corrosive to metals



2.16.4.2 *Guidance*

The corrosion rate can be measured according to the test method of sub-section 37.4 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of tests and Criteria.* The specimen to be used for the test should be made of the following materials:

(a) For the purposes of testing steel, steel types
S235JR+CR (1.0037 resp.St 37-2),
S275J2G3+CR (1.0144 resp.St 44-3), ISO 3574, Unified Numbering System (UNS) G 10200, or SAE 1020.

(b) For the purposes of testing aluminium: non-clad types 7075-T6 or AZ5GU-T6.

PART 3

HEALTH AND ENVIRONMENTAL HAZARDS

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CHAPTER 3.1

ACUTE TOXICITY

3.1.1 Definition

Acute toxicity refers to those adverse effects occurring following oral or dermal administration of a single dose of a substance, or multiple doses given within 24 hours, or an inhalation exposure of 4 hours.

3.1.2 Classification criteria for substances

3.1.2.1 Chemicals can be allocated to one of five toxicity categories based on acute toxicity by the oral, dermal or inhalation route according to the numeric criteria expressed as (approximate) LD50 (oral, dermal) or LC50 (inhalation) values as shown in the table below. Explanatory notes are shown following the table.

Table 3.1.1: Acute toxicity hazard categories and (approximate) LD50/LC50 values defining the respective categories

Exposure Route	**Category 1**	**Category 2**	**Category 3**	**Category 4**	**Category 5**
Oral (mg/kg bodyweight)	5	50	300	2000	5000
Dermal (mg/kg bodyweight)	50	200	1000	2000	
Gases (ppmV) *see: Note (a)*	100	500	2500	5000	*See detailed criteria in Note (e)*
Vapours (mg/l) *see: Note (a)* *Note (b)* *Note (c)*	0.5	2.0	10	20	
Dusts and Mists (mg/l) *see: Note (a)* *Note (d)*	0.05	0.5	1.0	5	

***NOTE**: Gases concentration are expressed in parts per million per volume (ppmV).*

Notes to Table 3.1.1:

(a) Inhalation cut-off values in the table are based on 4 hour testing exposures. Conversion of existing inhalation toxicity data which has been generated according to 1 hour exposures should be by dividing by a factor of 2 for gases and vapours and 4 for dusts and mists;

(b) It is recognised that saturated vapour concentration may be used as an additional element by some regulatory systems to provide for specific health and safety protection. (e.g. UN Recommendations for the Transport of Dangerous Goods);

(c) For some chemicals the test atmosphere will not just be a vapour but will consist of a mixture of liquid and vapour phases. For other chemicals the test atmosphere may consist of a vapour which is near the gaseous phase. In these latter cases, classification should be based on ppmV as follows: Category 1 (100 ppmV), Category 2 (500 ppmV), Category 3 (2500 ppmV), Category 4 (5000 ppmV). Work in the OECD Test Guidelines Programme should be undertaken to better define the terms "dusts", "mists" and "vapours" in relation to inhalation toxicity testing;

(d) The values for dusts and mists should be reviewed to adapt to any future changes to OECD Test Guidelines with respect to technical limitation in generating, maintaining and measuring dust and mist concentrations in respirable form;

(e) Criteria for Category 5 are intended to enable the identification of substances which are of relatively low acute toxicity hazard but which under certain circumstances may present a danger to vulnerable populations. These substances are anticipated to have an oral or dermal LD_{50} in the range of 2000-5000 mg/kg bodyweight and equivalent doses for inhalation. The specific criteria for Category 5 are:

(i) The substance is classified in this Category if reliable evidence is already available that indicates the LD_{50} (or LC_{50}) to be in the range of Category 5 values or other animal studies or toxic effects in humans indicate a concern for human health of an acute nature.

(ii) The substance is classified in this Category, through extrapolation, estimation or measurement of data, if assignment to a more hazardous category is not warranted, and:

- *reliable information is available indicating significant toxic effects in humans; or*
- *any mortality is observed when tested up to Category 4 values by the oral, inhalation, or dermal routes; or*
- *where expert judgement confirms significant clinical signs of toxicity, when tested up to Category 4 values, except for diarrhoea, piloerection or an ungroomed appearance; or*
- *where expert judgement confirms reliable information indicating the potential for significant acute effects from other animal studies.*

Recognising the need to protect animal welfare, testing in animals in Category 5 ranges is discouraged and should only be considered when there is a strong likelihood that results of such a test would have a direct relevance for protecting human health.

3.1.2.2 The harmonized classification system for *acute toxicity* has been developed in such a way as to accommodate the needs of existing systems. A basic principle set by the IOMC Coordinating Group/Harmonization of Chemical Classification Systems (CG/HCCS) is that "harmonization means establishing a common and coherent basis for chemical hazard classification and communication from which the appropriate elements relevant to means of transport, consumer, worker and environment protection can be selected". To that end, five categories have been included in the acute toxicity scheme.

3.1.2.3 The preferred test species for evaluation of acute toxicity by the oral and inhalation routes is the rat, while the rat or rabbit are preferred for evaluation of acute dermal toxicity. Test data already generated for the classification of chemicals under existing systems should be accepted when reclassifying these chemicals under the harmonized system. When experimental data for acute toxicity are available in several animal species, scientific judgement should be used in selecting the most appropriate LD_{50} value from among valid, well-performed tests.

3.1.2.4 Category 1, the highest toxicity category, has cut-off values (see Table 3.1.1) currently used primarily by the transport sector for classification for packing groups.

3.1.2.5 Category 5 is for chemicals which are of relatively low acute toxicity but which, under certain circumstances, may pose a hazard to vulnerable populations. Criteria for identifying substances in Category 5 are provided in addition to the table. These substances are anticipated to have an oral or dermal LD_{50} value in the range 2000 - 5000 mg/kg bodyweight and equivalent doses for inhalation exposure[1]. In light of animal welfare considerations, testing in animals in Category 5 ranges is discouraged and should only be considered when there is a strong likelihood that results of such testing would have a direct relevance to the protection of human health.

3.1.2.6 *Specific considerations for inhalation toxicity*

3.1.2.6.1 Values for *inhalation toxicity* are based on 4 hours tests in laboratory animals. When experimental values are taken from tests using a 1 hour exposure, they can be converted to a 4 hour equivalent by dividing the 1 hour value by a factor of 2 for gases and vapours and 4 for dusts and mists.

3.1.2.6.2 Units for inhalation toxicity are a function of the form of the inhaled material. Values for dusts and mists are expressed in mg/l. Values for gases are expressed in ppmV. Acknowledging the difficulties in testing vapours, some of which consist of mixtures of liquid and vapour phases, the table provides values in units of mg/l. However, for those vapours which are near the gaseous phase, classification should be based on ppmV. As inhalation test methods are updated, the OECD and other test guideline programs will need to define vapours in relation to mists for greater clarity.

3.1.2.6.3 Vapour inhalation values are intended for use in classification of acute toxicity for all sectors. It is also recognised that the saturated vapour concentration of a chemical is used by the transport sector as an additional element in classifying chemicals for packing groups.

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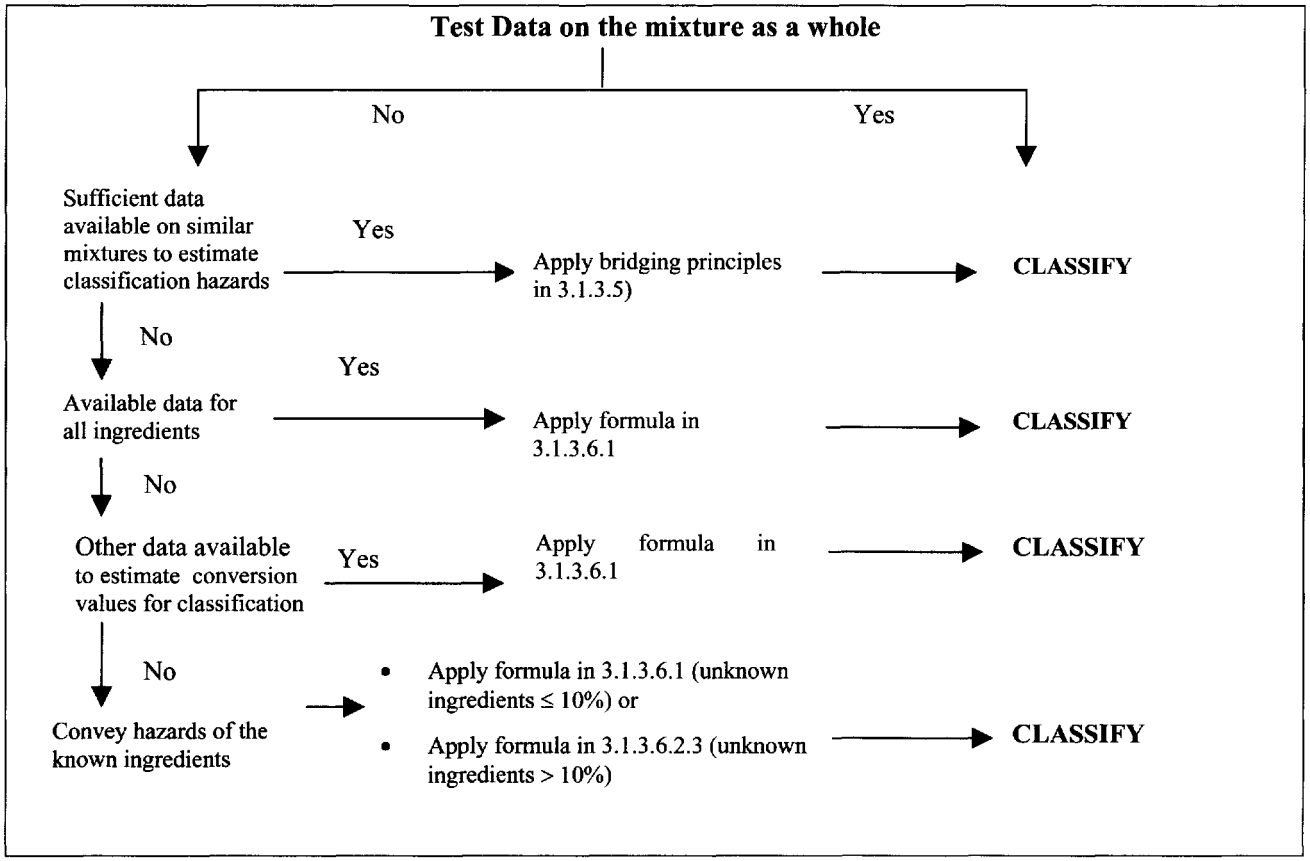
[1] *Guidance on Category 5 Inhalation Values: The OECD Task Force on Harmonisation of Classification and Labelling (HCL) did not include numerical values in Table 3.1.1 above for acute inhalation toxicity class 5 but instead specified doses "equivalent" to the range of 2000-5000 mg/kg bodyweight by the oral or dermal route(see Note (e) of Table 3.1.1). In some systems, the competent authority may prescribe values.*

3.1.3 Classification criteria for mixtures

3.1.3.1 The criteria for substances classify acute toxicity by use of lethal dose data (tested or derived). For mixtures, it is necessary to obtain or derive information that allows the criteria to be applied to the mixture for the purpose of classification. The approach to classification for acute toxicity is tiered, and is dependent upon the amount of information available for the mixture itself and for its ingredients. The flow chart of Figure 3.1.1 below outlines the process to be followed:

Figure 3.1.1: Tiered approach to classification of mixtures for acute toxicity



3.1.3.2 Classification of mixtures for acute toxicity can be carried out for each route of exposure, but is only needed for one route of exposure as long as this route is followed (estimated or tested) for all ingredients. If the acute toxicity is determined for more than one route of exposure, the more severe hazard category will be used for classification. All available information should be considered and all relevant routes of exposure should be identified for hazard communication.

3.1.3.3 In order to make use of all available data for purposes of classifying the hazards of mixtures, certain assumptions have been made and are applied where appropriate in the tiered approach:

(a) The "relevant ingredients" of a mixture are those which are present in concentrations of 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a reason to suspect that an ingredient present at a concentration of less than 1% is still relevant for classifying the mixture for acute toxicity. This point is particularly relevant when classifying untested mixtures which contain ingredients that are classified in Category 1 and Category 2;

(b) The acute toxicity estimate (ATE) for an ingredient in a mixture is derived using:

- The LD_{50}/LC_{50} where available,
- The appropriate conversion value from Table 3.1.2 that relates to the results of a range test for an ingredient, or
- The appropriate conversion value from Table 3.1.2 that relates to a classification category of the ingredient;

(c) Where a classified mixture is used as an ingredient of another mixture, the actual or derived acute toxicity estimate (ATE) for that mixture may be used when calculating the classification of the new mixture using the formulas in 3.1.3.6.1 and 3.1.3.6.2.3.

Table 3.1.2: Conversion from experimentally obtained acute toxicity range values (or acute toxicity hazard categories) to acute toxicity point estimates for the respective routes of exposure

Exposure routes	Classification category or experimentally obtained acute toxicity range estimate (*see Note 1*)	Converted Acute Toxicity point estimate (*see Note 2*)
Oral (mg/kg bodyweight)	0 < Category 1 ≤ 5 5 < Category 2 ≤ 50 50 < Category 3 ≤ 300 300 < Category 4 ≤ 2000 *2000 < Category 5 ≤ 5000*	0.5 5 100 500 2500
Dermal (mg/kg bodyweight)	0 < Category 1 ≤ 50 50 < Category 2 ≤ 200 200 < Category 3 ≤ 1000 1000 < Category 4 ≤ 2000 *2000 < Category 5 ≤ 5000*	5 50 300 1100 2500
Gases (ppmV)	0 < Category 1 ≤ 100 100 < Category 2 ≤ 500 500 < Category 3 ≤ 2500 2500 < Category 4 ≤ 5000 *Category 5 - See footnote to 3.1.2.5.*	10 100 700 3000
Vapours (mg/l)	0 < Category 1 ≤ 0.5 0.5 < Category 2 ≤ 2.0 2.0 < Category 3 ≤ 10.0 10.0 < Category 4 ≤ 20.0 *Category 5 - See footnote to 3.1.2.5.*	0.05 0.5 3 11
Dust/mist (mg/l)	0 < Category 1 ≤ 0.05 0.05 < Category 2 ≤ 0.5 0.5 < Category 3 ≤ 1.0 1.0 < Category 4 ≤ 5.0 *Category 5 - See footnote to 3.1.2.5.*	0.005 0.05 0.5 1.5

***Note**: Gases concentration are expressed in parts per million per volume (ppmV).*

***NOTE 1**: Category 5 is for mixtures which are of relatively low acute toxicity but which under certain circumstances may pose a hazard to vulnerable populations. These mixtures are anticipated to have an oral or dermal LD_{50} value in the range of 2000-5000 mg/kg bodyweight or equivalent dose for other routes of exposure. In light of animal welfare considerations, testing in animals in Category 5 ranges is discouraged and should only be considered when there is a strong likelihood that results of such testing would have a direct relevance for protecting human health.*

***NOTE 2**: These values are designed to be used in the calculation of the ATE for a mixture based on its components and do not represent test results. The values are conservatively set at the lower end of the range of Categories 1 and 2, and at a point approximately $1/10^{th}$ from the lower end of the range for Categories 3 – 5.*

3.1.3.4 *Classification of mixtures where acute toxicity test data are available for the complete mixture*

Where the mixture itself has been tested to determine its acute toxicity, it will be classified according to the same criteria as those used for substances, presented in Table 3.1.1. If test data for the mixture are not available, the procedures presented below should be followed.

3.1.3.5 *Classification of mixtures where acute toxicity test data are not available for the complete mixture: Bridging principles*

3.1.3.5.1 Where the mixture itself has not been tested to determine its acute toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data will be used in accordance with the following agreed bridging rules. This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity for additional testing in animals.

3.1.3.5.2 *Dilution*

If a mixture is diluted with a substance that has an equivalent or lower toxicity classification than the least toxic original ingredient, and which is not expected to affect the toxicity of other ingredients, then the new mixture may be classified as equivalent to the original mixture. Alternatively, the formula explained in paragraph 3.1.3.6.1 could be applied.

If a mixture is diluted with water or other totally non-toxic material, the toxicity of the mixture can be calculated from test data on the undiluted mixture. For example, if a mixture with an LD50 of 1000 mg/kg bodyweight were diluted with an equal volume of water, the LD50 of the diluted mixture would be 2000 mg/kg bodyweight.

3.1.3.5.3 *Batching*

The toxicity of one production batch of a complex mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product, and produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the toxicity of the batch has changed. If the latter occurs, new classification is necessary.

3.1.3.5.4 *Concentration of highly toxic mixtures*

If a mixture is classified in Category 1, and the concentration of the ingredients of the mixture that are in Category 1 is increased, the new mixture should be classified in Category 1 without additional testing.

3.1.3.5.5 *Interpolation within one toxicity category*

For three mixtures with identical ingredients, where A and B are in the same toxicity category and mixture C has the same toxicologically active ingredients with concentrations intermediate to the concentrations of those ingredients in mixtures A and B, then mixture C is assumed to be in the same toxicity category as A and B.

3.1.3.5.6 *Substantially similar mixtures*

Given the following:

(a) Two mixtures: (i) A + B
(ii) C + B;

(b) The concentration of ingredient B is essentially the same in both mixtures;

(c) The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);
(d) Data on toxicity for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the toxicity of B;

If mixture (i) is already classified based on test data, then mixture (ii) can be assigned the same hazard category.

3.1.3.5.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested, non-aerosolised form of the mixture for oral and dermal toxicity provided the added propellant does not affect the toxicity of the mixture on spraying. Classification of aerosolised mixtures for inhalation toxicity should be considered separately.

3.1.3.6 *Classification of mixtures based on ingredients of the mixture (Additivity formula)*

3.1.3.6.1 *Data available for all ingredients*

In order to ensure that classification of the mixture is accurate, and that the calculation need only be performed once for all systems, sectors, and categories, the acute toxicity estimate (ATE) of ingredients should be considered as follows:

- Include ingredients with a known acute toxicity, which fall into any of the GHS acute toxicity categories;
- Ignore ingredients that are presumed not acutely toxic (e.g. water, sugar);
- Ignore ingredients if the oral limit test does not show acute toxicity at 2000 mg/kg bodyweight.

Ingredients that fall within the scope of this paragraph are considered to be ingredients with a known acute toxicity estimate (ATE).

The ATE of the mixture is determined by calculation from the ATE values for all relevant ingredients according to the following formula below for Oral, Dermal or Inhalation Toxicity:

$$\frac{100}{ATEmix} = \sum_{n} \frac{Ci}{ATE_i}$$

where:

C_i = concentration of ingredient i
n ingredients and i is running from 1 to n
ATE_i = Acute Toxicity Estimate of ingredient i.

3.1.3.6.2 *Data are not available for one or more ingredients of the mixture*

3.1.3.6.2.1 Where an ATE is not available for an individual ingredient of the mixture, but available information such as listed below can provide a derived conversion value, the formula in 3.1.3.6.1 may be applied.

This may include evaluation of:

(a) Extrapolation between oral, dermal and inhalation acute toxicity estimates[2]. Such an evaluation could require appropriate pharmacodynamic and pharmacokinetic data;
(b) Evidence from human exposure that indicates toxic effects but does not provide lethal dose data;
(c) Evidence from any other toxicity tests/assays available on the substance that indicates toxic acute effects but does not necessarily provide lethal dose data; or
(d) Data from closely analogous substances using structure/activity relationships.

This approach generally requires substantial supplemental technical information, and a highly trained and experienced expert, to reliably estimate acute toxicity. If such information is not available, proceed to the provisions of 3.1.3.6.2.3.

3.1.3.6.2.2 In the event that an ingredient without any useable information at all is used in a mixture at a concentration of 1% or greater, it is concluded that the mixture cannot be attributed a definitive acute toxicity estimate. In this situation the mixture should be classified based on the known ingredients only, with the additional statement that x percent of the mixture consists of ingredient(s) of unknown toxicity.

3.1.3.6.2.3 If the total concentration of the ingredient(s) with unknown acute toxicity is ≤ 10% then the formula presented in 3.1.3.6.1 should be used. If the total concentration of the ingredient(s) with unknown toxicity is >10%, the formula presented in 3.1.3.6.1 should be corrected to adjust for the total percentage of the unknown ingredient(s) as follows:

$$\frac{100-(\Sigma C_{unknown} \text{ if } >10\%)}{ATEmix}=\sum_{n}\frac{Ci}{ATE_i}$$

[2] *For ingredients with acute toxicity estimates available for other than the most appropriate exposure route, values may be extrapolated from the available exposure route to the most relevant route. Dermal and inhalation route data are not always required for ingredients. However, in case data requirements for specific ingredients include acute toxicity estimates for the dermal and inhalation route, the values to be used in the formula need to be from the required exposure route.*

3.1.4 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. The table below presents specific label elements for substances and mixtures that are classified into acute toxicity Categories 1-5 based on the criteria set forth in this chapter.

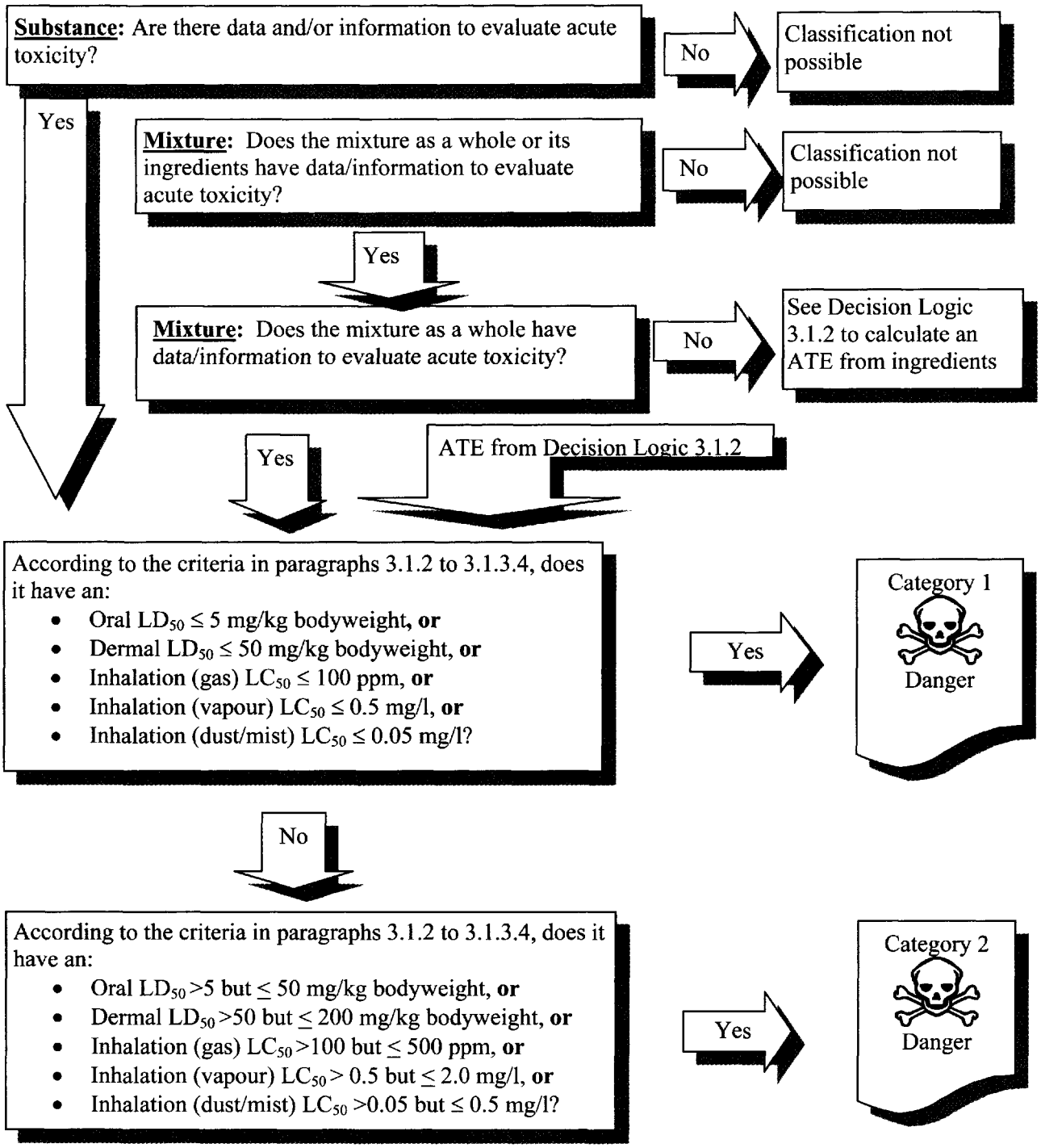
Table 3.1.3: Acute toxicity label elements

	Category 1	Category 2	Category 3	Category 4	Category 5
Symbol	Skull and crossbones	Skull and crossbones	Skull and crossbones	Exclamation mark	No symbol is used
Signal word	Danger	Danger	Danger	Warning	Warning
Hazard statement: **--Oral**	Fatal if swallowed	Fatal if swallowed	Toxic if swallowed	Harmful if swallowed	May be harmful if swallowed
--Dermal	Fatal in contact with skin	Fatal in contact with skin	Toxic in contact with skin	Harmful in contact with skin	May be harmful in contact with skin
--Inhalation	Fatal if inhaled	Fatal if inhaled	Toxic if inhaled	Harmful if inhaled	May be harmful if inhaled

3.1.5 Decision logic

The decision logic which follow is not part of the harmonized classification system but is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

Decision logic 3.1.1 for acute toxicity



Continued on next page

No

According to the criteria in paragraphs 3.1.2 to 3.1.3.4, does it have an:

- Oral LD_{50} >50 but ≤ 300 mg/kg bodyweight, **or**
- Dermal LD_{50} > 200 but ≤ 1000 mg/kg bodyweight, **or**
- Inhalation (gas) LC_{50} >500 but ≤ 2500 ppm, **or**
- Inhalation (vapour) LC_{50} >2 but ≤ 10.0 mg/l, **or**
- Inhalation (dust/mist) LC_{50} >0.5 but ≤ 1.0 mg/l?

Yes → Category 3

Danger

No

According to the criteria in paragraphs 3.1.2 to 3.1.3.4, does it have an:

- Oral LD_{50} >300 but ≤ 2000 mg/kg bodyweight, **or**
- Dermal LD_{50} >1000 but ≤ 2000 mg/kg bodyweight, **or**
- Inhalation (gas) LC_{50} >2500 but ≤ 5000 ppm, **or**
- Inhalation (vapour) LC_{50} >10 but ≤ 20 mg/l, **or**
- Inhalation (dust/mist) LC_{50} >1 but ≤ 5 mg/l?

Yes → Category 4

Warning

No

According to the criteria in paragraphs3.1.2 to 3.1.3.4, does it have an:

- Oral LD_{50} >2000 but ≤ 5000 mg/kg bodyweight, **or**
- Dermal LD_{50} >2000 but ≤ 5000 mg/kg bodyweight, **or**
- Inhalation (gas, vapour and/or dust/mist) LC_{50} in the equivalent range of the oral and dermal LD_{50} (i.e., 2000-5000 mg/kg body weight)?

Yes → Category 5

Warning

No

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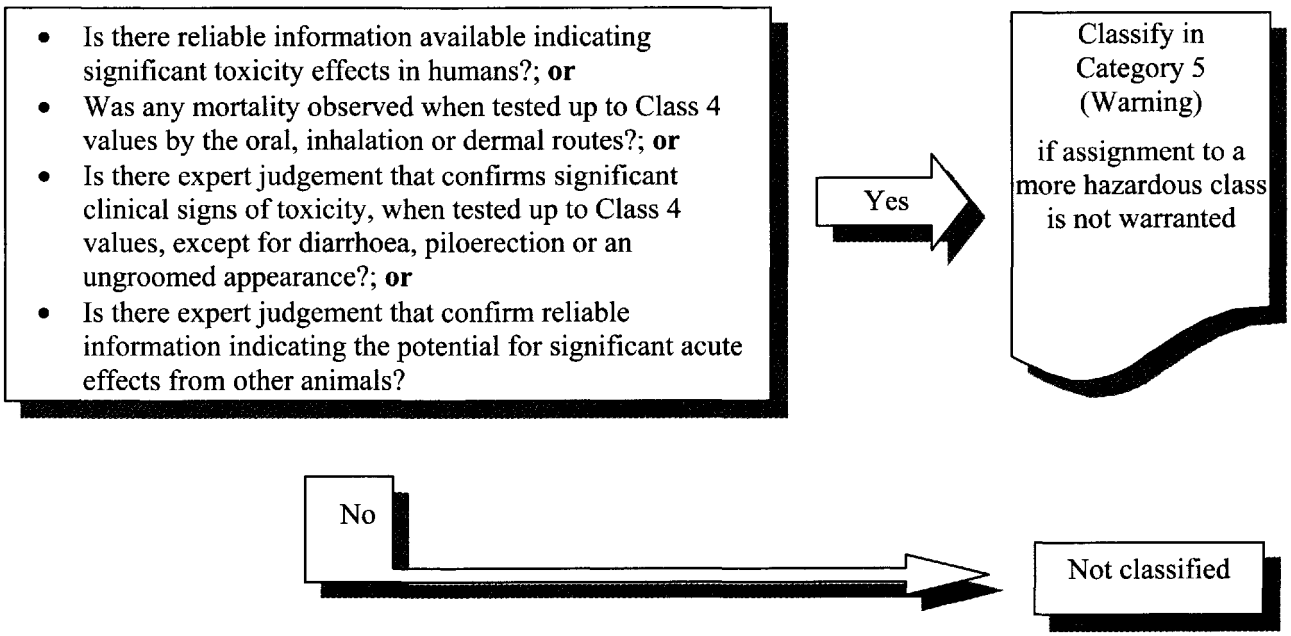
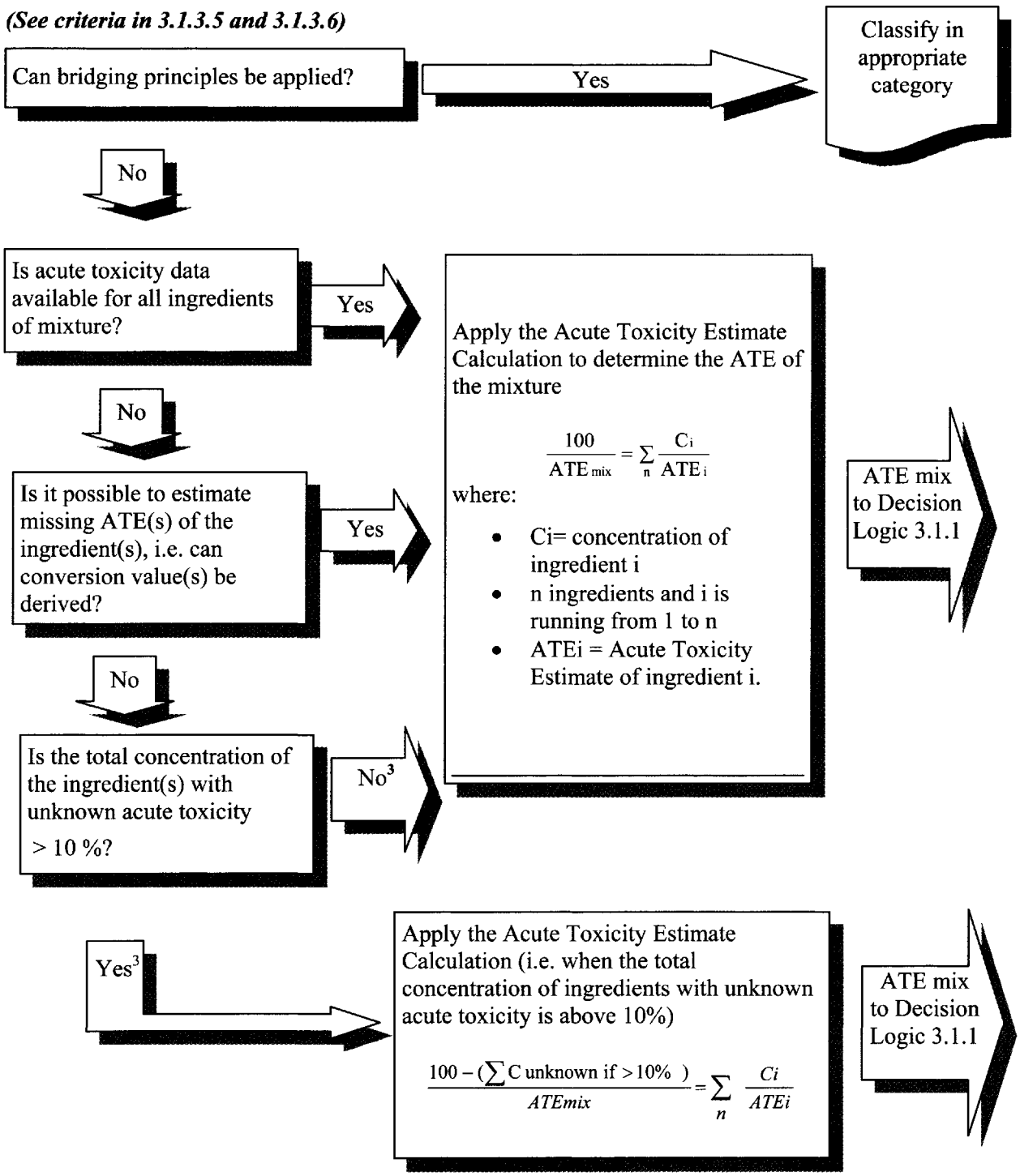

• Is there reliable information available indicating significant toxicity effects in humans?; **or**
• Was any mortality observed when tested up to Class 4 values by the oral, inhalation or dermal routes?; **or**
• Is there expert judgement that confirms significant clinical signs of toxicity, when tested up to Class 4 values, except for diarrhoea, piloerection or an ungroomed appearance?; **or**
• Is there expert judgement that confirm reliable information indicating the potential for significant acute effects from other animals?
Yes
Classify in Category 5 (Warning)
if assignment to a more hazardous class is not warranted
No
Not classified

Decision logic 3.1.2 for acute toxicity

(See criteria in 3.1.3.5 and 3.1.3.6)



[3] *In the event that an ingredient without any useable information is used in a mixture at a concentration ≥ 1%, the classification should be based on the ingredients with the known acute toxicity only, and an additional statement on the label should identify the fact that the acute toxicity of x percent of the mixture is unknown.*

CHAPTER 3.2

SKIN CORROSION/IRRITATION

3.2.1 Definitions

Skin Corrosion is the production of irreversible damage to the skin; namely, visible necrosis through the epidermis and into the dermis, following the application of a test substance for up to 4 hours[1]. Corrosive reactions are typified by ulcers, bleeding, bloody scabs, and, by the end of observation at 14 days, by discolouration due to blanching of the skin, complete areas of alopecia, and scars. Histopathology should be considered to evaluate questionable lesions.

Skin Irritation is the production of reversible damage to the skin following the application of a test substance for up to 4 hours[1].

3.2.2 Classification criteria for substances

3.2.2.1 The harmonized system includes guidance on the use of data elements that are evaluated before animal testing for skin corrosion and irritation is undertaken. It also includes hazard categories for corrosion and irritation.

3.2.2.2 Several factors should be considered in determining the corrosion and irritation potential of chemicals before testing is undertaken. Existing human experience and data including from single or repeated exposure and animal observations and data should be the first line of analysis, as they give information directly relevant to effects on the skin. In some cases enough information may be available from structurally related compounds to make classification decisions. Likewise, pH extremes like ≤ 2 and ≥ 11.5 may indicate skin effects, especially when buffering capacity is known, although the correlation is not perfect. Generally, such agents are expected to produce significant effects on the skin. It also stands to reason that if a chemical is highly toxic by the dermal route, a skin irritation/corrosion study may not be practicable since the amount of test substance to be applied would considerably exceed the toxic dose and, consequently, would result in the death of the animals. When observations are made of skin irritation/corrosion in acute toxicity studies and are observed up through the limit dose, additional testing would not be needed, provided that the dilutions used and species tested are equivalent. *In vitro* alternatives that have been validated and accepted may also be used to help make classification decisions.

All the above information that is available on a chemical should be used in determining the need for *in vivo* skin irritation testing. Although information might be gained from the evaluation of single parameters within a tier (see 3.2.2.3), e.g. caustic alkalis with extreme pH should be considered as skin corrosives, there is merit in considering the totality of existing information and making an overall weight of evidence determination. This is especially true when there is information available on some but not all parameters. Generally, primary emphasis should be placed upon existing human experience and data, followed by animal experience and testing data, followed by other sources of information, but case-by-case determinations are necessary.

3.2.2.3 A *tiered approach* to the evaluation of initial information should be considered, where applicable (Figure 3.2.1), recognising that all elements may not be relevant in certain cases.

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1 *This is a working definition for the purpose of this document.*

Figure 3.2.1: Tiered testing and evaluation of skin corrosion and irritation potential

Step	Parameter	Finding	Conclusion
1a	Existing human or animal experience [g]	Corrosive →	Classify as corrosive [a]
	↓ Not corrosive or no data		
1b	Existing human or animal experience [g]	Irritant →	Classify as irritant [a]
	↓ Not irritant or no data		
1c	Existing human or animal experience	Not corrosive or irritant →	No further testing, not classified
	↓ No data		
2a	Structure-activity relationships or structure-property relationships [b]	Corrosive →	Classify as corrosive [a]
	↓ Not corrosive or no data		
2b	Structure-activity relationships or structure-property relationships [b]	Irritant →	Classify as irritant [a]
	↓ Not irritating or no data		
3	pH with buffering [c]	pH ≤ 2 or ≥ 11.5 →	Classify as corrosive [a]
	↓ Not pH extreme or no data		
4	Existing skin data in animals indicate no need for animal testing [d]	Yes →	Possibly no further testing may be deemed corrosive/ irritant
	↓ No indication or no data		
5	Valid and accepted *in vitro* skin corrosion test [e]	Positive response →	Classify as corrosive [a]
	↓ Negative response or no data		
	↓		

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Figure 3.2.1 *(cont'd):* **Tiered testing and evaluation of skin corrosion and irritation potential**

Step	Parameter	Finding	Conclusion
6	Valid and accepted *in vitro* skin irritation test [(f)]	Positive response	Classify as irritant [(a)]
	↓ Negative response or no data		
7	*In vivo* skin corrosion test (1 animal)	Corrosive response	Classify as corrosive [(a)]
	↓ Negative response		
8	*In vivo* skin irritation test (3 animals total) [(h)]	Non-irritant response	Classify as irritant [(a)]
	↓ Negative response	No further testing	No further testing, not classified
9	When it is ethical to perform human patch testing [(g)]	Irritant response	Classify as irritant [(a)]
	↓ Not as above	Non-irritant response	No further testing, not classified

(a) Classify in the appropriate harmonized category, as shown in Table 3.2.1;

(b) Structure-activity and structure-property relationships are presented separately but would be conducted in parallel;

(c) Measurement of pH alone may be adequate, but assessment of acid or alkali reserve is preferable; methods are needed to assess buffering capacity;

(d) Pre-existing animal data should be carefully reviewed to determine if in vivo skin corrosion/irritation testing is needed. For example, testing may not be needed when a test material has not produced any skin irritation in an acute skin toxicity test at the limit dose, or produces very toxic effects in an acute skin toxicity test. In the latter case, the material would be classified as being very hazardous by the dermal route for acute toxicity; it is moot whether the material is also irritating or corrosive on the skin. It should be kept in mind in evaluating acute skin toxicity information that the reporting of skin lesions may be incomplete, testing and observations may be made on a species other than the rabbit, and species may differ in sensitivity in their responses;

(e) Examples of internationally accepted validated in vitro test methods for skin corrosion are OECD Test Guidelines 430 and 431;

(f) Presently there are no validated and internationally accepted in vitro test methods for skin irritation;

(g) This evidence could be derived from single or repeated exposures. There is no internationally accepted test method for human skin irritation testing, but an OECD guideline has been proposed;

(h) Testing is usually conducted in 3 animals, one coming from the negative corrosion test.

3.2.2.4 *Corrosion*

3.2.2.4.1 A single harmonized *corrosion category* is provided in Table 3.2.1, using the results of animal testing. A corrosive is a test material that produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least_1 of 3 tested animals after exposure up to a 4 hour duration. Corrosive reactions are typified by ulcers, bleeding, bloody scabs and, by the end of observation at 14 days, by discoloration due to blanching of the skin, complete areas of alopecia and scars. Histopathology should be considered to discern questionable lesions.

3.2.2.4.2 For those authorities wanting more than one designation for corrosivity, up to three subcategories are provided within the corrosive category (Category 1, see Table 3.2.1): subcategory 1A - where responses are noted following up to 3 minutes exposure and up to 1 hour observation; subcategory 1B - where responses are described following exposure between 3 minutes and 1 hour and observations up to 14 days; and subcategory 1C - where responses occur after exposures between 1 hour and 4 hours and observations up to 14 days.

Table 3.2.1 Skin corrosive category and subcategories [a]

Category 1: Corrosive	**Corrosive subcategories**	**Corrosive in ≥ 1 of 3 animals**	
(applies to authorities not using subcategories)	(only applies to some authorities)	**Exposure**	**Observation**
corrosive	1A	≤ 3 minutes	≤ 1 hour
	1B	> 3 minutes -- ≤ 1 hour	≤ 14 days
	1C	> 1 hour -- ≤ 4 hours	≤ 14 days

[a] The *use of human data is discussed in 3.2.2.1 and in "Classification of Hazardous Substances and Mixtures" (para. 1.3.2.4.7.1).*

3.2.2.5 *Irritation*

3.2.2.5.1 A single *irritant category* is provided in Table 3.2.2 that

(a) is centrist in sensitivity among existing classifications;
(b) recognises that some test materials may lead to effects which persist throughout the length of the test; and
(c) acknowledges that animal responses in a test may be quite variable. An additional mild irritant category is available for those authorities that want to have more than one skin irritant category.

3.2.2.5.2 Reversibility of skin lesions is another consideration in evaluating irritant responses. When inflammation persists to the end of the observation period in 2 or more test animals, taking into consideration alopecia (limited area), hyperkeratosis, hyperplasia and scaling, then a material should be considered to be an irritant.

3.2.2.5.3 Animal irritant responses within a test can be quite variable, as they are with corrosion. A separate irritant criterion accommodates cases when there is a significant irritant response but less than the mean score criterion for a positive test. For example, a test material might be designated as an irritant if at least 1 of 3 tested animals shows a very elevated mean score throughout the study, including lesions persisting at the end of an observation period of normally 14 days. Other responses could also fulfil this criterion. However, it should be ascertained that the responses are the result of chemical exposure. Addition of this criterion increases the sensitivity of the classification system.

3.2.2.5.4 A single irritant category (Category 2) is presented in the table using the results of animal testing. Authorities (e.g. pesticides) also have available a less severe mild irritant category (Category 3). Several criteria distinguish the two categories (Table 3.2.2). They mainly differ in the severity of skin reactions. The major criterion for the irritant category is that at least 2 tested animals have a mean score of $\geq 2.3 - \leq 4.0$. For the mild irritant category, the mean score cut-off values are $\geq 1.5 - < 2.3$ for at least 2 tested animals. Test materials in the irritant category would be excluded from being placed in the mild irritant category.

Table 3.2.2 Skin irritation categories[a]

Categories	Criteria
Irritant **(Category 2)** (applies to all authorities)	(1) Mean value of $\geq 2.3 - < 4.0$ for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or (2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or (3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.
Mild irritant **(Category 3)** (applies to only some authorities)	Mean value of $\geq 1.5 - < 2.3$ for erythema/eschar or for oedema from gradings in at least 2 of 3 tested animals from grades at 24, 48 and 72 hours or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions (when not included in the irritant category above).

[a] *The use of human data is discussed in 3.2.2.1 and in the "Classification of Hazardous Substances and Mixtures" (1.3.2.4.7.1).*

3.2.3 Classification criteria for mixtures

3.2.3.1 *Classification of mixtures when data are available for the complete mixture*

3.2.3.1.1 The mixture will be classified using the criteria for substances, and taking into account the testing and evaluation strategies to develop data for these hazard classes.

3.2.3.1.2 Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of chemicals that can give an accurate result for classification purposes, as well as being simple and relatively inexpensive to perform. When considering testing of the mixture classifiers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for skin corrosion and irritation to help ensure an accurate classification, as well as avoid unnecessary animal testing. A mixture is considered corrosive (Skin Category 1) if it has a pH of 2 or less or a pH of 11.5 or greater. If consideration of alkali/acid reserve suggests the substance or preparation may not be corrosive despite the low or high pH value, then further testing needs to be carried out to confirm this, preferably by use of an appropriate validated *in vitro* test.

3.2.3.2 *Classification of mixtures when data are not available for the complete mixture: Bridging principles*

3.2.3.2.1 Where the mixture itself has not been tested to determine its skin irritation/corrosion, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data will be used in accordance with the following agreed bridging rules. This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity for additional testing in animals.

3.2.3.2.2 *Dilution*

If a mixture is diluted with a diluent which has an equivalent or lower corrosivity/irritancy classification than the least corrosive/irritant original ingredient and which is not expected to affect the corrosivity/irritancy of other ingredients, then the new mixture may be classified as equivalent to the original mixture. Alternatively, the method explained in section 3.2.3.3 could be applied.

3.2.3.2.3 *Batching*

The irritation/corrosion potential of one production batch of a complex mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product and produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the toxicity of the batch has changed. If the latter occurs, new classification is necessary.

3.2.3.2.4 *Concentration of mixtures of the highest corrosion / irritation category*

If a tested mixture classified in the highest subcategory for corrosion is concentrated, a more concentrated mixture should be classified in the highest corrosion subcategory without additional testing. If a tested mixture classified in the highest category for skin irritation is concentrated and does not contain corrosive ingredients, a more concentrated mixture should be classified in the highest irritation category without additional testing.

3.2.3.2.5 *Interpolation within one toxicity category*

For three mixtures with identical ingredients, where A and B are in the same irritation/ corrosion toxicity category and mixture C has the same toxicologically active ingredients with concentrations intermediate to the concentrations of those ingredients in mixtures A and B, then mixture C is assumed to be in the same irritation/corrosion category as A and B.

3.2.3.2.6 *Substantially similar mixtures*

Given the following:

(a) Two mixtures
  (i) A +B
  (ii) C + B;
(b) The concentration of ingredient B is essentially the same in both mixtures;
(c) The concentration of ingredient A in mixture(i) equals that of ingredient C in mixture (ii);
(d) Data on irritation/corrosion for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the toxicity of B.

If mixture (i) is already classified based on test data, then mixture (ii) can be classified in the same category.

3.2.3.2.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested non-aerosolised form of mixture provided that the added propellant does not affect the irritation or corrosive properties of the mixture upon spraying.

3.2.3.3 *Classification of mixtures when data are available for all components or only for some components of the mixture*

3.2.3.3.1 In order to make use of all available data for purposes of classifying the skin irritation/corrosion hazards of mixtures, the following assumption has been made and is applied where appropriate in the tiered approach:

The "relevant ingredients" of a mixture are those which are present in concentrations of 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a presumption (e.g. in the case of corrosive ingredients) that an ingredient present at a concentration of less than 1% can still be relevant for classifying the mixture for skin irritation/corrosion.

3.2.3.3.2 In general, the approach to classification of mixtures as irritant or corrosive to skin when data are available on the components, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or irritant component contributes to the overall irritant or corrosive properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive components when they are present at a concentration below the concentration limit for classification with Category 1, but are at a concentration that will contribute to the classification of the mixture as an irritant. The mixture is classified as corrosive or irritant when the sum of the concentrations of such components exceeds a cut-off value/concentration limit.

3.2.3.3.3 Table 3.2.3 below provides the cut-off value/concentration limits to be used to determine if the mixture is considered to be an irritant or a corrosive to the skin.

3.2.3.3.4 Particular care must be taken when classifying certain types of chemicals such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in 3.2.3.3.1 and 3.2.3.3.2 might not work given that many of such substances are corrosive or irritant at concentrations < 1%. For mixtures containing strong acids or bases the pH should be used as classification criteria (see 3.2.3.1.2) since pH will be a better indicator of corrosion than the concentration limits of Table 3.2.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach shown in Table 3.2.3, due to chemical characteristics that make this approach unworkable, should be classified as Skin Category 1 if it contains ≥ 1% of a corrosive ingredient and as Skin Category 2/3 when it contains ≥ 3% of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3.2.3 does not apply is summarised in Table 3.2.4 below.

3.2.3.3.5 On occasion, reliable data may show that the skin corrosion/irritation of an ingredient will not be evident when present at a level above the generic concentration cut-off levels mentioned in Tables 3.2.3 and 3.2.4. In these cases the mixture could be classified according to those data (see also *Classification of Hazardous Substances and Mixtures* – Use of Cut-Off Values/Concentration Limits (1.3.3.2)). On occasion, when it is expected that the skin corrosion/irritation of an ingredient will not be evident when present at a level above the generic concentration cut-off levels mentioned in Tables 3.2.3 and 3.2.4, testing of the mixture may be considered. In those cases the tiered weight of evidence strategy should be applied as described in 3.2.3.1.4 and illustrated in Figure 3.2.1.

3.2.3.3.6 If there are data showing that (an) ingredient(s) may be corrosive or irritant at a concentration of < 1% (corrosive) or < 3% (irritant), the mixture should be classified accordingly (see also *Classification of Hazardous Substances and Mixtures – The Use of Cut-Off Values/Concentration Limits* (1.3.3.2)).

Table 3.2.3: Concentration of ingredients of a mixture classified as skin Category 1, 2 or 3 that would trigger classification of the mixture as hazardous to skin (Category 1, 2 or 3)

Sum of ingredients classified as:	**Concentration triggering classification of a mixture as:**		
	Skin corrosive	**Skin irritant**	
	Category 1 (see note below)	**Category 2**	**Category 3**
Skin Category 1	≥5%	≥1% but < 5%	
Skin Category 2		≥10%	≥1% but < 10%
Skin Category 3			≥10%
(10 x Skin Category 1) + Skin Category 2		≥10%	≥1% but <10%
(10 x Skin Category 1) + Skin Category 2 + Skin Category 3			≥10%

***NOTE**: Only some authorities will use the subcategories of Skin Category 1 (corrosive). In these cases, the sum of all ingredients of a mixture classified as Skin Category 1A, 1B or 1C respectively, should each be ≥ 5% in order to classify the mixture as either Skin Category 1A, 1B or 1C. In case the sum of the Skin Category 1A ingredients is < 5% but the sum of Skin Category ingredients 1A+1B is ≥ 5%, the mixture should be classified as Skin Category 1B. Similarly, in case the sum of Skin Category 1A+1B is <5% but the sum of Category 1A+1B+1C is ≥5% the mixture would be classified as Category 1C.*

Table 3.2.4: Concentration of ingredients of a mixture for which the additivity approach does not apply, that would trigger classification of the mixture as hazardous to skin

Ingredient:	Concentration:	Mixture classified as: Skin
Acid with pH ≤ 2	≥ 1%	Category 1
Base with pH ≥11.5	≥ 1%	Category 1
Other corrosive (Category 1) ingredients for which additivity does not apply	≥ 1%	Category 1
Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

3.2.4 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. The table below presents specific label elements for substances and mixtures that are classified as irritating or corrosive to the skin based on the criteria set forth in this chapter.

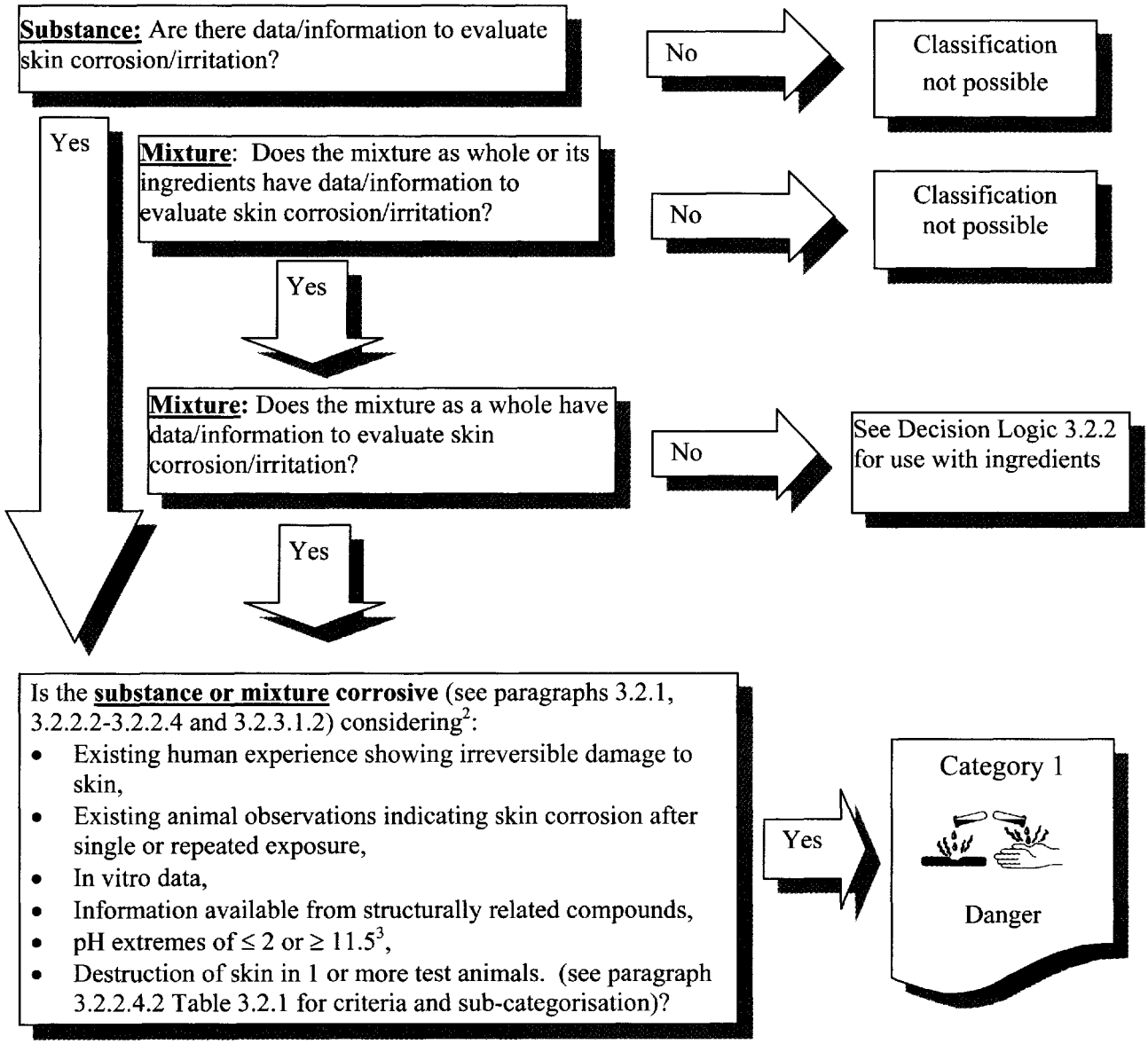
Table 3.2.5: Label elements for skin corrosion/irritation.

	Category 1			Category 2	Category 3
	1 A	**1 B**	**1 C**		
Symbol	Corrosion	Corrosion	Corrosion	Exclamation mark	No symbol is used
Signal word	Danger	Danger	Danger	Warning	Warning
Hazard statement	Causes severe skin burns and eye damage	Causes severe skin burns and eye damage	Causes severe skin burns and eye damage	Causes skin irritation	Causes mild skin irritation

3.2.5 Decision logic

The decision logic which follows is not part of the harmonized classification system but is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

Decision logic 3.2.1 for skin corrosion/irritation:



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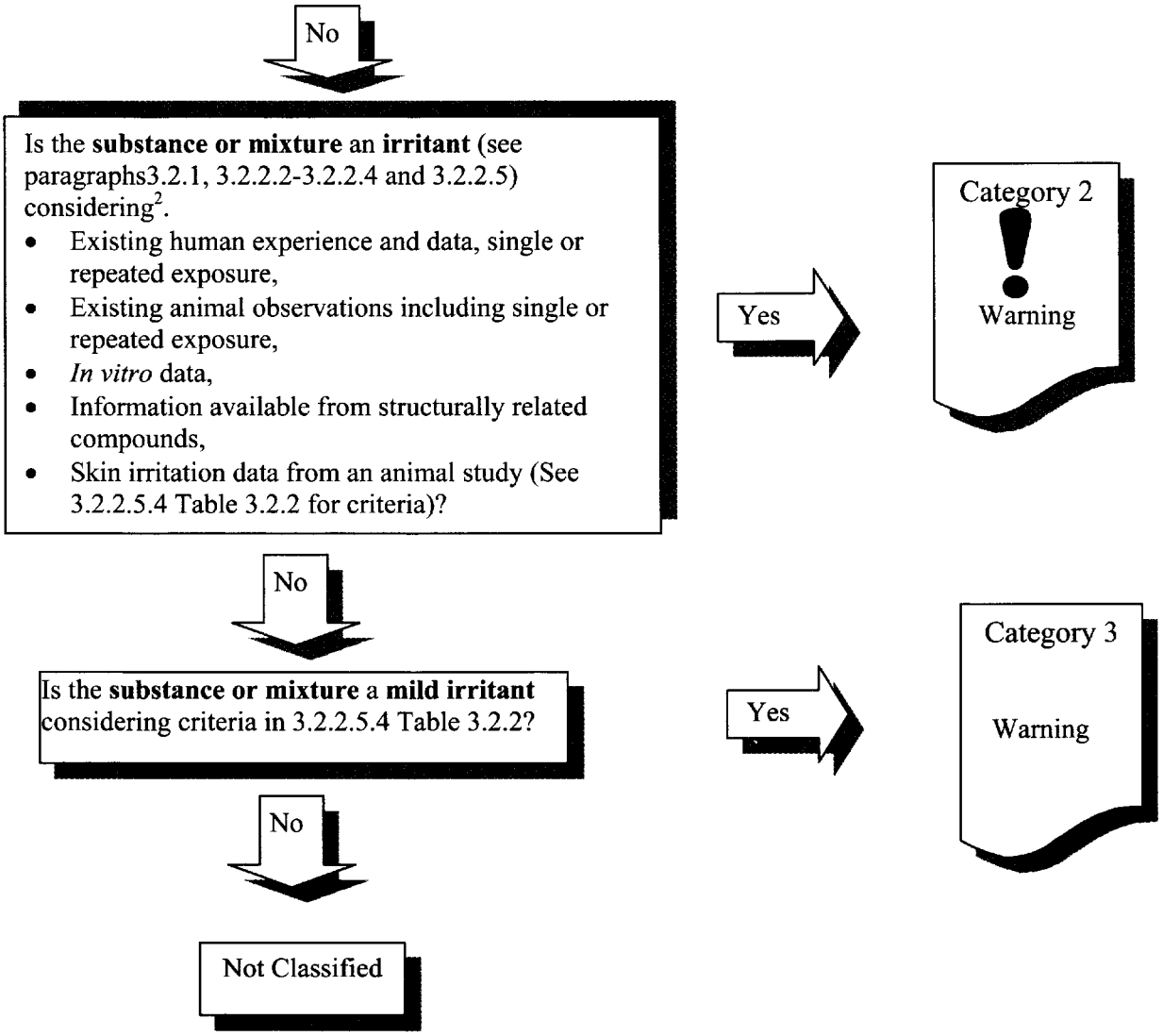
[2] *Figure 3.2.1 contains details for testing and evaluation.*

[3] *Including consideration of acid/alkali reserve capacity, if appropriate.*



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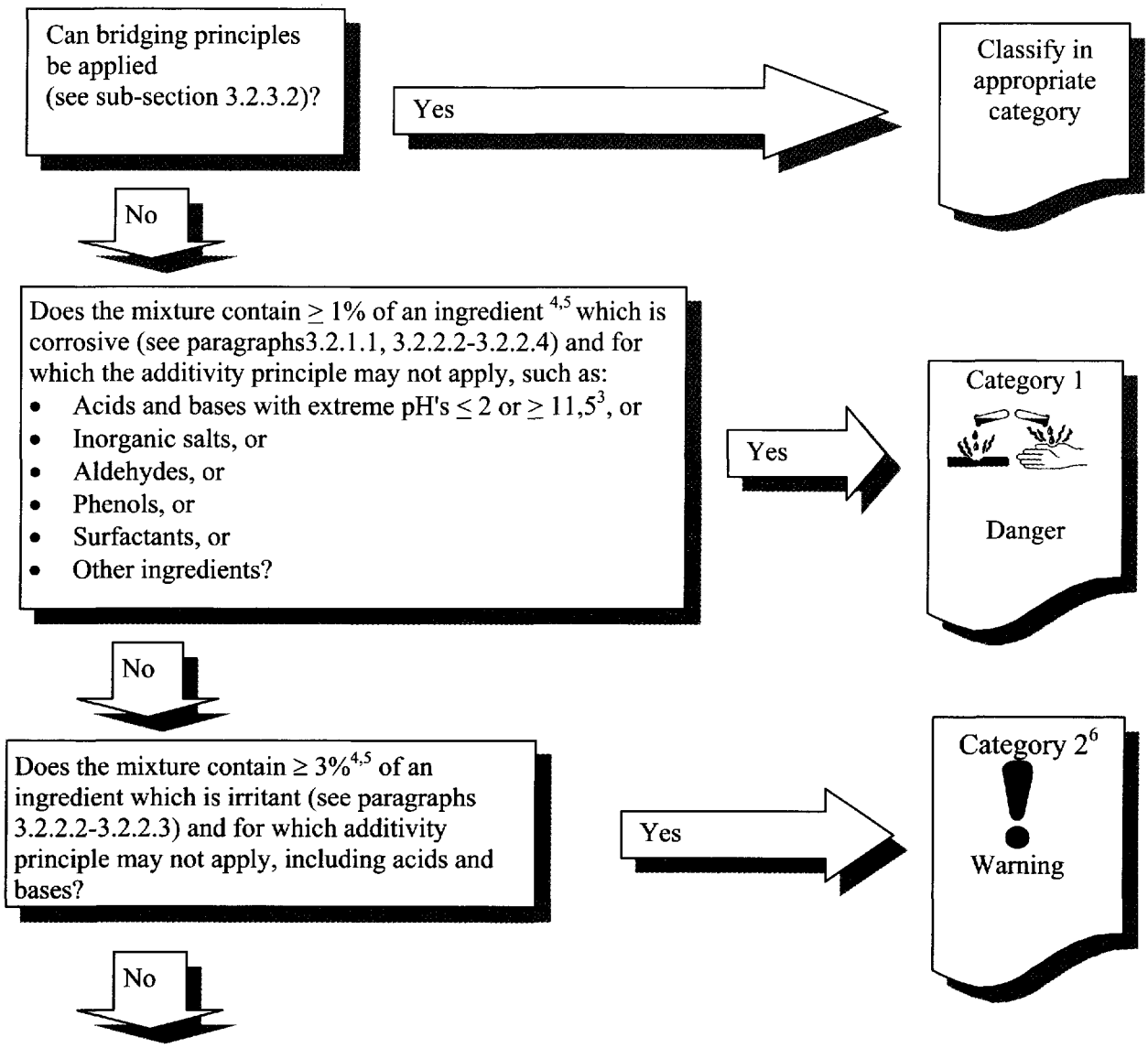
[2] *Figure 3.2.1 contains details for testing and evaluation.*

Decision logic 3.2.2 for skin corrosion/irritation:
Classification of mixtures on the basis of information/data on ingredients



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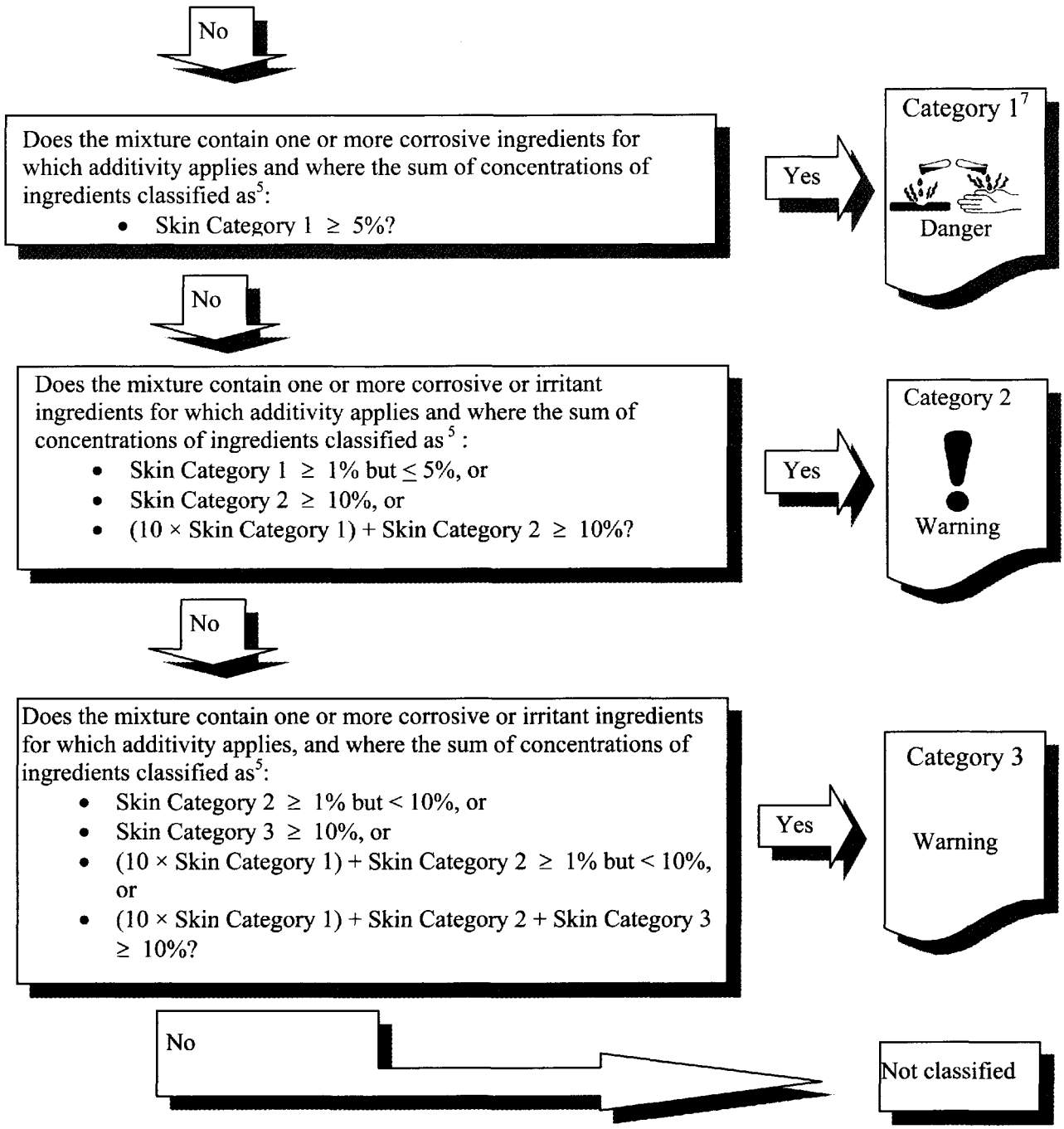
3 *Including consideration of acid/alkali reserve capacity, if appropriate.*

4 *Or where relevant < 1 %, see paragraph 3.2.3.3.1.*

5 *For specific concentration limits, see paragraph 3.2.3.3.6 of this chapter. See also Chapter 1.3, para. 1.3.3.2 for "The use of Cut-off Values/Concentration Limits".*

6 *If the mixture also contains corrosive or irritant ingredient(s) for which additivity applies, move to the box below.*



[5] *For specific concentration limits, see paragraph 3.2.3.3.6 of this chapter. See also Chapter 1.3, para. 1.3.3.2, for "The Use of Cut-off Values/Concentration Limits".*

[7] *See note to Table 3.2.3 for details on use of Category 1 subcategories.*

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CHAPTER 3.3

SERIOUS EYE DAMAGE /EYE IRRITATION

3.3.1 Definitions

Serious eye damage is the production of tissue damage in the eye, or serious physical decay of vision, following application of a test substance to the anterior surface of the eye, which is not fully reversible within 21 days of application [1].

Eye irritation is the production of changes in the eye following the application of test substance to the anterior surface of the eye, which are fully reversible within 21 days of application[1]

3.3.2 Classification criteria for substances

3.3.2.1 A tiered testing and evaluation scheme is presented that combines pre-existing information on serious ocular tissue damage and on eye irritation (including data relating to historical human or animal experience) as well as considerations on structure-activity relationships (SAR) or structure-property relationships (SPR) and the output of validated *in vitro* tests in order to avoid unnecessary animal testing.

3.3.2.2 The proposals for classification of eye irritation and serious damage to the eye include elements that are harmonized and will be used by all authorities as well as optional subcategories that will be applied by only some authorities (e.g. authorities classifying pesticides).

The harmonized system includes guidance on the data elements that must be evaluated before animal testing for eye damaging effects is undertaken. It also includes hazard categories for local lesions on the eyes.

3.3.2.3 Before there is any *in vivo* testing for serious eye damage/ eye irritation, all existing information on a test material should be reviewed. Preliminary decisions can often be made from existing data as to whether an agent causes serious (i.e. irreversible) damage to the eyes. If a test material can be classified, no testing is required. A highly recommended way of evaluating existing information on agents or of approaching new uninvestigated substances, is to utilise a tiered testing strategy for serious eye damage and eye irritation.

3.3.2.4 Several factors should be considered in determining the serious eye damage or irritation potential of chemicals before testing is undertaken. Accumulated human and animal experience should be the first line of analysis, as it gives information directly relevant to effects on the eye. In some cases enough information may be available from structurally related compounds to make hazard decisions. Likewise, pH extremes like ≤ 2 and ≥ 11.5, may produce serious eye damage, especially when associated with significant buffering capacity. Such agents are expected to produce significant effects on the eyes. Possible skin corrosion has to be evaluated prior to consideration of serious eye damage/eye irritation in order to avoid testing for local effects on eyes with skin corrosive substances. *In vitro* alternatives that have been validated and accepted may be used to make classification decisions.

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[1] *This is a working definition for the purpose of this document.*

3.3.2.5 All the above information that is available on a chemical should be used in determining the need for *in vivo* eye irritation testing. Although information might be gained from the evaluation of single parameters within a tier (e.g. caustic alkalis with extreme pH should be considered as local corrosives), there is merit in considering the totality of existing information and making an overall weight of evidence determination. This is especially true when there is information available on some but not all parameters. Generally, primary emphasis should be placed upon expert judgement, considering human experience with the substance, followed by the outcome of skin irritation testing and of well validated alternative methods. Animal testing with corrosive substances should be avoided whenever possible.

3.3.2.6 A tiered approach to the evaluation of initial information should be considered where applicable, recognising that all elements may not be relevant in certain cases. The tiered approach explained in Figure 3.3.1 was developed with contributions from (inter)national centres and committees for the testing and validation of alternatives to animal testing during a workshop in Solna, Sweden[2].

3.3.2.7 Where data needed for such a testing strategy cannot be required, the proposed tiered testing approach provides good guidance on how to organise existing information on a test material and to make a weight-of-evidence decision about hazard assessment and hazard classification - ideally without conducting new animal tests.

Figure 3.3.1: Testing and evaluation strategy for serious eye damage and eye irritation

(see also: "Testing and evaluation strategy for skin irritation/corrosion" Figure 3.2.1)

Step	Parameter	Findings	Conclusions
1a	Data relating to historical human or animal experience ↓	Serious eye damage →	Category 1
		Eye irritant →	Category 2
	No or don't know ↓		
1b	Data relating to historical human or animal experience ↓	Skin corrosive →	No evaluation of effects on eyes; deemed to be Category 1
	No or don't know ↓		

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[2] *OECD (1996). Final Report of the OECD Workshop on Harmonisation of Validation and Acceptance Criteria for Alternative Toxicological Test Methods. Document ENV/MC/TG(96)9 (http://www.oecd.org/ehs/test/background.htm).*

Figure 3.3.1 *(cont'd)*: **Testing and evaluation strategy for serious eye damage and eye irritation**

	Parameter	Findings	Conclusions
1c	Data relating to historical human or animal experience →	Skin irritant →	No evaluation of effects on eyes; deemed to be Category 2
	↓ No or don't know ↓		
2a	Structure activity relationships/Structure property relationships (SAR/SPR) →	Severe damage to eyes →	Category 1
	↓ No or don't know ↓		
2b	Structure activity relationships/Structure property relationships (SAR/SPR) →	Eye irritant →	No evaluation of effects on eyes; deemed to be Category 2
	↓ No or don't know ↓		
2c	Structure activity relationships/Structure property relationships (SAR/SPR) →	Skin corrosive →	No evaluation of effects on eyes; deemed to be Category 1
	↓ No or don't know ↓		
3a	pH/acid or alkaline reserve →	PH ≥ 11.5 or pH ≤ 2 (considering acid or alkaline reserve) →	Category 1
	↓		
3b	2 < pH < 11.5 (no buffering potential) ↓		
4	Other information indicating the material is a skin corrosive →	Yes →	No evaluation of effects on eyes; deemed to be Category 1
	↓ No		

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Figure 3.3.1 *(cont'd)*: **Testing and evaluation strategy for serious eye damage and eye irritation**

Step	Parameter	Findings	Conclusions
	No ↓		
5	Is a valid *in vitro* test available to assess severe damage to eyes ↓	→ No	→ Go to step 6
5a	*In vitro* test for severe eye irritation ↓	→ Severe damage to eyes	→ Category 1
	Not a severe eye irritant ↓		
6	Is a valid *in vitro* test for eye irritation available → No ↓	- But *in vitro* test for severe eye irritancy was negative - In the absence of any *in vitro* test	→ Go to step 8 → Go to Step 7
	Yes ↓		
6a	*In vitro* eye irritation test ↓	→ Eye irritant	→ Category 2
	No indication of eye irritant properties ↓		
7	Experimentally assess skin corrosion potential (see Testing Strategy for Skin Irritation/Corrosion) ↓	→ Skin corrosive	→ No evaluation of effects on eyes, deemed to be category 1
	Not corrosive ↓		
8	1 rabbit eye test ↓	→ Serious damage to eyes	→ Category 1
	No serious damage ↓		
9	1 or 2 further rabbits →	Eye irritant	→ Category 2
	↓ →	Not an eye irritant	→ Not classified

NOTES to Figure 3.3.1:

Step 1a/b: *Data relating to historical human or animal experience: pre-existing information on eye irritation and skin corrosion are shown separately because evaluation of skin corrosion has to be considered if there is no information on local effects on eyes. Analysis of pre-existing experience with the chemical may identify serious eye damage, corrosion and irritation potential for both skin and eye effects:*

(i) *Step 1a - reliable determination of eye irritancy basing on human or animal experience - depends on expert judgement: in most cases human experience is based on accidental events and thus, the local effects detected after an accident have to be compared with classification criteria created for evaluation of animal test data;*

(ii) *Step 1b - evaluation of data on skin corrosivity - skin corrosive substances should not be instilled into the eyes of animals; such substances should be considered as leading to serious damage to the eyes as well (Category 1).*

Step 2a/b: *SAR (Structure Activity Relationships) / SPR (Structure Property Relationships) for eye irritation and skin corrosion are shown separately but in reality would probably be done in parallel. This stage should be completed using validated and accepted SAR/SPR approaches. The SAR/SPR analysis may identify serious eye damage, corrosion and irritation potential for both skin and eye effects: i) Step 2a - reliable determination of eye irritancy only by theoretical evaluations - in most cases it will only be appropriate for substances that are homologous to agents with very well known properties. ii) Step 2c - theoretical evaluation of skin corrosivity - skin corrosive substances should not be instilled into the eyes of animals; such substances should be considered as leading to serious damage to the eyes as well (Category 1).*

Step 3: *pH extremes like <2 and >11.5 may indicate strong local effects, especially in combination with assessment of acid or alkaline reserve, substances exhibiting such physico-chemical properties should be considered as leading to serious damage to eyes (Category 1).*

Step 4: *All attainable information should be used, including human experience. But this information should be restricted to that which pre-exists (e.g. the results of a skin LD_{50} test or historical information on skin corrosion).*

Step 5: *These must be alternative methods for the assessment of eye irritation/ or serious damage to eyes (e.g. irreversible corneal opacity) which have been validated in accordance with internationally agreed principles and criteria (see para. 1.3.2 in Chapter 1.3).*

Step 6: *At present this step seems not to be achievable in the near future. Validated alternative methods for the reliable assessment of (reversible) eye irritation need to be developed.*

Step 7: *In the absence of any other relevant information, it is essential to obtain this via an internationally recognised corrosion/irritation test before proceeding to a rabbit eye irritation test. This must be conducted in a staged manner. If possible, this should be achieved using a validated, accepted in vitro skin corrosivity assay. If this is not available, then the assessment should be completed using animal tests (see the skin irritation/ corrosion strategy, para 3.2.2).*

Step 8: *Staged assessment of eye irritation in vivo. If in a limit test with one rabbit serious damage to eyes is detected no further testing is needed.*

Step 9: *Only two animals may be employed for irritation testing (including the one used for evaluation of possible serious effects) if these two animals give concordant clearly irritant or clearly non-irritant responses. In the case of different or borderline responses a third animal is needed. Depending on the result of this three-animal test, classification may be required or not.*

3.3.2.8 *Irreversible effects on the eye / serious damage to eyes (Category 1)*

A single harmonized hazard category is adopted for substances that have the potential to seriously damage the eyes. This hazard category - Category 1 (irreversible effects on the eye) - includes the criteria listed below. These observations include animals with grade 4 cornea lesions and other severe reactions (e.g. destruction of cornea) observed at any time during the test, as well as persistent corneal opacity, discoloration of the cornea by a dye substance, adhesion, pannus, and interference with the function of the iris or other effects that impair sight. In this context, persistent lesions are considered those which are not fully reversible within an observation period of normally 21 days. Hazard classification: Category 1 also contains substances fulfilling the criteria of corneal opacity ≥ 3 or iritis > 1.5 detected in a Draize eye test with rabbits, because severe lesions like these usually do not reverse within a 21 days observation period.

Table 3.3.1: Irreversible eye effects categories

An eye irritant Category 1 (irreversible effects on the eye) is a test material that produces:
- at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or - at least in 2 of 3 tested animals, a positive response of: corneal opacity ≥ 3 and/or iritis > 1.5 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the testmaterial.

The use of human data is discussed in *Purpose, Scope and Application* (Chapter 1.1, para. 1.1.2.5 (c)) and *Classification of Hazardous Substances and Mixtures* (Chapter 1.3, para. .3.2.4.7).

3.3.2.9 *Reversible effects on the eye (Category 2)*

A single category is adopted for substances that have the potential to induce reversible eye irritation. This single hazard category provides the option to identify within the category a sub-category for substances inducing eye irritant effects reversing within an observation time of 7 days.

Those authorities desiring one single category for classification of "eye irritation" may use the overall harmonized Category 2 (irritating to eyes); others may want to distinguish between Category 2A (irritating to the eyes) and Category 2B (mildly irritating to eyes).

Table 3.3.2: Reversible eye effects categories

An eye irritant Category 2A (irritating to eyes) is a test material that produces: - at least in 2 of 3 tested animals a positive response of: corneal opacity ≥ 1 and/or iritis ≥ 1, and/or conjunctival redness ≥ 2, and/or conjunctival oedema (chemosis) ≥ 2 - calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and - which fully reverses within an observation period of normally 21 days Within this category an eye irritant is considered **mildly irritating to eyes (Category 2B)** when the effects listed above are fully reversible within 7 days of observation.

For those chemicals where there is pronounced variability among animal responses, this information may be taken into account in determining the classification.

3.3.3 Classification criteria for mixtures

3.3.3.1 *Classification of mixtures when data are available for the complete mixture*

The mixture will be classified using the criteria for substances, and taking into account the testing and evaluation strategies used to develop data for these hazard classes.

Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of chemicals that can give an accurate result for classification purposes, as well as being simple and relatively inexpensive to perform. When considering testing of the mixture manufacturers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for skin corrosion and serious eye damage and eye irritation to help ensure an accurate classification, as well as avoid unnecessary animal testing. A mixture is considered to cause serious eye damage (Eye Category 1) if it has a pH of 2 or less or 11.5 or greater. If consideration of alkali/acid reserve suggests the substance or preparation may not have the potential to cause serious eye damage despite the low or high pH value, then further testing needs to be carried out to confirm this, preferably by use of an appropriate validated *in vitro* test.

3.3.3.2 *Classification of mixtures when data are not available for the complete mixture: Bridging principles*

3.3.3.2.1 Where the mixture itself has not been tested to determine its skin corrosivity or potential to cause serious eye damage or irritation, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data will be used in accordance with the following agreed bridging rules. This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity for additional testing in animals.

3.3.3.2.2 *Dilution*

If a mixture is diluted with a diluent which has an equivalent or lower classification for serious eye damage/irritancy classification than the least damaging/irritant original ingredient and which is not expected to affect the corrosivity/irritancy of other ingredients, then the new mixture may be classified as equivalent to the original mixture. Alternatively, the method explained in 3.3.3.3 could be applied.

3.3.3.2.3 *Batching*

The irritation/serious eye damage potential of one production batch of a complex mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product and produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the toxicity of the batch has changed. If the latter occurs, new classification is necessary.

3.3.3.2.4 *Concentration of mixtures of the highest serious eye damage/ irritation class*

If a tested mixture classified in the highest category for serious eye damage is concentrated, a more concentrated mixture should be classified in the highest serious eye damage category without additional testing. If a tested mixture classified in the highest subcategory for skin/eye irritation is concentrated and does not contain serious eye damage ingredients, a more concentrated mixture should be classified in the highest irritation category without additional testing.

3.3.3.2.5 *Interpolation within one toxicity category*

For three mixtures with identical ingredients, where A and B are in the same irritation/ serious eye damage toxicity category and mixture C has the same toxicologically active ingredients with concentrations intermediate to the concentrations of those ingredients in mixtures A and B, then mixture C is assumed to be in the same irritation/serious eye damage category as A and B.

3.3.3.2.6 *Substantially similar mixtures*

Given the following:

(a) Two mixtures (i) A +B
(ii) C + B;
(b) The concentration of ingredient B is essentially the same in both mixtures;
(c) The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);
(d) Data on irritation/serious eye damage for A and C are available and substantially equivalent, i.e. if mixture (i) is already classified by testing, mixture (ii) can be assigned in the same category.

3.3.3.2.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested non-aerosolised form of mixture provided that the added propellant does not affect the irritation or corrosive properties of the mixture upon spraying[3].

[3] *Bridging principles apply for the intrinsic hazard classification of aerosols, however, the need to evaluate the potential for "mechanical" eye damage from the physical force of the spray is recognised.*

3.3.3.3 *Classification of mixtures when data are available for all components or only for some components of the mixture*

3.3.3.3.1 In order to make use of all available data for purposes of classifying the eye irritation/serious eye damaging properties of the mixtures, the following assumption has been made and is applied where appropriate in the tiered approach:

The "relevant ingredients" of a mixture are those which are present in concentrations of 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a presumption (e.g. in the case of corrosive ingredients) that an ingredient present at a concentration of less than 1% can still be relevant for classifying the mixture for eye irritation/serious eye damage.

3.3.3.3.2 In general, the approach to classification of mixtures as eye irritant or seriously damaging to the eye when data are available on the components, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or irritant component contributes to the overall irritant or corrosive properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive components when they are present at a concentration below the concentration limit for classification with Category 1, but are at a concentration that will contribute to the classification of the mixture as an irritant. The mixture is classified as seriously damaging to the eye or eye irritant when the sum of the concentrations of such components exceeds a threshold cut-off value/concentration limit.

3.3.3.3.3 Table 3.3.3 provides the cut-off value/concentration limits to be used to determine if the mixture should be classified an irritant or a seriously damaging to the eye.

3.3.3.3.4 Particular care must be taken when classifying certain types of chemicals such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in paragraphs 3.3.3.3.1 and 3.3.3.3.2 might not work given that many of such substances are corrosive or irritant at concentrations < 1 %. For mixtures containing strong acids or bases the pH should be used as classification criteria (see paragraph 3.3.3.1) since pH will be a better indicator of serious eye damage than the concentration limits of Table 3.3.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach applied in Table 3.3.3 due to chemical characteristics that make this approach unworkable, should be classified as Eye Category 1 if it contains ≥ 1% of a corrosive ingredient and as Eye Category 2 when it contains ≥ 3% of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3.3.3 does not apply is summarised in Table 3.3.4.

3.3.3.3.5 On occasion, reliable data may show that the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic cut-off values/concentration limits mentioned in Tables 3.3.3 and 3.3.4. In these cases the mixture could be classified according to those data (see also paragraph 1.3.3.2 – *"Use of Cut-Off Values/Concentration Limits"*). On occasion, when it is expected that the skin corrosion/irritation or the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic concentration/ cut-off levels mentioned in Tables 3.3.3 and 3.3.4, testing of the mixture may be considered. In those cases, the tiered weight of evidence strategy should be applied as referred to in paragraph 3.3.2, Figure 3.3.1 and explained in detail in this chapter.

3.3.3.3.6 If there are data showing that (an) ingredient(s) may be corrosive or irritant at a concentration of < 1% (corrosive) or < 3% (irritant), the mixture should be classified accordingly (see also paragraph 1.3.3.2 *"Use of Cut-Off Values/Concentration Limits"*).

Table 3.3.3: Concentration of ingredients of a mixture classified as skin Category 1 and/or eye Category 1 or 2 that would trigger classification of the mixtures as hazardous to the eye (Category 1 or 2)

Sum of ingredients classified as:	Concentration triggering classification of a mixture as	
	Irreversible Eye Effects	Reversible Eye Effects
	Category 1	Category 2
Eye or Skin Category 1	≥ 3%	≥1% but < 3%
Eye Category 2/2A		≥10%
(10 x Eye Category 1) + Eye Category 2/2A		≥10%
Skin Category 1 + Eye Category 1	≥ 3%	≥1% but <3%
10 x (Skin Category 1 + Eye Category 1) + Eye Category 2A/2B		≥10%

Table 3.3.4: Concentration of ingredients of a mixture for which the additivity approach does not apply, that would trigger classification of the mixture as hazardous to the eye

Ingredient:	Concentration:	Mixture classified as: Eye
Acid with pH ≤ 2	≥ 1%	Category 1
Base with pH ≥11.5	≥ 1%	Category 1
Other corrosive (Category 1) ingredients for which additivity does not apply	≥ 1%	Category 1
Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

3.3.4 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. Additional reference sources providing advice on the use of precautionary information is also included.

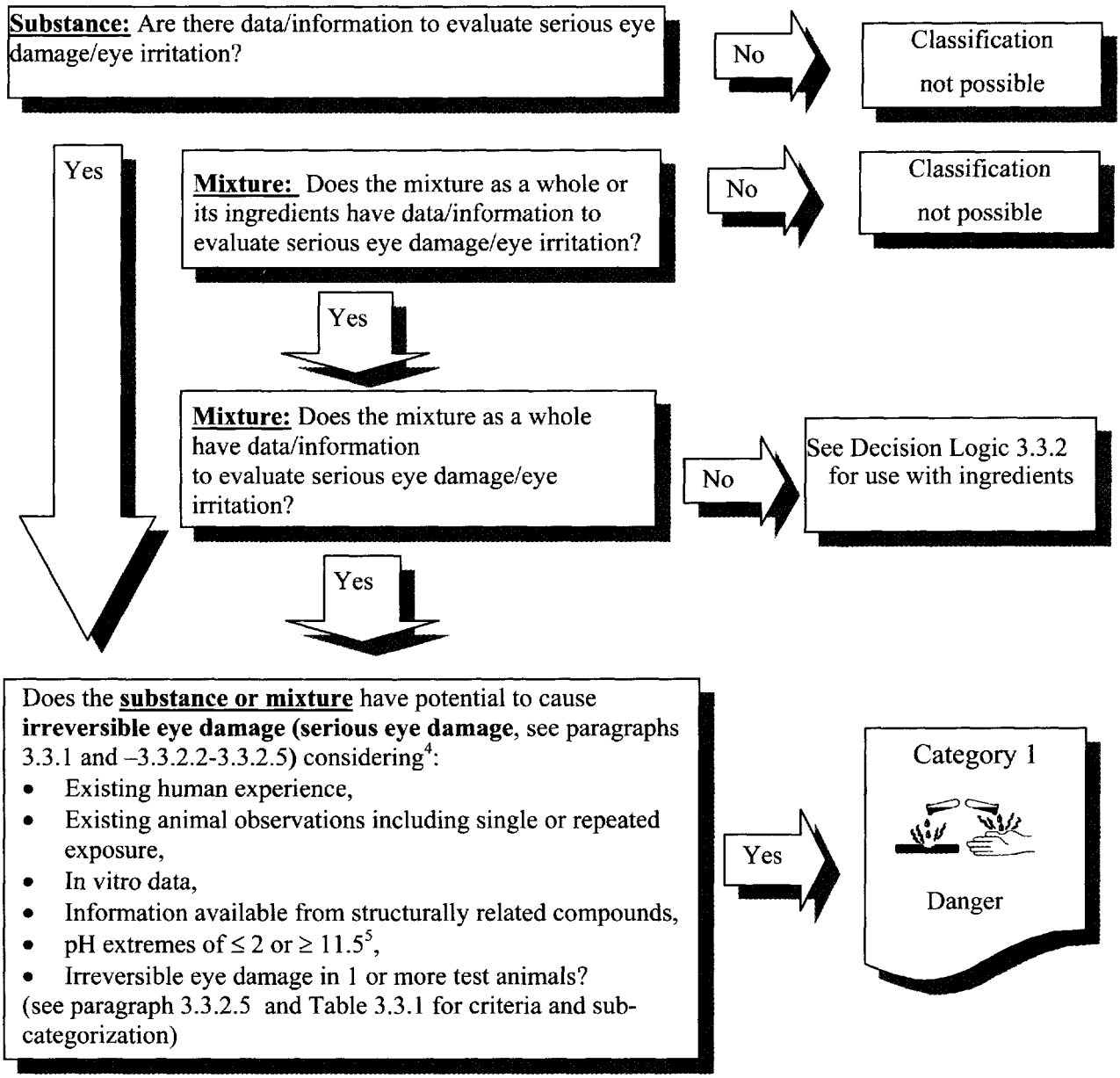
Table 3.3.5: Label elements for serious eye damage/eye irritation

	Category 1	Category 2A	Category 2B
Symbol	Corrosive symbol	Exclamation mark	No symbol is used
Signal word	Danger	Warning	Warning
Hazard statement	Causes severe eye damage	Causes severe eye irritation	Causes eye irritation

3.3.5 Decision logic

The decision logic which follows is not part of the harmonized classification system but is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

Decision logic 3.3.1 for serious eye damage / eye irritation



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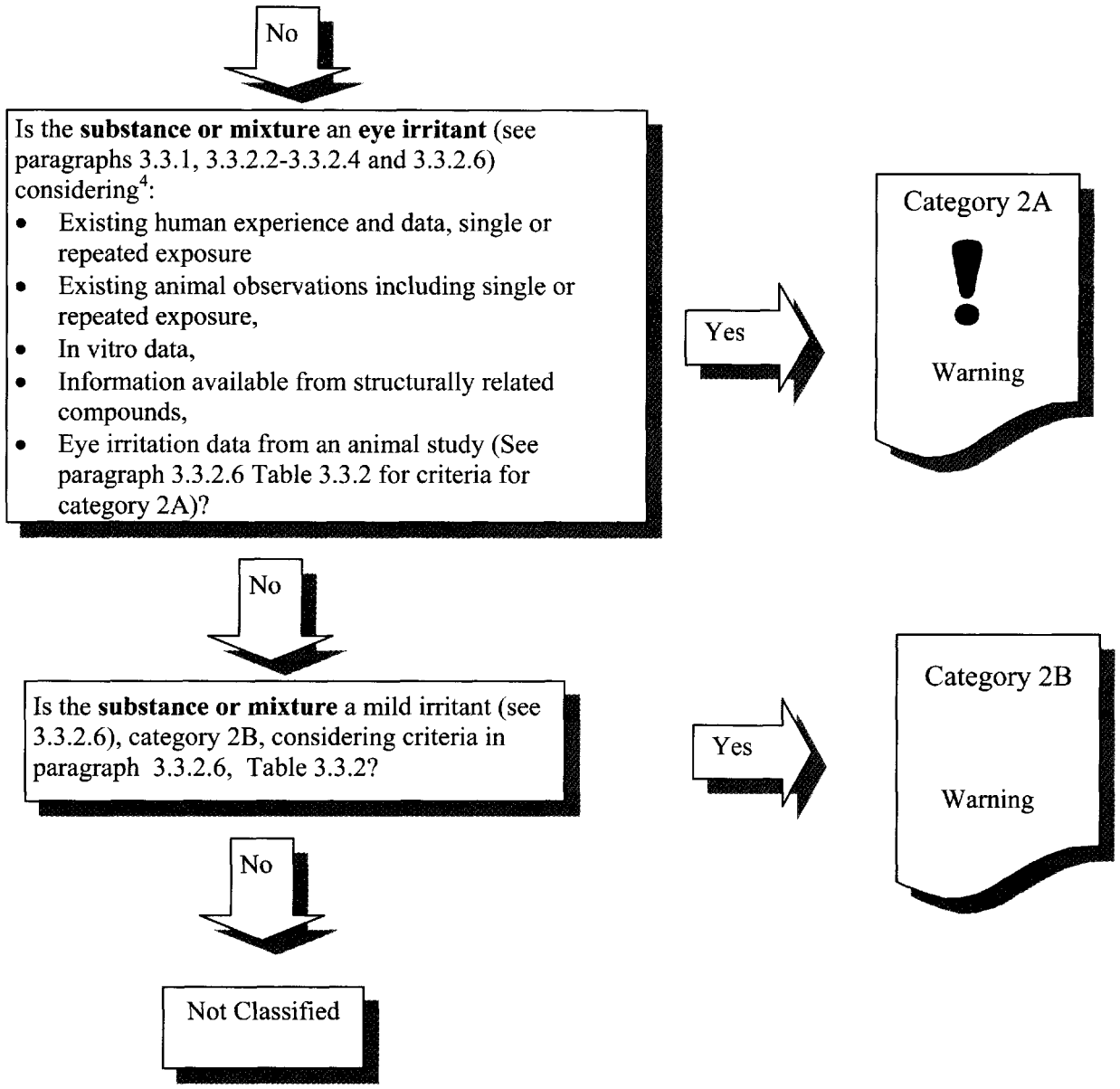
[4] *Figure 3.3.1 contains details for testing and evaluation.*

[5] *Including consideration of acid/alkali reserve capacity, if appropriate.*



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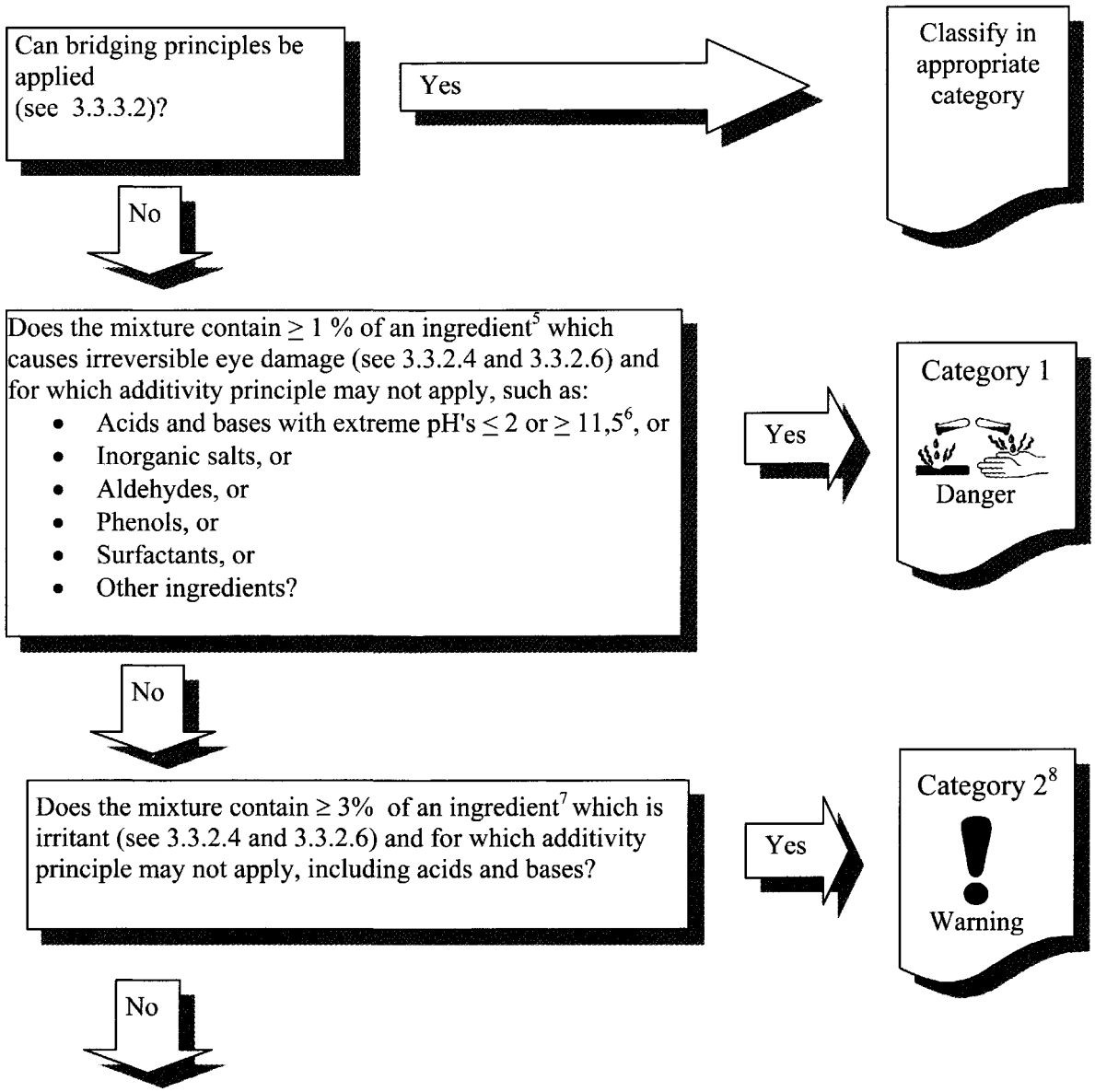
[4] *Figure 3.3.1 contains details for testing and evaluation.*

Decision logic 3.3.2 for serious eye damage / eye irritation:
Classification of mixtures on the basis of information/data on ingredients



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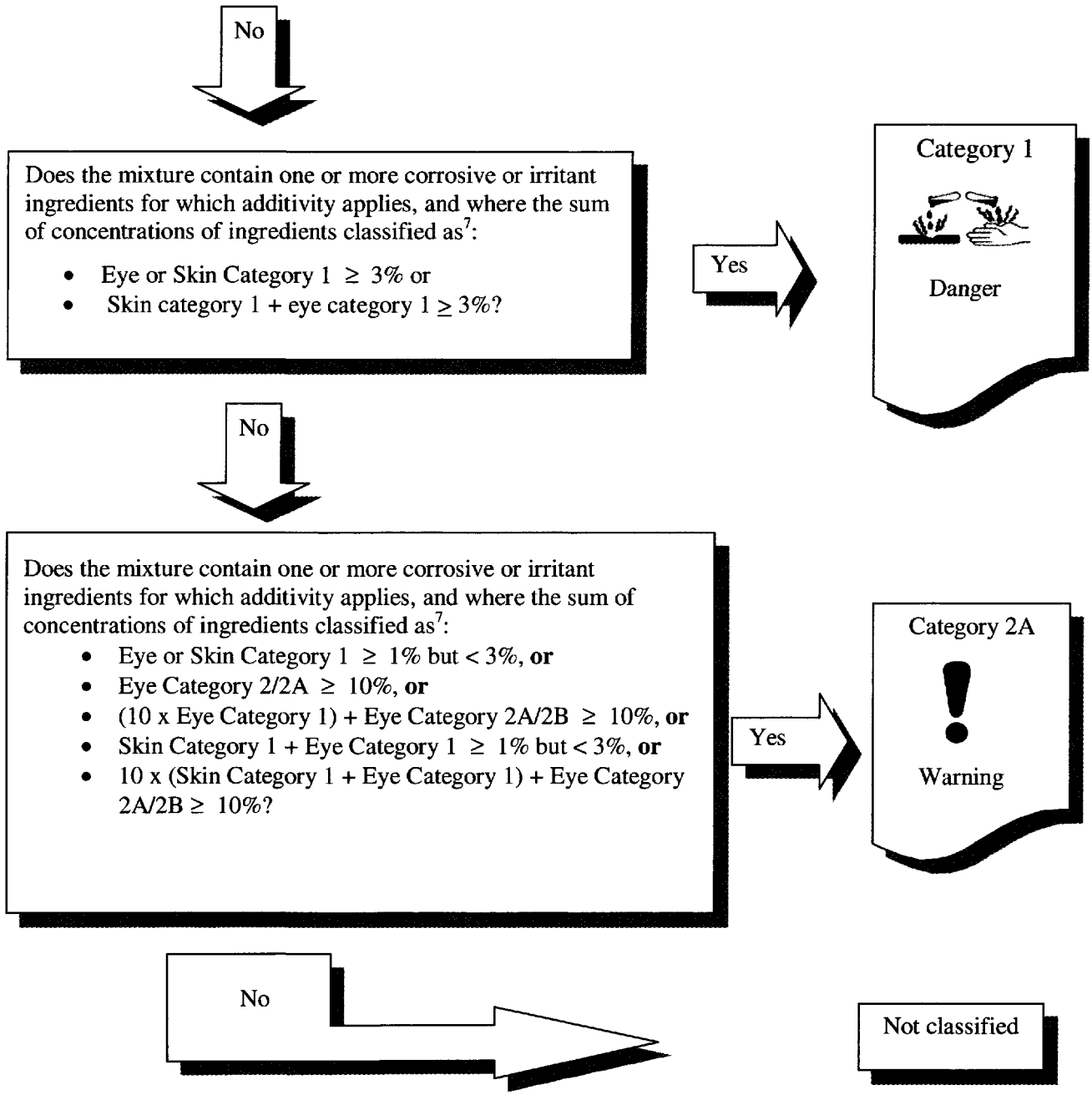
5 *Or where relevant < 1 %, see para. 3.3.3.3.1.*

6 *Including consideration of acid/alkali reserve capacity, if appropriate.*

7 *For specific concentration limits, see para. 3.3.3.3.4 of this chapter. See also Chapter 1.3, para. 1.3.3.2 for "The Use of Cut-Off Values/Concentration Limits".*

8 *If the mixture also contains other corrosive or irritant ingredient(s) for which additivity applies move to the box below.*



[7] *For specific concentration limits, see para. 3.3.3.3.4 of this chapter. See also Chapter 1.3, para. 13.3.2, for "The Use of Cut-off Values/Concentration Limits.*

CHAPTER 3.4

RESPIRATORY OR SKIN SENSITIZATION

3.4.1 Definitions

A *respiratory sensitizer* is a substance that will induce hypersensitivity of the airways following inhalation of the substance.[1]

A *skin sensitizer* is a substance that will induce an allergic response following skin contact[1].

3.4.2 Classification criteria for substances

3.4.2.1 *Respiratory sensitizers*

3.4.2.1.1 *Hazard category*

Substances shall be classified as respiratory sensitizers (Category 1) in accordance with the criteria given below:

- If there is evidence in humans that the substance can induce specific respiratory hypersensitivity and/or
- If there are positive results from an appropriate animal test.

3.4.2.1.2 *Human evidence*

3.4.2.1.2.1 Evidence that a 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/conjunctivitis 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.

3.4.2.1.2.2 When considering the human evidence, 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.

3.4.2.1.2.3 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:
  - *in vivo* immunological test (e.g. skin prick test);
  - *in vitro* immunological test (e.g. serological analysis);
  - studies that may indicate other specific hypersensitivity reactions where immunological mechanisms of action have not been proven, e.g. repeated low-level irritation, pharmacologically mediated effects;

[1] *This is a working definition for the purpose of this document.*

- a chemical structure related to substances known to cause respiratory hypersensitivity;

- data from positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.

3.4.2.1.2.4 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.

3.4.2.1.2.5 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.

3.4.2.1.3 *Animal studies*

Data from appropriate animal studies[2] which may be indicative of the potential of a substance to cause sensitization by inhalation in humans[3] may include:

- measurements of Immunoglobulin E (IgE) and other specific immunological parameters, for example in mice;
- specific pulmonary responses in guinea pigs.

3.4.2.2 *Skin sensitizers*

3.4.2.2.1 *Hazard category*

Substances shall be classified as contact sensitizers (Category 1) in accordance with the criteria given below:

• If there is evidence in humans that the substance can induce sensitization by skin contact in a substantial number of persons, or
• If there are positive results from an appropriate animal test.

3.4.2.2.2 *Specific considerations*

3.4.2.2.2.1 For classification of a substance, evidence should include any or all of the following:

- Positive data from patch testing, normally obtained in more than one dermatology clinic;
- 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;
- Positive data from appropriate animal studies;
- Positive data from experimental studies in man (See Chapter1.3, paragraph 1.3.2.4.7);
- Well documented episodes of allergic contact dermatitis, normally obtained in more than one dermatology clinic.

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2 *At present recognised animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, animal testing may be used, e.g. a modification of the guinea pig maximisation test for determination of relative allergenicity of proteins. However, these tests still need further validation.*

3 *The mechanisms by which substances induce symptoms of asthma are not yet fully known. For preventative measures, these substances are considered respiratory sensitizers. However, if on the basis of the evidence, it can be demonstrated that these substances induce symptoms of asthma by irritation only in people with bronchial hyperreactivity, they should not be considered as respiratory sensitizers.*

3.4.2.2.2.2 Positive effects seen in either humans or animals will normally justify classification. Evidence from animal studies is usually much more reliable than evidence from human exposure. However, in cases where evidence is available from both sources, and there is conflict between the results, the quality and reliability of the evidence from both sources must be assessed in order to resolve the question of classification on a case-by-case basis. Normally, human data are not generated in controlled experiments with volunteers for the purpose of hazard classification but rather as part of risk assessment to confirm lack of effects seen in animal tests. Consequently, positive human data on contact sensitization are usually derived from case-control or other, less defined studies. Evaluation of human data must therefore be carried out with caution as the frequency of cases reflect, in addition to the inherent properties of the substances, factors such as the exposure situation, bioavailability, individual predisposition and preventive measures taken. Negative human data should not normally be used to negate positive results from animal studies.

3.4.2.2.2.3 If none of the above mentioned conditions are met the substance need not be classified as a contact sensitizer. However, a combination of two or more indicators of contact sensitization as listed below may alter the decision. This shall be considered on a case-by-case basis.

- Isolated episodes of allergic contact dermatitis;
- Epidemiological studies of limited power, e.g. where chance, bias or confounders have not been ruled out fully with reasonable confidence;
- Data from animal tests, performed according to existing guidelines, which do not meet the criteria for a positive result described in paragraph 3.4.2.2.4.1 of this chapter, but which are sufficiently close to the limit to be considered significant;
- Positive data from non-standard methods;
- Positive results from close structural analogues.

3.4.2.2.3 *Immunological contact urticaria*

Substances meeting the criteria for classification as respiratory sensitizers may in addition cause immunological contact urticaria. Consideration should be given to classifying these substances also as contact sensitizers. Substances which cause immunological contact urticaria without meeting the criteria for respiratory sensitizers should also be considered for classification as contact sensitizers.

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 sensitization.

3.4.2.2.4 *Animal studies*

3.4.2.2.4.1 When an adjuvant type test method for skin sensitization is used, a response of at least 30% of the animals is considered as positive. For a non-adjuvant test method a response of at least 15% of the animals is considered positive. Test methods for skin sensitization are described in the OECD Guideline 406 (the Guinea Pig Maximisation test and the Buehler guinea pig test) and Guideline 429 (Local Lymph Node Assay). Other methods may be used provided that they are well-validated and scientific justification is given. The Mouse Ear Swelling Test (MEST), appears to be a reliable screening test to detect moderate to strong sensitizers, and can be used as a first stage in the assessment of skin sensitization potential. In case of a positive result in this latter test it may not be necessary to conduct a further guinea pig test.

3.4.2.2.4.2 When evaluating animal data, produced by testing according to the OECD or equivalent Guidelines for skin sensitization, the rate of sensitized animals may be considered. This rate reflects the sensitizing capacity of a substance in relation to its mildly irritating dose. This dose may vary between substances. A more appropriate evaluation of the sensitizing capacity of a substance could be carried out if the dose-response relationship was known for the substance. This is an area that needs further development.

3.4.2.2.4.3 There are substances that are extremely sensitizing at low doses where others require high doses and long time of exposure for sensitization. For the purpose of hazard classification it may be preferable to distinguish between strong and moderate sensitizers. However, at present animal or other test systems to

subcategorise sensitizers have not been validated and accepted. Therefore, sub-categorisation should not yet be considered as part of the harmonized classification system.

3.4.3 Classification criteria for mixtures

3.4.3.1 *Classification of mixtures when data are available for the complete mixture*

When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture can be classified by weight of evidence evaluation of these data. Care should be exercised in evaluating data on mixtures, that the dose used does not render the results inconclusive. [For special labelling required by some competent authorities, see Notes 1, 3 and 5 to Table 3.4.1 of this chapter.]

3.4.3.2 *Classification of mixtures when data are not available for the complete mixture: Bridging Principles*

3.4.3.2.1 Where the mixture itself has not been tested to determine its sensitizing properties, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data will be used in accordance with the following agreed bridging rules. This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity for additional testing in animals.

3.4.3.2.2 *Dilution*

If a mixture is diluted with a diluent which is not a sensitizer and which is not expected to affect the sensitization of other ingredients, then the new mixture may be classified as equivalent to the original mixture.

3.4.3.2.3 *Batching*

The sensitizing properties of one production batch of a complex mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product and produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the sensitization of the batch has changed. If the latter occurs, new classification is necessary.

3.4.3.2.4 *Substantially similar mixtures*

Given the following:

(a) Two mixtures: (i) A + B
(ii) C + B;
(b) The concentration of ingredient B is essentially the same in both mixtures;
(c) The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);
(d) Ingredient B is a sensitizer and ingredients A and C are not sensitizers;
(e) A and C are not expected to affect the sensitizing properties of B.

If mixture (i) is already classified by testing, then mixture (ii) can be assigned the same hazard category.

3.4.3.2.5 *Aerosols*

An aerosol form of the mixture may be classified in the same hazard category as the tested non-aerosolised form of the mixture provided that the added propellant does not affect the sensitizing properties of the mixture upon spraying.

3.4.3.3 *Classification of mixtures when data are available for all components or only for some components of the mixture*

The mixture should be classified as a respiratory or skin sensitizer when at least one ingredient has been classified as a respiratory or skin sensitizer and is present at or above the appropriate cut-off value / concentration limit for the specific endpoint as shown in Table 3.4.1 for solid/liquid and gas respectively.

Table 3.4.1: Cut-off values/concentration limits of ingredients of a mixture classified as either skin sensitisers or respiratory sensitizers that would trigger classification of the mixture

Ingredient Classified as:	**Cut-off/concentration limits triggering classification of a mixture as:**		
	Skin Sensitizer	**Respiratory Sensitizer**	
	All physical states	Solid/Liquid	Gas
Skin Sensitizer	≥ 0.1% (Note 1)	-	-
	≥ 1.0% (Note 2)	-	-
Respiratory Sensitizer	-	≥ 0.1% (Note 3)	≥ 0.1% (Note 5)
	-	≥ 1.0 % (Note 4)	≥ 0.2% (Note 6)

***NOTE 1**: If a skin sensitizer is present in the mixture as an ingredient at a concentration between 0.1% and 1.0%, both an SDS and a label would generally be expected. In addition, some competent authorities may require supplemental labelling for mixtures containing a sensitising ingredient at concentrations above 0.1%. The label warning for skin sensitizers between 0.1% and 1.0% may differ from the label warning for skin sensitizers ≥ 1.0%, depending on competent authority requirements. While the current cut-off values reflect existing systems, all recognise that special cases may require information to be conveyed below that level.*

***NOTE 2**: If a skin sensitizer is present in the mixture as an ingredient at a concentration of ≥ 1.0%, both an SDS and a label would generally be expected.*

***NOTE 3**: If a solid or liquid respiratory sensitizer is present in the mixture as an ingredient at a concentration between 0.1% and 1.0%, both an SDS and a label would generally be expected. In addition, some competent authorities may require supplemental labelling for mixtures containing a sensitising ingredient at concentrations above 0.1%. The label warning for solid or liquid respiratory sensitizers between 0.1% and 1.0% may differ from the label warning for solid or liquid respiratory sensitizers ≥ 1.0%, depending on competent authority requirements. While the current cut-off values reflect existing systems, all recognise that special cases may require information to be conveyed below that level.*

***NOTE 4**: If a solid or liquid respiratory sensitizer is present in the mixture as an ingredient at a concentration of ≥ 1.0%, both an SDS and a label would generally be expected.*

***NOTE 5**: If a gaseous respiratory sensitizer is present in the mixture as an ingredient at a concentration between 0.1% and 0.2%, both an SDS and a label would generally be expected. In addition, some competent authorities may require supplemental labelling for mixtures containing a sensitising ingredient at concentrations above 0.1%. The label warning for a gaseous respiratory sensitizers between 0.1% and 0.2% may differ from the label warning for a gaseous respiratory sensitizers ≥ 0.2%, depending on competent authority requirements. While the current cut-off values reflect existing systems, all recognise that special cases may require information to be conveyed below that level.*

***NOTE 6**: If a gaseous respiratory sensitizer is present in the mixture as an ingredient at a concentration of ≥ 0.2%, both an SDS and a label would generally be expected.*

3.4.4 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. Table 3.4.2 below presents specific label elements for substances and mixtures that are classified as respiratory and skin sensitizers based on the criteria in this chapter.

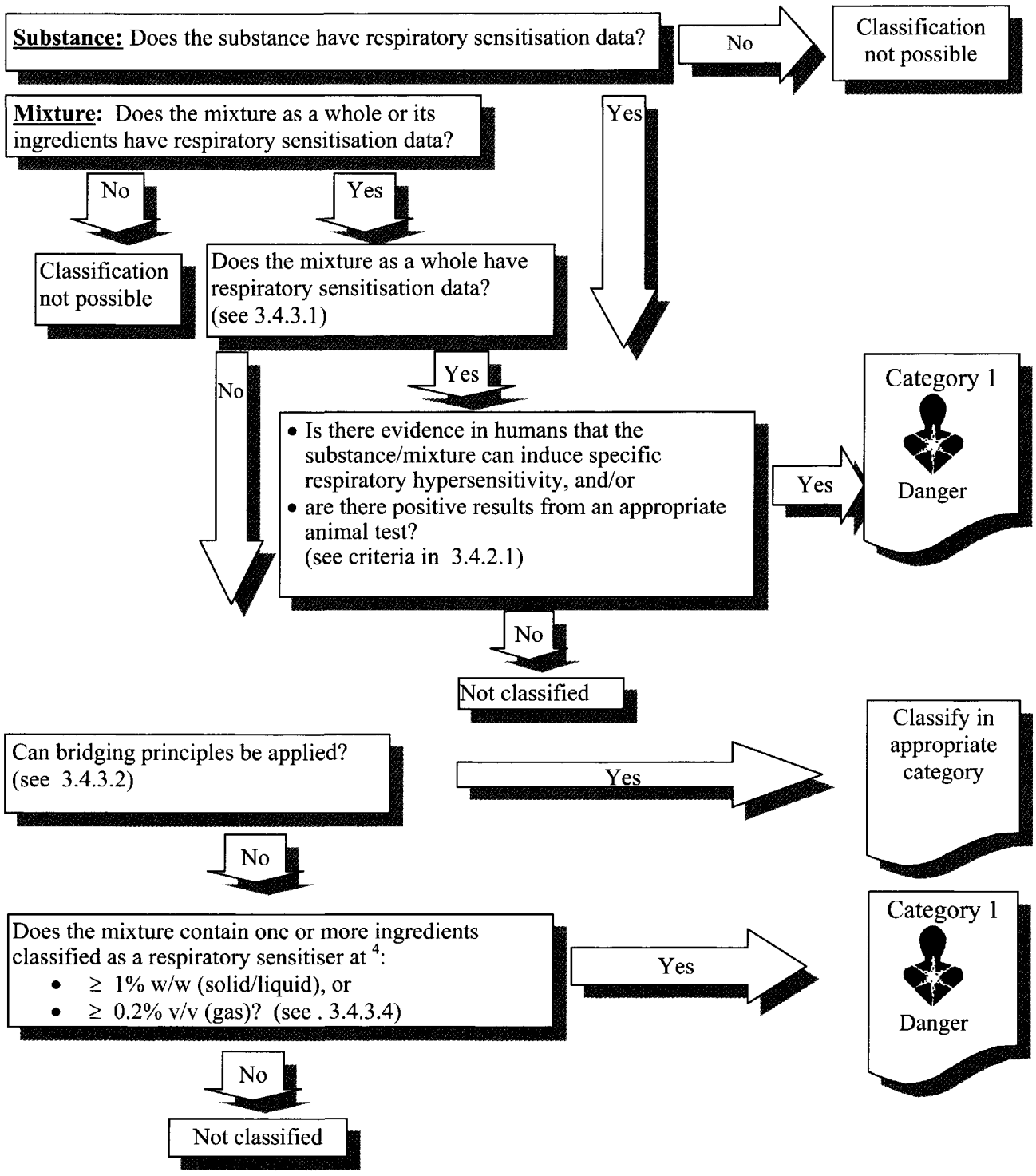
Table 3.4.2: Respiratory or skin sensitization label elements.

	Respiratory Sensitization Category 1	**Skin Sensitization Category 1**
Symbol	Health Hazard	Exclamation Mark
Signal Word	Danger	Warning
Hazard Statement	May cause allergy or asthma symptoms or breathing difficulties if inhaled	May cause an allergic skin reaction

3.4.5 Decision logic

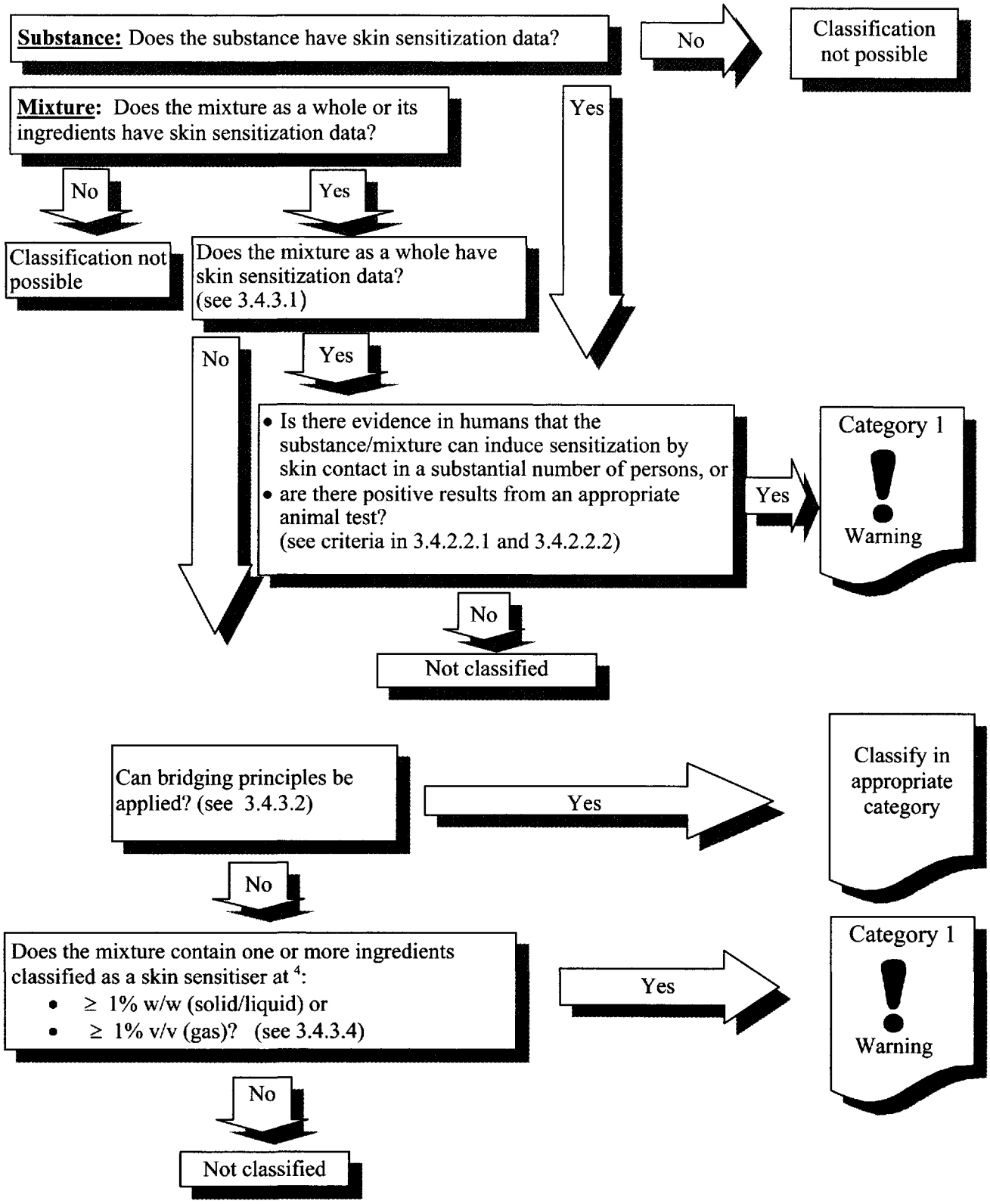
The decision logics which follow are not part of the harmonized classification system but are provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logics.

3.4.5.1 *Decision logic 3.4.1 for Respiratory Sensitization*



[4] *For specific concentration limits, see "The use of Cut-off Values/Concentration Limits" in Chapter 1.3, para. 1.3.3.2.*

3.4.5.2 *Decision logic 3.4.2 for Skin Sensitization*



[4] *For specific concentration limits, see "The use of Cut-off Values/Concentration Limits" in Chapter 1.3, para 1.3.3.2.*

CHAPTER 3.5

GERM CELL MUTAGENICITY

3.5.1 Definitions and general considerations

This hazard class is primarily concerned with chemicals that may cause mutations in the germ cells of humans that can be transmitted to the progeny. However, mutagenicity/genotoxicity tests *in vitro* and in mammalian somatic cells *in vivo* are also considered in classifying substances and mixtures within this hazard class.

In the present context, commonly found definitions of the terms mutagenic, mutagen, mutations and genotoxic are used. A *mutation* is defined as a permanent change in the amount or structure of the genetic material in a cell.

The term "mutation" applies both to heritable genetic changes that may be manifested at the phenotypic level and to the underlying DNA modifications when known (including, for example, specific base pair changes and chromosomal translocations). The term *mutagenic* and *mutagen* will be used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms.

The more general terms *genotoxic* and *genotoxicity* apply to agents or processes which alter the structure, information content, or segregation of DNA, including those which cause DNA damage by interfering with normal replication processes, or which in a non-physiological manner (temporarily) alter its replication. Genotoxicity test results are usually taken as indicators for mutagenic effects.

3.5.2 Classification criteria for substances

3.5.2.1 The classification system provides for two different categories of germ cell mutagens to accommodate the weight of evidence available. The two-category system is described in the following.

3.5.2.2 To arrive at a classification, test results are considered from experiments determining mutagenic and/or genotoxic effects in germ and/or somatic cells of exposed animals. Mutagenic and/or genotoxic effects determined in *in vitro* tests may also be considered.

3.5.2.3 The system is hazard based, classifying chemicals on the basis of their intrinsic ability to induce mutations in germ cells. The scheme is, therefore, not meant for the (quantitative) risk assessment of chemical substances.

3.5.2.4 Classification for heritable effects in human germ cells is made on the basis of well conducted, sufficiently validated tests, preferably as described in OECD Test Guidelines. Evaluation of the test results should be done using expert judgement and all the available evidence should be weighed for classification.

3.5.2.5 Examples of *in vivo* heritable germ cell mutagenicity tests are:

Rodent dominant lethal mutation test (OECD 478)
Mouse heritable translocation assay (OECD 485)
Mouse specific locus test

3.5.2.6 Examples of *in vivo* somatic cell mutagenicity tests are:

Mammalian bone marrow chromosome aberration test (OECD 475)
Mouse spot test (OECD 484)
Mammalian erythrocyte micronucleus test (OECD 474)

Figure 3.5.1: Hazard categories for germ cell mutagens

CATEGORY 1: Chemicals known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans

Category 1A: Chemicals known to induce heritable mutations in germ cells of humans

Criterion: Positive evidence from human epidemiological studies.

Category 1B: Chemicals which should be regarded as if they induce heritable mutations in the germ cells of humans

Criteria:

- Positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals; or
- Positive result(s) from *in vivo* somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. This supporting evidence may, for example, be derived from mutagenicity/genotoxic tests in germ cells *in vivo*, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or
- Positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.

CATEGORY 2: Chemicals which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans

Criteria:
Positive evidence obtained from experiments in mammals and/or in some cases from *in vitro* experiments, obtained from:

- Somatic cell mutagenicity tests *in vivo*, in mammals; or
- Other *in vivo* somatic cell genotoxicity tests which are supported by positive results from *in vitro* mutagenicity assays.

***NOTE*:**

- *Chemicals which are positive in in vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, should be considered for classification as Category 2 mutagens.*

3.5.2.7 Examples of mutagenicity/genotoxicity tests in germ cells are:

(a) Mutagenicity tests:
Mammalian spermatogonial chromosome aberration test (OECD 483)
Spermatid micronucleus assay

(b) Genotoxicity tests:
Sister chromatid exchange analysis in spermatogonia
Unscheduled DNA synthesis test (UDS) in testicular cells

3.5.2.8 Examples of genotoxicity tests in somatic cells are:

Liver Unscheduled DNA Synthesis (UDS) *in vivo* (OECD 486)
Mammalian bone marrow Sister Chromatid Exchanges (SCE)

3.5.2.9 Examples of *in vitro* mutagenicity tests are:

In vitro mammalian chromosome aberration test (OECD 473)
In vitro mammalian cell gene mutation test (OECD 476)
Bacterial reverse mutation tests (OECD 471)

3.5.2.10 The classification of individual substances should be based on the total weight of evidence available, using expert judgement. In those instances where a single well-conducted test is used for classification, it should provide clear and unambiguously positive results. If new, well validated, tests arise these may also be used in the total weight of evidence to be considered. The relevance of the route of exposure used in the study of the chemical compared to the route of human exposure should also be taken into account.

3.5.3 Classification criteria for mixtures

3.5.3.1 *Classification of mixtures when data are available for the complete mixture*

Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using cut-off values/concentration limits for the ingredients classified as germ cell mutagens. The classification may be modified on a case-by-case basis based on the available test data for the mixture as a whole. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of germ cell mutagenicity test systems. Adequate documentation supporting the classification should be retained and made available for review upon request.

3.5.3.2 *Classification of mixtures when data are not available for the complete mixture: Bridging principles*

3.5.3.2.1 Where the mixture itself has not been tested to determine its germ cell mutagenicity hazard, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data will be used in accordance with the following agreed bridging rules. This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity for additional testing in animals.

3.5.3.2.2 *Dilution*

If a mixture is diluted with a diluent which is not expected to affect the germ cell mutagenicity of other ingredients, then the new mixture may be classified as equivalent to the original mixture.

3.5.3.2.3 *Batching*

The germ cell mutagenic potential of one production batch of a complex mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product produced by and under the control of the same manufacturer unless there is reason to believe there is significant variation in composition such that the germ cell mutagenic potential of the batch has changed. If the latter occurs, a new classification is necessary.

3.5.3.2.4 *Substantially similar mixtures*

Given the following:

(a) Two mixtures: (i) A + B
(ii) C + B;
(b) The concentration of mutagen ingredient B is the same in both mixtures;
(c) The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);

(d) Data on toxicity for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the germ cell mutagenicity of B.

If mixture (i) is already classified by testing, then mixture (ii) can be classified in the same category.

3.5.3.3 *Classification of mixtures when data are available for all components or only for some components of the mixture*

The mixture will be classified as a mutagen when at least one ingredient has been classified as a Category 1 or Category 2 mutagen and is present at or above the appropriate cut-off value/concentration limit as shown in Table 3.5.1 below for Category 1 and 2 respectively.

Table 3.5.1: Cut-off values/concentration limits of ingredients of a mixture classified as germ cell mutagens that would trigger classification of the mixture.

Ingredient classified as:	Cut-off/concentration limits triggering classification of a mixture as:	
	Category 1 mutagen	Category 2 mutagen
Category 1 mutagen	≥ 0.1 %	-
Category 2 mutagen	-	≥ 1.0%

Note: The cut-off values/concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).

3.5.4 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. The table below presents specific label elements for substances and mixtures classified as germ cell mutagens based on the criteria in this chapter.

Table 3.5.2: Label elements of germ cell mutagenicity

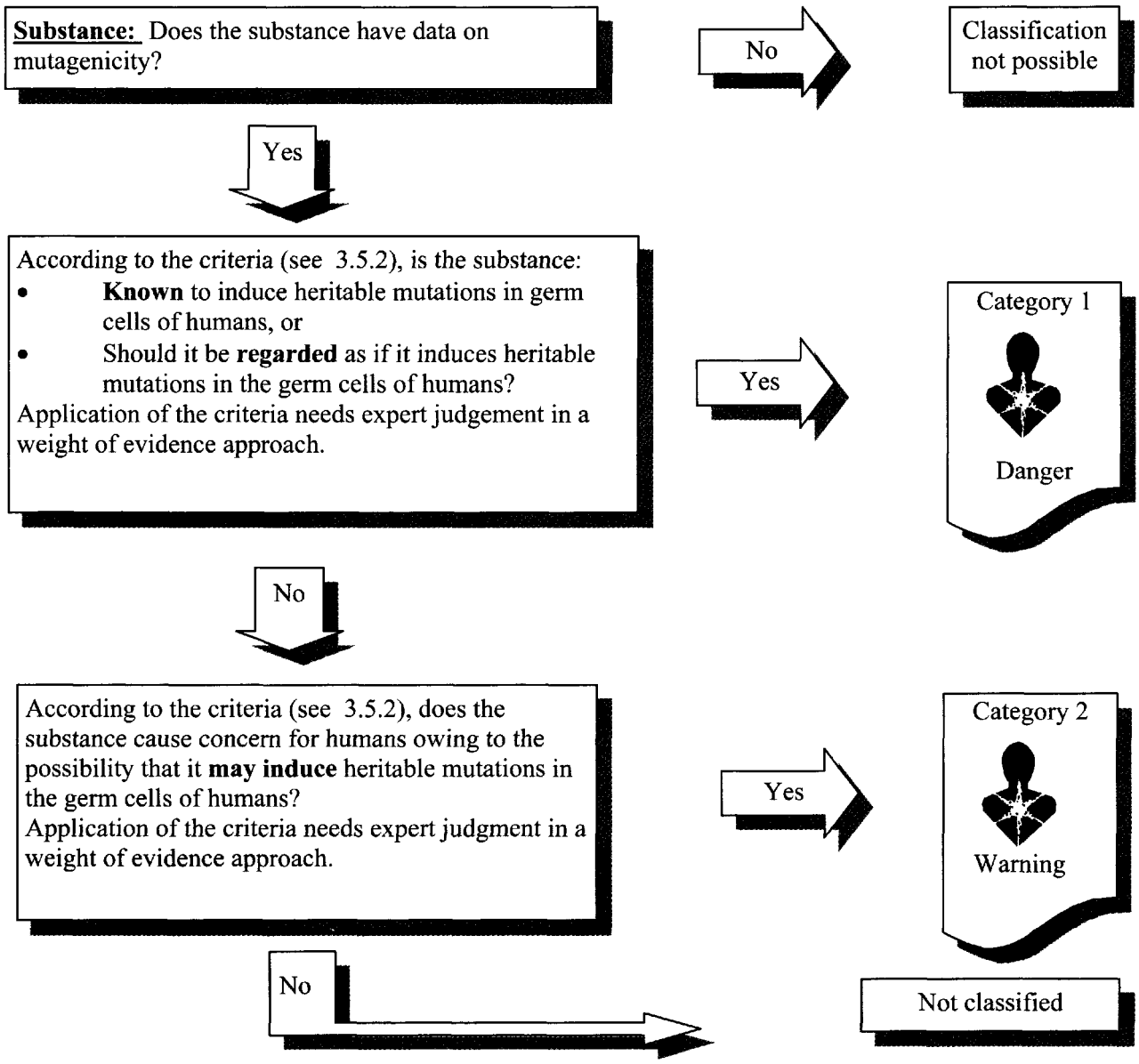
	Category 1A	Category 1B	Category 2
Symbol	Health Hazard	Health Hazard	Health Hazard
Signal Word	Danger	Danger	Warning
Hazard Statement	May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	Suspected of causing genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)

3.5.5 Decision logic and guidance

3.5.5.1 *Decision logic for Germ Cell Mutagenicity*

The decision logic which follows is not part of the harmonized classification system but is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

Decision logic 3.5.1 for Germ Cell Mutagenicity: substances



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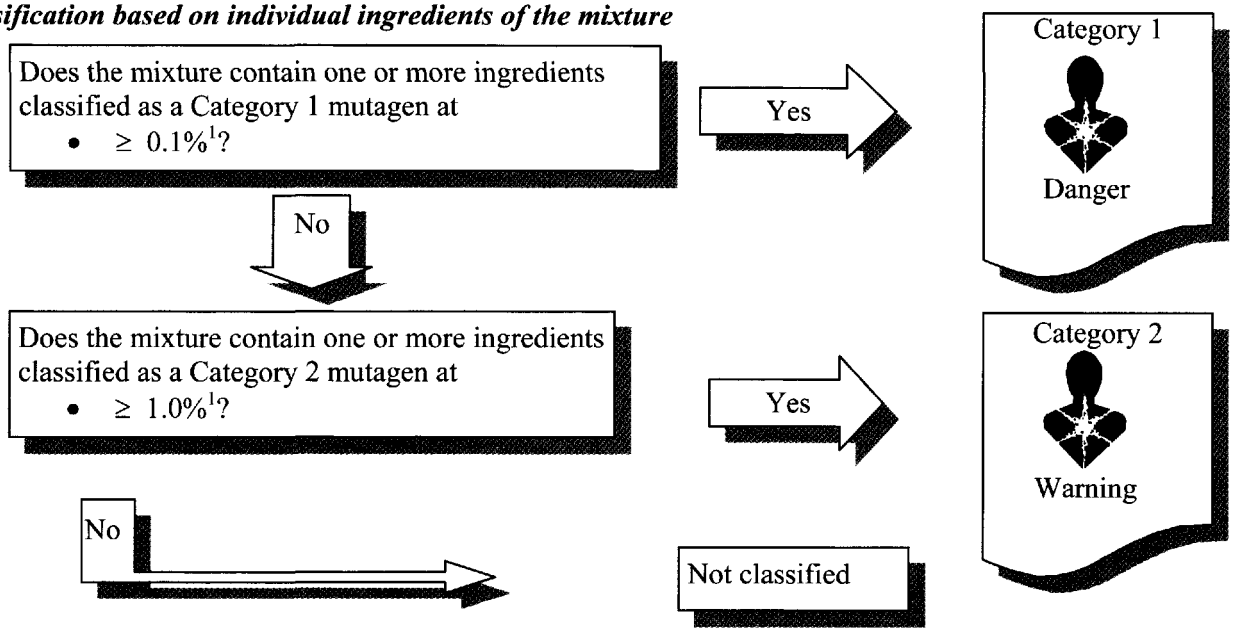
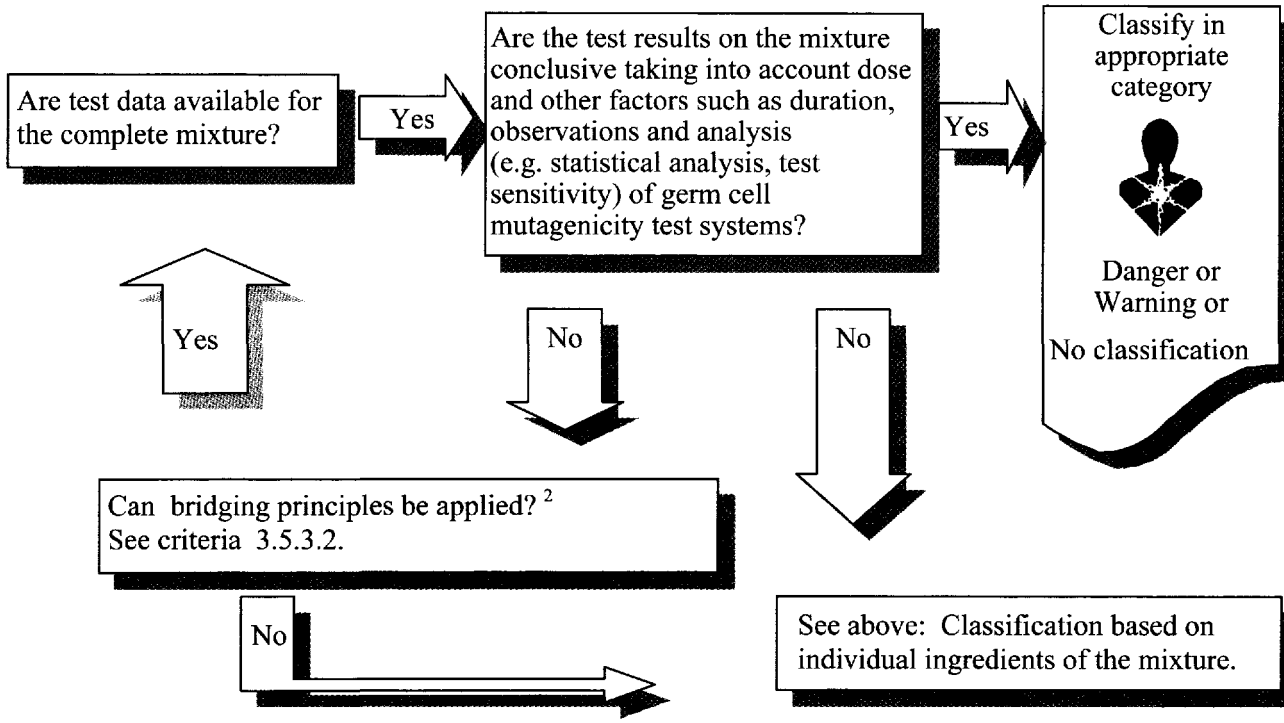
Decision logic 3.5.2 for Germ Cell Mutagenicity: mixtures

Mixture:
Classification of mixtures will be based on the available test data for the **individual ingredients** of the mixture, using cut-off values/concentration limits for those ingredients. The classification may **be modified on a case-by-case basis** based on the available test data for the mixture as a whole or based on bridging principles. See Modified classification on a case-by-case basis below. For further details see criteria (3.5.3).

Classification based on individual ingredients of the mixture



Modified classification on a case-by-case basis



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[1] *For specific concentration limits, see "The use of Cut-Off Valve Concentration limits in chapter 1.3, para.1.3.3.2 and Table 3.5.1 of this Chapter.*

[2] *If data on another mixture are used in the application of bridging principles, the data on that mixture must be conclusive in accordance with paragraph 3.5.3.1.*

3.5.5.2 *Guidance*

It is increasingly accepted that the process of chemical-induced tumorigenesis in man and animals involves genetic changes in proto-oncogenes and/or tumour suppresser genes of somatic cells. Therefore, the demonstration of mutagenic properties of chemicals in somatic and/or germ cells of mammals *in vivo* may have implications for the potential classification of these chemicals as carcinogens (See also Carcinogenicity, Chapter 3.6, paragraph 3.6.2.5.3).

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CHAPTER 3.6

CARCINOGENICITY

3.6.1 Definitions

The term *carcinogen* denotes a chemical substance or a mixture of chemical substances which induce cancer or increase its incidence. Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans.

Classification of a chemical as posing a carcinogenic hazard is based on the inherent properties of the substance and does not provide information on the level of the human cancer risk which the use of the chemical may represent.

3.6.2 Classification criteria for substances

3.6.2.1 For the purpose of classification for carcinogenicity, chemical substances are allocated to one of two categories based on strength of evidence and additional considerations (weight of evidence). In certain instances, route specific classification may be warranted.

Figure 3.6.1 : Hazard categories for carcinogens

CATEGORY 1: Known or presumed human carcinogens

The placing of a chemical in Category 1 is done on the basis of epidemiological and/or animal data. An individual chemical may be further distinguished:

Category 1A: Known to have carcinogenic potential for humans; the placing of a chemical is largely based on human evidence.

Category 1B: Presumed to have carcinogenic potential for humans; the placing of a chemical is largely based on animal evidence.

Based on strength of evidence together with additional considerations, such evidence may be derived from human studies that establish a causal relationship between human exposure to a chemical and the development of cancer (known human carcinogen). Alternatively, evidence may be derived from animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case by case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.

Classification: Category 1 (A and B) Carcinogen

CATEGORY 2: Suspected human carcinogens

The placing of a chemical in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the chemical in Category 1. Based on strength of evidence together with additional considerations, such evidence may be from either limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

Classification: Category 2 Carcinogen

3.6.2.2 Classification as a carcinogen is made on the basis of evidence from reliable and acceptable methods, and is intended to be used for chemicals which have an intrinsic property to produce such toxic effects. The evaluations should be based on all existing data, peer-reviewed published studies and additional data accepted by regulatory agencies.

3.6.2.3 *Carcinogen classification* is a one-step, criterion-based process that involves two interrelated determinations: evaluations of strength of evidence and consideration of all other relevant information to place chemicals with human cancer potential into hazard categories.

3.6.2.4 *Strength of evidence* involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance. Sufficient human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the agent and an increased incidence of tumours. Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated. Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient. The terms "sufficient" and "limited" are used here as they have been defined by the International Agency for Research on Cancer (IARC) and are outlined in 3.6.5.3.1.

3.6.2.5 *Additional considerations (weight of evidence)*: Beyond the determination of the strength of evidence for carcinogenicity, a number of other factors should be considered that influence the overall likelihood that an agent may pose a carcinogenic hazard in humans. The full list of factors that influence this determination is very lengthy, but some of the important ones are considered here.

3.6.2.5.1 The factors can be viewed as either increasing or decreasing the level of concern for human carcinogenicity. The relative emphasis accorded to each factor depends upon the amount and coherence of evidence bearing on each. Generally there is a requirement for more complete information to decrease than to increase the level of concern. Additional considerations should be used in evaluating the tumour findings and the other factors in a case-by-case manner.

3.6.2.5.2 Some important factors which may be taken into consideration, when assessing the overall level of concern are:

- Tumour type and background incidence
- Multisite responses
- Progression of lesions to malignancy
- Reduced tumour latency

Additional factors which may increase or decrease the level of concern include:

- Whether responses are in single or both sexes
- Whether responses are in a single species or several species
- Structural similarity or not to a chemical(s) for which there is good evidence of carcinogenicity
- Routes of exposure
- Comparison of absorption, distribution, metabolism and excretion between test animals and humans
- The possibility of a confounding effect of excessive toxicity at test doses
- Mode of action and its relevance for humans, such as mutagenicity, cytotoxicity with growth stimulation, mitogenesis, immunosuppression.

3.6.2.5.3 *Mutagenicity:* It is recognised that genetic events are central in the overall process of cancer development. Therefore evidence of mutagenic activity *in vivo* may indicate that a chemical has a potential for carcinogenic effects.

3.6.2.5.4 The following additional considerations apply to classification of chemicals into either Category 1 or Category 2. A chemical that has not been tested for carcinogenicity may in certain instances be classified in Category 1 or Category 2 based on tumour data from a structural analogue together with substantial support from consideration of other important factors such as formation of common significant metabolites, e.g. for benzidine congener dyes.

3.6.2.5.5 The classification should also take into consideration whether or not the chemical is absorbed by a given route(s); or whether there are only local tumours at the site of administration for the tested route(s), and adequate testing by other major route(s) show lack of carcinogenicity.

3.6.2.5.6 It is important that whatever is known of the physico-chemical, toxicokinetic and toxicodynamic properties of the substances, as well as any available relevant information on chemical analogues, i.e. structure activity relationship, is taken into consideration when undertaking classification.

3.6.2.6 It is realised that some regulatory authorities may need flexibility beyond that developed in the hazard classification scheme. For inclusion into Safety Data Sheets positive results in any carcinogenicity study performed according to good scientific principles with statistically significant results may be considered.

3.6.2.7 The relative hazard potential of a chemical is a function of its intrinsic potency. There is great variability in potency among chemicals, and it may be important to account for these potency differences. The work that remains to be done is to examine methods for potency estimation Carcinogenic potency as used here does not preclude risk assessment. The proceedings of a WHO/IPCS workshop on the *Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals, on Developing a Conceptual Framework for Cancer Risk Assessment (1999, Lyon, France)*, points to a number of scientific questions arising for classification of chemicals, e.g. mouse liver tumours, peroxisome proliferation, receptor-mediated reactions, chemicals which are carcinogenic only at toxic doses and which do not demonstrate mutagenicity. Accordingly, there is a need to articulate the principles necessary to resolve these scientific issues which have led to diverging classifications in the past. Once these issues are resolved, there would be a firm foundation for classification of a number of chemical carcinogens.

3.6.3 Classification criteria for mixtures

3.6.3.1 *Classification of mixtures when data are available for the complete mixture*

Classification of mixtures will be based on the available test data of the individual ingredients of the mixture using cut-off values/concentration limits for those ingredients. The classification may be modified on a case-by case basis based on the available test data for the mixture as a whole. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of carcinogenicity test systems. Adequate documentation supporting the classification should be retained and made available for review upon request.

3.6.3.2 *Classification of mixtures when data are not available for the complete mixture: Bridging Principles*

3.6.3.2.1 Where the mixture itself has not been tested to determine its carcinogenic hazard, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data will be used in accordance with the following agreed bridging rules. This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity for additional testing in animals.

3.6.3.2.2 *Dilution*

If a mixture is diluted with a diluent that is not expected to affect the carcinogenicity of other ingredients, then the new mixture may be classified as equivalent to the original mixture.

3.6.3.2.3 *Batching*

The carcinogenic potential of one production batch of a complex mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product produced by and under the control of the same manufacturer unless there is reason to believe there is significant variation in composition such that the carcinogenic potential of the batch has changed. If the latter occurs, a new classification is necessary.

3.6.3.2.4 *Substantially similar mixtures*

Given the following:

(a) Two mixtures: (i) A + B
(ii) C + B;
(b) The concentration of carcinogen ingredient B is the same in both mixtures;
(c) The concentration of ingredient A in mixture i equals that of ingredient C in mixture ii;
(d) Data on toxicity for A and C are available and substantially equivalent, i.e. they are inthe same hazard category and are not expected to affect the carcinogenicity of B.

If mixture (i) is already classified by testing, then mixture (ii) can be assigned the same category.

3.6.3.3 *Classification of mixtures when data are available for all components or only for some components of the mixture*

The mixture will be classified as a carcinogen when at least one ingredient has been classified as a Category 1 or Category 2 carcinogen and is present at or above the appropriate cut-off value/concentration limit as shown in Table 3.6.1 for Category 1 and 2 respectively.

Table 3.6.1: Cut-off values/concentration limits of ingredients of a mixture classified as carcinogen that would trigger classification of the mixture[1]

Ingredient Classified as:	**Cut-off/concentration limits triggering classification of a mixture as:**	
	Category 1 carcinogen	**Category 2 carcinogen**
Category 1 carcinogen	≥ 0.1 %	
Category 2 carcinogen	-	≥ 0.1% (note1)
		≥ 1.0% (note 2)

***NOTE 1**: If a Category 2 carcinogen ingredient is present in the mixture at a concentration between 0.1% and 1%, every regulatory authority would require information on the SDS for a product. However, a label warning would be optional. Some authorities will choose to label when the ingredient is present in the mixture between 0.1% and 1%, whereas others would normally not require a label in this case.*

***NOTE 2**: If a Category 2 carcinogen ingredient is present in the mixture at a concentration of ≥ 1%, both an SDS and a label would generally be expected.*

[1] *This compromise classification scheme involves consideration of differences in hazard communication practices in existing systems. It is expected that the number of affected mixtures will be small; the differences will be limited to label warnings; and the situation will evolve over time to a more harmonised approach.*

3.6.4 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. Table 3.6.2 below presents specific label elements for substances and mixtures that are classified as carcinogenic based on the criteria set forth in this chapter.

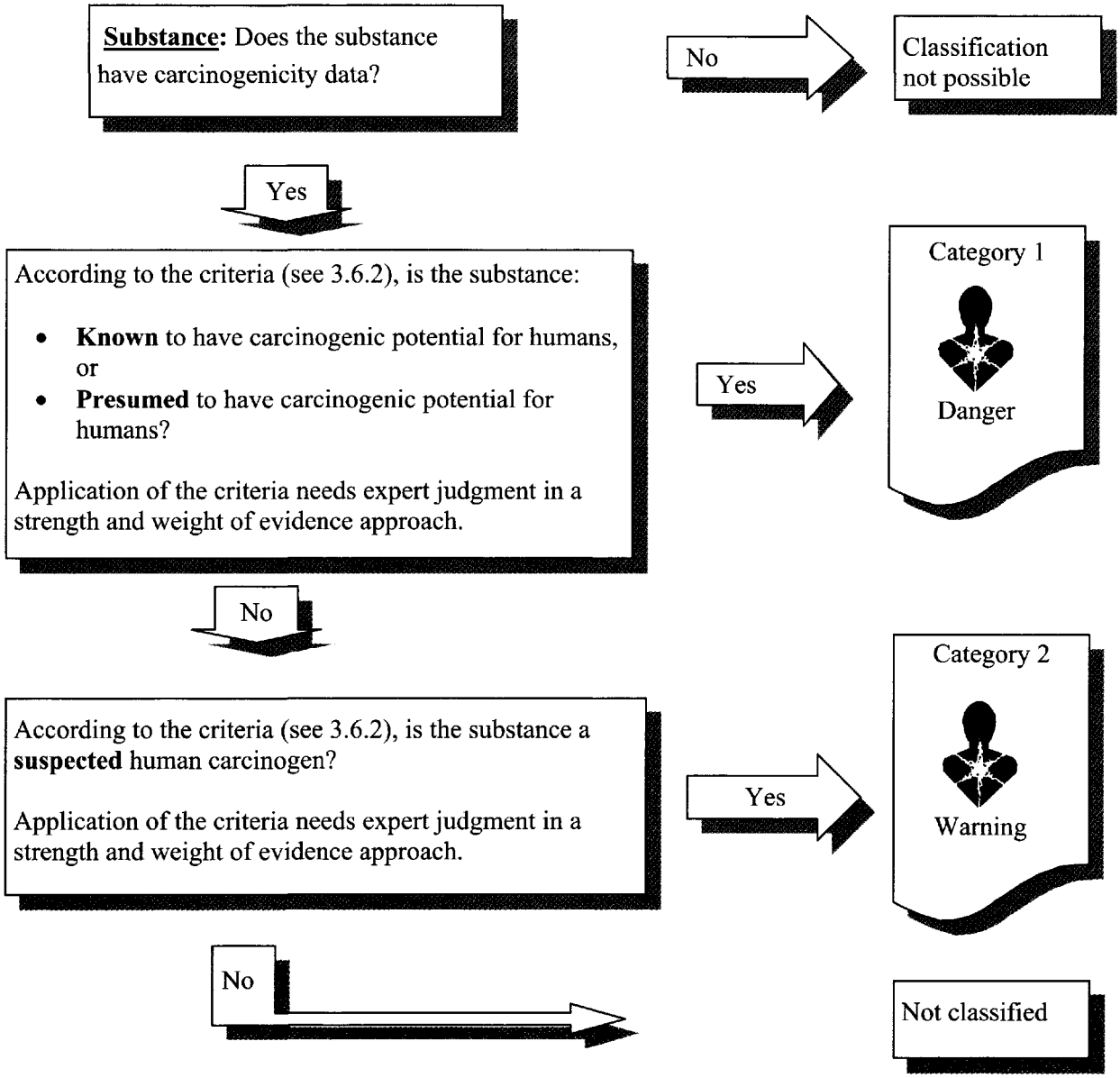
Table 3.6.2: Label elements for carcinogenicity

	Category 1A	Category 1B	Category 2
Symbol	Health Hazard	Health Hazard	Health Hazard
Signal Word	Danger	Danger	Warning
Hazard Statement	May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	Suspected of causing cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)

3.6.5 Decision logic and guidance for Carcinogenicity

The decision logic which follows is not part of the harmonized classification system but is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

3.6.5.1 *Decision logic 3.6.1 for substances*

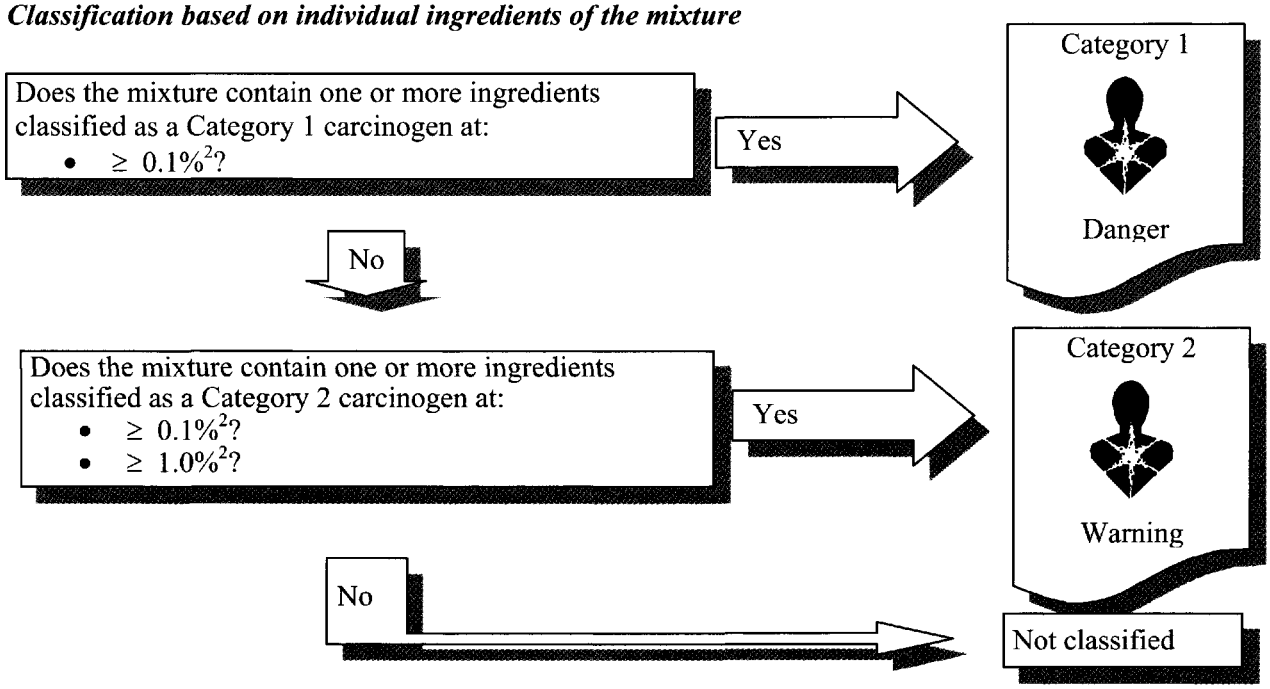


Continued on next page

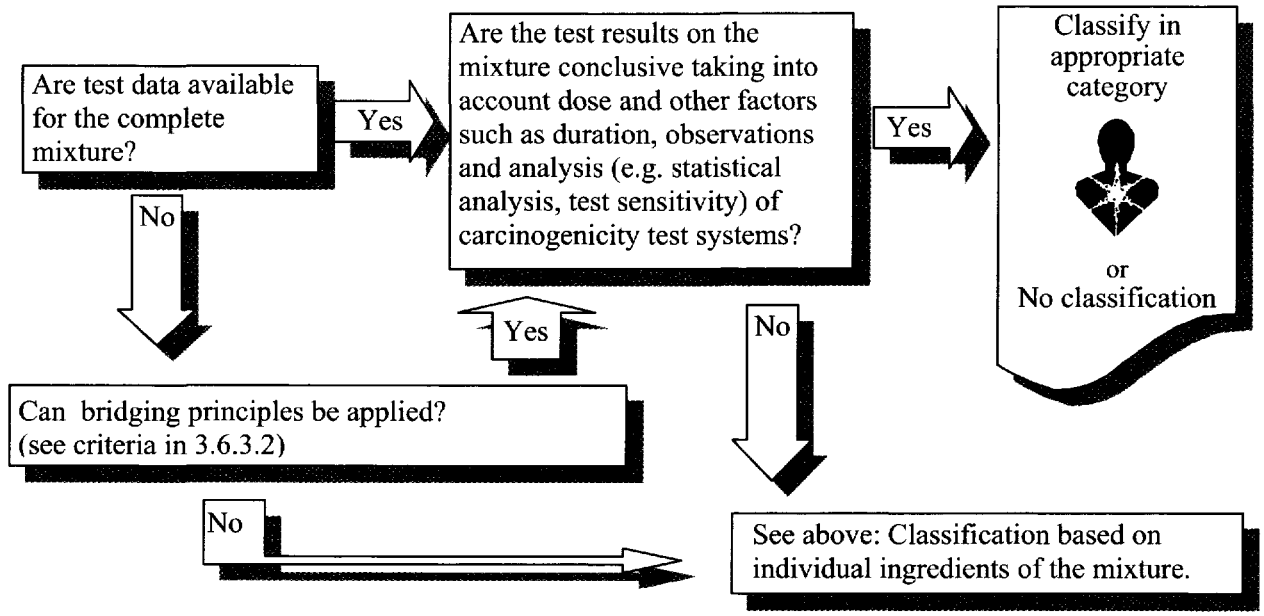
3.6.5.2 *Decision logic 3.6.2 for mixtures*

Mixture:
Classification of mixtures will be based on the available test data for the **individual ingredients** of the mixture, using cut-off values/concentration limits for those ingredients. The classification may be **modified on a case-by-case basis** based on the available test data for the mixture as a whole or based on bridging principles. See Modified classification on a case-by-case basis below. For further details see criteria (paragraphs 3.6.2.7, 3.6.3.1-3.6.3.2).

Classification based on individual ingredients of the mixture



Modified classification on a case-by-case basis



[2] *For specific concentration limits, see "The use of Cut-off Values/Concentration Limits" in Chapter 1.3, para. 1.3.3.2 and in Table 3.6.1 of this Chapter.*

3.6.5.3 *Background Guidance* [3]

Excerpts from monographs of the International Agency for Research on Cancer (IARC) Monographs Programme on the Evaluation of the Strength of Evidence of Carcinogenic Risks to Humans follow as in 3.6.5.2.1 and 3.6.5.2.2[4] .

3.6.5.3.1 *Carcinogenicity in humans*

3.6.5.3.1.1 The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

(a) Sufficient evidence of carcinogenicity: the Working Group on Carcinogenicity of the OECD Task Force on Harmonization of Classification and Labelling considered that a causal relationship has been established between exposure to the agent, mixture or exposure circumstance and human cancer. That is, a positive relationship has been observed between exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence;

(b) Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent, mixture or exposure circumstance and cancer for which a causal interpretation was considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

3.6.5.3.1.2 In some instances the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

3.6.5.3.2 Carcinogenicity in experimental animals

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

(a) Sufficient evidence of carcinogenicity: The OECD Working Group considered that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (i) two or more species of animals or (ii) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols;

(b) Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset;

(c) Limited evidence of carcinogenicity: the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (i) the evidence of carcinogenicity is restricted to a single experiment; or (ii) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study; or (iii) the agent or mixture increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains.

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[3] *The information and guidance which follows is taken from the OECD Integrated Document on Harmonisation of Classification and Labelling. It is not part of the agreed text on the harmonised classification system developed by the OECD Task Force-HCL, but has been provided here as additional.*

[4] *See para 3.6.2.4 of this Chapter.*

CHAPTER 3.7

REPRODUCTIVE TOXICITY

3.7.1 Definitions and general considerations

3.7.1.1 *Reproductive toxicity*

Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. The definitions presented below are adapted from those agreed at the IPCS/OECD Workshop for the Harmonization of Risk Assessment for Reproductive and Developmental Toxicity, Carshalton, UK, 17-21 October, 1994[1]. For classification purposes, the known induction of genetically based inheritable effects in the offspring is addressed in *Germ Cell Mutagenicity* (Chapter 3.5), since in the present classification system it is considered more appropriate to address such effects under the separate hazard class of germ-cell mutagenicity.

In this classification system, reproductive toxicity is subdivided under two main headings:

- Adverse effects on reproductive ability or capacity;
- Adverse effects on development of the offspring.

3.7.1.2 *Adverse effects on reproductive ability or capacity*

Any effect of chemicals that would interfere with reproductive ability or capacity. This may include, but not be limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.

Adverse effects on or via lactation are also included in reproductive toxicity, but for classification purposes, such effects are treated separately. (See 3.7.2.1) This is because it is desirable to be able to classify chemicals specifically for an adverse effect on lactation so that a specific hazard warning about this effect can be provided for lactating mothers.

3.7.1.3 *Adverse effects on development of the offspring*

Taken in its widest sense, developmental toxicity includes any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women and men and women of reproductive capacity. Therefore, for pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure. These effects can be manifested at any point in the life span of the organism. The major manifestations of developmental toxicity include (a) death of the developing organism, (b) structural abnormality, (c) altered growth, and (d) functional deficiency.

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1 *OECD Monograph Series on Testing and Assessment No. 17, 1998.*

3.7.2 Classification criteria for substances

3.7.2.1 *Hazard categories*

For the purpose of classification for reproductive toxicity, chemical substances are allocated to one of two categories. Effects on reproductive ability or capacity, and on development, are considered as separate issues. In addition, effects on lactation are allocated to a separate hazard category.

Figure 3.7.1 (a): Hazard categories for reproductive toxicants

CATEGORY 1: Known or presumed human reproductive or developmental toxicant

This Category includes substances which are known to have produced an adverse effect on reproductive ability or capacity or on development in humans or for which there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. For regulatory purposes, a substance can be further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).

CATEGORY 1A: Known to have produced an adverse effect on reproductive ability or capacity or on development in humans

The placing of the substance in this category is largely based on evidence from humans.

CATEGORY 1B: Presumed to produce an adverse effect on reproductive ability or capacity or on development in humans

The placing of the substance in this category is largely based on evidence from experimental animals. Data from animal studies should provide clear evidence of specific reproductive toxicity in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

CATEGORY 2: Suspected human reproductive or developmental toxicant

This Category includes substances for which there is some evidence from humans or experimental animals, - possibly supplemented with other information - of an adverse effect on reproductive ability or capacity, or on development, in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects, and where the evidence is not sufficiently convincing to place the substance in Category 1. For instance, deficiencies in the study may make the quality of evidence less convincing, and in view of this Category 2 could be the more appropriate classification.

Figure 3.7.1 (b): Hazard category for lactation effects

EFFECTS ON OR VIA LACTATION

Effects on or via lactation are allocated to a separate single category. It is appreciated that for many substances there is no information on the potential to cause adverse effects on the offspring via lactation. However, substances which are absorbed by women and have been shown to interfere with lactation, or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, should be classified to indicate this property hazardous to breastfed babies. This classification can be assigned on the basis of:

(a) absorption, metabolism, distribution and excretion studies that would indicate the likelihood the substance would be present in potentially toxic levels in breast milk; and/or

(b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or

(c) human evidence indicating a hazard to babies during the lactation period.

3.7.2.2 *Basis of classification*

3.7.2.2.1 Classification is made on the basis of the appropriate criteria, outlined above, and an assessment of the total weight of evidence. Classification as a reproductive or developmental toxicant is intended to be used for chemicals which have an intrinsic, specific property to produce an adverse effect on reproduction or development and chemicals should not be so classified if such an effect is produced solely as a non-specific secondary consequence of other toxic effects.

3.7.2.2.2 In the evaluation of toxic effects on the developing offspring, it is important to consider the possible influence of maternal toxicity.

3.7.2.2.3 For human evidence to provide the primary basis for a Category 1A classification there must be reliable evidence of an adverse effect on reproduction in humans. Evidence used for classification should ideally be from well conducted epidemiological studies which include the use of appropriate controls, balanced assessment, and due consideration of bias or confounding factors. Less rigorous data from studies in humans should be supplemented with adequate data from studies in experimental animals and classification in Category 1B should be considered.

3.7.2.3 *Weight of evidence*

3.7.2.3.1 Classification as a reproductive toxicant is made on the basis of an assessment of the total weight of evidence. This means that all available information that bears on the determination of reproductive toxicity is considered together. Included is information such as epidemiological studies and case reports in humans and specific reproduction studies along with sub-chronic, chronic and special study results in animals that provide relevant information regarding toxicity to reproductive and related endocrine organs. Evaluation of substances chemically related to the material under study may also be included, particularly when information on the material is scarce. The weight given to the available evidence will be influenced by factors such as the quality of the studies, consistency of results, nature and severity of effects, level of statistical significance for intergroup differences, number of endpoints affected, relevance of route of administration to humans and freedom from bias. Both positive and negative results are assembled together into a weight of evidence determination. However, a single, positive study performed according to good scientific principles and with statistically or biologically significant positive results may justify classification (see also paragraph 3.7.2.2.3).

3.7.2.3.2 Toxicokinetic studies in animals and humans, site of action and mechanism or mode of action study results may provide relevant information, which could reduce or increase concerns about the hazard to human health. If it can be conclusively demonstrated that the clearly identified mechanism or mode of action has no relevance for humans or when the toxicokinetic differences are so marked that it is certain that the hazardous property will not be expressed in humans then a substance which produces an adverse effect on reproduction in experimental animals should not be classified.

3.7.2.3.3 In some reproductive toxicity studies in experimental animals the only effects recorded may be considered of low or minimal toxicological significance and classification may not necessarily be the outcome. These include for example small changes in semen parameters or in the incidence of spontaneous defects in the foetus, small changes in the proportions of common foetal variants such as are observed in skeletal examinations, or in foetal weights, or small differences in postnatal developmental assessments.

3.7.2.3.4 Data from animal studies ideally should provide clear evidence of specific reproductive toxicity in the absence of other, systemic, toxic effects. However, if developmental toxicity occurs together with other toxic effects in the dam, the potential influence of the generalised adverse effects should be assessed to the extent possible. The preferred approach is to consider adverse effects in the embryo/foetus first, and then evaluate maternal toxicity, along with any other factors, which are likely to have influenced these effects, as part of the weight of evidence. In general, developmental effects that are observed at maternally toxic doses should not be automatically discounted. Discounting developmental effects that are observed at maternally toxic doses can only be done on a case-by-case basis when a causal relationship is established or refuted.

3.7.2.3.5 If appropriate information is available it is important to try to determine whether developmental toxicity is due to a specific maternally mediated mechanism or to a non-specific secondary mechanism, like maternal stress and the disruption of homeostasis. Generally, the presence of maternal toxicity should not be used to negate findings of embryo/foetal effects, unless it can be clearly demonstrated that the effects are secondary non-specific effects. This is especially the case when the effects in the offspring are significant, e.g. irreversible effects such as structural malformations. In some situations it is reasonable to assume that reproductive toxicity is due to a secondary consequence of maternal toxicity and discount the effects, for example if the chemical is so toxic that dams fail to thrive and there is severe inanition; they are incapable of nursing pups; or they are prostrate or dying.

3.7.2.4 *Maternal toxicity*

3.7.2.4.1 Development of the offspring throughout gestation and during the early postnatal stages can be influenced by toxic effects in the mother either through non-specific mechanisms related to stress and the disruption of maternal homeostasis, or by specific maternally-mediated mechanisms. So, in the interpretation of the developmental outcome to decide classification for developmental effects it is important to consider the possible influence of maternal toxicity. This is a complex issue because of uncertainties surrounding the relationship between maternal toxicity and developmental outcome. Expert judgement and a weight of evidence approach, using all available studies, should be used to determine the degree of influence that should be attributed to maternal toxicity when interpreting the criteria for classification for developmental effects. The adverse effects in the embryo/foetus should be first considered, and then maternal toxicity, along with any other factors which are likely to have influenced these effects, as weight of evidence, to help reach a conclusion about classification.

3.7.2.4.2 Based on pragmatic observation, it is believed that maternal toxicity may, depending on severity, influence development via non-specific secondary mechanisms, producing effects such as depressed foetal weight, retarded ossification, and possibly resorptions and certain malformations in some strains of certain species. However, the limited numbers of studies which have investigated the relationship between developmental effects and general maternal toxicity have failed to demonstrate a consistent, reproducible relationship across species. Developmental effects, which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case by case basis that the developmental effects are secondary to maternal toxicity. Moreover, classification should be considered where there is significant toxic effect in the offspring, e.g. irreversible effects such as structural malformations, embryo/foetal lethality, significant post-natal functional deficiencies.

3.7.2.4.3 Classification should not automatically be discounted for chemicals that produce developmental toxicity only in association with maternal toxicity, even if a specific maternally-mediated mechanism has been demonstrated. In such a case, classification in Category 2 may be considered more appropriate than Category 1. However, when a chemical is so toxic that maternal death or severe inanition results, or the dams are prostrate and incapable of nursing the pups, it may be reasonable to assume that developmental toxicity is produced solely as a secondary consequence of maternal toxicity and discount the developmental effects. Classification may not necessarily be the outcome in the case of minor developmental changes e.g. small reduction in foetal/pup body weight, retardation of ossification when seen in association with maternal toxicity.

3.7.2.4.4 Some of the end points used to assess maternal toxicity are provided below. Data on these end points, if available, need to be evaluated in light of their statistical or biological significance and dose response relationship.

Maternal mortality: an increased incidence of mortality among the treated dams over the controls should be considered evidence of maternal toxicity if the increase occurs in a dose-related manner and can be attributed to the systemic toxicity of the test material. Maternal mortality greater than 10% is considered excessive and the data for that dose level should not normally be considered for further evaluation.

Mating index (no. animals with seminal plugs or sperm/no. mated × 100) [2]

Fertility index (no. animals with implants/no. of matings × 100) [2]

Gestation length (if allowed to deliver)

Body weight and body weight change: consideration of the maternal body weight change and/or adjusted (corrected) maternal body weight should be included in the evaluation of maternal toxicity whenever such data are available. The calculation of an adjusted (corrected) mean maternal body weight change, which is the difference between the initial and terminal body weight minus the gravid uterine weight (or alternatively, the sum of the weights of the foetuses), may indicate whether the effect is maternal or intrauterine. In rabbits, the body weight gain may not be useful indicators of maternal toxicity because of normal fluctuations in body weight during pregnancy.

Food and water consumption (if relevant): the observation of a significant decrease in the average food or water consumption in treated dams compared to the control group may be useful in evaluating maternal toxicity, particularly when the test material is administered in the diet or drinking water. Changes in food or water consumption should be evaluated in conjunction with maternal body weights when determining if the effects noted are reflective of maternal toxicity or more simply, unpalatability of the test material in feed or water.

Clinical evaluations (including clinical signs, markers, haematology and clinical chemistry studies): The observation of increased incidence of significant clinical signs of toxicity in treated dams relative to the control group may be useful in evaluating maternal toxicity. If this is to be used as the basis for the assessment of maternal toxicity, the types, incidence, degree and duration of clinical signs should be reported in the study. Examples of frank clinical signs of maternal intoxication include: coma, prostration, hyperactivity, loss of righting reflex, ataxia, or laboured breathing.

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[2] *It is recognised that this index can also be affected by the male.*

Post-mortem data: increased incidence and/or severity of post-mortem findings may be indicative of maternal toxicity. This can include gross or microscopic pathological findings or organ weight data, e.g. absolute organ weight, organ-to-body weight ratio, or organ-to-brain weight ratio. When supported by findings of adverse histopathological effects in the affected organ(s), the observation of a significant change in the average weight of suspected target organ(s) of treated dams, compared to those in the control group, may be considered evidence of maternal toxicity.

3.7.2.5 *Animal and experimental data*

3.7.2.5.1 A number of internationally accepted test methods are available; these include methods for developmental toxicity testing (e.g. OECD Test Guideline 414, ICH Guideline S5A, 1993), methods for peri- and post-natal toxicity testing (e.g. ICH S5B, 1995) and methods for one or two-generation toxicity testing (e.g. OECD Test Guidelines 415, 416).

3.7.2.5.2 Results obtained from Screening Tests (e.g. OECD Guidelines 421 - Reproduction/ Developmental Toxicity Screening Test, and 422 - Combined Repeated Dose Toxicity Study with Reproduction/Development Toxicity Screening Test) can also be used to justify classification, although it is recognised that the quality of this evidence is less reliable than that obtained through full studies.

3.7.2.5.3 Adverse effects or changes, seen in short- or long-term repeated dose toxicity studies, which are judged likely to impair reproductive ability or capacity and which occur in the absence of significant generalised toxicity, may be used as a basis for classification, e.g. histopathological changes in the gonads.

3.7.2.5.4 Evidence from *in vitro* assays, or non-mammalian tests, and from analogous substances using structure-activity relationship (SAR), can contribute to the procedure for classification. In all cases of this nature, expert judgement must be used to assess the adequacy of the data. Inadequate data should not be used as a primary support for classification.

3.7.2.5.5 It is preferable that animal studies are conducted using appropriate routes of administration which relate to the potential route of human exposure. However, in practice, reproductive toxicity studies are commonly conducted using the oral route, and such studies will normally be suitable for evaluating the hazardous properties of the substance with respect to reproductive toxicity. However, if it can be conclusively demonstrated that the clearly identified mechanism or mode of action has no relevance for humans or when the toxicokinetic differences are so marked that it is certain that the hazardous property will not be expressed in humans then a substance which produces an adverse effect on reproduction in experimental animals should not be classified.

3.7.2.5.6 Studies involving routes of administration such as intravenous or intraperitoneal injection, which may result in exposure of the reproductive organs to unrealistically high levels of the test substance, or elicit local damage to the reproductive organs, e.g. by irritation, must be interpreted with extreme caution and on their own would not normally be the basis for classification.

3.7.2.5.7 There is general agreement about the concept of a limit dose, above which the production of an adverse effect may be considered to be outside the criteria which lead to classification. However, there was no agreement within the OECD Task Force regarding the inclusion within the criteria of a specified dose as a limit dose. Some Test Guidelines specify a limit dose, other Test Guidelines qualify the limit dose with a statement that higher doses may be necessary if anticipated human exposure is sufficiently high that an adequate margin of exposure would not be achieved. Also, due to species differences in toxicokinetics, establishing a specific limit dose may not be adequate for situations where humans are more sensitive than the animal model.

3.7.2.5.8 In principle, adverse effects on reproduction seen only at very high dose levels in animal studies (for example doses that induce prostration, severe inappetence, excessive mortality) would not normally lead to classification, unless other information is available, e.g. toxicokinetics information indicating that humans

may be more susceptible than animals, to suggest that classification is appropriate. Please also refer to the section on Maternal Toxicity for further guidance in this area.

3.7.2.5.9 However, specification of the actual 'limit dose' will depend upon the test method that has been employed to provide the test results, e.g. in the OECD Test Guideline for repeated dose toxicity studies by the oral route, an upper dose of 1000 mg/kg unless expected human response indicates the need for a higher dose level, has been recommended as a limit dose.

3.7.2.5.10 Further discussions are needed on the inclusion within the criteria of a specified dose as a limit dose.

3.7.3 Classification criteria for mixtures

3.7.3.1 *Classification of mixtures when data are available for the complete mixture*

Classification of mixtures will be based on the available test data of the individual constituents of the mixture using cut-off values/concentration limits for the components of the mixture. The classification may be modified on a case-by case basis based on the available test data for the mixture as a whole. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of reproduction test systems. Adequate documentation supporting the classification should be retained and made available for review upon request.

3.7.3.2 *Classification of mixtures when data are not available for the complete mixture: Bridging Principles*

3.7.3.2.1 Where the mixture itself has not been tested to determine its reproductive toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data will be used in accordance with the following agreed bridging rules. This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity for additional testing in animals.

3.7.3.2.2 *Dilution*

If a mixture is diluted with a diluent which is not expected to affect the reproductive toxicity of other ingredients, then the new mixture may be classified as equivalent to the original mixture.

3.7.3.2.3 *Batching*

The reproductive toxicity potential of one production batch of a complex mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product produced by and under the control of the same manufacturer unless there is reason to believe there is significant variation in composition such that the reproductive toxicity potential of the batch has changed. If the latter occurs, a new classification is necessary.

3.7.3.2.4 *Substantially similar mixtures*

Given the following:

(a) Two mixtures: (i) A + B
(ii) C + B;
(b) The concentration of Ingredient B, toxic to reproduction, is the same in both mixtures;
(c) The concentration of ingredient A in mixture i equals that of ingredient C in mixture ii;
(d) Data on toxicity for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the reproductive toxicity of B.

If mixture (i) is already classified by testing, then mixture (ii) can be assigned the same category.

3.7.3.3 *Classification of mixtures when data are available for all components or only for some components of the mixture*

The mixture will be classified as a reproductive toxicant when at least one ingredient has been classified as a Category 1 or Category 2 reproductive toxicant and is present at or above the appropriate cut-off value/concentration limit as shown in Table 3.7.1 below for Category 1 and 2 respectively.

Table 3.7.1: Cut-off values/concentration limits of ingredients of a mixture classified as reproductive toxicants that would trigger classification of the mixture[3]

Ingredient classified as:	**Cut-off/concentration limits triggering classification of a mixture as:**	
	Category 1 reproductive toxicant	**Category 2 reproductive toxicant**
Category 1 reproductive toxicant	≥ 0.1 % (note 1)	
	≥ 0.3 % (note 2)	
Category 2 reproductive toxicant		≥ 0.1 % (note 3)
		≥ 3.0 % (note 4)

***NOTE 1**: If a Category 1 reproductive toxicant is present in the mixture as an ingredient at a concentration between 0.1% and 0.3%, every regulatory authority would require information on the SDS for a product. However, a label warning would be optional. Some authorities will choose to label when the ingredient is present in the mixture between 0.1% and 0.3%, whereas others would normally not require a label in this case.*

***NOTE 2**: If a Category 1 reproductive toxicant is present in the mixture as an ingredient at a concentration of ≥ 0.3%, both an SDS and a label would generally be expected.*

***NOTE 3**: If a Category 2 reproductive toxicant is present in the mixture as an ingredient at a concentration between 0.1% and 3.0%, every regulatory authority would require information on the SDS for a product. However, a label warning would be optional. Some authorities will choose to label when the ingredient is present in the mixture between 0.1% and 3.0%, whereas others would normally not require a label in this case.*

***NOTE 4**: If a Category 2 reproductive toxicant is present in the mixture as an ingredient at a concentration of ≥ 3.0%, both an SDS and a label would generally be expected.*

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[3] *This compromise classification scheme involves consideration of differences in hazard communication practices in existing systems. It is expected that the number of affected mixtures will be small; the differences will be limited to label warnings; and the situation will evolve over time to a more harmonised approach.*

3.7.3.4 *Criteria for the classification of mixtures containing substances which have effects on lactation*[4]

Harmonized criteria for the classification of mixtures containing substances which have effects on lactation have to date not been developed. The data base for this hazard category is extremely limited, and experience will have to be gained in using the category in the harmonized system before the issue of classification of mixtures containing components which can contaminate breast milk can be addressed. This issue should be considered in the future.

3.7.4 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 3.7.2: Label elements for reproductive toxicity

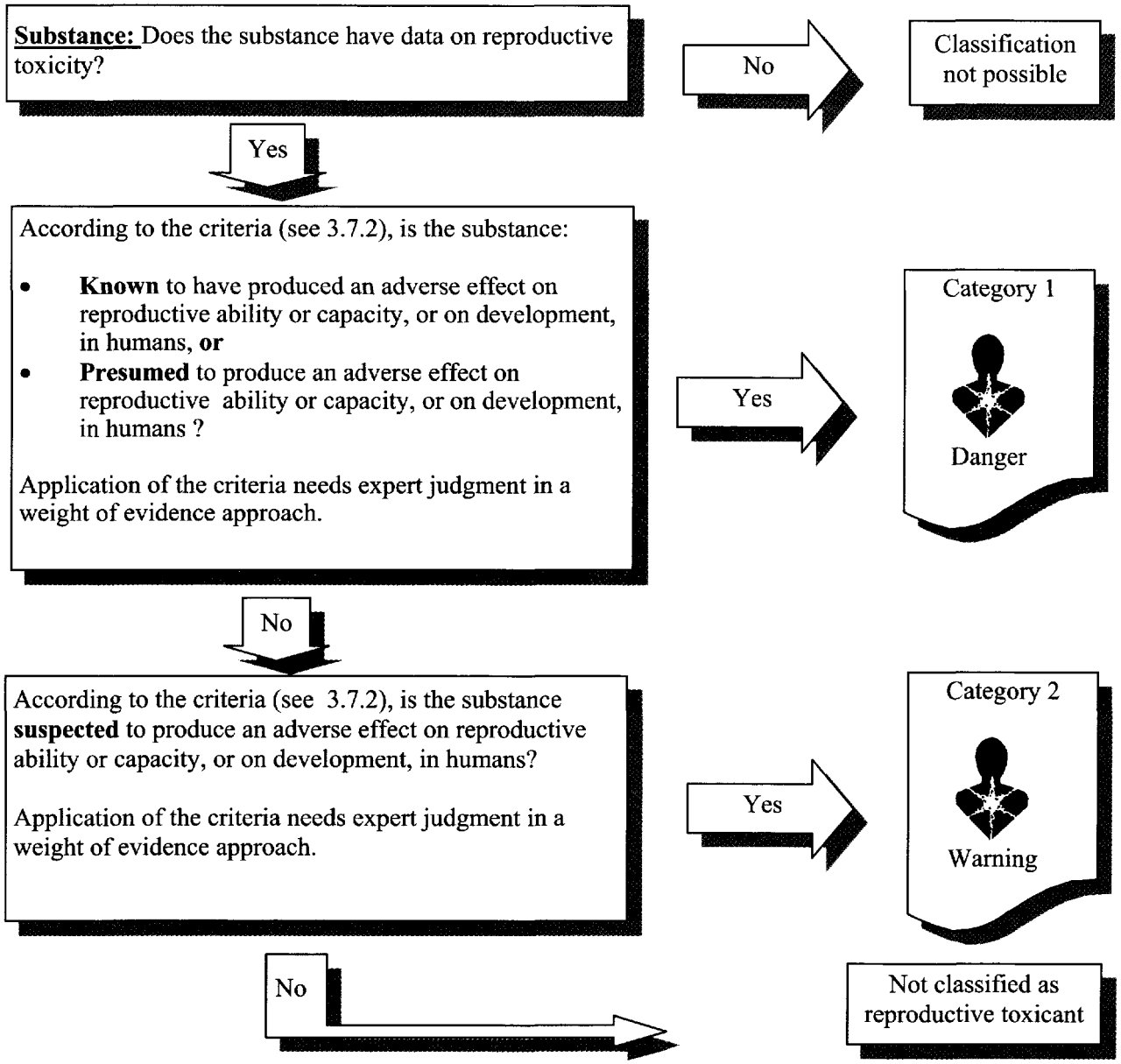
	Category 1A	**Category 1B**	**Category 2**	**Additional category for effects on or via lactation**
Symbol	Health Hazard	Health Hazard	Health Hazard	No symbol
Signal word	Danger	Danger	Warning	No signal word
Hazard statement	May damage fertility or the unborn child (state specific effect if known)or(route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	May damage fertility or the unborn child (state specific effect if known)or(route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	Suspected of damaging fertility or the unborn child (state specific effect if known)or(route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	May cause harm to breast-fed children.

[4] *This text has been provided here to draw attention to this issue, and is not part of the agreed text on the harmonized classification system developed by the OECD Task Force-HCL.*

3.7.5 Decision logic for classification of reproductive toxicity

The decision logic which follows is not part of the harmonized classification system but is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

3.7.5.1 *Decision logic 3.7.1 for substances*



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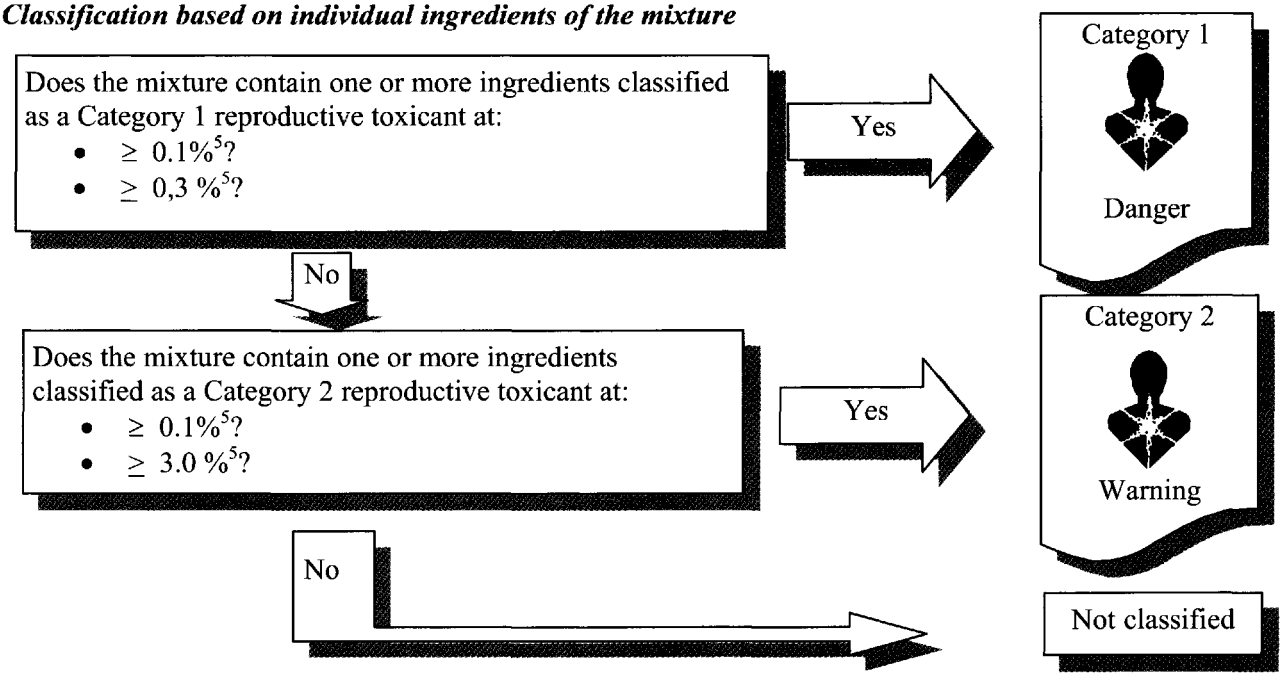
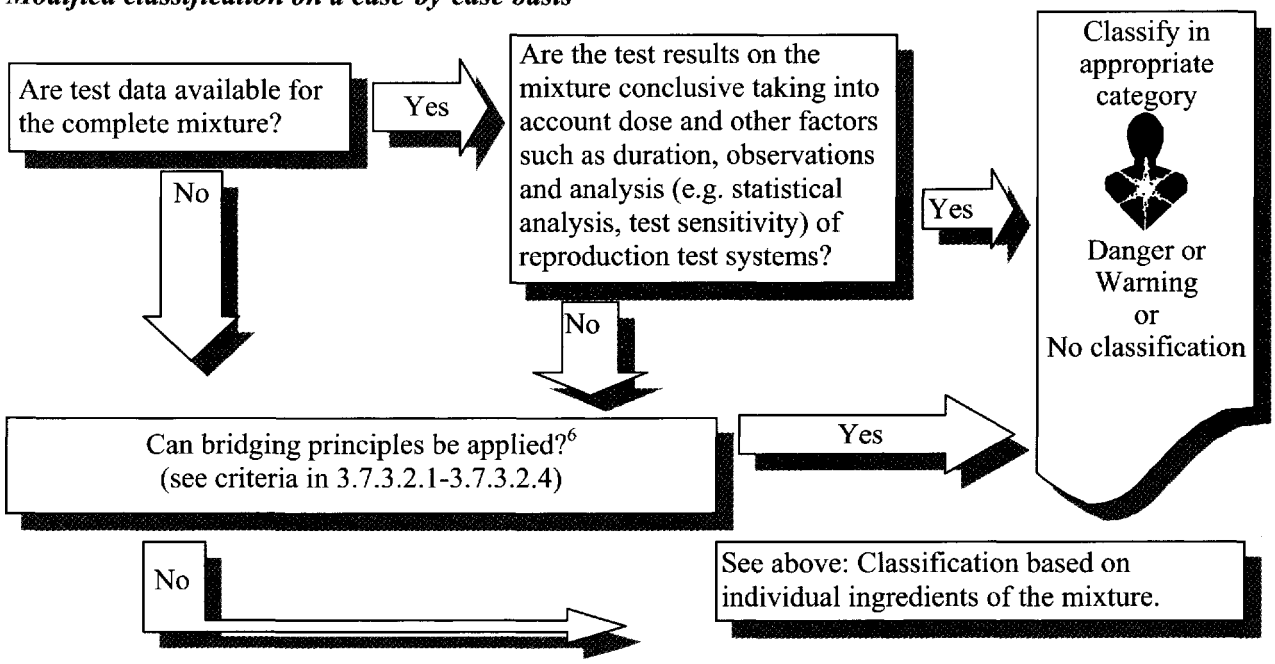
3.7.5.2 *Decision logic 3.7.2 for mixtures*

Mixture: Classification of mixtures will be based on the available test data for the **individual ingredients** of the mixture, using cut-off values/concentration limits for those ingredients. The classification may be **modified on a case-by-case basis** based on the available test data for the mixture as a whole or based on bridging principles. See modified classification on a case-by-case basis below. For further details see criteria (See 3.7.3.1, 3.7.3.2 and 3.7.3.3).

Classification based on individual ingredients of the mixture



Modified classification on a case-by-case basis



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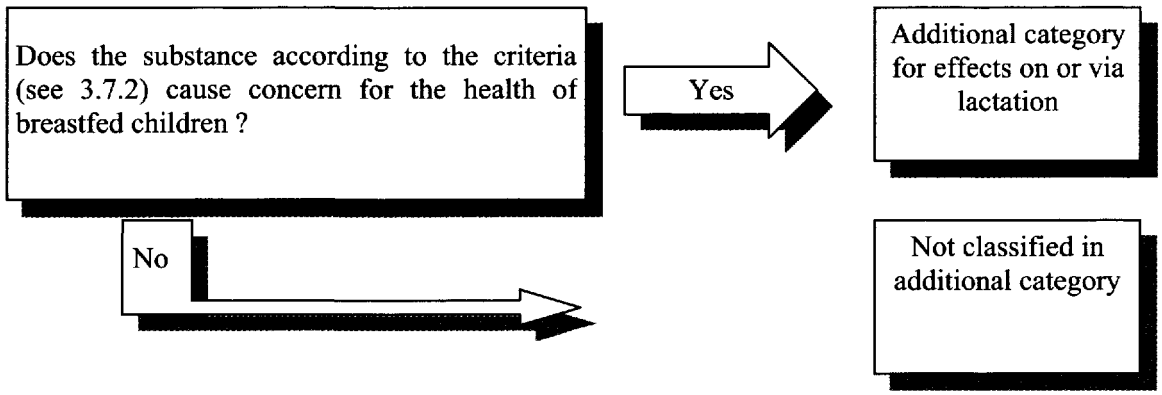
[5] *For specific concentration limits, see "The use of Cut-off Values/Concentration Limits" in Chapter1.3, para. 1.3.3.2, and in Table 3.7.of this Chapter.*

[6] *If data on another mixture are used in the application of bridging principles, the data on that mixture must be conclusive in accordance with paragraph 3.7.3.1.*

3.7.6 Decision logic for classification of effects on or via lactation

Decision logic 3.7.3



CHAPTER 3.8

SPECIFIC TARGET ORGAN SYSTEMIC TOXICITY - SINGLE EXPOSURE

3.8.1 Definitions and general considerations

3.8.1.1 The purpose of this chapter is to provide a means of classifying substances that produce specific, non lethal target organ/systemic toxicity arising from a single exposure. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included.

3.8.1.2 Classification identifies the chemical substance as being a specific target organ/systemic toxicant and, as such, it may present a potential for adverse health effects in people who are exposed to it.

3.8.1.3 Classification depends upon the availability of reliable evidence that a single exposure to the substance has produced a consistent and identifiable toxic effect in humans, or, in experimental animals, toxicologically significant changes which have affected the function or morphology of a tissue/organ, or has produced serious changes to the biochemistry or haematology of the organism and these changes are relevant for human health. It is recognised that human data will be the primary source of evidence for this hazard class.

3.8.1.4 Assessment should take into consideration not only significant changes in a single organ or biological system but also generalised changes of a less severe nature involving several organs.

3.8.1.5 Specific target organ/systemic toxicity can occur by any route that is relevant for humans, i.e. principally oral, dermal or inhalation.

3.8.1.6 Specific target organ/systemic toxicity following a repeated exposure is classified in the GHS as described in *Target Organ Systemic Toxicity – Repeated Exposure* (Chapter 3.9) and is therefore excluded from the present chapter. Other specific toxic effects, such as acute lethality/toxicity, serious damage to eyes/irritation and skin corrosivity/irritation, skin and respiratory sensitization, carcinogenicity, mutagenicity and reproductive toxicity are assessed separately in the GHS and consequently are not included here.

3.8.2 Classification criteria for substances

3.8.2.1 Substances are classified for immediate or delayed effects separately, by the use of expert judgement on the basis of the weight of all evidence available, including the use of recommended guidance values (see 3.8.2.9). Then substances are placed in one of two categories, depending upon the nature and severity of the effect(s) observed.

Figure 3.8.1: Categories for specific target organ systemic toxicity/single exposure

CATEGORY 1: Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following single exposure

Placing a substance in Category 1 is done on the basis of:

- reliable and good quality evidence from human cases or epidemiological studies; or,
- observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.9) to be used as part of weight-of-evidence evaluation.

CATEGORY 2: Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following single exposure

Placing a substance in Category 2 is done on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.9) in order to help in classification.
In exceptional cases, human evidence can also be used to place a substance in Category 2 (see 3.8.2.9).

NOTE: *For both categories the specific target organ/system that has been primarily affected by the classified substance may be identified, or the substance may be identified as a general systemic toxicant. Attempts should be made to determine the primary target organ of toxicity and classify for that purpose, e.g. hepatoxicants, neurotoxicants. One should carefully evaluate the data and, where possible, not include secondary effects, e.g. a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems.*

3.8.2.2 The relevant route of exposure by which the classified substance produces damage should be identified.

3.8.2.3 Classification is determined by expert judgement, on the basis of the weight of all evidence available including the guidance presented below.

3.8.2.4 Weight of evidence of all data, including human incidents, epidemiology, and studies conducted in experimental animals, is used to substantiate specific target organ/systemic toxic effects that merit classification.

3.8.2.5 The information required to evaluate specific target organ/systemic toxicity comes either from single exposure in humans, e.g. exposure at home, in the workplace or environmentally, or from studies conducted in experimental animals. The standard animal studies in rats or mice that provide this information are acute toxicity studies which can include clinical observations and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/organs to be identified. Results of acute toxicity studies conducted in other species may also provide relevant information.

3.8.2.6 In exceptional cases, based on expert judgement, it may be appropriate to place certain substances with human evidence of target organ/systemic toxicity in Category 2: (a) when the weight of human evidence is not sufficiently convincing to warrant Category 1 classification, and/or (b) based on the nature and severity of effects. Dose/concentration levels in humans should not be considered in the

classification and any available evidence from animal studies should be consistent with the Category 2 classification. In other words, if there are also animal data available on the chemical that warrant Category 1 classification, the chemical should be classified as Category 1.

3.8.2.7 *Effects considered to support classification*

3.8.2.7.1 Evidence associating single exposure to the substance with a consistent and identifiable toxic effect demonstrates support for classification.

3.8.2.7.2 It is recognised that evidence from human experience/incidents is usually restricted to reports of adverse health consequences, often with uncertainty about exposure conditions, and may not provide the scientific detail that can be obtained from well-conducted studies in experimental animals.

3.8.2.7.3 Evidence from appropriate studies in experimental animals can furnish much more detail, in the form of clinical observations, and macroscopic and microscopic pathological examination - and this can often reveal hazards that may not be life-threatening but could indicate functional impairment. Consequently all available evidence, and relevance to human health, must be taken into consideration in the classification process. Examples of relevant toxic effects in humans and/or animals are provided below:

- Morbidity resulting from single exposure;
- Significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (e.g. sight, hearing and sense of smell);
- Any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters;
- Significant organ damage that may be noted at necropsy and/or subsequently seen or confirmed at microscopic examination;
- Multifocal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;
- Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction;
- Evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

3.8.2.8 *Effects considered not to support classification*

It is recognised that effects may be seen that would not justify classification. Examples of such effects in humans and/or animals are provided below:

- Clinical observations or small changes in bodyweight gain, food consumption or water intake that may have some toxicological importance but that do not, by themselves, indicate "significant" toxicity;
- Small changes in clinical biochemistry, haematology or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance;
- Changes in organ weights with no evidence of organ dysfunction;
- Adaptive responses that are not considered toxicologically relevant;
- Substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, should not justify classification;

- Where there are only local effects, at the site of administration for the routes tested, and especially when adequate testing by other principal routes show lack of specific target organ/systemic toxicity.

3.8.2.9 *Guidance values to assist with classification based on the results obtained from studies conducted in experimental animals*

3.8.2.9.1 In order to help reach a decision about whether a substance should be classified or not, and to what degree it would be classified (Category 1 vs. Category 2), dose/concentration 'guidance values' are provided for consideration of the dose/concentration which has been shown to produce significant health effects. The principal argument for proposing such guidance values is that all chemicals are potentially toxic and there has to be a reasonable dose/concentration above which a degree of toxic effect is acknowledged.

3.8.2.9.2 Thus, in animal studies, when significant toxic effects are observed, that would indicate classification, consideration of the dose/concentration at which these effects were seen, in relation to the suggested guidance values, can provide useful information to help assess the need to classify (since the toxic effects are a consequence of the hazardous property(ies) and also the dose/concentration).

3.8.2.9.3 The guidance value ranges proposed for single-dose exposure which has produced a significant non-lethal toxic effect are those applicable to acute toxicity testing, as indicated in Table 3.8.1.

Table 3.8.1: Guidance value ranges for single-dose exposures

		Guidance value ranges for :	
Route of exposure	**Units**	**Category 1**	**Category 2**
Oral (rat)	mg/kg body weight	$C \leq 300$	$2000 \geq C > 300$
Dermal (rat or rabbit)	mg/kg body weight	$C \leq 1000$	$2000 \geq C > 1000$
Inhalation (rat) gas	ppm	$C \leq 2500$	$5000 \geq C > 2500$
Inhalation (rat) vapour	mg/1	$C \leq 10$	$20 > C > 10$
Inhalation (rat) dust/mist/fume	mg/l/4h	$C \leq 1.0$	$5.0 > C > 1.0$

The guidance values and ranges mentioned in Table 3.8.1 above are intended only for guidance purposes, i.e. to be used as part of the weight of evidence approach, and to assist with decision about classification. They are *not intended as strict demarcation values.*

3.8.2.9.4 Thus it is feasible that a specific profile of toxicity is seen to occur at a dose/concentration below the guidance value, e.g. <2000 mg/kg body weight by the oral route, however the nature of the effect may result in the decision not to classify. Conversely, a specific profile of toxicity may be seen in animal studies occurring at above a guidance value, eg. At or above 2000 mg/kg body weight by the oral route, and in addition there is supplementary information from other sources, e.g. other single dose studies, or human case experience, which supports a conclusion that, in view of the weight of evidence, classification would be the prudent action to take.

3.8.2.10 *Other considerations*

3.8.2.10.1 When a chemical is characterised only by use of animal data (typical of new chemicals, but also true for many existing chemicals), the classification process would include reference to dose/concentration guidance values as one of the elements that contribute to the weight of evidence approach.

3.8.2.10.2 When well-substantiated human data are available showing a specific target organ/systemic toxic effect that can be reliably attributed to single exposure to a chemical substance, the substance may be classified. Positive human data, regardless of probable dose, predominates over animal data. Thus, if a chemical is unclassified because specific target organ/systemic toxicity observed was considered not relevant or significant to humans, if subsequent human incident data become available showing a specific target organ/systemic toxic effect, the substance should be classified.

3.8.2.10.3 A chemical that has not been tested for specific target organ/systemic toxicity may in certain instances, where appropriate, be classified on the basis of data from a validated structure activity relationship and expert judgement-based extrapolation from a structural analogue that has previously been classified together with substantial support from consideration of other important factors such as formation of common significant metabolites.

3.8.2.10.4 It is recognised that saturated vapour concentration may be used as an additional element by some regulatory systems to provide for specific health and safety protection.

3.8.3 Classification criteria for mixtures

3.8.3.1 Mixtures are classified using the same criteria as for substances, or alternatively as described below. As with substances, mixtures may be classified for target organ/systemic toxicity following single exposure, repeated exposure, or both.

3.8.3.2 *Classification of mixtures when data are available for the complete mixture*

When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture can be classified by weight of evidence evaluation of this data. Care should be exercised in evaluating data on mixtures, that the dose, duration, observation or analysis, do not render the results inconclusive.

3.8.3.3 *Classification of mixtures when data are not available for the complete mixture: Bridging principles*

3.8.3.3.1 Where the mixture itself has not been tested to determine its target organ/systemic toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data can be used in accordance with the following bridging principles. This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity of additional testing in animals.

3.8.3.3.2 *Dilution*

If a mixture is diluted with a diluent which has the same or a lower toxicity classification as the least toxic original ingredient and which is not expected to affect the toxicity of other ingredients, then the new mixture may be classified as equivalent to the original mixture.

3.8.3.3.3 *Batching*

The toxicity of one production batch of a complex mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product and produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the toxicity of the batch has changed. If the latter occurs, a new classification is necessary.

3.8.3.3.4 *Concentration of highly toxic mixtures*

If in a mixture of category 1, the concentration of a toxic ingredient is increased, the concentrated mixture should be classified in category 1 without additional testing.

3.8.3.3.5 *Interpolation within one toxicity category*

For three mixtures with identical ingredients, where A and B are in the same toxicity category and mixture C has the same toxicologically active ingredients with concentrations intermediate to the concentrations of those ingredients in mixtures A and B, then mixture C is assumed to be in the same toxicity category as A and B.

3.8.3.3.6 *Substantially similar mixtures*

Given the following:

(a) Two mixtures: (i) A + B
(ii) C + B;
(b) The concentration of ingredient B is essentially the same in both mixtures;
(c) The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);
(d) Data on toxicity for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the toxicity of B.

If mixture (i) is already classified by testing, then mixture (ii) can be assigned the same category.

3.8.3.3.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested, non-aerosolised form of the mixture for oral and dermal toxicity provided the added propellant does not affect the toxicity of the mixture on spraying. Classification of aerosolised mixtures for inhalation toxicity should be considered separately.

3.8.3.4 *Classification of mixtures when data are available for all components or only for some components of the mixture*

3.8.3.4.1 Where there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredient substances. In this case, the mixture will be classified as a target organ/systemic toxicant (specific organ specified), following single exposure, repeat exposure, or both when at least one ingredient has been classified as a Category 1 or Category 2 target organ/systemic toxicant and is present at or above the appropriate cut-off value/concentration limit as mentioned in Table 3.8.2 below for Category 1 and 2 respectively.

Table 3.8.2: Cut-off values/concentration limits of ingredients of a mixture classified as a target organ/ systemic toxicant that would trigger classification of the mixture[1]

Ingredient **Classified as:**	**Cut-off/concentration limits triggering classification of a mixture as:**	
	Category 1	**Category 2**
Category 1 **Target Organ Systemic Toxicant**	≥ 1.0 % (note 1) ≥ 10 % (note 2)	1.0≤ ingredient < 10% (note 3)
Category 2 **Target Organ Systemic Toxicant**		≥ 1.0 % (note 4) ≥ 10 % (note 5)

NOTE 1: *If a Category 1 target organ/systemic toxicant is present in the mixture as an ingredient at a concentration between 1.0% and 10%, every regulatory authority would require information on the SDS for a product. However, a label warning would be optional. Some authorities will choose to label when the ingredient is present in the mixture between 1.0% and 10%, whereas others would normally not require a label in this case.*

NOTE 2: *If a Category 1 target organ/systemic toxicant is present in the mixture as an ingredient at a concentration of ≥ 10%, both an SDS and a label would generally be expected.*

NOTE 3: *If a Category 1 target organ/systemic toxicant is present in the mixture as an ingredient at a concentration between 1.0% and 10%, some authorities classify this mixture as a Category 2 target organ/systemic toxicant, whereas others would not.*

NOTE 4: *If a Category 2 target organ/systemic toxicant is present in the mixture as an ingredient at a concentration between 1.0% and 10%, every regulatory authority would require information on the SDS for a product. However, a label warning would be optional. Some authorities will choose to label when the ingredient is present in the mixture between 1.0% and 10%, whereas others would normally not require a label in this case.*

NOTE 5: *If a Category 2 target organ/systemic toxicant is present in the mixture as an ingredient at a concentration of ≥ 10%, both an SDS and a label would generally be expected.*

These cut-off values and consequent classifications should be applied equally and appropriately to both single- and repeated-dose target organ toxicants.

3.8.3.4.3 Mixtures should be classified for either or both single- and repeated-dose toxicity independently.

3.8.3.4.4 Care should be exercised when toxicants affecting more than one organ system are combined that the potentiation or synergistic interactions are considered, because certain substances can cause target organ toxicity at <1% concentration when other ingredients in the mixture are known to potentiate its toxic effect.

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[1] *This compromise classification scheme involves consideration of differences in hazard communication practices in existing systems. It is expected that the number of affected mixtures will be small; the differences will be limited to label warnings; and the situation will evolve over time to a more harmonised approach.*

3.8.4 Hazard communication

3.8.4.1 General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

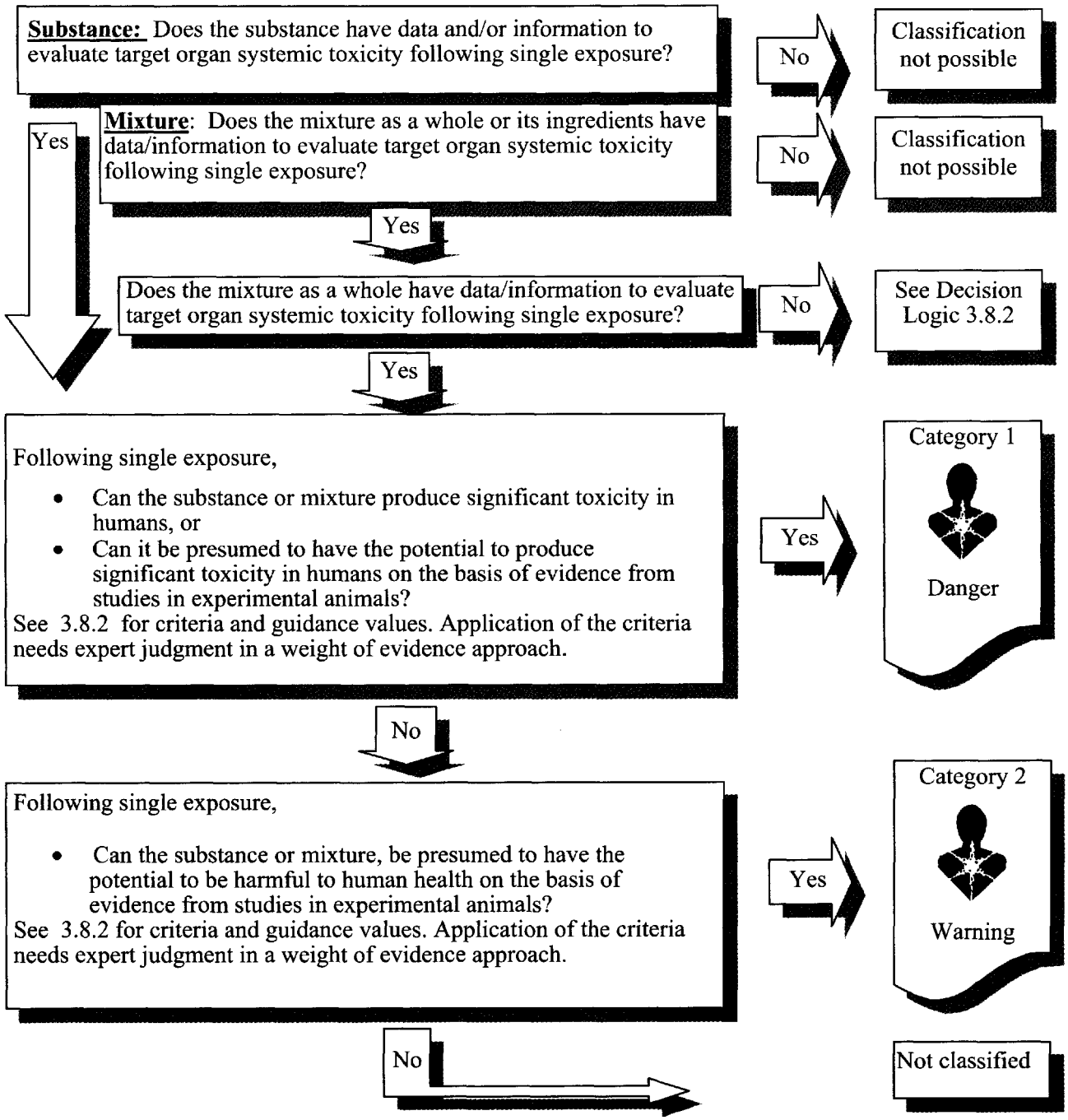
Table 3.8.3: Label elements for target organ systemic toxicity after single exposure

	Category 1	**Category 2**
Symbol	Health Hazard	Health Hazard
Signal word	Danger	Warning
Hazard statement	Causes damage to organs (or state all organs affected, if known) if (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	May cause damage to organs (or state all organs affected, if known) if (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)

3.8.5 Decision logic for Target Organ Systemic Toxicity from single exposure

The decision logic which follows is not part of the harmonized classification system but is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

Decision logic 3.8.1



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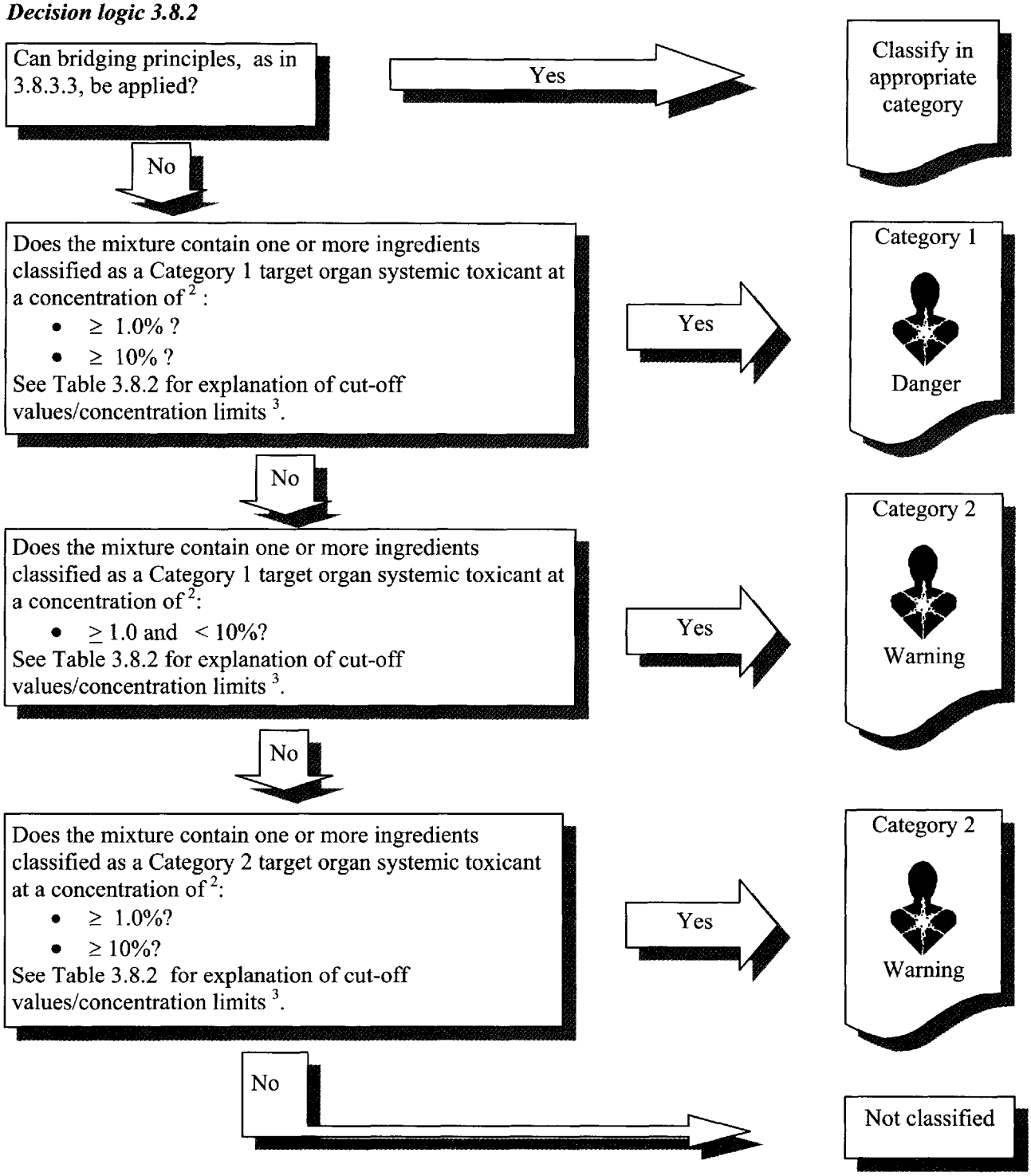
Decision logic 3.8.2



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[2] *See 3.8.2 of this Chapter and "The Use of Cut-off Values/Concentration Limits" in Chapter 1.3, para. 1.3.3.2.*

[3] *See 3.8.3.4 and Table 3.8.2 for explanation and guidance.*

CHAPTER 3.9

SPECIFIC TARGET ORGAN SYSTEMIC TOXICITY - REPEATED EXPOSURE

3.9.1 Definitions and general considerations

3.9.1.1 The purpose of this document is to provide a means of classifying substances that produce specific target organ/systemic toxicity arising from a repeated exposure. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included.

3.9.1.2 Classification identifies the chemical substance as being a specific target organ/systemic toxicant and, as such, it may present a potential for adverse health effects in people who are exposed to it.

3.9.1.3 Classification depends upon the availability of reliable evidence that a repeated exposure to the substance has produced a consistent and identifiable toxic effect in humans, or, in experimental animals, toxicologically significant changes which have affected the function or morphology of a tissue/organ, or has produced serious changes to the biochemistry or haematology of the organism and these changes are relevant for human health. It is recognised that human data will be the primary source of evidence for this hazard class.

3.9.1.4 Assessment should take into consideration not only significant changes in a single organ or biological system but also generalised changes of a less severe nature involving several organs.

3.9.1.5 Specific target organ/systemic toxicity can occur by any route that is relevant for humans, i.e. principally oral, dermal or inhalation.

3.9.1.6 Non-lethal toxic effects observed after a single-event exposure are classified in the GHS as described in *Specific Target Organ Systemic Toxicity – Single Exposure* (Chapter 3.8) and are therefore excluded from the present chapter._Other specific toxic effects, such as acute lethality/toxicity, serious damage to eyes/eye irritation and skin corrosivity/irritation, skin and respiratory sensitization, carcinogenicity, mutagenicity and reproductive toxicity are assessed separately in the GHS and consequently are not included here.

3.9.2 Classification criteria for substances

3.9.2.1 Substances are classified as specific target organ/systemic toxicant by expert judgement on the basis of the weight of all evidence available, including the use of recommended guidance values which take into account the duration of exposure and the dose/concentration which produced the effect(s), (see 3.9.2.9), and are placed in one of two categories, depending upon the nature and severity of the effect(s) observed.

Figure 3.9.1: Categories for specific target organ systemic toxicity/repeated exposure

CATEGORY 1: Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following repeated exposure

Placing a substance in Category 1 is done on the basis of:

- reliable and good quality evidence from human cases or epidemiological studies; or,
- observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) to be used as part of weight-of- evidence evaluation.

CATEGORY 2: Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure

Placing a substance in Category 2 is done on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) in order to help in classification.

In exceptional cases human evidence can also be used to place a substance in Category 2 (see 3.9.2.6).

NOTE: *For both categories the specific target organ/system that has been primarily affected by the classified substance may be identified, or the substance may be identified as a general systemic toxicant. Attempts should be made to determine the primary target organ of toxicity and classify for that purpose, e.g. hepatoxicants, neurotoxicants. One should carefully evaluate the data and, where possible, not include secondary effects, e.g. a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems.*

3.9.2.2 The relevant route of exposure by which the classified substance produces damage should be identified.

3.9.2.3 Classification is determined by expert judgement, on the basis of the weight of all evidence available including the guidance presented below.

3.9.2.4 Weight of evidence of all data, including human incidents, epidemiology, and studies conducted in experimental animals, is used to substantiate specific target organ/systemic toxic effects that merit classification. This taps the considerable body of industrial toxicology data collected over the years. Evaluation should be based on all existing data, including peer-reviewed published studies and additional data acceptable to regulatory agencies.

3.9.2.5 The information required to evaluate specific target organ/systemic toxicity comes either from repeated exposure in humans, e.g. exposure at home, in the workplace or environmentally, or from studies conducted in experimental animals. The standard animal studies in rats or mice that provide this information are 28 day, 90 day or lifetime studies (up to 2 years) that include haematological, clinicochemical and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/organs to be

identified. Data from repeat dose studies performed in other species may also be used. Other long-term exposure studies, eg. for carcinogenicity, neurotoxicity or reproductive toxicity, may also provide evidence of specific target organ/systemic toxicity that could be used in the assessment of classification.

3.9.2.6 In exceptional cases, based on expert judgement, it may be appropriate to place certain substances with human evidence of target organ/systemic toxicity in Category 2: (a) when the weight of human evidence is not sufficiently convincing to warrant Category 1 classification, and/or (b) based on the nature and severity of effects. Dose/concentration levels in humans should not be considered in the classification and any available evidence from animal studies should be consistent with the Category 2 classification. In other words, if there are also animal data available on the chemical that warrant Category 1 classification, the chemical should be classified as Category 1.

3.9.2.7 ***Effects considered to support classification***

3.9.2.7.1 Reliable evidence associating repeated exposure to the substance with a consistent and identifiable toxic effect demonstrates support for classification.

3.9.2.7.2 It is recognised that evidence from human experience/incidents is usually restricted to reports of adverse health consequences, often with uncertainty about exposure conditions, and may not provide the scientific detail that can be obtained from well-conducted studies in experimental animals.

3.9.2.7.3 Evidence from appropriate studies in experimental animals can furnish much more detail, in the form of clinical observations, haematology, clinical chemistry, macroscopic and microscopic pathological examination - and this can often reveal hazards that may not be life-threatening but could indicate functional impairment. Consequently all available evidence, and relevance to human health, must be taken into consideration in the classification process. Examples of relevant toxic effects in humans and/or animals are provided below:

- Morbidity or death resulting from repeated or long-term exposure. Morbidity or death may result from repeated exposure, even to relatively low doses/concentrations, due to bioaccumulation of the substance or its metabolites, or due to the overwhelming of the de-toxification process by repeated exposure;
- Significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (e.g. sight, hearing and sense of smell);
- Any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters;
- Significant organ damage that may be noted at necropsy and/or subsequently seen or confirmed at microscopic examination;
- Multifocal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;
- Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g. severe fatty change in the liver);
- Evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

3.9.2.8 ***Effects considered not to support classification***

It is recognised that effects may be seen that would not justify classification. Examples of such effects in humans and/or animals are provided below:

- Clinical observations or small changes in bodyweight gain, food consumption or water intake that may have some toxicological importance but that do not, by themselves, indicate "significant" toxicity;
- Small changes in clinical biochemistry, haematology or urinalysis parameters and /or transient effects, when such changes or effects are of doubtful or minimal toxicological importance;
- Changes in organ weights with no evidence of organ dysfunction;
- Adaptive responses that are not considered toxicologically relevant;
- Substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, should not justify classification.

3.9.2.9 *Guidance values to assist with classification based on the results obtained from studies conducted in experimental animals*

3.9.2.9.1 In studies conducted in experimental animals, reliance on observation of effects alone, without reference to the duration of experimental exposure and dose/concentration, omits a fundamental concept of toxicology, i.e. all substances are potentially toxic, and what determines the toxicity is a function of the dose/concentration and the duration of exposure. In most studies conducted in experimental animals the test guidelines use an upper limit dose value.

3.9.2.9.2 In order to help reach a decision about whether a substance should be classified or not, and to what degree it would be classified (Category 1 vs. Category 2), dose/concentration 'guidance values' are provided in Table 3.9.1 for consideration of the dose/concentration which has been shown to produce significant health effects. The principal argument for proposing such guidance values is that all chemicals are potentially toxic and there has to be a reasonable dose/concentration above which a degree of toxic effect is acknowledged. Also, repeated-dose studies conducted in experimental animals are designed to produce toxicity at the highest dose used in order to optimise the test objective - and so most studies will reveal some toxic effect at least at this highest dose. What is therefore to be decided is not only what effects have been produced, but also at what dose/concentration they were produced and how relevant is that for humans.

3.9.2.9.3 Thus, in animal studies, when significant toxic effects are observed, that would indicate classification, consideration of the duration of experimental exposure and the dose/concentration at which these effects were seen, in relation to the suggested guidance values, can provide useful information to help assess the need to classify (since the toxic effects are a consequence of the hazardous property(ies) and also the duration of exposure and the dose/concentration).

3.9.2.9.4 The decision to classify at all can be influenced by reference to the dose/concentration guidance values at or below which a significant toxic effect has been observed.

3.9.2.9.5 The guidance values proposed refer basically to effects seen in a standard 90-day toxicity study conducted in rats. They can be used as a basis to extrapolate equivalent guidance values for toxicity studies of greater or lesser duration, using dose/exposure time extrapolation similar to Haber's rule for inhalation, which states essentially that the effective dose is directly proportional to the exposure concentration and the duration of exposure. The assessment should be done on a case-by-case basis; e.g. for a 28-day study the guidance values below would be increased by a factor of three.

3.9.2.9.6 Thus for Category 1 classification, significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals and seen to occur at or below the (suggested) guidance values as indicated in Table 3.9.1 would justify classification:

Table 3.9.1: Guidance values to assist in Category 1 classification

Route of exposure	Units	Guidance values (dose/concentration)
Oral (rat)	mg/kg bw/d	10
Dermal (rat or rabbit)	mg/kg bw/d	20
Inhalation (rat)gas	ppm/6h/d	50
Inhalation (rat)vapour	mg/litre/6h/d	0.2
Inhalation (rat) dust/mist/fume	mg/litre/6h/d	0.02

Note: "bw" is for "body weight", "h" for" hour" and "d" for "day".

3.9.2.9.7 For Category 2 classification, significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals and seen to occur within the (suggested) guidance value ranges as indicated in Table 3.9.2 would justify classification:

Table 3.9.2: Guidance values to assist in Category 2 classification

Route of Exposure	Units	Guidance Value Ranges: (dose/concentration)
Oral (rat)	mg/kg bw/d	10 - 100
Dermal (rat or rabbit)	mg/kg bw/d	20 - 200
Inhalation (rat) gas	ppm/6h/d	50 - 250
Inhalation (rat)vapour	mg/litre/6h/d	0.2 - 1.0
Inhalation (rat) dust/mist/fume	mg/litre/6h/d	0.02 - 0.2

Note: bw is for body weight, "h" for" hour" and "d" for "day".

3.9.2.9.8 The guidance values and ranges mentioned in paragraphs 3.2.9.9.6 and 3.2.9.9.7 are intended only for guidance purposes, i.e. to be used as part of the weight of evidence approach, and to assist with decisions about classification. They are not intended as strict demarcation values.

3.9.2.9.9 Thus it is feasible that a specific profile of toxicity is seen to occur in repeat-dose animal studies at a dose/concentration below the guidance value, eg. <100 mg/kg bw/day by the oral route, however the nature of the effect, e.g. nephrotoxicity seen only in male rats of a particular strain known to be susceptible to this effect, may result in the decision not to classify. Conversely, a specific profile of toxicity may be seen in animal studies occurring at above a guidance value, eg. at or above 100 mg/kg bw/day by the oral route, and in addition there is supplementary information from other sources, e.g. other long-term administration studies, or human case experience, which supports a conclusion that, in view of the weight of evidence, classification would be the prudent action to take.

3.9.2.10 *Other considerations*

3.9.2.10.1 When a chemical is characterised only by use of animal data (typical of new chemicals, but also true for many existing chemicals), the classification process would include reference to dose/concentration guidance values as one of the elements that contribute to the weight of evidence approach.

3.9.2.10.2 When well-substantiated human data are available showing a specific target organ/systemic toxic effect that can be reliably attributed to repeated or prolonged exposure to a chemical substance, the substance may be classified. Positive human data, regardless of probable dose, predominates over animal

data. Thus, if a chemical is unclassified because no specific target organ/systemic toxicity was seen at or below the proposed dose/concentration guidance value for animal testing, if subsequent human incident data become available showing a specific target organ/systemic toxic effect, the substance should be classified.

3.9.2.10.3 A chemical that has not been tested for specific target organ/systemic toxicity may in certain instances, where appropriate, be classified on the basis of data from a validated structure activity relationship and expert judgement-based extrapolation from a structural analogue that has previously been classified together with substantial support from consideration of other important factors such as formation of common significant metabolites.

3.9.2.10.4 It is recognised that saturated vapour concentration may be used as an additional element by some regulatory systems to provide for specific health and safety protection.

3.9.3 Classification criteria for mixtures

3.9.3.1 Mixtures are classified using the same criteria as for substances, or alternatively as described below. As with substances, mixtures may be classified for target organ/systemic toxicity following single exposure, repeated exposure, or both.

3.9.3.2 *Classification of mixtures when data are available for the complete mixture*

When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture can be classified by weight of evidence evaluation of this data. Care should be exercised in evaluating data on mixtures, that the dose, duration, observation or analysis, do not render the results inconclusive.

3.9.3.3 *Classification of mixtures when data are not available for the complete mixture: Bridging principles*

3.9.3.3.1 Where the mixture itself has not been tested to determine its target organ/systemic toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data can be used in accordance with the following bridging principles. This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity of additional testing in animals.

3.9.3.3.2 *Dilution*

If a mixture is diluted with a diluent which has the same or a lower toxicity classification as the least toxic original ingredient and which is not expected to affect the toxicity of other ingredients, then the new mixture may be classified as equivalent to the original mixture.

3.9.3.3.3 *Batching*

The toxicity of one production batch of a complex mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product and produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the toxicity of the batch has changed. If the latter occurs, new classification is necessary.

3.9.3.3.4 *Concentration of highly toxic mixtures*

If in a mixture of category 1, the concentration of a toxic ingredient is increased, the concentrated mixture should be classified in category 1 without additional testing

3.9.3.3.5 *Interpolation within one toxicity category*

For three mixtures with identical ingredients, where A and B are in the same toxicity category and mixture C has the same toxicologically active ingredients with concentrations intermediate to the concentrations of those ingredients in mixtures A and B, then mixture C is assumed to be in the same toxicity category as A and B.

3.9.3.3.6 *Substantially similar mixtures*

Given the following:

(a) Two mixtures: (i) A + B
(ii) C + B;
(b) The concentration of ingredient B is essentially the same in both mixtures;
(c) The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);
(d) Data on toxicity for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the toxicity of B.

If mixture (i) is already classified by testing, then mixture (ii) can assigned the same category.

3.9.3.3.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested, non-aerosolised form of the mixture for oral and dermal toxicity provided the added propellant does not affect the toxicity of the mixture on spraying. Classification of aerosolised mixtures for inhalation toxicity should be considered separately.

3.9.3.4 *Classification of mixtures when data are available for all components or only for some components of the mixture*

3.9.3.4.1 Where there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredient substances. In this case, the mixture will be classified as a target organ/systemic toxicant (specific organ specified), following single exposure, repeat exposure, or both when at least one ingredient has been classified as a Category 1 or Category 2 target organ/systemic toxicant and is present at or above the appropriate cut-off value/concentration limit as mentioned in Table 3.9.3 for Category 1 and 2 respectively.

Table 3.9.3: Cut-off values/concentration limits of ingredients of a mixture classified as a target organ/ systemic toxicant that would trigger classification of the mixture.[1]

Ingredient **Classified as:**	**Cut-off/concentration limits triggering classification of a mixture as:**	
	Category 1	**Category 2**
Category 1 **Target Organ Systemic Toxicant**	≥ 1.0 % (note 1)	1.0≤ ingredient < 10% (note 3)
	≥ 10 % (note 2)	1.0≤ ingredient < 10% (note 3)
Category 2 **Target Organ Systemic Toxicant**		≥ 1.0 % (note 4)
		≥ 10 % (note 5)

***NOTE 1**: If a Category 1 target organ/systemic toxicant is present in the mixture as an ingredient at a concentration between 1.0% and 10%, every regulatory authority would require information on the SDS for a product. However, a label warning would be optional. Some authorities will choose to label when the ingredient is present in the mixture between 1.0% and 10%, whereas others would normally not require a label in this case.*

***NOTE 2**: If a Category 1 target organ/systemic toxicant is present in the mixture as an ingredient at a concentration of ≥ 10%, both an SDS and a label would generally be expected.*

***NOTE 3**: If a Category 1 target organ/systemic toxicant is present in the mixture as an ingredient at a concentration between 1.0% and 10%, some authorities classify this mixture as a Category 2 target organ/systemic toxicant, whereas others would not.*

***NOTE 4**: If a Category 2 target organ/systemic toxicant is present in the mixture as an ingredient at a concentration between 1.0% and 10%, every regulatory authority would require information on the SDS for a product. However, a label warning would be optional. Some authorities will choose to label when the ingredient is present in the mixture between 1.0% and 10%, whereas others would normally not require a label in this case.*

***NOTE 5**: If a Category 2 target organ/systemic toxicant is present in the mixture as an ingredient at a concentration of ≥ 10%, both an SDS and a label would generally be expected.*

3.9.3.4.2 These cut-off values and consequent classifications should be applied equally and appropriately to both single- and repeated-dose target organ toxicants.

3.9.3.4.3 Mixtures should be classified for either or both single- and repeated-dose toxicity independently.

3.9.3.4.4 Care should be exercised when toxicants affecting more than one organ system are combined that the potentiation or synergistic interactions are considered, because certain substances can cause target organ toxicity at <1% concentration when other ingredients in the mixture are known to potentiate its toxic effect.

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[1] *This compromise classification scheme involves consideration of differences in hazard communication practices in existing systems. It is expected that the number of affected mixtures will be small; the differences will be limited to label warnings; and the situation will evolve over time to a more harmonised approach.*

3.9.4 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

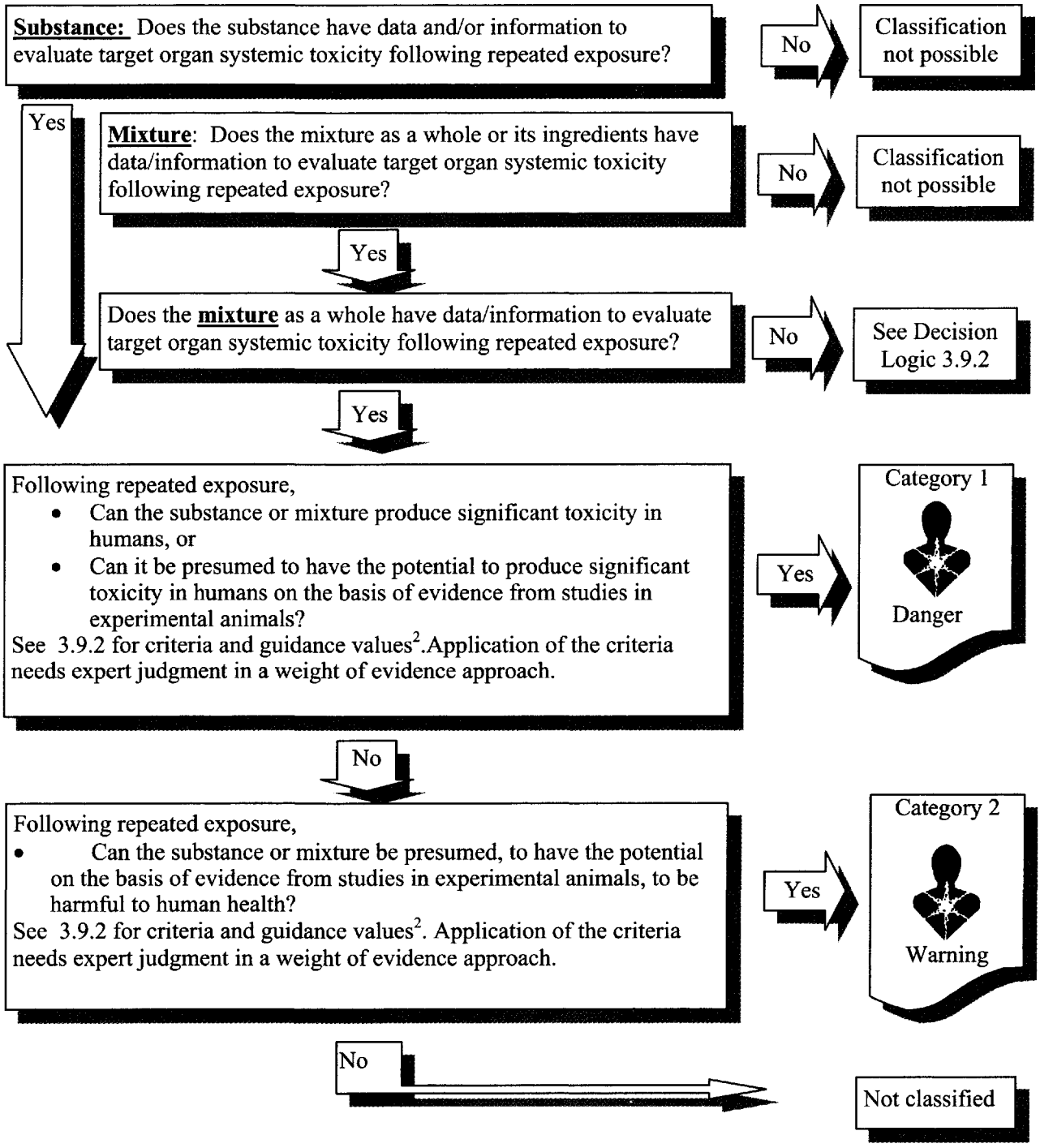
Table 3.9.4: Label elements for target organ systemic toxicity after repeated exposure

	Category 1	**Category 2**
Symbol	Health Hazard	Health Hazard
Signal word	Danger	Warning
Hazard statement	Causes damage to organs (state all organs affected, if known) through prolonged or repeated exposure (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	May cause damage to organs (state all organs affected, if known) through prolonged or repeated exposure (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)

3.9.5 Decision logic for target organ systemic toxicity following repeated exposure

The decision logic which follows is not part of the harmonized classification system but is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

Decision logic 3.9.1



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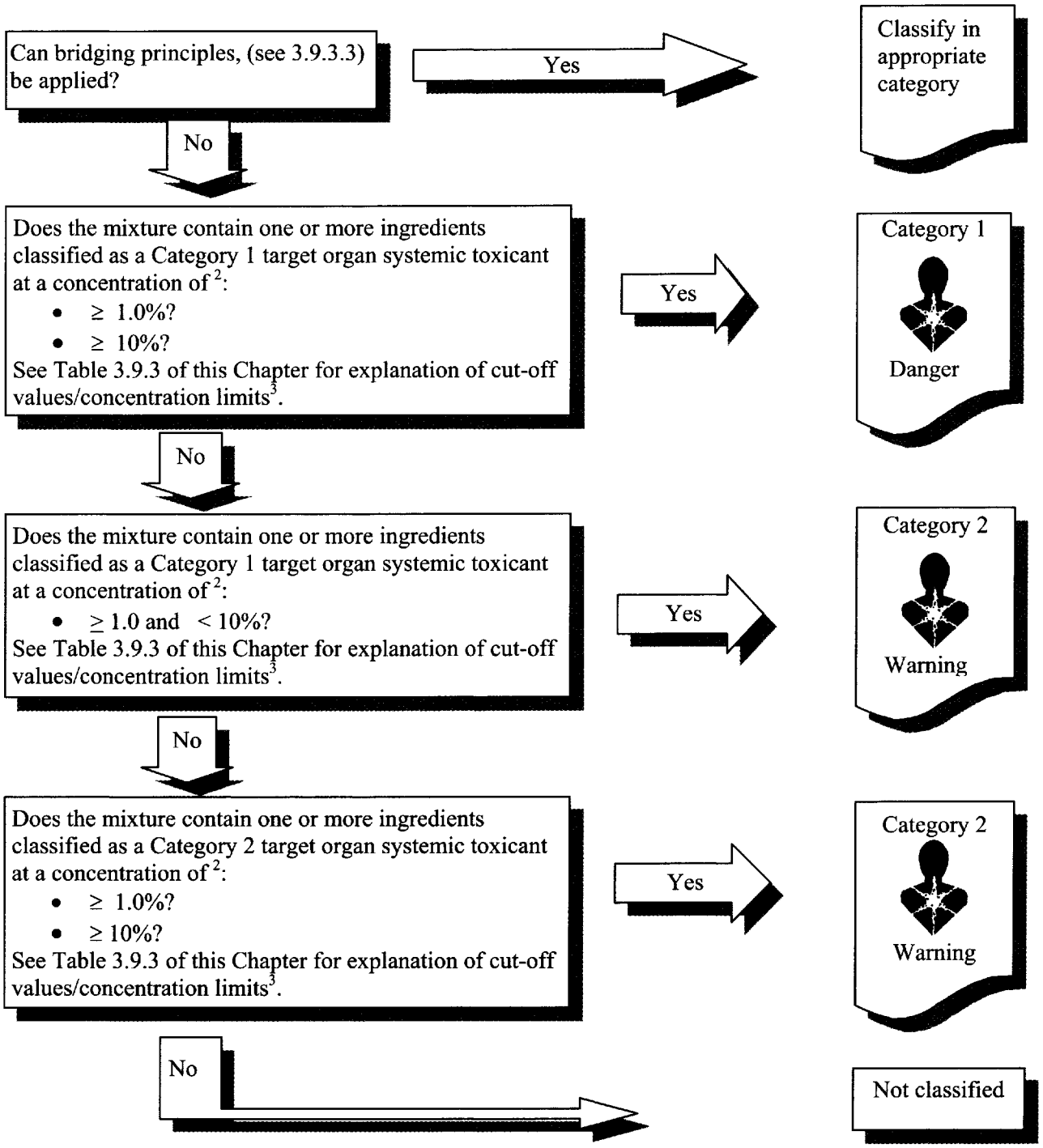
[2] *In this chapter, see 3.9.2, Tables 3.9.1 and 3.9.2, and in Chapter 1.3, para. 1.3.3.2, see "The Use of Cut-off Values/Concentration Limits".*

Decision logic 3.9.2



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[2] *In this chapter, see 3.9.2, Tables 3.9.1 and 3.9.2, and in Chapter 1.3, para. 1.3.3.2, see "The Use of Cut-off Values/Concentration Limits".*

[3] *See 3.9.3.4 and 3.9.4 and Table 3.9.3 for explanation and guidance.*

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CHAPTER 3.10

HAZARDOUS TO THE AQUATIC ENVIRONMENT

3.10.1 Definitions and general considerations

3.10.1.1 *Definitions*

Acute aquatic toxicity means the intrinsic property of a substance to be injurious to an organism in a short-term exposure to that substance.

Availability of a substance means the extent to which this substance becomes a soluble or disaggregate species. For metal availability, the extent to which the metal ion portion of a metal (M°) compound can disaggregate from the rest of the compound (molecule).

Bioavailability (or biological availability) means the extent to which a substance is taken up by an organism, and distributed to an area within the organism. It is dependent upon physico-chemical properties of the substance, anatomy and physiology of the organism, pharmacokinetics, and route of exposure. Availability is not a prerequisite for bio availability.

Bioaccumulation means net result of uptake, transformation and elimination of a substance in an organism due to all routes of exposure (i.e. air, water, sediment/soil and food)

Bioconcentration means net result of uptake, transformation and elimination of a substance in an organism due to waterborne exposure.

Chronic aquatic toxicity means potential or actual properties of a substance to cause adverse effects to aquatic organisms during exposures which are determined in relation to the life-cycle of the organism.

Complex mixtures or multi-component substances or complex substances means mixtures comprising a complex mix of individual substances with different solubilities and physico-chemical properties. In most cases, they can be characterised as a homologous series of substances with a certain range of carbon chain length/number of degree of substitution.

Degradation means the decomposition of organic molecules to smaller molecules and eventually to carbon dioxide, water and salts.

3.10.1.2 *Basic elements*

3.10.1.2.1 The basic elements for use within the harmonized system are:

- acute aquatic toxicity;
- potential for or actual bioaccumulation;
- degradation (biotic or abiotic) for organic chemicals; and
- chronic aquatic toxicity.

3.10.1.2.2 While data from internationally harmonized test methods are preferred, in practice, data from national methods may also be used where they are considered as equivalent. In general, it has been agreed that freshwater and marine species toxicity data can be considered as equivalent data and are preferably to be derived using OECD Test Guidelines or equivalent according to the principles of Good Laboratory Practices (GLP). Where such data are not available classification should be based on the best available data.

3.10.1.3 *Acute aquatic toxicity*

Acute aquatic toxicity would normally be determined using a fish 96 hour LC_{50} (OECD Test Guideline 203 or equivalent), a crustacea species 48 hour EC_{50} (OECD Test Guideline 202 or equivalent) and/or an algal species 72 or 96 hour EC_{50} (OECD Test Guideline 201 or equivalent). These species are considered as surrogate for all aquatic organisms and data on other species such as Lemna may also be considered if the test methodology is suitable.

3.10.1.4 *Bioaccumulation potential*

The potential for bioaccumulation would normally be determined by using the octanol/water partition coefficient, usually reported as a log K_{ow} determined by OECD Test Guideline 107 or 117. While this represents a potential to bioaccumulate, an experimentally determined Bioconcentration Factor (BCF) provides a better measure and should be used in preference when available. A BCF should be determined according to OECD Test Guideline 305.

3.10.1.5 *Rapid degradability*

3.10.1.5.1 Environmental degradation may be biotic or abiotic (e.g. hydrolysis) and the criteria used reflect this fact (See 3.10.2.10.3). Ready biodegradation can most easily be defined using the OECD biodegradability tests OECD Test Guideline 301 (A - F). A pass level in these tests can be considered as indicative of rapid degradation in most environments. These are freshwater tests and thus the use of the results from OECD Test Guideline 306 which is more suitable for marine environments has also been included. Where such data are not available, a BOD(5 days)/COD ratio > 0.5 is considered as indicative of rapid degradation.

3.10.1.5.2 Abiotic degradation such as hydrolysis, primary degradation, both abiotic and biotic, degradation in non-aquatic media and proven rapid degradation in the environment may all be considered in defining rapid degradability. Special guidance on data interpretation is provided in the Guidance Document (Annex 8).

3.10.1.6 *Chronic aquatic toxicity*

Chronic toxicity data are less available than acute data and the range of testing procedures less standardised. Data generated according to the OECD Test Guidelines 210 (Fish Early Life Stage), or 211 (Daphnia Reproduction) and 201 (Algal Growth Inhibition) can be accepted (See also Chapter 3.3.2 of Annex 8). Other validated and internationally accepted tests could also be used. The NOECs or other equivalent L(E)Cx should be used.

3.10.1.7 *Other considerations*

3.10.1.7.1 The harmonized system for classifying chemical substances for the hazards they present to the aquatic environment is based on a consideration of systems existing listed in 3.10.1.7.4. The aquatic environment may be considered in terms of the aquatic organisms that live in the water, and the aquatic ecosystem of which they are part. To that extent, the proposal does not address aquatic pollutants for which there may be a need to consider effects beyond the aquatic environment such as the impacts on human health etc. The basis, therefore, of the identification of hazard is the aquatic toxicity of the substance, although this may be modified by further information on the degradation and bioaccumulation behaviour.

3.10.1.7.2 While the scheme is intended to apply to all substances and mixtures, it is recognised that for some substances, e.g. metals, poorly soluble substances, etc., special guidance will be necessary. For instance, application of the criteria to metals and metal compounds is contingent on completion of an appropriate validation exercise, as provided in OECD series on Testing and Assessment No 29 .

3.10.1.7.3 Two Guidance Documents (see Annexes 8 and 9) have been prepared to cover issues such as data interpretation and the application of the criteria defined below to such groups of substances.

Considering the complexity of this endpoint and the breadth of the application of the system, the Guidance Documents are considered an important element in the operation of the harmonized scheme. (As noted above, Annex 9 is subject to validation.)

3.10.1.7.4 Consideration has been given to existing classification systems as currently in use, including the EU Supply and Use Scheme, the revised GESAMP hazard evaluation procedure, IMO Scheme for Marine Pollutant, the European Road and Rail Transport Scheme (RID/ADR), the Canadian and US Pesticide systems and the US Land Transport Scheme. The harmonized scheme is considered suitable for use for packaged goods in both supply and use and multimodal transport schemes, and elements of it may be used for bulk land transport and bulk marine transport under MARPOL 73/78 Annex II insofar as this uses aquatic toxicity.

3.10.2 Classification criteria for substances

3.10.2.1 The harmonized classification system for substances consists of three acute classification categories and four chronic classification categories (see Figure 3.10.1). The acute and the chronic classification categories are applied independently. The criteria for classification of a substance in acute categories I to III are defined on the basis of the acute toxicity data only (EC_{50} or LC_{50}). The criteria for classification of a substance into chronic categories combine two types of information, i.e. acute toxicity data and environmental fate data (degradability and bioaccumulation data). For assignment of mixtures to chronic categories, degradation and bioaccumulation properties are derived from tests on components.

3.10.2.2 Substances classified under the following criteria will be categorised as "hazardous to the aquatic environment". These criteria describe in detail the classification categories. They are diagrammatically summarised in Table 3.10.1.

Figure 3.10.1: Categories for substances hazardous to the aquatic environment

Acute toxicity

Category: Acute I	
96 hr LC50 (for fish)	≤1 mg/L and/or
48 hr EC50 (for crustacea)	≤1 mg/L and/or
72 or 96hr ErC_{50} (for algae or other aquatic plants)	≤1 mg/L.
Category: Acute I may be subdivided for some regulatory systems to include a lower band at $L(E)C_{50}$ ≤0 1 mg/L.	
Category: Acute II	
96 hr LC_{50} (for fish)	>1 - ≤10 mg/L and/or
48 hr EC_{50} (for crustacea)	>1 - ≤10 mg/L and/or
72 or 96hr ErC_{50} (for algae or other aquatic plants)	>1 - ≤10 mg/L.
Category: Acute III	
96 hr LC_{50} (for fish)	>10 - ≤100 mg/L and/or
48 hr EC_{50} (for crustacea)	>10 - ≤100 mg/L and/or
72 or 96hr ErC_{50} (for algae or other aquatic plants)	>10 - ≤100 mg/L.
Some regulatory systems may extend this range beyond an $L(E)C_{50}$ of 100 mg/L through the introduction of another category.	

Figure 3.10.1: Categories for substances hazardous to the aquatic environment *(cont'd)*

Chronic toxicity

Category: Chronic I	
96 hr LC_{50} (for fish)	≤1 mg/L and/or
48 hr EC50 (for crustacea)	≤1 mg/L and/or
72 or 96hr ErC_{50} (for algae or other aquatic plants)	≤1 mg/L
and the substance is not rapidly degradable and/or the log K_{ow} ≥ 4 (unless the experimentally determined BCF <500).	
Category: Chronic II	
96 hr LC_{50} (for fish)	>1 to ≤10 mg/L and/or
48 hr EC_{50} (for crustacea)	>1 to ≤10 mg/L and/or
72 or 96hr ErC_{50} (for algae or other aquatic plants)	>1 to ≤10 mg/L
and the substance is not rapidly degradable and/or the log K_{ow}	≥4 (unless the experimentally
determined BCF <500), unless the chronic toxicity NOECs are	> 1 mg/L.
Category: Chronic III	
96 hr LC_{50} (for fish)	>10 to ≤100 mg/L and/or
48 hr EC_{50} (for crustacea)	>10 to ≤100 mg/L and/or
72 or 96hr ErC_{50} (for algae or other aquatic plants)	>10 to ≤100 mg/L
and the substance is not rapidly degradable and/or the log K_{ow}	≥4 (unless the experimentally
determined BCF <500) unless the chronic toxicity NOECs are	>1 mg/L.
Category: Chronic IV	
Poorly soluble substances for which no acute toxicity is recorded at levels up to the water solubility, and which are not rapidly degradable and have a log K_{ow} ≥ 4, indicating a potential to bioaccumulate, will be classified in this category unless other scientific evidence exists showing classification to be unnecessary. Such evidence would include an experimentally determined BCF <500, or a chronic toxicity NOECs > 1 mg/L, or evidence of rapid degradation in the environment.	

Table 3.10.1: Classification scheme for substances hazardous to the aquatic environment

Classification criterion elements				Classification categories	
Toxicity		**Degradability** (*Note 3*)	**Bioaccumulation** (*Note 4*)		
Acute (*Note 1a and 1b*)	**Chronic** (*Note 2a and 2b*)			**Acute**	**Chronic**
Box 1: value ≤ 1.00 mg/L		**Box 5:**	**Box 6:**	**Category: Acute I** **Box 1**	**Category: Chronic I** **Boxes 1+5+6** **Boxes 1+5** **Boxes 1+6**
Box 2: 1.00 < value ≤ 10.0 mg/L		lack of rapid degradability	BCF ≥ 500 or, if absent log K_{ow}≥ 4	**Category: Acute II** **Box 2**	**Category: Chronic II** **Boxes 2+5+6** **Boxes 2+5** **Boxes 2+6** **Unless Box 7**
Box 3: 10.0 < value ≤ 100 mg/L				**Category: Acute III** **Box 3**	**Category: Chronic III** **Boxes 3+5+6** **Boxes 3+5** **Boxes 3+6** **Unless Box 7**
Box 4: No acute toxicity (*Note 5*)	**Box 7:** value > 1.00 mg/L				**Category: Chronic IV** **Boxes 4+5+6** **Unless Box 7**

Notes to Table 3.10.1:

NOTE 1a: *Acute toxicity band based on L(E)C-50 values in mg/L for fish, crustacea and/or algae or other aquatic plants (or QSAR estimation if no experimental data).*

NOTE 1b: *Where the algal toxicity ErC-50 [= EC-50 (growth rate)] falls more than 100 times below the next most sensitive species and results in a classification based solely on this effect, consideration should be given to whether this toxicity is representative of the toxicity to aquatic plants. Where it can be shown that this is not the case, professional judgement should be used in deciding if classification should be applied. Classification should be based on the ErC-50. In circumstances where the basis of the EC-50 is not specified and no ErC-50 is recorded, classification should be based on the lowest EC-50 available.*

NOTE 2a: *Chronic toxicity band based on NOEC values in mg/L for fish or crustacea or other recognised measures for long-term toxicity.*

NOTE 2b: *It is the intention that the system be further developed to include chronic toxicity data.*

NOTE 3. *Lack of rapid degradability is based on either a lack of Ready Biodegradability or other evidence of lack of rapid degradation.*

NOTE 4: *Potential to bioaccumulate, based on an experimentally derived BCF ≥ 500 or, if absent, a log K_{ow} ≥ 4 provided log K_{ow} is an appropriate descriptor for the bioaccumulation potential of the substance. Measured log K_{ow} values take precedence over estimated values and measured BCF values take precedence over log K_{ow} values.*

NOTE 5: *"No acute toxicity" is taken to mean that the L(E)C-50 is above the water solubility. Also for poorly soluble substances, (w.s. < 1.00 mg/L), where there is evidence that the acute test would not have provided a true measure of the intrinsic toxicity.*

3.10.2.3 The system for classification recognises that the core intrinsic hazard to aquatic organisms is represented by both the acute and chronic toxicity of a substance, the relative importance of which is determined by the specific regulatory system in operation. Distinction can be made between the acute hazard and the chronic hazard and therefore separate hazard categories are defined for both properties representing a gradation in the level of hazard identified. The lowest of the available toxicity values will normally be used to define the appropriate hazard category(ies). There may be circumstances, however, when a weight of evidence approach may be used. Acute toxicity data are the most readily available and the tests used are the most standardised. For that reason, these data form the core of the classification system.

3.10.2.4 Acute toxicity represents a key property in defining the hazard where transport of large quantities of a substance may give rise to short-term dangers arising from accidents or major spillages. Hazards categories up to L(E)C_{50} values of 100 mg/L are thus defined although categories up to 1000 mg/L may be used in certain regulatory frameworks. The Acute Category I may be further sub-divided to include an additional category for acute toxicity L(E)C_{50} $\leq$0.1 mg/L in certain regulatory systems such as that defined by MARPOL 73/78 Annex II. It is anticipated that their use would be restricted to regulatory systems concerning bulk transport.

3.10.2.5 For packaged substances it is considered that the principal hazard is defined by chronic toxicity, although acute toxicity at L(E)C_{50} levels $\leq$1 mg/L are also considered hazardous. Levels of substances up to 1 mg/L are considered as possible in the aquatic environment following normal use and disposal. At toxicity levels above this, it is considered that the short-term toxicity itself does not describe the principal hazard, which arises from low concentrations causing effects over a longer time scale. Thus, a number of hazard categories are defined which are based on levels of chronic aquatic toxicity. Chronic toxicity data are not available for many substances, however, and it is necessary to use the available data on acute toxicity to estimate this property. The intrinsic properties of a lack of rapid degradability and/or a potential to bioconcentrate in combination with acute toxicity may be used to assign a substance to a chronic hazard category. Where chronic toxicity is available showing NOECs >1 mg/L, this would indicate that no classification in a chronic hazard category would be necessary. Equally, for substances with an L(E)C_{50} >100 mg/L, the toxicity is considered as insufficient to warrant classification in most regulatory systems.

3.10.2.6 While the current system will continue to rely on the use of acute toxicity data in combination with a lack of rapid degradation and/or a potential to bioaccumulate as the basis for classification for assigning a chronic hazard category, it is recognised that actual chronic toxicity data would form a better basis for classification where these data are available. It is thus the intention that the scheme should be further developed to accommodate such data. It is anticipated that in such a further development, the available chronic toxicity data would be used to classify in the chronic hazard in preference to that derived from their acute toxicity in combination with a lack of rapid degradation and/or a potential to bioaccumulate.

3.10.2.7 Recognition is given to the classification goals of MARPOL 73/78 Annex II, which covers the transport of bulk quantities in ships tanks, which are aimed at regulating operational discharges from ships and assigning of suitable ship types. They go beyond that of protecting aquatic ecosystems, although that clearly is included. Additional hazard categories may thus be used which take account of factors such as physico-chemical properties and mammalian toxicity.

3.10.2.8 ***Aquatic toxicity***

3.10.2.8.1 The organisms fish, crustacea and algae are tested as surrogate species covering a range of trophic levels and taxa, and the test methods are highly standardised. Data on other organisms may also be considered, however, provided they represent equivalent species and test endpoints. The algal growth inhibition test is a chronic test but the EC_{50} is treated as an acute value for classification purposes. This EC_{50} should normally be based on growth rate inhibition. If only the EC_{50} based on reduction in biomass is available, or it is not indicated which EC_{50} is reported, this value may be used in the same way.

3.10.2.8.2 Aquatic toxicity testing, by its nature, involves the dissolution of the substance under test in the water media used and the maintenance of a stable bioavailable exposure concentration over the course of the test. Some substances are difficult to test under standard procedures and thus special guidance will be

developed on data interpretation for these substances and how the data should be used when applying the classification criteria.

3.10.2.9 *Bioaccumulation*

It is the bioaccumulation of substances within the aquatic organisms that can give rise to toxic effects over longer time scales even when actual water concentrations are low. The potential to bioaccumulate is determined by the partitioning between n-octanol and water. The relationship between the partition coefficient of an organic substance and its bioconcentration as measured by the BCF in fish has considerable scientific literature support. Using a cut-off value of log $K_{ow} \geq 4$ is intended to identify only those substances with a real potential to bioconcentrate. In recognition that the log K_{ow} is only an imperfect surrogate for a measured BCF, such a measured value would always take precedence. A BCF in fish of <500 is considered as indicative of a low level of bioconcentration.

3.10.2.10 *Rapid degradability*

3.10.2.10.1 Substances that rapidly degrade can be quickly removed from the environment. While effects can occur, particularly in the event of a spillage or accident, they will be localised and of short duration. The absence of rapid degradation in the environment can mean that a substance in the water has the potential to exert toxicity over a wide temporal and spatial scale. One way of demonstrating rapid degradation utilises the biodegradation screening tests designed to determine whether a substance is "readily biodegradable". Thus a substance which passes this screening test is one that is likely to biodegrade "rapidly" in the aquatic environment, and is thus unlikely to be persistent. However, a fail in the screening test does not necessarily mean that the substance will not degrade rapidly in the environment. Thus a further criterion was added which would allow the use of data to show that the substance did actually degrade biotically or abiotically in the aquatic environment by >70% in 28 days. Thus, if degradation could be demonstrated under environmentally realistic conditions, then the definition of 'rapid degradability' would have been met. Many degradation data are available in the form of degradation half-lives and these can also be used in defining rapid degradation. Details regarding the interpretation of these data are further elaborated in the Guidance Document of Annex 8. Some tests measure the ultimate biodegradation of the substance, i.e. full mineralisation is achieved. Primary biodegradation would not normally qualify in the assessment of rapid degradability unless it can be demonstrated that the degradation products do not fulfill the criteria for classification as hazardous to the aquatic environment.

3.10.2.10.2 It must be recognised that environmental degradation may be biotic or abiotic (e.g. hydrolysis) and the criteria used reflect this fact. Equally, it must be recognised that failing the ready biodegradability criteria in the OECD tests does not mean that the substance will not be degraded rapidly in the real environment. Thus where such rapid degradation can be shown, the substance should be considered as rapidly degradable. Hydrolysis can be considered if the hydrolysis products do not fulfil the criteria for classification as hazardous to the aquatic environment. A specific definition of rapid degradability is shown below. Other evidence of rapid degradation in the environment may also be considered and may be of particular importance where the substances are inhibitory to microbial activity at the concentration levels used in standard testing. The range of available data and guidance on its interpretation are provided in the Guidance Document of Annex 8.

3.10.2.10.3 Substances are considered rapidly degradable in the environment if the following criteria hold true:

(a) if in 28-day ready biodegradation studies, the following levels of degradation are achieved;

- tests based on dissolved organic carbon: 70%
- tests based on oxygen depletion or carbon dioxide generation: 60% of theoretical maxima

These levels of biodegradation must be achieved within 10 days of the start of degradation which point is taken as the time when 10% of the substance has been degraded; or

(b) if, in those cases where only BOD and COD data are available, when the ratio of BOD5/COD is ≥0.5; or

(c) if other convincing scientific evidence is available to demonstrate that the substance can be degraded (biotically and/or abiotically) in the aquatic environment to a level >70% within a 28 day period.

3.10.2.11 *Inorganic compounds and metals*

3.10.2.11.1 For inorganic compounds and metals, the concept of degradability as applied to organic compounds has limited or no meaning. Rather the substance may be transformed by normal environmental processes to either increase or decrease the bioavailability of the toxic species. Equally the use of bioaccumulation data should be treated with care. Specific guidance will be provided on how these data for such materials may be used in meeting the requirements of the classification criteria.

3.10.2.11.2 Poorly soluble inorganic compounds and metals may be acutely or chronically toxic in the aquatic environment depending on the intrinsic toxicity of the bioavailable inorganic species and the rate and amount of this species which may enter solution. A protocol for testing these poorly soluble materials is included in Annex 9. This protocol is undergoing validation testing under the auspices of the OECD.

3.10.2.12 *Category Chronic IV*

The system also introduces as "safety net" classification (Category: Chronic IV) for use when the data available do not allow classification under the formal criteria but there are nevertheless some grounds for concern. The precise criteria are not defined with one exception. For poorly water soluble organic substances for which no toxicity has been demonstrated, classification can occur if the substance is both not rapidly degraded and has a potential to bioaccumulate. It is considered that for such poorly soluble substances, the toxicity may not have been adequately assessed in the short-term test due to the low exposure levels and potentially slow uptake into the organism. The need for this classification can be negated by demonstrating the absence of long-term effects, i.e. a long-term NOECs > water solubility or 1 mg/L, or rapid degradation in the environment.

3.10.2.13 *Use of QSARs*

While experimentally derived test data are preferred, where no experimental data are available, validated Quantitative Structure Activity Relationships (QSARs) for aquatic toxicity and log K_{ow} may be used in the classification process. Such validated QSARs may be used without modification to the agreed criteria, if restricted to chemicals for which their mode of action and applicability are well characterised. Reliable calculated toxicity and log K_{ow} values should be valuable in the safety net context. QSARs for predicting ready biodegradation are not yet sufficiently accurate to predict rapid degradation.

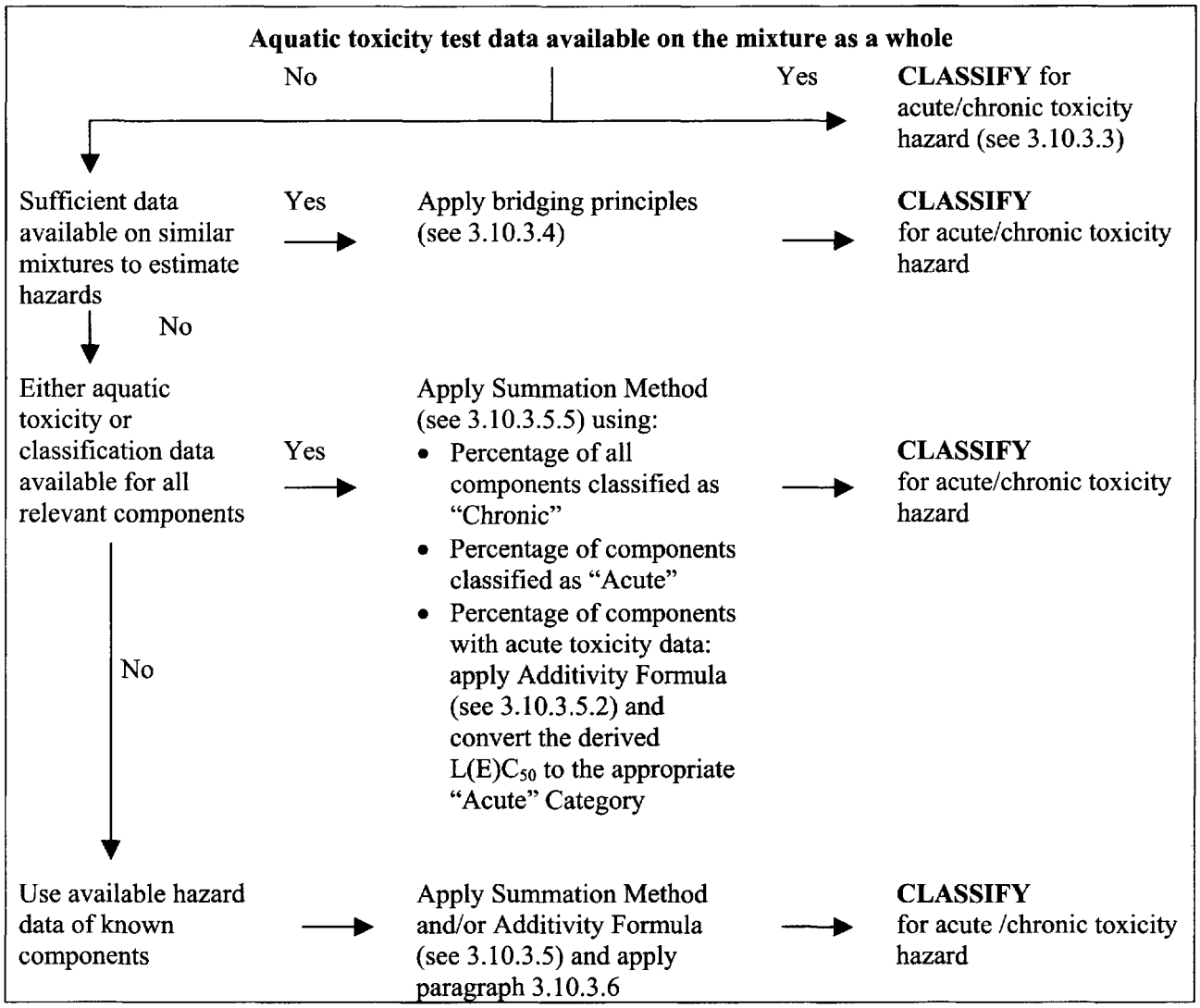
3.10.3 Classification criteria for mixtures

3.10.3.1 The classification system for mixtures covers all classification categories which are used for substances meaning acute categories I to III and chronic categories I to IV. In order to make use of all available data for purposes of classifying the aquatic environmental hazards of the mixture, the following assumption has been made and is applied where appropriate.

The "relevant components" of a mixture are those which are present in a concentration of 1% (w/w) or greater, unless there is a presumption (e.g. in the case of highly toxic components) that a component present at less than 1% can still be relevant for classifying the mixture for aquatic environmental hazards.

3.10.3.2 The approach for classification of aquatic environmental hazards is tiered, and is dependent upon the type of information available for the mixture itself and for its components. Elements of the tiered approach include: (a) classification based on tested mixtures; (b) classification based on bridging principles, (c) the use of "summation of classified components" and /or an "additivity formula". Figure 3.10.2 outlines the process to be followed.

Figure 3.10.2: Tiered approach to classification of mixtures for acute and chronic aquatic environmental hazards



3.10.3.3 *Classification of mixtures when data are available for the complete mixture*

3.10.3.3.1 When the mixture as a whole has been tested to determine its aquatic toxicity, it can be classified according to the criteria that have been agreed for substances, but only for acute toxicity. The classification should be based on the data for fish, crustacea and algae/plants. Classification of mixtures by using LC_{50} or EC_{50} data for the mixture as a whole is not possible for chronic categories since both toxicity data and environmental fate data are needed, and there are no degradability and bioaccumulation data for mixtures as a whole. It is not possible to apply the criteria for chronic classification because the data from degradability and bio-accumulation tests of mixtures cannot be interpreted; they are meaningful only for single substances.

3.10.3.3.2 When there is acute toxicity test data (LC_{50} or EC_{50}) available for the mixture as a whole, this data as well as information with respect to the classification of components for chronic toxicity should be used to complete the classification for tested mixtures as follows. When chronic (long-term) toxicity data (NOEC) is also available, this should be used as well.

- $L(E)C_{50}$ (LC_{50} or EC_{50}) of the tested mixture ≤ 100mg/L and NOEC of the tested mixture ≤ 1.0 mg/L or unknown:
  - → Classify mixture as Category Acute I, II or III
  - → Apply Summation of Classified Components approach (see 3.10.3.5.5) for chronic classification (Chronic I, II, III, IV or no need of chronic classification).

- $L(E)C_{50}$ of the tested mixture ≤ 100mg/L and NOEC of the tested mixture > 1.0 mg/L:
  - → Classify mixture as Category Acute I, II or III
  - → Apply Summation of Classified Components approach (see 3.10.3.5.5) for classification as Category Chronic I. If the mixture is not classified as Category Chronic I, then there is no need for chronic classification.

- $L(E)C_{50}$ of the tested mixture >100mg/L, or above the water solubility, and NOEC of the tested mixture ≤ 1.0mg/L or unknown:
  - → No need to classify for acute toxicity hazard
  - → Apply Summation of Classified Components approach (see 3.10.3.5.5) for Chronic classification (Category Chronic IV or no need for chronic classification).

- $L(E)C_{50}$ of the tested mixture >100mg/L, or above the water solubility, and NOEC of the tested mixture > 1.0 mg/L:
  - → No need to classify for acute or chronic toxicity hazard

3.10.3.4 *Classification of mixtures when data are not available for the complete mixture: Bridging principles*

3.10.3.4.1 Where the mixture itself has not been tested to determine its aquatic environmental hazard, but there are sufficient data on the individual components and similar tested mixtures to adequately characterise the hazards of the mixture, this data will be used in accordance with the following agreed bridging rules. This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity for additional testing in animals.

3.10.3.4.2 *Dilution*

If a mixture is formed by diluting another classified mixture or a substance with a diluent which has an equivalent or lower aquatic hazard classification than the least toxic original component and which is not expected to affect the aquatic hazards of other components, then the mixture may be classified as equivalent to the original mixture or substance.

If a mixture is formed by diluting another classified mixture or a substance with water or other totally non-toxic material, the toxicity of the mixture can be calculated from the original mixture or substance.

3.10.3.4.3 *Batching*

The aquatic hazard classification of one production batch of a complex mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product and produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the aquatic hazard classification of the batch has changed. If the latter occurs, new classification is necessary.

3.10.3.4.4 *Concentration of mixtures which are classified with the most severe classification categories (Chronic I and Acute I)*

If a mixture is classified as Chronic I and/or Acute I, and components of the mixture which are classified as Chronic I and/or Acute I are further concentrated, the more concentrated mixture should be classified with the same classification category as the original mixture without additional testing.

3.10.3.4.5 *Interpolation within one toxicity category*

If mixtures A and B are in the same classification category and mixture C is made in which the toxicologically active components have concentrations intermediate to those in mixtures A and B, then mixture C is assumed to be in the same category as A and B. Note that the identity of the components is the same in all three mixtures.

3.10.3.4.6 *Substantially similar mixtures*

Given the following:

(a) Two mixtures: (i) A + B
(ii) C + B;
(b) The concentration of component B is the same in both mixtures;
(c) The concentration of component A in mixture (i) equals that of component C in mixture (ii);
(d) Classification for A and C are available and are the same, i.e. they are in the same hazard category and are not expected to affect the aquatic toxicity of B.

Then there is no need to test mixture (ii) if mixture (i) is already characterised by testing and both mixtures would be classified in the same category.

3.10.3.5 *Classification of mixtures when data are available for all components or only for some components of the mixture*

3.10.3.5.1 The classification of a mixture is based on summation of the classification of its components. The percentage of components classified as "Acute" or "Chronic" will feed straight into the summation method. Details of the summation method are described in 3.10.3.5.5.

3.10.3.5.2 Mixtures can be made of a combination of both components that are classified (as Acute I, II, III and/or Chronic I, II, III, IV) and those for which adequate test data is available. When adequate toxicity data is available for more than one component in the mixture, the combined toxicity of those components may be calculated using the following additivity formula, and the calculated toxicity may be used to assign that portion of the mixture an acute hazard category which is then subsequently used in applying the summation method.

$$\frac{\sum Ci}{L(E)C_{50m}} = \sum_{n} \frac{Ci}{L(E)C_{50i}}$$

where:

C_i	=	concentration of component i (weight percentage)
$L(E)C_{50i}$	=	(mg/L) LC_{50} or EC_{50} for component i
n	=	number of components, and i is running from 1 to n
$L(E)C_{50m}$	=	L(E) C_{50} of the part of the mixture with test data

3.10.3.5.3 When applying the additivity formula for part of the mixture, it is preferable to calculate the toxicity of this part of the mixture using for each substance toxicity values that relate to the same species (i.e. fish, daphnia or algae) and then to use the highest toxicity (lowest value) obtained (i.e. use the most sensitive of the three species). However, when toxicity data for each component are not available in the same species, the toxicity value of each component should be selected in the same manner that toxicity values are selected for the classification of substances, i.e. the higher toxicity (from the most sensitive test organism) is used. The calculated acute toxicity may then be used to classify this part of the mixture as Acute I, II or III using the same criteria described for substances.

3.10.3.5.4 If a mixture is classified in more than one way, the method yielding the more conservative result should be used.

3.10.3.5.5 *Summation method*

3.10.3.5.5.1 Rationale

3.10.3.5.5.1.1 In case of the substance classification categories Acute I/Chronic I to Acute III/ Chronic III, the underlying toxicity criteria differ by a factor of 10 in moving from one category to another. Substances with a classification in a high toxicity band may therefore contribute to the classification of a mixture in a lower band. The calculation of these classification categories therefore needs to consider the contribution of all substances classified Acute I/Chronic I to Acute III/Chronic III together.

3.10.3.5.5.1.2 When a mixture contains components classified as Acute Category I, attention should be paid to the fact that such components, when their acute toxicity is well below 1 mg/L contribute to the toxicity of the mixture even at a low concentration. (See also *Classification of Hazardous Substances and Mixtures* in Chapter 1.3,1.3.3.2.1). Active ingredients in pesticides often possess such high aquatic toxicity but also some other substances like organometallic compounds. Under these circumstances the application of the normal cut-off values/concentration limits may lead to an "underclassification" of the mixture. Therefore, multiplying factors should be applied to account for highly toxic components, as described in paragraph 3.10.3.5.5.5.

3.10.3.5.5.2 Classification procedure

In general a more severe classification for mixtures overrides a less severe classification, e.g. a classification with Chronic I overrides a classification with Chronic II. As a consequence the classification procedure is already completed if the result of the classification is Chronic I. A more severe classification than chronic I is not possible therefore it is not necessary to undergo the further classification procedure.

3.10.3.5.5.3 Classification for the Acute Categories I, II and III

3.10.3.5.5.3.1 First, all components classified as Acute I are considered. If the sum of these components is greater than 25% the whole mixture is classified as Category Acute I. If the result of the calculation is a classification of the mixture as Category Acute I, the classification process is completed.

3.10.3.5.5.3.2 In cases where the mixture is not classified as Acute I, classification of the mixture as Acute II is considered. A mixture is classified as Acute II if ten times the sum of all components classified as Acute I plus the sum of all components classified as Acute II is greater than 25%. If the result of the calculation is classification of the mixture as Category Acute II, the classification process is completed.

3.10.3.5.5.3.3 In cases where the mixture is not classified either as Acute I or Acute II, classification of the mixture as Acute III is considered. A mixture is classified as Acute III if 100 times the sum of all components classified as Acute I plus 10 times the sum of all components classified as Acute II plus the sum of all components classified as Acute III is greater than 25%.

3.10.3.5.5.3.4 The classification of mixtures for acute hazards based on this summation of classified components, is summarised in Table 3.10.2.

Table 3.10.2: Classification of a mixture for acute hazards, based on summation of classified components

Sum of components classified as:		**Mixture is classified as:**
Acute I × M[a]	>25%	Acute I
(M × 10 × Acute I) +Acute II	>25%	Acute II
(M × 100 × Acute I)+ (10 × Acute II) + Acute III	>25%	Acute III

[a] *For explanation of the M factor, see paragraph 3.10.3.5.5.5.*

3.10.3.5.5.4 Classification for the Chronic Categories I, II, III and IV

3.10.3.5.5.4.1 First all components classified as Chronic I are considered. If the sum of these components is greater than 25% the mixture is classified as Category Chronic I. If the result of the calculation is a classification of the mixture as Category Chronic I the classification procedure is completed.

3.10.3.5.5.4.2 In cases where the mixture is not classified as Chronic I, classification of the mixture as Chronic II is considered. A mixture is classified as Chronic II if 10 times the sum of all components classified as Chronic I plus the sum of all components classified as Chronic II is greater than 25%. If the result of the calculation is classification of the mixture as Chronic II, the classification process is completed.

3.10.3.5.5.4.3 In cases where the mixture is not classified either as Chronic I or Chronic II, classification of the mixture as Chronic III is considered. A mixture is classified as Chronic III if 100 times the sum of all components classified as Chronic I plus 10 times the sum of all components classified with Chronic II plus the sum of all components classified as Chronic III is greater than 25%.

3.10.3.5.5.4.4 If the mixture is still not classified in either Category Chronic I, II or III, classification of the mixture as Chronic IV should be considered. A mixture is classified as Chronic IV if the sum of the percentages of components classified as Chronic I, II, III and IV is greater than 25%.

3.10.3.5.5.4.5 The classification of mixtures for chronic hazards, based on this summation of classified components, is summarised in Table 3.10.3.

Table 3.10.3: Classification of a mixture for chronic hazards, based on summation of classified components

Sum of components classified as:	**Mixture is classified as:**
Chronic I × M[a] >25%	Chronic I
(M × 10 × Chronic I)+Chronic II >25%	Chronic II
(M × 100 × Chronic I)+(10 × Chronic II)+Chronic III >25%	Chronic III
Chronic I + Chronic II + Chronic III +Chronic IV > 25%	Chronic IV

[a] *For explanation of the M factor, see paragraph 3.10.3.5.5.5.*

3.10.3.5.5.5 Mixtures with highly toxic components

Acute Category 1 components with toxicities well below 1 mg/L may influence the toxicity of the mixture and should be given increased weight in applying the summation of classification approach. When a mixture contains components classified as Acute or Chronic Category I, the tiered approach described in 3.10.3.5.5.3 and 3.10.3.5.5.4 should be applied using a weighted sum by multiplying the concentrations of Acute Category I components by a factor, instead of merely adding up the percentages. This means that the concentration of "Acute I" in the left column of Table 3.10.2 and the concentration of "Chronic I" in the left column of Table 3.10.3 are multiplied by the appropriate multiplying factor. The multiplying factors to be applied to these components are defined using the toxicity value, as summarised in Table 3.10.4 below. Therefore, in order to classify a mixture containing Acute/Chronic I components, the classifier needs to be informed of the value of the M factor in order to apply the summation method. Alternatively, the additivity formula (paragraph 3.10.3.5.2) may be used when toxicity data are available for all highly toxic components in the mixture and there is convincing evidence that all other components, including those for which specific acute toxicity data are not available, are of low or no toxicity and do not significantly contribute to the environmental hazard of the mixture.

Table 3.10.4: Multiplying factors for highly toxic components of mixtures

L(E)C50 value	**Multiplying factor (M)**
$0.1 < L(E)C_{50} \leq 1$	1
$0.01 < L(E)C_{50} \leq 0.1$	10
$0.001 < L(E)C_{50} \leq 0.01$	100
$0.0001 < L(E)C_{50} \leq 0.001$	1000
$0.00001 < L(E)C_{50} \leq 0.0001$	10000
(continue in factor 10 intervals)	

3.10.3.6 *Classification of mixtures with components without any useable information*

In the event that no useable information on acute and/or chronic aquatic hazard is available for one or more relevant components, it is concluded that the mixture cannot be attributed (a) definitive hazard category(ies). In this situation the mixture should be classified based on the known components only, with the additional statement that: "x percent of the mixture consists of components(s) of unknown hazards to the aquatic environment".

3.10.4 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard Communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

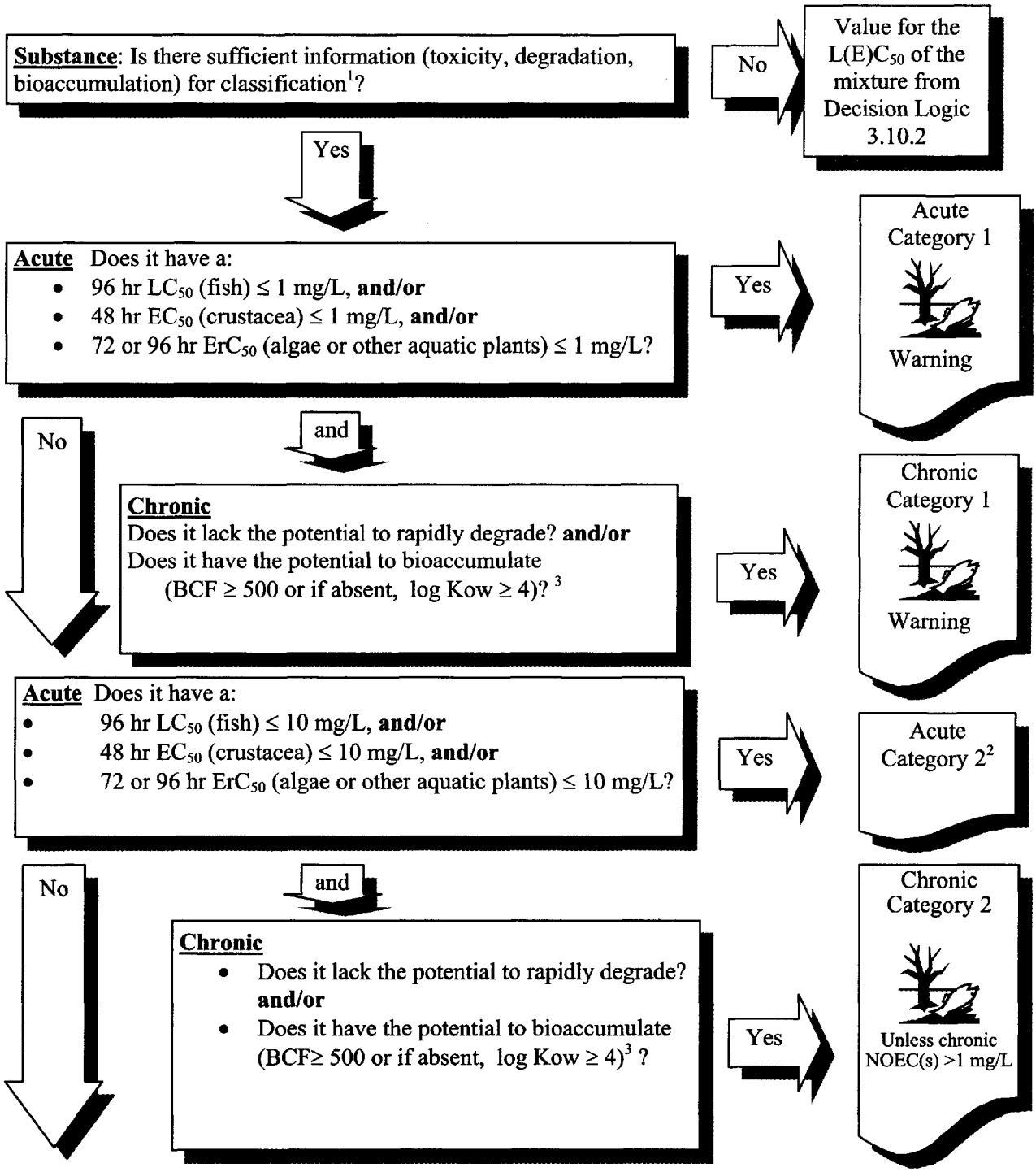
Table 3.10.5: Label elements for hazardous to the aquatic environment

ACUTE				
	Category 1	**Category 2**	**Category 3**	
Symbol	Fish and tree	No symbol is used	No symbol is used	
Signal word	Warning	No signal word is used	No signal word is used	
Hazard Statement	Very toxic to aquatic life	Toxic to aquatic life	Harmful to aquatic life	
CHRONIC				
	Category 1	**Category 2**	**Category 3**	**Category 4**
Symbol	Fish and tree	Fish and tree	No symbol is used	No symbol is used
Signal word	Warning	No signal word is used	No signal word is used	No signal word is used
Hazard statement	Very toxic to aquatic life with long lasting effects	Toxic to aquatic life with long lasting effects	Harmful to aquatic life with long lasting effects	May cause long lasting harmful effects to aquatic life

3.10.5 Decision logic

The decision logic which follows is not part of the harmonized classification system but is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic

3.10.5 *Decision logic 3.10.1 for Hazardous to the Aquatic Environment*



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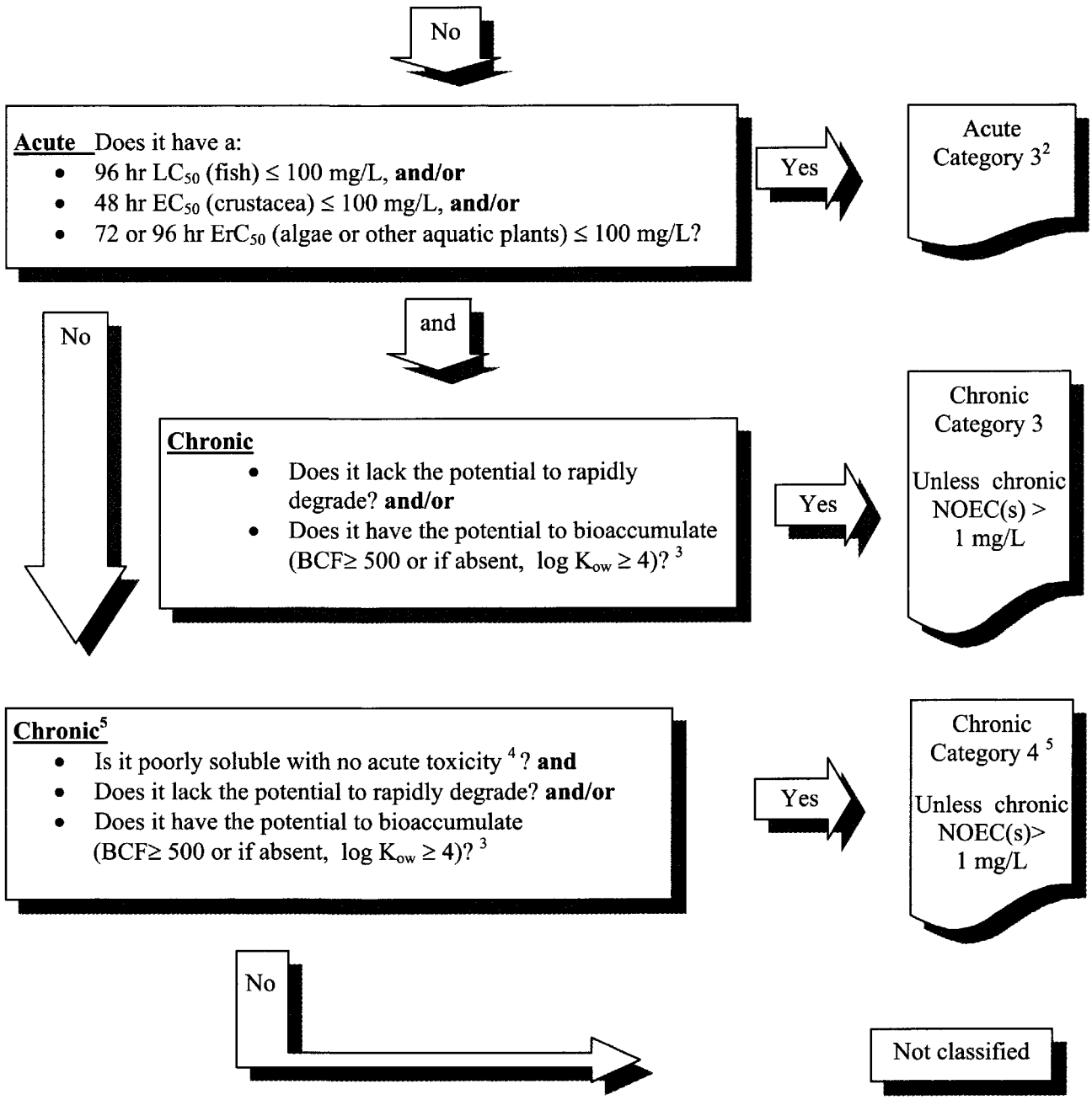
1 *Classification can be based on either measured data and/or calculated data (see paragraph 3.10.2.13 of this chapter and Annex 8) and/or analogy decisions (see paragraph A8.6.4.5 of Annex 8).*

2 *Labelling requirements differ from on regulatory system to another, and certain classification categories may only be used in one or a few regulations*

3 *See Note 4 of Table 3.10.1 and Chapter A8.5 of Annex 8.*



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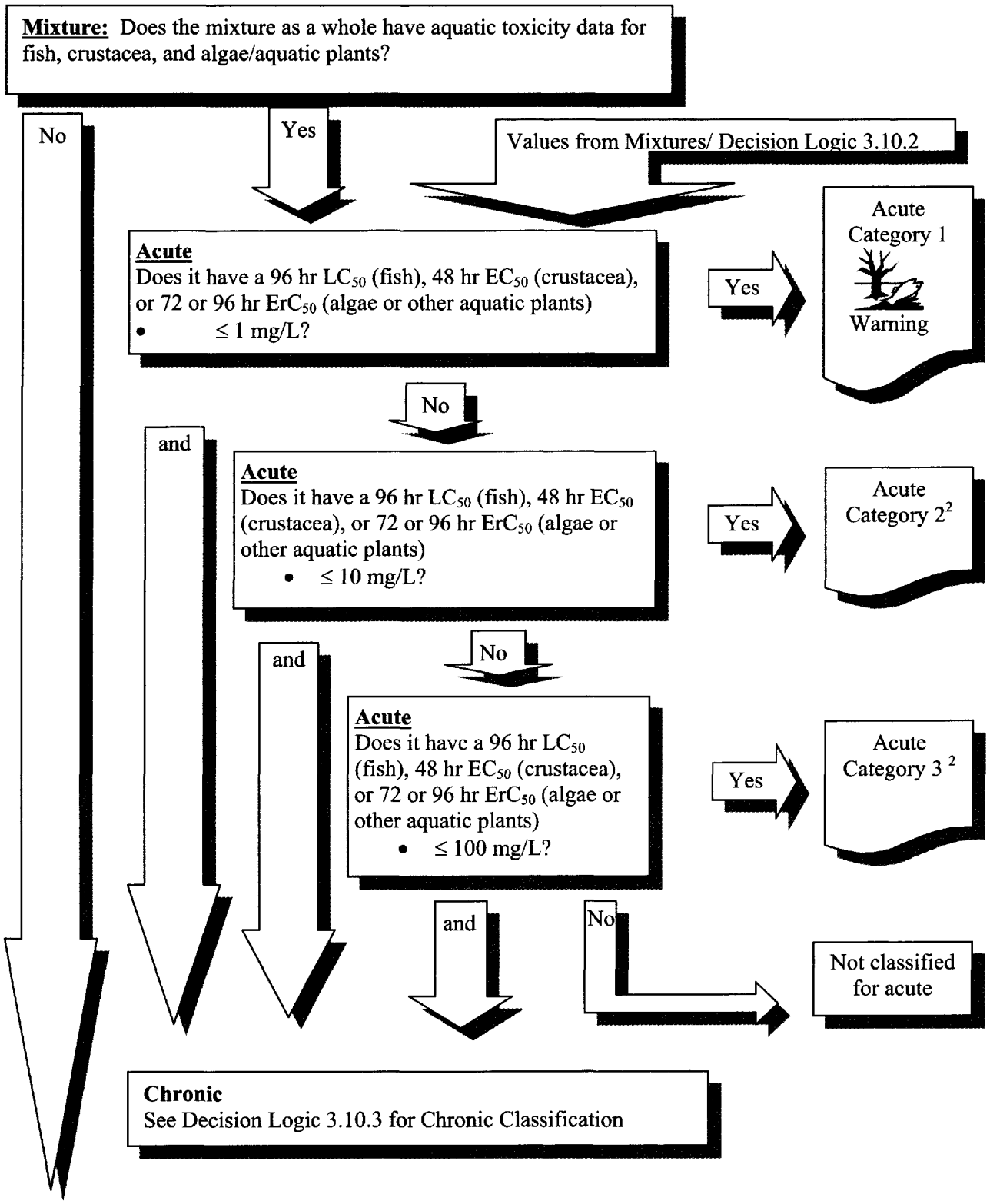
2 *Labelling requirements differ from one regulatory system to another, and certain classification categories may only be used in one or a few regulations.*

3 *See Note 4 of Table 3.10.1 and Chapter A8.5 of Annex 8.*

4 *See Table 3.10.1, Note 5 further developed in Annex8, sub-section A8.3.5.7.*

5 *See paragraph 3.10.2.12.*



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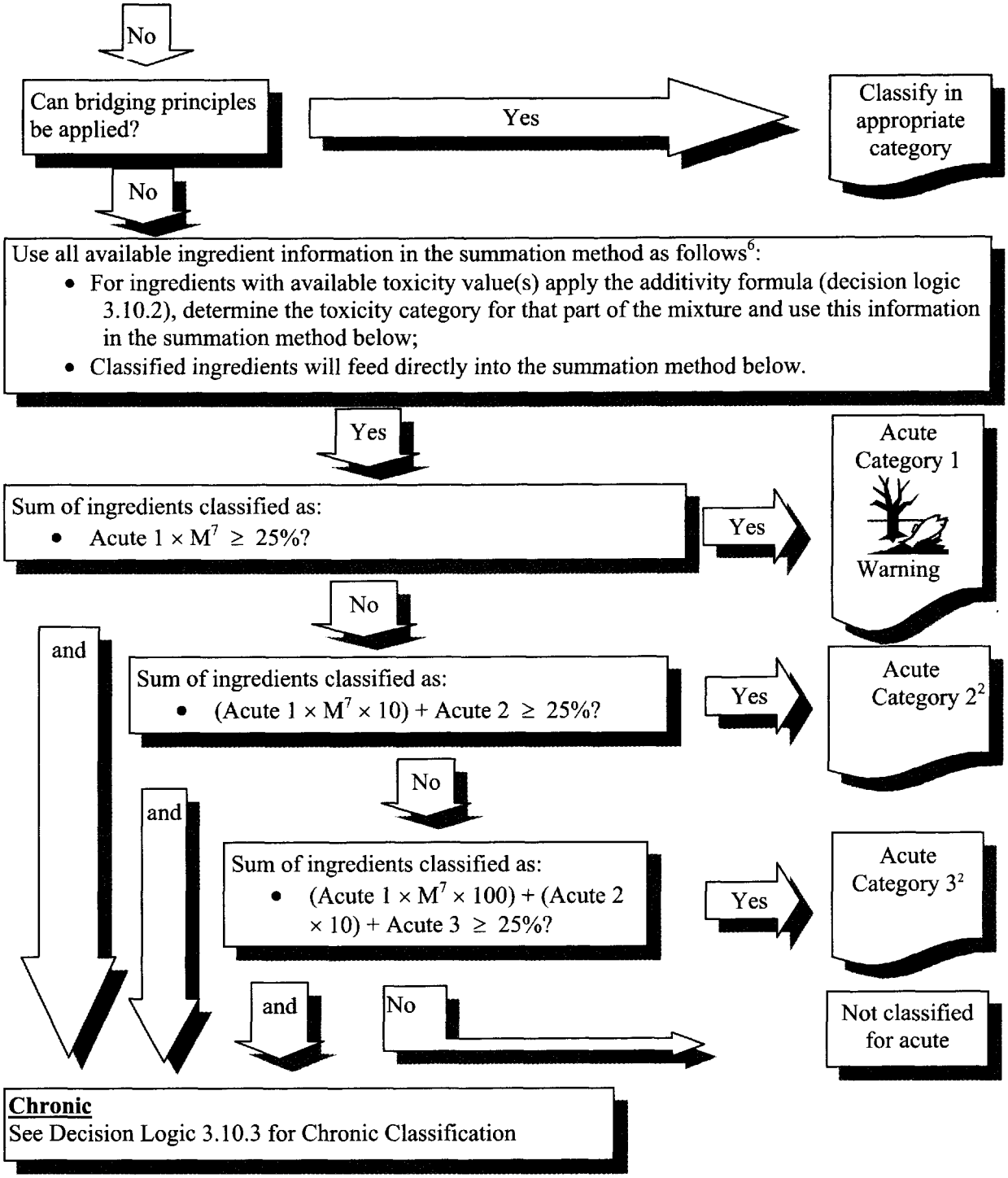
[2] *Labelling requirements differ from one regulatory system to another, and certain classification categories may only be used in one or a few regulations.*



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2 *Labelling requirements differ from one regulatory system to another, and certain classification categories may only be used in one or a few regulations.*

6 *If not all components have information, include the statement "x percent of the mixture consists of ingredients(s) of unknown hazards to the aquatic environment" on the label. Alternatively, in the case of a mixture with highly toxic ingredients, if toxicity values are available for these highly toxic ingredients and all other ingredients do not significantly contribute to the hazard of the mixture, than the additivity formula may be applied. (See paragraph 3.10.3.5.5.5). In this case and other cases where toxicity values are available for all ingredients, the acute classification may be made solely on the basis of the additivity formula.*

7 *For explanation of M factor see paragraph 3.10.3.5.5.5.*

Mixtures decision logic 3.10.2 (Additivity method)

Apply the Additivity Method:

$$\frac{\sum Ci}{L(E)C_{50m}} = \sum_{n} \frac{Ci}{L(E)C_{occ}}$$

where:

C_i = concentration of component i (weight percentage)
$L(E)C_{occ}$ = (mg/L) LC_{50} or EC_{50} for component I
n = number of components
$L(E)C_{50m}$ = $L(E)C_{50}$ of the part of the mixture with test data

→ Value to Mixture Decision Logic 3.10.1

Mixtures decision logic 3.10.3 (Chronic classification)

Sum of ingredients classified as:
• Chronic 1 × M^7 ≥ 25%?

Yes → Chronic Category 1 Warning

No

Sum of ingredients classified as:
• (Chronic 1 × M^7 × 10) + Chronic 2 ≥ 25%?

Yes → Chronic Category 2

No

Sum of ingredients classified as:
• (Chronic 1 × M^7 × 100) + (Chronic 2 x 10) + Chronic 3 ≥ 25%?

Yes → Chronic Category 3

No

Sum of ingredients classified as:
• Chronic 1 + Chronic 2 + Chronic 3 + Chronic 4 ≥ 25%?

Yes → Chronic Category 4

No → Not classified chronic

7 *For explanation of M factor see paragraph 3.10.3.5.5.5.*

ANNEXES

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ANNEX 1

ALLOCATION OF LABEL ELEMENTS

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Annex 1

ALLOCATION OF LABEL ELEMENTS

For the GHS, the assigned pictogram, signal word and hazard statement are given in that order for each hazard category of the hazard class. Where the hazard class and or categories are covered under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations*, the assigned corresponding pictogram is given for each category below the GHS requirements.

<table>
<tr><th colspan="6">EXPLOSIVES</th></tr>
<tr><th>Unstable/
Division 1.1</th><th>Division 1.2</th><th>Division 1.3</th><th>Division 1.4</th><th>Division 1.5</th><th>Division 1.6</th></tr>
<tr><td> </td><td> </td><td> </td><td>1.4 *

Warning

Fire or projection hazard</td><td>1.5 *

Warning

May explode in fire</td><td>1.6 *</td></tr>
<tr><td>Danger

Explosive; mass explosion hazard</td><td>Danger

Explosive; severe projection hazard</td><td>Danger

Explosive; fire, blast or projection hazard</td><td colspan="3">* Apply only to substances or mixtures subject to UN Recommendations on the Transport of Dangerous Goods, Model Regulations, requirements (see also par. 1.4.10.5.1 (d) (ii))</td></tr>
<tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr>
<tr><td colspan="6"><u>Notes</u> on colours of UN Recommendations on the Transport of Dangerous Goods, Model Regulations, pictogram elements:
(1) For Divisions 1.1, 1.2 and 1.3: Symbol exploding bomb: black; background: orange; figure "1" in bottom corner.
(2) For Divisions 1.4, 1.5, 1.6: Background: orange; Figures: black; figure "1" in bottom corner.</td></tr>
</table>

FLAMMABLE GASES				
Category 1	Category 2	-	-	Note
 Danger Extremely flammable gas	No symbol Warning Flammable gas			Under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations*, the symbol, number and border line may be shown in black instead of white. The background colour stays red in both cases.
	Not required under the *UN Model Regulations*			

FLAMMABLE AEROSOLS				
Category 1	Category 2	-	-	Note
 Danger Extremely flammable aerosol	 Warning Flammable aerosol			Under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations*, the symbol, number and border line may be shown in black instead of white. The background colour stays red in both cases.

OXIDIZING GASES				
Category 1	-	-	-	Note
 Danger May cause or intensify fire; oxidizer				
				Pictogram colours: Symbol and number: black. Background: yellow.

GASES UNDER PRESSURE				
Compressed gas	Liquefied gas	Refrigerated liquefied gas	Dissolved gas	Note Under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations*, pictogram elements:
 Warning Contains gas under pressure; may explode if heated	 Warning Contains gas under pressure; may explode if heated	 Warning Contains refrigerated gas; may cause cryogenic burns or injury	 Warning Contains gas under pressure; may explode if heated	(1) Not required for toxic or flammable gases. (2) The symbol, number and border line may be shown in white instead of black. The background stays green in both cases.

FLAMMABLE LIQUIDS				
Category 1	**Category 2**	**Category 3**	**Category 4**	**Note**
			No symbol	Under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations*, the symbol, number and border line may be shown in black instead of white. The background colour stays red in both cases.
Danger **Extremely flammable liquid and vapour**	**Danger** **Highly flammable liquid and vapour**	**Warning** **Flammable liquid and vapour**	**Warning** **Combustible liquid**	
			Not required under the *UN Recommendations on the Transport of Dangerous Goods Model Regulations*	

FLAMMABLE SOLIDS				
Category 1	**Category 2**	**-**	**-**	**Note**
				Colours for pictogram *under the UN Recommendations on the Transport of Dangerous Goods, Model Regulations*: Symbol and figure: black. Background: white with seven vertical red stripes.
Danger **Flammable solid**	**Warning** **Flammable solid**			

SELF-REACTIVE SUBSTANCES				
Type A	**Type B**	**Types C and D**	**Types E and F**	**Type G**
				No label elements are allocated for this category
Danger **Heating may cause an explosion**	**Danger** **Heating may cause a fire or explosion**	**Danger** **Heating may cause a fire**	**Warning** **Heating may cause a fire**	
Same as for explosives (follow same symbol selection process)				**Not required under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations***

Notes: (1) **For Type B, under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations*, special provision 181 may apply (Exemption of explosive label with competent authority approval. See Chapter 3.3 of *UN Model Regulations* for more details).**

(2) **For colours of *UN Model Regulations* pictograms see descriptions for Flammable Solids and Explosives.**

PYROPHORIC LIQUIDS				
Category 1	-	-	-	Note
 Danger Catches fire spontaneously if exposed to air				Colours of *UN Recommendations on the Transport of Dangerous Goods , Model Regulations,* pictogram: Symbol and figure: black. Background: upper half: white; lower half: red.

PYROPHORIC SOLIDS				
Category 1	-	-	-	Note
 Danger Catches fire spontaneously if exposed to air				Colours of *UN Recommendations on the Transport of Dangerous Goods, Model Regulations,* pictogram: Symbol and figure: black. Background: upper half: white; lower half: red.

SELF-HEATING SUBSTANCES				
Category 1	**Category 2**	**-**	**-**	**Note**
 Danger **Self-heating; may catch fire**	 **Warning** **Self-heating in large quantities; may catch fire**			**Colours of *UN Recommendations on the Transport of Dangerous Goods, Model Regulations*, pictogram:** **Symbol and figure: black.** **Background: upper half: white; lower half: red.**

SUBSTANCES, WHICH IN CONTACT WITH WATER, EMIT FLAMMABLE GASES

Category 1	Category 2	Category 3	-	Note
 Danger **In contact with water releases flammable gases which may ignite spontaneously**	 **Danger** **In contact with water releases flammable gases**	 **Warning** **In contact with water releases flammable gases**		**Under the UN Recommendations on the Transport of Dangerous Goods, Model Regulations, the symbol, number and border line may be shown in black instead of white. The background stays blue in both cases.**

OXIDIZING LIQUIDS				
Category 1	Category 2	Category 3	-	Note
				Under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations*, pictogram colours: Symbol and number: black. Background: yellow.
Danger May cause fire or explosion; strong oxidizer	Danger May intensify fire; oxidizer	Warning May intensify fire; oxidizer		

OXIDIZING SOLIDS				
Category 1	Category 2	Category 3	-	Note
				Under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations*, pictogram colours: Symbol and number: black. Background: yellow.
Danger May cause fire or explosion; strong oxidizer	Danger May intensify fire; oxidizer	Warning May intensify fire; oxidizer		

ORGANIC PEROXIDES

Type A	Type B	Types C and D	Types E and F	Type G
				There are no label elements allocated to this hazard class.
Danger Heating may cause an explosion	Danger Heating may cause a fire or explosion	Danger Heating may cause a fire	Warning Heating may cause a fire	
Same as for explosives (follow same symbol selection process)				Not required under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations*.

Notes: (1) For Type B, under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations*, special provision 181 may apply (Exemption of explosive label with competent authority approval. See Chapter 3.3 of UN Model Regulations for more details).

(2) UN Model Regulations pictogram colours: See tables for Oxidizing liquids and Explosives.

CORROSIVE TO METALS

Category 1	-	-	-	Note
Warning May be corrosive to metals				Under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations*, pictogram colours: Symbol: black background: upper half: white; lower half: black with white border; Figure 8: white.

ACUTE TOXICITY: ORAL				
Category 1	Category 2	Category 3	Category 4	Category 5
				No symbol
Danger	**Danger**	**Danger**	**Warning**	**Warning**
Fatal if swallowed	**Fatal if swallowed**	**Toxic if swallowed**	**Harmful if swallowed**	**May be harmful if swallowed**
			Not required under the *UN Recommendations on the Transport of Dangerous Goods , Model Regulations.* **Note:** **For gases under the UN Model Regulations , replace the number 6 in the bottom corner of the pictogram by 2.** **UN Model Regulations pictogram colours:** **Symbol and figure: black.** **Background: white.**	

ACUTE TOXICITY: SKIN				
Category 1	Category 2	Category 3	Category 4	Category 5
				No symbol
Danger	**Danger**	**Danger**	**Warning**	**Warning**
Fatal in contact with skin	**Fatal in contact with skin**	**Toxic in contact with skin**	**Harmful in Contact with skin**	**May be harmful in contact with skin**
			Not required under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations.* **Note:** **For gases under the UN Model Regulations, replace the number 6 in the bottom corner of the pictogram by 2.** **For UN Model Regulations pictogram colours:** **Symbol and figure: black.** **Background: white.**	

ACUTE TOXICITY: INHALATION				
Category 1	Category 2	Category 3	Category 4	Category 5
				No symbol
Danger Fatal if inhaled	Danger Fatal if inhaled	Danger Toxic if inhaled	Warning Harmful if inhaled	Warning May be harmful if inhaled
			Not required under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations.* Note: For gases under the UN Model Regulations, replace the number 6 in the bottom corner of the pictogram by 2. For UN Model Regulations pictogram colours: Symbol and figure: black. Background: white.	

SKIN CORROSION/IRRITATION				
Category 1A	Category 1B	Category 1C	Category 2	Category 3
				No symbol
Danger Causes severe skin burns and eye damage	Danger Causes severe skin burns and eye damage	Danger Causes severe skin burns and eye damage	Warning Causes skin irritation	Warning Causes mild skin irritation
			Not required under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations.* Note: UN Model Regulations pictogram colours: Symbol: black background: upper half: white; lower half: black with white border; Figure 8: white.	

SERIOUS EYE DAMAGE/ EYE IRRITATION				
Category 1	Category 2A	Category 2B	-	-
 Danger Causes serious eye damage	 Warning Causes serious eye irritation	No symbol Warning Causes eye irritation		
Not required under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations.*				

RESPIRATORY SENSITIZATION *				
Category 1	-	-	-	-
 Danger May cause allergy or asthma symptoms or breathing difficulties if inhaled				
Not required under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations.*				

* *Further work is included in the work programme of the Sub-Committee of Experts on the GHS.*

SKIN SENSITIZATION *				
Category 1	-	-	-	-
 Warning **May cause an allergic skin reaction**				
Not required under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations.*				

* *Further work is included in the work programme of the Sub-Committee of Experts on the GHS.*

GERM CELL MUTAGENICITY				
Category 1A	**Category 1B**	**Category 2**	-	-
Danger **May cause genetic defects** (*state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard*)	**Danger** **May cause genetic defects** (*state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard*)	**Warning** **Suspected of causing genetic defects** (*state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard*)		
Not required under the ***UN Recommendations on the Transport of Dangerous Goods, Model Regulations.***				

CARCINOGENICITY				
Category 1A	**Category 1B**	**Category 2**	-	-
Danger **May cause cancer** (*state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard*)	**Danger** **May cause cancer** (*state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard*)	**Warning** **Suspected of causing cancer** (*state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard*)		
Not required under the ***UN Recommendations on the Transport of Dangerous Goods, Model Regulations.***				

TOXIC TO REPRODUCTION				
Category 1A	**Category 1B**	**Category 2**	**Additional Category**	**-**
 Danger **May damage fertility or the unborn child** (*state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard*)	 **Danger** **May damage fertility or the unborn child** (*state specific effect if known)(state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard*)	 **Warning** **Suspected of damaging fertility or the unborn child** (*state specific effect if known)(state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard*)	**Effects on or via lactation** **May cause harm to breast-fed children.**	
Not required under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations.*				

TARGET ORGAN SYSTEMIC TOXICITY (SINGLE EXPOSURE)				
Category 1	Category 2	-	-	-
 Danger **Causes damage to (*state all organs affected, or use a general statement where there is no definite evidence that other organs are not affected*) if (*state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard*)**	 **Warning** **May cause damage to (*state all organs affected, or use a general statement where there is no definite evidence that other organs are not affected*) if (*state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard*)**			
Not required under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations.*				

TARGET ORGAN SYSTEMIC TOXICITY (REPEATED EXPOSURE)				
Category 1	Category 2	-	-	-
 Danger **Causes (*state all organs affected, or use a general statement where there is no definite evidence that other organs are not affected*) damage through prolonged or repeated exposure (*state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard*)**	 **Warning** **May cause (*state all organs affected, or use a general statement where there is no definite evidence that other organs are not affected*) damage through prolonged or repeated exposure (*state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard*)**			
Not required under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations.*				

AQUATIC TOXICITY (ACUTE)				
Category 1	**Category 2**	**Category 3**	**-**	**Note**
	No symbol	No symbol		**Presently not covered under the *UN Recommendations on the Transport of Dangerous Goods, Model Regulations* if the substance presents any other hazards covered by *UN Model Regulations* . If no other hazard is presented, the UN Model Regulations Class 9 label is applicable. The UN Model Regulations requirements are being revised.**
Warning	**No signal word**	**No signal word**		
Very toxic to aquatic life	**Toxic to aquatic life**	**Harmful to aquatic life**		

AQUATIC TOXICITY (CHRONIC)				
Category 1	Category 2	Category 3	Category 4	Note
		No symbol	No symbol	Presently not covered under the *UN Recommendations on the Transport of Dangerous Goods , Model Regulations* if the substance presents any other hazards covered by UN Model Regulations . If no other hazard is presented, UN Model Regulations Class 9 label is applicable. The UN Model Regulations requirements are being revised.
Warning	No signal word	No signal word	No signal word	
Very toxic to aquatic life with long lasting effects	Toxic to aquatic life with long lasting effects	Harmful to aquatic life with long lasting effects	May cause long lasting harmful effects to aquatic life	

ANNEX 2

CLASSIFICATION AND LABELLING

SUMMARY TABLES

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Annex 2

CLASSIFICATION AND LABELLING SUMMARY TABLES

A2.1 **Explosives** (see Chapter 2.1 for details)

Hazard category	Criteria	Hazard communication elements	
Division 1.1	According to the results of the test in Part I of the *Manual of Tests and Criteria, UN Recommendations on the Transport of Dangerous Goods.*	Symbol	
		Signal word	Danger
		Hazard statement	Explosive; mass explosion hazard
Division 1.2	According to the results of the test in Part I of the *Manual of Tests and Criteria, UN Recommendations on the Transport of Dangerous Goods.*	Symbol	
		Signal word	Danger
		Hazard statement	Explosive; severe projection hazard
Division 1.3	According to the results of the test in Part I of the *Manual of Tests and Criteria, UN Recommendations on the Transport of Dangerous Goods.*	Symbol	
		Signal word	Danger
		Hazard statement	Explosive; fire, blast or projection hazard
Division 1.4	According to the results of the test in Part I of the *Manual of Tests and Criteria, UN Recommendations on the Transport of Dangerous Goods.*	Symbol	**1.4**
		Signal word	Warning
		Hazard statement	Fire or projection hazard
Division 1.5	According to the results of the test in Part I of the *Manual of Tests and Criteria , UN Recommendations on the Transport of Dangerous Goods.*	Symbol	**1.5**
		Signal word	Warning
		Hazard statement	May explode in fire
Division 1.6	According to the results of the test in Part I of the *Manual of Tests and Criteria, UN Recommendations on the Transport of Dangerous Goods.*	Symbol	**1.6**
		Signal word	No signal word
		Hazard statement	No hazard statement

A2.2 **Flammable gases** (See Chapter 2.2 for details)

Hazard category	Criteria	Hazard communication elements	
1	Gases and gas mixtures, which at 20 °C and a standard pressure of 101.3 kPa: (a) are ignitable when in a mixture of 13% or less by volume in air; or (b) have a flammable range with air of at least 12 percentage points regardless of the lower flammable limit.	Symbol	
		Signal word	Danger
		Hazard statement	Extremely flammable gas
2	Gases or gas mixtures, other than those of category 1, which, at 20 °C and a standard pressure of 101.3 kPa, have a flammable range while mixed in air.	Symbol	No symbol used
		Signal word	Warning
		Hazard statement	Flammable gas

A2.3 **Flammable aerosols** (See Chapter 2.3 for details)

Hazard category	Criteria	Hazard communication elements	
1	On the basis of its components, of its chemical heat of combustion and, if applicable, of the results of the foam test, for foam aerosols, and of the ignition distance test and enclosed space test, for spray aerosols (see decision logic in 2.3.4.1 of Chapter 2.3).	Symbol	
		Signal word	Danger
		Hazard statement	Extremely flammable aerosol
2	On the basis of its components, of its chemical heat of combustion and, if applicable, of the results of the foam test, for foam aerosols, and of the ignition distance test and enclosed space test, for spray aerosols (see decision logic in 2.3.4.1 of Chapter 2.3).	Symbol	
		Signal word	Warning
		Hazard statement	Flammable aerosol

A2.4 Oxidizing gases (See Chapter 2.4 for details)

Hazard category	Criteria	Hazard communication elements	
1	Any gas which may, generally by providing oxygen, cause or contribute to the combustion of other material more than air does.	Symbol	
		Signal word	Danger
		Hazard statement	May cause or intensify fire; oxidizer

A2.5 Gases under pressure (See Chapter 2.5 for details)

Hazard category	Criteria	Hazard communication elements	
Compressed gas	A gas, which when packaged under pressure is entirely gaseous at -50 °C; including all gases with a critical temperature ≤ -50 °C.	Symbol	
		Signal word	Warning
		Hazard statement	Contains gas under pressure; may explode if heated
Liquefied gas	A gas which when packaged under pressure, is partially liquid at temperatures above -50 °C. A distinction is made between: *i) High pressure liquefied gas*: a gas with a critical temperature between –50 °C and +65 °C; and *ii) Low pressure liquefied gas*: a gas with a critical temperature above +65 °C.	Symbol	
		Signal word	Warning
		Hazard statement	Contains gas under pressure; may explode if heated
Refrigerated liquefied gas	A gas which when packaged is made partially liquid because of its low temperature.	Symbol	
		Signal word	Warning
		Hazard statement	Contains refrigerated gas; may cause cryogenic burns or injury
Dissolved gas	A gas which when packaged under pressure is dissolved in a liquid phase solvent.	Symbol	
		Signal Word	Warning
		Hazard statement	Contains gas under pressure; may explode if heated

A2.6 **Flammable liquids** (See Chapter 2.6 for details)

Hazard category	Criteria	Hazard communication elements	
1	Flash point < 23 °C and initial boiling point ≤ 35 °C.	Symbol	
		Signal word	Danger
		Hazard statement	Extremely flammable liquid and vapour
2	Flash point < 23 °C and initial boiling point >35 °C.	Symbol	
		Signal word	Danger
		Hazard statement	Highly flammable liquid and vapour
3	Flash point ≥ 23 °C and ≤ 60 °C.	Symbol	
		Signal word	Warning
		Hazard statement	Flammable liquid and vapour
4	Flash point > 60 °C and ≤ 93 °C.	Symbol	No symbol used
		Signal word	Warning
		Hazard statement	Combustible liquid

A.2.7 **Flammable solids** (See Chapter 2.7 for details)

Hazard category	Criteria	Hazard communication elements	
1	Burning rate test: Substances other than metal powders: - wetted zone does not stop fire and - burning time < 45 seconds or burning rate > 2.2 mm/s Metal powders: - burning time ≤ 5 minutes.	Symbol	
		Signal word	Danger
		Hazard statement	Flammable solid
2	Burning rate test: Substances other than metal powders: - wetted zone stops the fire for at least 4 minutes and - burning time < 45 seconds or burning rate > 2.2 mm/second Metal powders : - burning time > 5 minutes and ≤ 10 minutes.	Symbol	
		Signal word	Warning
		Hazard statement	Flammable solid

A2.8 Self-reactive substances (See Chapter 2.8 for details)

Hazard category	Criteria	Hazard communication elements	
Type A	According to the results of tests in the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* Part II and the application of the decision logic under 2.8.4.1 of Chapter 2.8.	Symbol	
		Signal word	Danger
		Hazard statement	Heating may cause an explosion
Type B	According to the results of tests in the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* Part II and the application of the decision logic under para. 2.8.4.1 of Chapter 2.8.	Symbol	
		Signal word	Danger
		Hazard statement	Heating may cause a fire or explosion
Type C and D	According to the results of tests in the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* Part II and the application of the decision logic under para. 2.8.4.1 of Chapter 2.8.	Symbol	
		Signal word	Danger
		Hazard statement	Heating may cause a fire
Type E and F	According to the results of tests in the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* Part II and the application of the decision logic under para. 2.8.4.1 of Chapter 2.8.	Symbol	
		Signal word	Warning
		Hazard statement	Heating may cause a fire
Type G	According to the results of tests in the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* Part II and the application of the decision logic under para. 2.8.4.1 of Chapter 2.8.	Signal word	There are no label elements allocated to this hazard category
		Symbol	
		Hazard statement	

A2.9 Pyrophoric liquids (See Chapter 2.9 for details)

Hazard category	Criteria	Hazard communication elements	
1	The liquid ignites within 5 min when added to an inert carrier and exposed to air, or it ignites or chars a filter paper on contact with air within 5 min.	Symbol	
		Signal word	Danger
		Hazard statement	Catches fire spontaneously if exposed to air

A2.10 Pyrophoric solids (See Chapter 2.10 for details)

Hazard category	Criteria	Hazard communication elements	
1	The solid ignites within 5 minutes of coming into contact with air.	Symbol	
		Signal word	Danger
		Hazard statement	Catches fire spontaneously if exposed to air

A2.11 Self-heating substances (See Chapter 2.11 for details)

<table>
<tr><th>Hazard category</th><th>Criteria</th><th colspan="2">Hazard communication elements</th></tr>
<tr><td rowspan="3">1</td><td rowspan="3">A positive result is obtained in a test using a 25 mm sample cube at 140 °C.</td><td>Symbol</td><td> </td></tr>
<tr><td>Signal word</td><td>Danger</td></tr>
<tr><td>Hazard statement</td><td>Self-heating; may catch fire</td></tr>
<tr><td rowspan="3">2</td><td rowspan="3">(a) A positive result is obtained in a test using a 100 mm sample cube at 140 °C and a negative result is obtained in a test using a 25 mm cube sample at 140 °C <u>and</u> the substance is to be packed in packages with a volume of more than 3 m^3; or
(b) A positive result is obtained in a test using a 100 mm sample cube at 140 °C and a negative result is obtained in a test using a 25 mm cube sample at 140 °C, a positive result is obtained in a test using a 100 mm cube sample at 120 °C <u>and</u> the substance is to be packed in packages with a volume of more than 450 litres; or
(c) A positive result is obtained in a test using a 100 mm sample cube at 140 °C and a negative result is obtained in a test using a 25 mm cube sample at 140 °C <u>and</u> a positive result is obtained in a test using a 100 mm cube sample at 100 °C.</td><td>Symbol</td><td> </td></tr>
<tr><td>Signal word</td><td>Warning</td></tr>
<tr><td>Hazard statement</td><td>Self-heating in large quantities; may catch fire</td></tr>
</table>

A2.12 Substances, which on contact with water, emit flammable gases (See Chapter 2.12 for details)

Hazard category	Criteria	Hazard communication elements	
1	Any substance which reacts vigorously with water at ambient temperatures and demonstrates generally a tendency for the gas produced to ignite spontaneously, or which reacts readily with water at ambient temperatures such that the rate of evolution of flammable gas is equal to or greater than 10 litres per kilogram of substance over any one minute.	Symbol	
		Signal word	Danger
		Hazard statement	In contact with water releases flammable gases which may ignite spontaneously
2	Any substance which reacts readily with water at ambient temperatures such that the maximum rate of evolution of flammable gas is equal to or greater than 20 litres per kilogram of substance per hour, and which does not meet the criteria for category 1.	Symbol	
		Signal word	Danger
		Hazard statement	In contact with water releases flammable gases
3	Any substance which reacts slowly with water at ambient temperatures such that the maximum rate of evolution of flammable gas is equal to or greater than 1 litre per kilogram of substance per hour, and which does not meet the criteria for categories 1 and 2.	Symbol	
		Signal word	Warning
		Hazard statement	In contact with water releases flammable gases

A2.13 Oxidizing liquids (See Chapter 2.13 for details)

Hazard category	Criteria	Hazard communication elements	
1	Any substance which, in the 1:1 mixture, by mass, of substance and cellulose tested, spontaneously ignites; or the mean pressure rise time of a 1:1 mixture, by mass, of substance and cellulose is less than that of a 1:1 mixture, by mass, of 50% perchloric acid and cellulose.	Symbol	
		Signal word	Danger
		Hazard statement	May cause fire or explosion; strong oxidizer
2	Any substance which, in the 1:1 mixture, by mass, of substance and cellulose tested, exhibits a mean pressure rise time less than or equal to the mean pressure rise time of a 1:1 mixture, by mass, of 40% aqueous sodium chlorate solution and cellulose; and the criteria for category 1 are not met.	Symbol	
		Signal word	Danger
		Hazard statement	May intensify fire; oxidizer
3	Any substance which, in the 1:1 mixture, by mass, of substance and cellulose tested, exhibits a mean pressure rise time less than or equal to the mean pressure rise time of a 1:1 mixture, by mass, of 65% aqueous nitric acid and cellulose; and the criteria for categories 1 and 2 are not met.	Symbol	
		Signal word	Warning
		Hazard statement	May intensify fire; oxidizer

A2.14 Oxidizing solids (See Chapter 2.14 for details)

Hazard category	Criteria	Hazard communication elements	
1	Any substance which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning time less than the mean burning time of a 3:2 mixture, by mass, of potassium bromate and cellulose.	Symbol	
		Signal word	Danger
		Hazard statement	May cause fire or explosion; strong oxidizer
2	Any substance which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning time equal to or less than the mean burning time of a 2:3 mixture (by mass) of potassium bromate and cellulose and the criteria for category 1 are not met.	Symbol	
		Signal word	Danger
		Hazard statement	May intensify fire; oxidizer
3	Any substance which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning time equal to or less than the mean burning time of a 3:7 mixture (by mass) of potassium bromate and cellulose and the criteria for categories 1 and 2 are not met.	Symbol	
		Signal word	Warning
		Hazard statement	May intensify fire; oxidizer

A2.15 Organic peroxides (See Chapter 2.15 for details)

Hazard category	Criteria	Hazard communication elements	
Type A	According to the results of test series A to H in the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* Part II and the application of the decision logic under 2.15.4.1 of Chapter 2.15.	Symbol	
		Signal word	Danger
		Hazard statement	Heating may cause an explosion
Type B	According to the results of test series A to H in the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* Part II and the application of the decision logic under 2.15.4.1 of Chapter 2.15.	Symbol	
		Signal word	Danger
		Hazard statement	Heating may cause a fire or explosion
Type C and D	According to the results of test series A to H in the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* Part II and the application of the decision logic under 2.15.4.1 of Chapter 2.15.	Symbol	
		Signal word	Danger
		Hazard statement	Heating may cause a fire
Type E and F	According to the results of test series A to H in the *UN Recommendations on the Transport of Dangerous Good, Manual of Tests and Criteria,* Part II and the application of the decision logic under 2.15.4.1 of Chapter 2.15.	Symbol	
		Signal word	Warning
		Hazard statement	Heating may cause a fire
Type G	According to the results of test series A to H in the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria,* Part II and the application of the decision logic under 2.15.4.1 of Chapter 2.15.	Signal word	There are no label elements allocated to this hazard category
		Symbol	
		Hazard statement	

A2.16 Corrosive to metals (See Chapter 2.16 for details)

Hazard category	Criteria	Hazard communication elements	
1	Corrosion rate on steel or aluminium surfaces exceeding 6.25 mm per year at a test temperature of 55 °C.	Symbol	
		Signal word	Warning
		Hazard statement	May be corrosive to metals

A2.17 Acute toxicity (See Chapter 3.1 for details)

Hazard category	Criteria	Hazard communication elements	
1	$LD_{50} \leq 5$ mg/kg bodyweight (oral) $LD_{50} \leq 50$ mg/kg bodyweight (skin/dermal) $LC_{50} \leq 100$ ppm (gas) $LC_{50} \leq 0.5$ (mg/l) (vapour) $LC_{50} \leq 0.05$ (mg/l) (dust,mist)	Symbol	
		Signal word	Danger
		Hazard statement	Fatal if swallowed. (oral) Fatal in contact with skin (dermal) Fatal if inhaled (gas, vapour, dust, mist)
2	LD_{50} between 5 and less than 50 mg/kg bodyweight (oral) LD50 between 50 and less than 200 mg/kg bodyweight (skin/dermal) LC50 between 100 and less than 500 ppm (gas) LC50 between 0.5 and less than2.0 (mg/l) (vapour) LC50 between 0.05 and less than 0.5 (mg/l) (dust, mist)	Symbol	
		Signal word	Danger
		Hazard Statement	Fatal if swallowed. (oral) Fatal in contact with skin (dermal) Fatal if inhaled (gas, vapour, dust, mist)
3	LD_{50} between 50 and less than 300 mg/kg bodyweight (oral) LD_{50} between 200 and less than 1000 mg/kg bodyweight (skin/dermal) LC_{50} between 500 and less than 2500 ppm (gas) LC_{50} between 2.0 and less than 10.0 (mg/l) (vapour) LC_{50} between 0.5 and less than 1.0 (mg/l) (dust, mist)	Symbol	
		Signal word	Danger
		Hazard statement	Toxic if swallowed. (oral) Toxic in contact with skin (dermal) Toxic if inhaled (gas, vapour, dust, mist)

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Hazard category	Criteria	Hazard communication elements	
(cont'd)			
4	LD_{50} between 300 and less than 2000 mg/kg bodyweight (oral) LD_{50} between 1000 and less than 2000 mg/kg bodyweight (skin/dermal) LC_{50} between 2500 and less than 5000 ppm (gas) LC50 between 10.0 and less than 20.0 (mg/l) (vapour) LC50 between 1.0 and less than 5.0 (mg/l) (dust, mist)	Symbol	
		Signal word	Warning
		Hazard statement	Harmful if swallowed. (oral) Harmful in contact with skin (dermal) Harmful if inhaled (gas, vapour, dust, mist)
5	LD_{50} between 2000 and 5000 (oral or skin/dermal) For gases, vapours, dusts, mists, LC_{50} in the equivalent range of the oral and dermal LD_{50} (i.e., between 2000 and 5000 mg/kg bodyweight). See also the additional criteria • Indication of significant effect in humans • Any mortality at Category 4 • Significant clinical signs at Category 4 • Indication from other studies.	Symbol	No symbol
		Signal word	Warning
		Hazard statement	May be harmful if swallowed (oral) May be harmful in contact with skin (dermal) May be harmful if inhaled (gas, vapour, dust, mist)

A2.18 Skin corrosion/irritation (See Chapter 3.2 for details)

Hazard category	Criteria	Hazard communication elements	
1 **Corrosive Including sub-categories A, B, and C; see Chapter 3.2, Table 3.2.1**	1. *For Substances and Tested Mixtures*: • Human experience showing irreversible damage to the skin; • Structure/activity or structure property relationship to a substance or mixture already classified as corrosive; • pH extremes of ≤ 2 and ≥ 11.5 including acid/alkali reserve capacity; • Positive results in a valid and accepted *in vitro* skin corrosion test; or • Animal experience or test data that indicate that the substance/mixture causes irreversible damage to the skin following exposure of up to 4 hours (See Table 3.2.1). 2. *If data for a mixture are not available*, use bridging principles in 3.2.3.2. 3. *If bridging principles do not apply,* (a) For mixtures where substances can be added: Classify as corrosive if the sum of the concentrations of corrosive substances in the mixture is ≥ 5% (for substances with additivity); or (b) For mixtures where substances cannot be added:≥ 1%. See 3.2.3.3.4.	Symbol	
		Signal word	Danger
		Hazard statement	Causes severe skin burns and eye damage

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Hazard category (cont'd)	Criteria	Hazard communication elements	
2 **Irritant** **(applies to all authorities)**	1. *For Substances and Tested Mixtures* • Human experience or data showing reversible damage to the skin following exposure of up to 4 hours; • Structure/activity or structure property relationship to a substance or mixture already classified as an irritant; • Positive results in a valid and accepted *in vitro* skin irritation test; or • Animal experience or test data that indicate that the substance/mixture causes reversible damage to the skin following exposure of up to 4 hours , mean value of ≥ 2.3 < 4.0 for erythema/eschar or for oedema , or inflammation that persists to the end of the observation period, in 2 of 3 tested animals (Table3.2.2). 2. *If data for a mixture are not available*, use bridging principles in 3.2.3.2. 3. *If bridging principles do not apply*, classify as an irritant if: (a) For mixtures where substances can be added: the sum of concentrations of corrosive substances in the mixture is ≥ 1% but ≤ 5%; the sum of the concentrations of irritant substances is ≥ 10%; or the sum of (10 x the concentrations of corrosive ingredients) + (the concentrations of irritant ingredients) is ≥ 10%; or (b) For mixtures where substances cannot be added: ≥ 3%. (See 3.2.3.3.4).	Symbol	
		Signal word	Warning
		Hazard statement	Causes skin irritation

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Hazard category (cont'd)	**Criteria**	**Hazard communication elements**	
3 **Mild Irritant** **(applies to some authorities)**	1. *For Substances and Tested Mixtures* • Animal experience or test data that indicates that the substance/mixture causes reversible damage to the skin following exposure of up to 4 hours, mean value of $\geq 1.5 < 2.3$ for erythema/eschar in 2 of 3 tested animals (See Table 3.2.2). 2. *If data for a mixture are not available* and the bridging principles in 3.2.3.2. 3. *If bridging principles do not apply*, classify as mild irritant if: • For mixtures where substances can be added the sum of the concentrations of irritant substances in the mixture is $\geq$ 1% but $\leq$ 10%; • For mixtures where substances cannot be added: the sum of the concentrations of mild irritant substances is $\geq$ 10%; • the sum of (10 x the concentrations of corrosive substances) + (the concentrations of irritant substances) is $\geq$ 1% but $\leq$ 10%; or • the sum of (10 x the concentrations of corrosive substances) + (the concentrations of irritant substances) + (the concentrations of mild irritant substances) is $\geq$ 10%.	Symbol	None
		Signal word	Warning
		Hazard statement	Causes mild skin irritation

A2.19 Serious eye damage / eye irritation (See Chapter 3.3 for details)

Hazard category	Criteria	Hazard communication elements	
1 **Irrever-sible Effects**	1. *For Substances and Tested Mixtures* • Classification as corrosive to skin; • Human experience or data showing damage to the eye which is not fully reversible within 21 days; • Structure/activity or structure property relationship to a substance or mixture already classified as corrosive; • pH extremes of < 2 and > 11.5 including buffering capacity; • Positive results in a valid and accepted *in vitro* test to assess serious damage to eyes; or • Animal experience or test data that the substance or mixture produces either (1) in at least one animal, effects on the cornea, iris or conjunctiva that are not expected to reverse or have not reversed; or (2) in at least 2 of 3 tested animals a positive response of corneal opacity ≥ 3 and/or iritis >1.5 (see Table3.3.1). 2. *If data for a mixture are not available*, use bridging principles in 3.3.3.2. 3. *If bridging principles do not apply,* (a) For mixtures where substances can be added: Classify as Category 1 if the sum of the concentrations of substances classified as corrosive to the skin and/or eye Category 1 substances in the mixture is ≥ 3%; or (b) For mixtures where substances cannot be added:≥ 1 (see 3.3.3.3.4).	Symbol	
		Signal word	Danger
		Hazard statement	Causes serious eye damage

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Hazard category (cont'd)	Criteria	Hazard communication elements	
2A **Irritant**	1. *Substances and tested mixtures* • Classification as severe skin irritant; • Human experience or data showing production of changes in the eye which are fully reversible within 21 days; • Structure/activity or structure property relationship to a substance or mixture already classified as an eye irritant; • Positive results in a valid and accepted *in vitro* eye irritation test; or • Animal experience or test data that indicate that the substance/mixture produces a positive response in at least 2 of 3 tested animals of : corneal opacity ≥1, iritis ≥1, or conjunctival edema (chemosis) ≥2 (Table 3.3.2). 2. *If data for a mixture are not available*, use bridging principles in 3.3.3.2. 3. *If bridging does not apply*, classify as an irritant (2A) if: (a) For mixtures where substances can be added: the sum of the concentrations of skin and/or eye Category 1 substances in the mixture is ≥ 1% but ≤ 3%; the sum of the concentrations of eye irritant substances is ≥ 10%; or the sum of (10 x the concentrations of skin and/or eye category 1 substances) + (the concentrations of eye irritants) is ≥ 10%; (b) For mixtures where substances cannot be added: the sum of the concentrations of eye irritant ingredients is ≥ 3% (see 3.3.3.3.4).	Symbol	
		Signal word	Warning
		Hazard statement	Causes serious eye irritation
2B **Mild Irritant**	1. *For Substances and tested mixtures* • Human experience or data showing production of mild eye irritation; • Animal experience or test data that indicate that the lesions are fully reversible within 7 days (see Table 3.3.2). 2. *If data for a mixture are not available*, use bridging principles in 3.3.3.2. 3. *If bridging does not apply*, classify as an irritant (2B) if: (a)For mixtures where substances can be added: the sum of the concentrations of skin and/or eye Category 1 substances in the mixture is ≥ 1% but ≤ 3%; the sum of the concentrations of eye irritant substances is ≥ 10%; or the sum of (10 x the concentrations of skin and/or eye category 1 substances) + (the concentrations of eye irritants) is ≥ 10%; (b) For mixtures where substances cannot be added: the sum of the concentrations of eye irritant ingredients is ≥ 3% (see 3.3.3.3.4).	Symbol	No symbol
		Signal word	Warning
		Hazard statement	Causes eye irritation

A2.20 Respiratory sensitizer (See Chapter 3.4 for details)

<table>
<tr><th>Hazard category</th><th>Criteria</th><th colspan="2">Hazard communication element</th></tr>
<tr><td rowspan="3">1</td><td rowspan="3">1. For Substances and Tested Mixture
If there is human evidence that the individual substance induces specific respiratory hypersensitivity, and/or
Where there are positive results from an appropriate animal test.
2. If these mixture meets the criteria set forth in the "Bridging Principles" through one of the following:
(a) Dilution;
(b) Batching;
(c) Substantially Similar Mixture.
3. If bridging principles do not apply, classify if any individual respiratory sensitizer in the mixture has a concentration of:
≥ 1.0% Solid/Liquid
≥ 0.2% Gas.</td><td>Symbol</td><td> </td></tr>
<tr><td>Signal word</td><td>Danger</td></tr>
<tr><td>Hazard statement</td><td>May cause allergic or asthmatic symptoms or breathing difficulties if inhaled</td></tr>
</table>

A2.21 Skin sensitizer (See Chapter 3.4 for details)

Hazard category	Criteria	Hazard communication element	
1	1. *For Substances and tested mixture* If there is evidence in humans that the individual substance can induce sensitization by skin contact in a substantial number of persons, or Where there are positive results from an appropriate animal test. 2. *If the mixture meets the criteria* set forth in the "Bridging Principles" through one of the following: (a) Dilution; (b) Batching; (c) Substantially similar mixture. 4. *If bridging principles do not apply*, classify if any individual skin sensitizer in the mixture has a concentration of: ≥ 1.0% Solid/Liquid/Gas.	Symbol	
		Signal word	Warning
		Hazard Statement	May cause allergic skin reaction

A2.22 Mutagenicity (See Chapter 3.5 for details)

Hazard Category	Criteria for classification	Hazard communication elements	
1 (Both 1A and 1B)	Known to induce heritable mutations or regarded as if it induces heritable mutations in the germ cells of humans (see criteria in 3.5.2) or mixtures containing ≥0.1 % of such a substance.	Symbol	
		Signal word	Danger
		Hazard statement	May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)
2	Causes concern for man owing to the possibility that it may induce heritable mutations in the germ cells of humans (see criteria in 3.5.2) or mixtures containing ≥1.0 % of such a substance.	Symbol	
		Signal word	Warning
		Hazard Statement	Suspected of causing genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)

A2.23 Carcinogenicity (See Chapter 3.6 for details)

Hazard category	Criteria	Hazard communication elements	
1 (both 1A and 1B)	Known or Presumed Human Carcinogen including mixtures containing ≥ 0.1% of such a substance.	Symbol	
		Signal word	Danger
		Hazard statement	May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard.
2	Suspected human carcinogen Including mixtures containing more than ≥ 0.1 or ≥1.0 % of such a substance (see Notes 1 and 2 in Table 3.6.1 of Chapter 3.6).	Symbol	
		Signal word	Warning
		Hazard statement	Suspected of causing cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard*)

* *Some authorities will choose to label according to this provision, others may not.*

A2.24 (a) Toxic to reproduction (See Chapter 3.7 for details)

Hazard category	Criteria	Hazard communication elements	
1 (Both 1A and 1B)	Known or presumed human reproductive toxicants (see criteria in 3.7.2.2.1 to 3.7.2.6.0 of Chapter 3.7) or mixtures containing ≥ 0.1% or ≥0.3 % of such a substance (see notes 1 and 2 of Table 3.7.1, Chapter 3.7).	Symbol	
		Signal word	Danger
		Hazard statement	May damage fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)
2	Suspected human reproductive toxicants (see criteria in 3.7.2.2.1 to 3.7.2.6.0 of Chapter 3.7) or mixtures containing ≥ 0.1% or ≥3.0 % of such a substance (see Notes 3 and 4 of Table 3.7.1, Chapter 3.7).	Symbol	
		Signal word	Warning
		Hazard statement	Suspected of damaging fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)

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A2.24 (b) Effects on or via lactation (See Chapter 3.7)

Hazard category (cont'd)	**Criteria**	**Hazard communication elements**	
Special category	Substances which cause concern for the health of breastfed children (see criteria in 3.7.2.2.1 to 3.7.2.6.0 and 3.7.3.4 of Chapter 3.7).	Symbol	No symbol
		Signal word	No signal word
		Hazard Statement	May cause harm to breast-fed children

A2.25 Target organ systemic toxicity following single exposure (See Chapter 3.8 for details)

Hazard category	Criteria	Hazard communication elements	
1	Reliable evidence on the substance or mixture (including bridging) of an adverse effect on specific organ/systems or systemic toxicity in humans or animals. May use guidance values in Table 3.8.1, Category 1 criteria as part of weight of evidence evaluation. May be named for specific organ/system. Mixture that lacks sufficient data, but contains Category 1 ingredient at a concentration of ≥ 1.0 to ≤ 10.0% for some authorities; and ≥10.0% for all authorities.	Symbol	
		Signal word	Danger
		Hazard statement	Causes damage to organs (state all organs affected, if known) through prolonged or repeated exposure (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)
2	Evidence on the substance or mixture (including bridging) of an adverse effect on specific organ/systems or systemic toxicity from animal studies or humans considering weight of evidence and guidance values in Table 3.8.1, Category 2 criteria. May be named for specific organ/system affected. Mixture that lacks sufficient data, but contains Category 1 ingredient: ≥ 1 but ≤10% for some authorities; and /or contains Category 2 ingredient: ≥ 1 to ≤10% for some authorities; and ≥10% for all authorities.	Symbol	
		Signal word	Warning
		Hazard statement	May causes amage to organs (state all organs affected, if known) through prolonged or repeated exposure (state oute of exposure if it is conclusively proven that no other routes of exposure cause the hazard)

A2.26 Target organ systemic toxicity following repeat exposure (See Chapter 3.9 for details)

Hazard category	Criteria	Hazard communication elements	
1	Reliable evidence on the substance or mixture (including bridging) of an adverse effect on specific organ/systems or systemic toxicity in humans or animals. May use guidance values in Table 3.91 as part of weight of evidence evaluation. May be named for specific organ/system. Mixture that lacks sufficient data, but contains Category 1 ingredient: ≥ 1 to ≤ 10% for some authorities; and ≥10% for all authorities.	Symbol	
		Signal word	Danger
		Hazard statement	Causes damage to organs (state all organs affected, if known) through prolonged or repeated exposure (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)
2	Evidence on the substance or mixture (including bridging) of an adverse effect on specific organ/systems or systemic toxicity from animal studies or humans considering weight of evidence and guidance values in Table 3.9.2 criteria. May be named for specific organ/system. Mixture that lacks sufficient data, but contains Category 1 ingredient: ≥ 1.0 but ≤10% for some authorities (see Note 3 of Table 3.9.3) and /or contains Category 2 ingredient: ≥ 1.0 or ≥10%.	Symbol	
		Signal word	Warning
		Hazard statement	May cause damage to organs (state all organs affected, if known) through prolonged or repeated exposure (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)

A2.27 Acute hazards to the aquatic environment (See Chapter 3.10 for details)

Hazard category	Criteria	Hazard communication elements	
1	*1. For Substances and Tested Mixtures:* • $L(E)C_{50} \leq 1mg/L$ where $L(E)C_{50}$ is either fish 96hr LC_{50}, crustacea 48hr EC LC_{50} or aquatic plant 72 or 96hr ErC_{50}. *2. If data for a mixture are not available,* use bridging principles (see 3.10.3.4). *3. If bridging principles do not apply,* (a) For mixtures with classified ingredients: The summation method (see 3.10.3.10.3.5.5) reveals: • [Concentration of Acute 1] × M > 25% where M is a multiplying factor (see 3.10.3.5.5.5). (b) For mixtures with tested ingredients: The additivity formula (see 3.10.3.5.2 and 3.10.3.5.3) reveals: • $L(E)C_{50} \leq 1mg/L$. (c) For mixtures with both classified and tested ingredients: The combined additivity formula and summation method (see paragraphs 3.10.3.5.2 to 3.10.3.5.5.3) reveal: • Concentration of Acute 1 × M > 25%. *4. For mixtures with no usable information for one or more relevant ingredients,* classify using the available information and add the statement: "x percent of the mixture consists of component(s) of unknown hazards to the aquatic environment".	Symbol	
		Signal word	Warning
		Hazard statement	Very toxic to aquatic life

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Hazard category (cont'd)	Criteria	Hazard communication elements	
2	1. *For Substances and Tested Mixtures:* • 1mg/L < L(E)C_{50} ≤ 10mg/L where L(E)C_{50} is either fish 96hr LC_{50}, crustacea 48hr EC LC_{50} or aquatic plant 72 or 96hr ErC_{50}. 2. *If data for a mixture are not available,* use bridging principles (see 3.10.3.4). 3. *If bridging principles do not apply,* (a) For mixtures with classified ingredients: The summation method (see 3.10.3.5.5.1 to 3.10.3.5.5.3) reveals: • [Concentration of Acute 1] × M × 10 + (Concentration of Acute 2] > 25% where M is a multiplying factor (see 3.10.3.5.5.5). (b) For mixtures with tested ingredients: The additivity formula (see 3.10.3.5.2-3.10.3.5.3) reveals: • 1mg/L < L(E)C_{50} ≤ 10mg/L. (c) For mixtures with both classified and tested ingredients: The combined additivity formula and summation method (see 3.10.3.5.2-3.10.3.5.5.3) reveal: • [Concentration of Acute 1] × M x 10 + [Concentration of Acute 2] > 25%. 4. *For mixtures with no usable information for one or more relevant ingredients,* classify using the available information and add the statement: "x percent of the mixture consists of component(s) of unknown hazards to the aquatic environment".	Symbol	No symbol used
		Signal word	No signal word
		Hazard statement	Toxic to aquatic life

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Hazard category (cont'd)	**Criteria**	**Hazard communication elements**	
3	*1. For Substances and Tested Mixtures:* • 10mg/L < L(E)C_{50} ≤ 100mg/L where L(E)C_{50} is either fish 96hr LC_{50}, crustacea 48hr EC LC_{50} or aquatic plant 72 or 96hr ErC_{50}. *2. If data for a mixture are not available,* use bridging principles (see 3.10.3.4). *3. If bridging principles do not apply,* (d) For mixtures with classified ingredients: The summation method (see 3.10.3.5.5.1 to 3.10.3.5.5.3) reveals: • [Concentration of Acute 1] × M x 100 + [Concentration of Acute 2] × 10 + [Concentration of Acute 3] > 25% where M is a multiplying factor (see 3.10.3.5.5.5). (e) For mixtures with tested ingredients: The additivity formula (see 3.10.3.5.2-3.10.3.5.3) reveals: • 10mg/L < L(E)C_{50} ≤ 100mg/L. (f) For mixtures with both classified and tested ingredients: The combined additivity formula and summation method (see 3.10.3.5.2 to 3.10.3.5.5.3) reveal: • [Concentration of Acute 1] × M x 100 + [Concentration of Acute 2] × 10 + [Concentration of Acute 3] > 25%. *4. For mixtures with no usable information for one or more relevant ingredients,* classify using the available information and add the statement: "x percent of the mixture consists of component(s) of unknown hazards to the aquatic environment".	Symbol	No symbol used
		Signal word	No signal word
		Hazard statement	Harmful to aquatic life

A2.28 Chronic hazards to the aquatic environment (See Chapter 3.10 for details)

Hazard category	Criteria	Hazard communication elements	
1	*1. For Substances:* • $L(E)C_{50} \leq 1mg/L$; and • Lack the potential to rapidly biodegrade and/or have the potential to bioaccumulate (BCF≥ 500 or if absent log Kow ≥ 4) where $L(E)C_{50}$ is either fish 96hr LC_{50}, crustacea 48hr EC LC_{50} or aquatic plant 72 or 96hr ErC_{50}. *2. For Mixtures,* use bridging principles (see 3.10.3.4). *3. If bridging principles do not apply,* • [Concentration of Chronic 1] x M > 25% where M is a multiplying factor (see 3.10.3.5.5.5). *4. For mixtures with no usable information for one or more relevant ingredients,* classify using the available information and add the statement: "x percent of the mixture consists of component(s) of unknown hazards to the aquatic environment".	Symbol	
		Signal word	Warning
		Hazard statement	Very toxic to aquatic life with long lasting effects
2	*1. For Substances:* • 1 mg/L < $L(E)C_{50} \leq 10$ mg/L; and • Lack the potential to rapidly biodegrade and/or have the potential to bioaccumulate (BCF≥ 500 or if absent log Kow ≥ 4); unless • Chronic NOECs > 1mg/L. *2. For Mixtures,* use bridging (see 3.10.3.4). *3. If bridging principles do not apply,* • [Concentration of Chronic 1] x M x 10 + [Concentration of Chronic 2] > 25% where M is a multiplying factor (see 3.10.3.5.5.5). *4. For mixtures with no usable information for one or more relevant ingredients,* classify using the available information and add the statement: "x percent of the mixture consists of component(s) of unknown hazards to the aquatic environment".	Symbol	
		Signal word	No signal word
		Hazard statement	Toxic to aquatic life with long lasting effects

Continued on next page

Hazard category (Cont'd)	**Criteria**	**Hazard communication elements**	
3	*1. For Substances:* • 10 mg/L < L(E)C_{50} ≤ 100 mg/L; and • Lack the potential to rapidly biodegrade and/or have the potential to bioaccumulate (BCF≥ 500 or if absent log Kow ≥ 4); unless • Chronic NOECs > 1mg/L. *2. For Mixtures,* use bridging principles (see 3.10.3.4). *3. If bridging principles do not apply,* • [Concentration of Chronic 1] × M × 100 + [Concentration of Chronic 2] × 10 + [Concentration of Chronic 3] > 25% where M is a multiplying factor (see 3.10.3.5.5.5). *4. For mixtures with no usable information for one or more relevant ingredients,* classify using the available information and add the statement: "x percent of the mixture consists of component(s) of unknown hazards to the aquatic environment".	Symbol	No symbol used
		Signal word	No signal word
		Hazard statement	Harmful to aquatic life with long lasting effects
4	*1. For Substances:* • poorly soluble and no acute toxicity is observed up the water solubility • Lack the potential to rapidly biodegrade and/or have the potential to bioaccumulate (BCF≥ 500 or if absent log Kow ≥ 4); unless • Chronic NOECs > 1mg/L. *2. For Mixtures,* use bridging principles (see 3.10.3.4). *3. If bridging principles do not apply,* • Sum of concentrations of components classified as Chronic 1, 2, 3 or 4 > 25%. *4. For mixtures with no usable information for one or more relevant ingredients,* classify using the available information and add the statement: "x percent of the mixture consists of component(s) of unknown hazards to the aquatic environment".	Symbol	No symbol used
		Signal word	No signal word
		Hazard statement	May cause long lasting harmful effects to aquatic life

ANNEX 3

PRECAUTIONARY STATEMENTS, PICTOGRAMS

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Annex 3

PRECAUTIONARY STATEMENTS, PICTOGRAMS

This annex lists statements that are frequently used in existing systems to provide precautionary information. It is not an exhaustive list, rather it is designed to provide examples of statements that may be appropriate to the label provided for the specific substance or mixture. Systems or suppliers should make use of those which are most appropriate to the particular situation.

Where a statement contains words in brackets, any of the words in brackets may be used in addition to the core information contained in the phrase, or instead of some of this information, as appropriate. e.g. "Keep away from heat" or "Keep away from heat and sparks" or "Keep away from heat, sparks, and flame" or "Keep away from sparks and flame", etc. Similarly, statements from different groups may be used in combination, e.g. "Keep away from heat and ignition sources and store in a cool well-ventilated place".

The IPCS Chemical Safety Cards Programme includes a compilers guide, which provides some explanation of precautionary statements and the context for their use.

A3.1 Statements for physical hazards

A3.1.1 *Flammable liquids, solids and gases*

(a) Avoidance of ignition sources

Keep away from fire {– No Smoking}.
Keep away from heat, {sparks} {and flame} {– No Smoking}.
Keep away from heat and ignition sources {– No Smoking}.
Keep away from sources of ignition – No Smoking.
Avoid contact with heat and ignition sources {and oxidizers} {– No Smoking}.
No open flames, no sparks and no smoking.
Take precautionary measures against static charges.
Do not use sparking tools.
Keep from direct sunlight.
Keep away from fire, sparks and heated surfaces.
Do not use or store near heat or open flame.

(b) Precautions regarding the container

Keep container closed.
Keep container tightly closed.
Keep container closed when not in use.
Store in a tightly closed container.
Keep only in the original container.

(c) Storage of the container or package

Keep in a cool place.
Keep at a temperature not exceeding {...}°C.
Decomposes below boiling point at { } °C.
Decomposes below melting point at { } °C.
Keep container/package in a well-ventilated place.
Keep container/package tightly closed in a cool {, well-ventilated} place.
Keep only in the original container/package in a cool well-ventilated place.
Keep container/package tightly closed and in a well-ventilated place.
Store in a cool/low-temperature, well-ventilated {dry} place {away from heat and ignition sources}.
Store and transport according to packing list of dangerous chemicals.
Explosive limit ranges.
Exposure to temperatures about 130 degrees F may cause bursting.

(d) Storage separately from incompatible materials
Do not store and transport with oxidizers etc.
Separate from oxidizers {oxygen}, {explosives}, {halogens}, {compressed air} {acids}, {bases} {and food chemicals} etc. in transport {and storage}.
Do not store and transport with oxidizers, {acids} {and bases}, etc.

(e) Fire-fighting
Use CO_2, dry chemical, or foam.
In case of fire, use {..}.

A3.1.2 *Pyrophoric liquids and solids*

Use any combination of the phrases in A3.1.1 plus one or more of the following:
Keep under {insert name of inert gas}.
Do not allow contact with air.
Protect from light, moisture and damage.

A3.1.3 *Self-heating substances*

Use any combination of the phrases in A3.1.1, in particular phrases relating to storage separately from incompatible materials, plus the following:
Keep at a temperature not exceeding { }.

A3.1.4 *Substances which, in contact with water, emit flammable gases*

Use any combination of the phrases in A3.1.1 as appropriate, plus one or more of the following:
Keep away from water.
Keep container dry.
Never add water to this product.
Keep from any possible contact with water.
No contact with water.
Do not add water to contents while in a container because of violent reaction and possible flash fire.
Store in a dry place, {protect from moisture}.
Protect from moisture and damage.
Handle under nitrogen, {protect from moisture}.

A3.1.5 *Oxidising liquids, solids and gases*

Use any combination of the phrases in A3.1.1 relating to precautions regarding the container and storage of the container or package as appropriate, plus one or more of the following:
Keep away from combustible material.
Keep away from (incompatible material to be specified by manufacturer).
Keep from contact with clothing and other combustible materials to avoid fire.
Prevent contamination with readily oxidizable materials and polymerization accelerators.
Do not store near combustible materials.
Drying of this product on clothing or combustible materials may cause fire.
Put safety caps and shockproof rubber rings on cylinders in transport.
Do not store and transport with flammable/combustible materials etc.
Isolate from reducers and flammable/ combustible materials etc in storage.
Do not store and transport with halogens and acids, etc.
Separate from reducers and finely powdered metals etc in storage and transport.

A3.1.6 *Organic peroxides*

Use any combination of the phrases in A3.1.1 relating to precautions regarding the container and storage of the container or package as appropriate, plus one or more of the following:
Keep away from heat.
Keep away from combustible material.
Keep away from (incompatible material to be specified by manufacturer).
Keep from contact with clothing and other combustible materials to avoid fire.
Prevent contamination with readily oxidizable materials and polymerization accelerators.
Do not store near combustible materials.
Drying of this product on clothing or combustible materials may cause fire.
Put safety caps and shockproof rubber rings on cylinders in transport.
Do not store and transport with flammable/combustible materials etc.
Isolate from reducers and flammable/ combustible materials etc in storage.
Do not store and transport with halogens and acids, etc.
Separate from reducers and finely powdered metals etc in storage and transport.

A3.1.7 *Self reactive substances*

Keep away from heat
Keep at temperature not exceeding .....°C.
Keep away from fire.
Keep away from heat, {sparks} {and flame}.
Keep away from heat and ignition sources.
Keep away from sources of ignition.
Avoid contact with heat and ignition sources.
No open flames, no sparks and no smoking.
Keep away from combustible material.
Keep away from (incompatible material to be specified by manufacturer).
Keep from contact with clothing and other combustible materials to avoid fire.
Prevent contamination with readily oxidizable materials and polymerization accelerators.
Do not store near combustible materials.
Drying of this product on clothing or combustible materials may cause fire.
Put safety caps and shockproof rubber rings on cylinders in transport.
Do not store and transport with flammable/combustible materials, etc.

A3.1.8 *Explosives*

Use any combination of the phrases in A3 1.1 relating to avoidance of sources of ignition, plus one or more of the following:
Avoid shock, {impact},{friction} {and rough handling}.
Keep away from fire.
No open flames, no sparks and no smoking.
Keep away from sources of ignition – No Smoking.
Do not use sparking tools.
Store and transport according to packing list of dangerous chemicals.
Above { } explosive vapour/air mixtures may be formed.
Gas/air or vapour/air mixtures are explosive.
Finely dispersed particles form explosive mixtures with air.
Do not use compressed air for filling, discharging or handling.

A3.1.9 *Corrosive to metal*

Store and transport according to packing list of dangerous chemicals.
Suitable materials for containment (storage and transport) are listed in the (M)SDS.
Avoid contact with skin and eyes.
Do not get on skin.
Do not get in eyes.

A3.2 Statements to prevent potential misuse and exposure to health

A3.2.1 *Ventilation controls*

Use only in well ventilated areas.
Use only with adequate ventilation {or closed system ventilation}.
Do not enter areas where used or stored until adequately ventilated.
Use only with adequate ventilation to keep exposures (airborne levels of dust, fume, vapour etc) below recommended exposure limits.
Use adequate ventilation to remove vapours (fumes, dust etc).
Use adequate ventilation and/or engineering controls in high temperature processing to prevent exposure to vapours.
Prevent vapour build up by providing adequate ventilation during and after use.
{Use with} {ventilation}, local exhaust ventilation {or breathing protection}.
Do not use in areas without adequate ventilation.
Do not breathe (dust, vapour or spray mist).

A3.2.2 *Hygiene measures*

When using do not {smoke}{eat} {or drink}.
Do not eat, drink or smoke during work.
Wash hands before eating {drinking} {or smoking}.
Wash thoroughly after handling.
Avoid all contact. Strict hygiene.
Avoid contact with skin and eyes
Do not get on skin.
Do not get in eyes.
Wash thoroughly with soap and water after handling and before eating, drinking, or using tobacco.
Wash thoroughly with soap and water after handling.
Avoid contact with skin, eyes or clothing.
Avoid contact with skin (eyes or clothing).
Do not get in eyes (skin) or on clothing.

A3.2.3 *Personal protective equipment*

Wear suitable {protective clothing} {gloves} {and eye/face protection}.
Wear protective clothing and gloves (specify protective clothing and type of gloves).
Wear protective eyewear (goggles, face shield, or safety glasses).
Wear appropriate personal protective equipment, avoid direct contact.

A3.2.4 *Respiratory protective equipment*

In case of insufficient ventilation, wear suitable respiratory equipment.
During fumigation/spraying, wear suitable respiratory equipment (appropriate wording to be specified by the manufacturer).
Have available emergency self-contained breathing apparatus or full-face airline respirator when using this chemical.
Always wear a self-contained breathing apparatus or full-face airline respirator when using this chemical.
Wear a mask or pesticide respirator jointly approved by the Mine Safety and Health Administration and NIOSH {US EPA}.
Wear (identify specific respiratory device approved by the Mine Safety and Health Administration and NIOSH). {US EPA}.
Use NIOSH approved respiratory protection (US requirements).

A3.3 Statements explaining appropriate action in the event of an accident

A3.3.1 *Spills*

In event of a spill, evacuate danger area.
In event of a spill, consult an expert.
To clean the floor and all objects contaminated by this material use (to be specified by manufacturer).
Cover with absorbent or contain. Collect and dispose.
Cover the spilled material with {....}.
Absorb remaining liquid in sand or inert absorbent and remove to safe place.
Treat remaining liquid with {.....}.
Wash away spilled liquid {remainder} with plenty of water.
Do NOT wash away into sewer.
Avoid run off to waterways and sewers.
Clean up spill immediately.
Allow product to cool/solidify and pick up as a solid.
Sweep up and remove immediately.
Use non-sparking equipment when picking up flammable spill, {remove all ignition sources.
Ensure adequate ventilation to remove vapours, fumes, dust etc.
Collect leaking liquid in sealable (metal/plastic) containers.
Cautiously neutralize spilled liquid.
Collect leaking and spilled liquid in sealable (metal/plastic) containers as far as possible.
Do not place spilled materials back in the original container.
Vacuum spilled material.
Sweep spilled substances into { } containers.
Sweep spilled substances into { } containers; if appropriate moisten first to prevent dusting.
Cautiously neutralize remainder. Then wash away with plenty of water.
Carefully collect remainder.
Wipe up remainder in { } then remove to safe place.
Do NOT absorb in saw-dust or other combustible absorbents.
NEVER direct water jet on liquid.

A3.3.2 *Fire-fighting*

In case of fire, use (indicate the precise type of fire fighting equipment).
If water increases the risk, never use water.
Use CO_2, dry chemical, or foam.
Water can be used to cool and protect exposed material.
Allow gas to burn if flow cannot be shut off.
Shut off supply; if not possible and no risk to surroundings, let the fire burn itself out; in other cases, extinguish with (select appropriate medium from list).
In case of fire in the surroundings: all extinguishing agents allowed.
In case of fire in the surroundings: (use the appropriate agent).
Fire fighters should wear complete protective clothing including self-contained breathing apparatus.

A3.3.3 *First aid*

A3.3.3.1 General

In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).
Have the product container or label with you when calling a poison control center or doctor, or going for treatment.

A3.3.3.2 Accident caused by inhalation

In case of accident by inhalation, remove casualty to fresh air and keep at rest.
Obtain medical attention immediately if inhaled.
{Remove person to} fresh air, {rest}.
Remove to fresh air immediately. Get medical attention immediately.
If signs/symptoms continue, get medical attention.
If breathing has stopped, apply artificial respiration.
If breathing is labored, administer oxygen.
Half upright position.
Artificial respiration if indicated.
No mouth-to-mouth respiration.
If inhaled, give oxygen or artificial respiration, call a physician.
If inhaled, give amylis nitris, call a physician.
Move person to fresh air.
If person is not breathing, call 911 or an ambulance, then give artificial respiration, preferably mouth-to-mouth if possible.
Call a poison control centre or doctor for further treatment advice.

A3.3.3.3 Accident caused by ingestion

Obtain medical attention immediately if ingested.
If swallowed, do not induce vomiting: seek medical advice immediately and show this container or label.
If swallowed, seek medical advice immediately and show this container or label.
If swallowed, rinse mouth with water (only if the person is conscious).
If swallowed, and the victim is conscious and alert, induce vomiting immediately, as directed by medical personnel.
{Do not induce vomiting}. {If conscious, give 2 glasses of water. Get immediate medical attention}.
Drink (one glass) (two glasses) of water. Call a physician (or poison control center immediately).
Rinse mouth.
Give a slurry of activated charcoal in water to drink.
Induce vomiting (only in conscious persons).
Do NOT induce vomiting.
Give nothing to drink.
Give plenty of water to drink.
Rest.
Wear protective gloves when inducing vomiting.
If ingested, drink lukewarm, induce vomiting, gastric irrigate, call a physician.
If ingested, drink lukewarm, induce vomiting, gastric irrigate, catharsis, call a physician.
If ingested, drink plant oil, induce vomiting, call a physician.
If ingested, wash out mouth with water, drink milk or egg white.
If ingested, flush the material in stomach with 5% sodium thiosulfate.
If ingested, flush the material in stomach with 1% sodium thiosulfate.
If ingested, induce vomiting, flush the material in stomach with sodium bicarbonate solution.
If ingested, induce vomiting, clyster and flush the material in stomach with plant oil.
If ingested, flush the material in stomach immediately with 2% copper sulfate.
If ingested, flush the material in stomach with sodium sulfate solution, catharsis.
If ingested, induce vomiting, flush the material in stomach with potassium permanganate solutions.
If ingested, drink milk or egg white, gastric irrigate, call a physician.
If ingested, call control center or doctor immediately for treatment advice.
Have person sip a glass of water if able to swallow.
Do not induce vomiting wash out mouth with water. Flush with water the material in stomach of victim, which has not corrosion symptoms.
If ingested, induce vomiting, flush the material in stomach with 60 ml of 1% potassium iodide.
Call a poison control center or doctor.
Do not give anything by mouth to an unconscious person.

A3.3.3.4 Accident caused by skin contact

After contact with skin, take off immediately all contaminated clothing and wash immediately with plenty of (to be specified by manufacturer). {If irritation develops and persists, get medical attention}.
If irritation develops and persists, get medical attention.
Immediately wash with tincture of green soap in flowing water for 15 minutes. Flush skin with large amounts of water. {If irritation develops and persists, get medical attention}.
Immediately flush skin with large amounts of water. Remove contaminated clothing. If irritation (redness, rash, blistering) develops, get medical attention.
Wash contaminated clothing before reuse.
Remove clothing and wash thoroughly before use.
Remove contaminated clothing and wash clothing before reuse Flush the contaminated area of body with large amounts of water.
Wash the contaminated area of body with soap and fresh water.

If contact with body directly, immediately obtain medical attention.
Flush with fresh water if contact with skin or eyes.
If frostbite, call a physician.
If skin contact, spread immediately with 2% silver nitrate.
Take off contaminated clothing.
Rinse skin immediately with plenty of water for 15-20 minutes.

A3.3.3.5 Accident caused by contact with eyes

In case of contact with eyes rinse immediately with plenty of (to be specified by manufacturer)
Immediately flush eyes for at least 15 minutes. Get medical attention.
Flush eyes with water for at least 15 minutes. Get medical attention if eye irritation develops or persists.
Hold eyelids apart and flush eyes with plenty of water for at least 15 minutes. Get medical attention.
Flush eyes with water for at least 15 minutes while holding eyelids open.
Remove contact lenses if worn. Get medical attention immediately.
First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
If contact with eyes directly, flush with gently flowing fresh water thoroughly.
Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first five minutes, then continue rinsing eye.

A3.4 Statements for environmental protection and appropriate disposal

A3.4.1 *Environment protection*

Use appropriate containment to avoid environmental contamination.
Avoid release to the environment. Refer to special instructions/safety data sheet.
Avoid release to the environment.
Prevent release to the environment.
Use appropriate containment.
Do not let this chemical/product enter the environment.
Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark.
Do not contaminate water when cleaning equipment or disposing of equipment washwaters.
Do not apply directly to water.
This chemical has properties and characteristics associated with chemicals detected in ground water. The use of this chemical in areas where soils are permeable, particularly where the water table is shallow, may result in ground-water contamination.
This chemical is known to leach through soil into ground water under certain conditions.
Use of this chemical in areas where soils are permeable, particularly where the water table is shallow, may result in ground-water contamination.

A3.4.2 *Disposal*

Dispose of this container to hazardous or special waste collection point.
Dispose of this material and its container as hazardous waste.
This material and its container must be disposed of as hazardous waste.
Do not dispose of with household waste, trash or other solid waste.
Dispose of wastes in an approved waste disposal facility.
Do not empty into drains.
Do not empty into drains; dispose of this material and its container in a safe way.
Do not empty into drains; dispose of this material and its container to hazardous or special waste collection point.
This material and its container must be disposed of in a safe way.

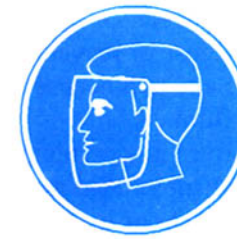
Do not contaminate water, food, or feed by storage disposal.
Do not allow into any sewer on the ground, or into any body of water.
Refer to manufacturer/supplier for information on recovery/recycling.
The (preferred) waste management option(s) is (are) to (select the appropriate statement listed below):
Reuse.
Recycle.
Reuse or recycle.
Send to a licensed recycler, reclaimer or incinerator.
Burn.
Burn in a municipal incinerator.
Dispose of in an approved landfill.
Call your local solid waste agency or (toll free phone number) for disposal information.
Never place unused product down any indoor or outdoor drain.

A3.5 Special statements for consumer products

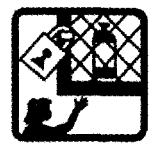
Keep locked up.
Keep out of the reach of children.
Keep locked up and out of the reach of children.
Keep away from food, drink, and animal feedstuffs.
Keep out of the reach of children.
Avoid exposure during pregnancy.

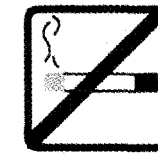
A3.6 Precautionary pictograms

From European Union (COUNCIL DIRECTIVE **92/58/EEC** of 24 June 1992)



From South African Bureau of Standards (**SABS 0265:1999)**





ANNEX 4

CONSUMER PRODUCT LABELLING BASED

ON THE LIKELIHOOD OF INJURY

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Annex 4

CONSUMER PRODUCT LABELLING BASED ON THE LIKELIHOOD OF INJURY

A4.1 Introduction

A4.1.1 The Globally Harmonized System of Classification and Labelling of Chemicals is based on an assessment of the intrinsic hazardous properties of the chemicals involved. However, it has been recognized that some systems provide information about chronic health hazards in consumer products only after considering additional data regarding potential exposures to consumers under normal conditions of use or foreseeable misuse. These systems thus provide information based on an assessment of risk, or the likelihood of injury occurring from exposure to these products. Where this exposure assessment and determination of likelihood of injury reveal that the potential for harm to occur as a result of the expected exposures is insignificant, chronic health hazards may not be included on the product label for consumer use. This type of system was recognized in a paper clarifying the scope of the GHS work in 1998[1]:

"The application of the components of the system may vary by type of product or stage of the life cycle. Once a chemical is classified, the likelihood of adverse effects may be considered in deciding what informational or other steps should be taken for a given product or use setting".

A4.1.2 The work on the GHS has not addressed harmonisation of this type of approach. Therefore, specific procedures to apply this approach would have to be developed and applied by the competent authority. However, in recognition that it is an approach that has been used, and will continue to be used in the future, this annex is being provided to give additional guidance on how such an approach may work in practice.

A4.1.3 Exposure assessments for some consumer products are used to determine what information is included on a label in this type of approach. Regulators and manufacturers obtain exposure data or generate hypothetical exposure data based on customary use or foreseeable misuse. These assumptions are then used to determine whether a chronic health hazard is included on a consumer product label, and what precautions are to be followed, under a risk-based approach. These decisions are thus made on the basis of considerations regarding the likelihood of harm occurring in the consumer exposure situations that have been identified.

A4.1.4 Consumer product labels in some systems are based on a combination of hazard and risk. However, acute and physical hazards may be indicated on the label, while chronic health effects labelling based on risk is not indicated. This may be due in part to the expectation that exposures to some consumer products are of short duration, and thus may not be sufficient to lead to the development of chronic health effects as a result of those exposures. These expectations may not be accurate where consumer products are used in a workplace, e.g. paints or adhesives used by construction workers on a regular basis

A4.1.5 While intrinsic hazards of a chemical can be determined for all sectors, information about exposure, and thus risk, varies significantly among the sectors covered by the GHS. The vehicle by which this information is then transmitted to the user also varies. In some cases, particularly in the consumer setting, the label is the sole source of information, while in others, especially the workplace, it is one piece of a comprehensive system, supplemented by SDSs and worker training. In transport, a label transmits the primary information, but additional information is provided by the transport documentation.

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1 *IOMC Description and Further Clarification of the Anticipated Application of the Globally Harmonized System (GHS), IFCS/ISG3/98.32B.*

A4.2 General principles

A4.2.1 While the specific risk assessment approach has not been addressed or harmonized in the GHS, certain general principles are as follows:

(a) All chemicals should be classified based on GHS classification criteria

The first step in the process of classifying hazards and communicating information should always be classification of intrinsic hazards based on the GHS criteria for substances and mixtures;

(b) Risk-based labelling can only be applied by the competent authorities to the chronic health hazards of chemicals in the consumer product setting. All acute health, environmental and physical hazards should be labelled based on intrinsic hazards

The hazard classification should lead directly to labelling of acute health effects, environmental and physical hazards. The labelling approach that involves a risk assessment should only be applied to chronic health hazards, e.g. carcinogenicity, reproductive toxicity, or target organ systemic toxicity based on repeated exposure. The only chemicals it may be applied to are those in the consumer product setting where consumer exposures are generally limited in quantity and duration;

(c) Estimates of possible exposures and risks to consumers should be based on conservative, protective assumptions to minimise the possibility of underestimating exposure or risk

Exposure assessments or estimates should be based on data and/or conservative assumptions.

Assessment of the risk and the approach to extrapolating animal data to humans should also involve a conservative margin of safety through establishment of uncertainty factors.

A4.2.2 *An example of risk-based labelling used in the United States Consumer Product Safety Commission*

A4.2.2.1 In general, consumers rely on product labels for information about the effects of a chemical product. Whereas other sectors have additional sources of information (e.g. safety data sheets, transport documents) to expand upon or refine product information and relate risk to the hazard information provided, the consumer sector generally does not.

A4.2.2.2 As noted above, the general rule for the GHS is that the label information will be based on intrinsic properties (hazards) of the chemical in all sectors. The rationale for hazard based labelling in the GHS has been described earlier in this document, and may be applied to consumer products as well as products in other sectors.

A4.2.2.3 In particular, the principle of the user's "right-to-know" about the intrinsic hazards of the chemical is important and widely supported by many stakeholders. Hazard information is an incentive to choose less hazardous chemicals for use. It may not be possible to accurately predict the exposures when the products are used, and consumer protective measures are less certain than those in other more structured sectors.

A4.2.2.4 On the other hand some research has indicated [2-7] that a consumer's attention can be diverted by too much information on a label regarding all potential hazards. It appears there is some evidence that warnings focused on specific hazards that are likely to cause injury enhance consumer protection.

A4.2.2.5 To ensure that consumers have the information needed to take appropriate protective measures, a risk-based labelling approach examines likely or possible exposures and communicates information related to the actual risks of exposure. Consumer exposures from use, foreseeable use and accidents can be estimated since products are designed for specific use(s).

A4.2.2.6 The following process has not been harmonized in the GHS. It is consistent with US Consumer Product Safety Commission Guidelines[8] and with other national and international guidelines on conducting risk assessments[9-11]. A substance or product under evaluation for chronic hazard labelling for consumer use in the US must satisfy a two-part test. First, it must present one of the chronic hazards covered, i.e. be classified as a chronic hazard based on specific criteria. Second, a risk assessment must be carried out to establish whether it has the potential to cause substantial illness or injury during or as a result of "reasonably foreseeable handling or use or from ingestion by children". If the result of the risk assessment indicates the risk is very low, the substance or product need not be labelled for chronic hazard. In other words, whether a given substance is labelled for a chronic effect depends not only on whether it is hazardous, but also on exposure and risk.

A4.2.2.7 The extent of the exposure assessment would depend on the hazard. For example, for non-cancer chronic endpoints, an "acceptable daily intake" (ADI) would be calculated from the "no observed adverse effect level" (NOAEL). For a conservative estimate of exposure, one can assume that the consumer will use the entire consumer product in a day and/or assume that all of the hazardous substance/mixture that the consumer is exposed to will be absorbed. If the resulting exposure is lower than the "acceptable daily intake" no hazard communication would be required. If the exposure level is higher than the ADI, then a more refined quantitative assessment could be performed before making a final labelling decision. If refined data are not available, or a refined analysis is not done, the hazard would be communicated on the label.

A4.2.2.8 For carcinogens, a unit risk from exposure to the carcinogen would be calculated based on linear extrapolation with the multistage model as a default model. Life time exposures can be calculated either by assuming worst case scenarios (such as all of the substance in a product is reaching the target tissue at each use, exposure is daily/weekly/monthly), or by determining actual exposures during use, or some combination of these approaches.

A4.2.2.9 The competent authority will need to establish what level of risk is acceptable to implement such an approach to consumer product labelling for chronic effects. For example, CPSC recommends labelling for a cancer hazard if the lifetime excess risk exceeds one-in-a-million from exposure during "reasonably foreseeable handling and use."

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ANNEX 5

COMPREHENSIBILITY TESTING METHODOLOGY

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Annex 5

COMPREHENSIBILITY TESTING METHODOLOGY *

A5.1 This instrument aims to provide a methodology for the assessment of the comprehensibility of labels and Safety Data Sheets (SDS's) for chemical hazards. The tool has been developed with a particular focus on addressing the needs of workers and consumers in developing countries. The emphasis of instrument development has been to provide a tool that is, as far as possible, globally applicable taking into account varied levels of literacy and differences in cultural experience.

A5.2 Overview of the Instrument

A5.2.1 The instrument is organized into a number of modules, directions for each of which is covered in this Annex. Broadly speaking, the instrument consists of four parts:

(a) Module 1: This is a focus group, whose main purpose is to ensure that the instruments used in modules 2 to 11 are sensible across diverse cultures and settings. Its use is recommended in all categories of target populations (see Table A5.2 below) but it should be mandatory to commence with this module in groups of workers and community members from cultures different to the settings in which labels and SDS's have been produced;

(b) Modules 2 to 8: These include a general questionnaire (module 2) and a set of label and Safety Data Sheet questions and exercises (modules 3 to 8). Depending on whether the subject is a worker and makes use of a Safety Data Sheet, some elements of these modules may not apply;

(c) Module 9: This is a simulation exercise. One version is intended for workers and is applicable to most people involved in production, while the other version (module 9a) is adapted for a consumer setting;

(d) Module 10: Module 10 contains a final post-test questionnaire. It is applicable to all participants in the questionnaires (modules 2 to 8) and the simulations (module 9). It is also administered to participants in the group exercise (Module 11). The questionnaire is focused on training, and past experience, and offers an opportunity for open-ended feedback and comment on the testing process;

(e) Module 11: This is a group_exercise for workers that draws on all elements contained in previous modules and is intended to test comprehensibility in the context of group learning. It is designed to complement modules 2 to 10 but is carried out on different subjects to those in modules 1, 2 to 8, and 9.

A5.2.3 It is further proposed that follow-up testing be conducted at one and twelve months after comprehensibility testing. This testing should be repeated on the same subjects who underwent initial testing. Depending on resources and logistics, it may be possible to avoid re-testing on all the modules completed at baseline. Repeat testing would be important to gain insight into retention and real benefits of exposure to hazard messages.

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* *Developed, by a multidisciplinary team at the University of Cape Town, for the International Labour Office (ILO) Working Group on Hazard Communication as part of international efforts to promote a Global Harmonised System (GHS) for hazard communication.*

A5.2.4 Table A5.1 summarizes the modules in the instrument, the main activities in the modules, and the objectives and outcomes to be derived from each module.

A5.2.5 Although the testing instrument has been designed as a self-contained package, it may be possible to make use of selective modules from the battery where there are local priorities and needs. Moreover, it is recognized that as global harmonization of hazard communication evolves, new needs for testing may arise. The instrument may be adapted to take account of new testing priorities over time by using adapted testing materials (labels and SDS's) in the same testing formats. For example, if new icons for hazard symbols are under consideration, module 4 can be amended to include new symbols.

A5.3 Use of Annex 5 and of the Testing Instrument

A5.3.1 Each module is the actual test questionnaire for a specific set of comprehensibility testing objectives. The layout of the modules is such that instructions are clearly marked in the questionnaires for those administering the comprehensibility tests. Accompanying each module, but presented separately, is a set of detailed guidance notes comprising the manual for the particular module. The manuals also outline the different labels and/or SDS's to be used in each module and the outputs and time requirements of each module.

A5.3.2 To avoid rendering the modules to lengthy, instructions on the modules have been kept to a minimum in the text of the modules, reserving the elaboration on instructions for the manual sections. Where key instructions are present in modules 3 to 11, they are listed in bold text within shaded boxes to improve ease of administration. Italic font is used throughout the modules for all text to be read out to the subject.

A5.3.3 Some modules (Modules 3, 4, 6, 7, 8 and 9) require random selection of labels and/or SDS's. A box of cards is provided to the interviewer to expedite the selection of a random label/SDS or set of labels/SDS's. The interviewer will have a specific box of such cards marked for every relevant module.

A5.3.4 Labels and Safety Data Sheets are provided but should be to conform to the normative styles and presentations existing in the countries in which the tool is to be applied. The GHS will bring a certain degree of standardization in the content and layout of hazard communication methods but a great deal of variation will still arise in relation to local traditions, styles, size and preferences. Labels and SDS's used in testing must as far as possible reflect the typical local usage patterns. Therefore, although sample labels and SDS's are provided with this manual, users are encouraged to adapt the test materials within the limits of the experimental design requirements so that the materials appear as authentic as possible to local subjects.

A5.3.5 Notwithstanding attempts to simplify the relatively complex testing procedures required to measure hazard communication comprehensibility, the test instrument require careful administration and quality control. Training of interviewers is therefore critical. This is dealt with in more detail in the manuals for modules 1 and 2.

Table A5.1 Comprehensibility Testing: Objectives and Outcomes by Module

Module	Contents	Objectives	Outcome
Module 1	**Focus Groups**	To shape research tool to the context, language, and cultural interpretations of the specific target group. To identify cultural specific definitions of words. To test whether ranking, the use of colour for attributing hazard, and the quantitative estimation of ambiguous variables are culturally transferable. Testing strategies used in subsequent modules are piloted for face validity and identify alternatives. To identify potential biases in the testing situation arising from cultural use of items.	Culturally consistent explanations for difficult words. Appropriate use of colour in local context. Account of cultural factors that would bias comprehensibility tests. Validation of colour blindness test methods. Interpretability of psychometric scales for non-Western populations. Contextual testing. Instruments to capture workers' experience. "Dummy" symbols.
Module 2	**General Interview**	To ascertain demographic and other data as a basis for analysis of comprehensibility. To clarify competence in colour and visual acuity necessary for some of the subsequent tests. To collect data on work experience, critical to interpretation of comprehensibility assessments.	Relevant demographic and other data for linking to study results and analysis. Colour and visual acuity assessed. Role work experience plays in comprehensibility.
Module 3	**Recall, reading, and comprehensi-bility of labels and SDS's**	To evaluate subjects' familiarity with a label and an SDS. To test subjects' recall of label elements. To evaluate the sequence used to look at label elements. To test the comprehensibility of signal words, colours, symbols and hazard statements. To assess the impact of the label on the subjects': - Ranking of hazard, both to self and to spouse or child - Intention to use, store and dispose of the chemical Whether ranking and reporting change after questions on comprehensibility Can subjects correctly identify the appropriate SDS? Can subjects correctly identify information on chemical name, health hazard, physical hazard and use of protective clothing?	Identify a priori familiarity with labels and SDS's. An assessment of the impact of different label fonts. Identification of poorly understood elements terms. Identify statements with highest comprehensibility. Hazard ranking, and intention to behave as a result of the label The effect of detailed questions on comprehensibility on subjects' perceptions of hazard as a proxy for training. The impact of the Hawthorne effect will be gauged. Comparison of ranking of hazard to self differs from ranking of hazard to a close relative. Identifying whether subjects can link data from a label to an appropriate SDS in a meaningful way.

Table A5.1 Comprehensibility Testing: Objectives and Outcomes by Module *(cont'd)*

Module	Contents	Objectives	Outcome
Module 4	**Rating and understanding of hazards:** **Signal words, Colours, and Symbols**	To test subjects' relative ranking for severity of hazard for: - Signal words, colours and symbols. - combinations of symbols and multiple symbols - selected combinations of symbols, colour and signal words. To test understanding of signal words, colours, and symbols. To test opinion on the ability of signal words, colours, and symbols to attract attention. To test whether subjects' perception of the label will influence their reported intention to use, store or dispose of the chemical. To explore subjects' views as to why hazard elements are present on a label.	Signal words, Colours and Symbols will be rated for ability to denote level of hazard, and for comprehension both separately, and for selected combinations of elements. Quality control assessment of face validity of ranking. Ability of label elements to attract attention. Label rated highest for attracting attention will be explored for its ability to: Prompt the subject to identify further information, particularly health hazard information. Influence reported intention to behave in safe ways.
Module 5	**Comprehension of hazard symbols with and without text**	To test subjects' understanding of symbols representing hazard classes. To test subjects' understanding of concepts of hazard classes. To identify whether adding text words improves understanding of selected symbols representing hazard classes: reproductive, carcinogenic, and mutagenic. To identify whether adding signal words improve understanding of symbols representing classes.	Ability to identify the correct symbol for a hazard class. Identification of hazard classes for which symbols perform poorly; and of symbols which perform poorly as indicators of a hazard class. Identify symbols with ambiguous interpretations. The effectiveness of adding text to symbols for reproductive, carcinogenic and mutagenic hazards. The effectiveness of adding signal words to symbols denoting hazard class.
Module 6	**Size, Placement, Background colour and Border of symbols /Pictograms**	To test the impact of varying symbol size, border and placement. To test the impact of varying background colour and varying icon size in a pictogram relative to border.	Impact of the symbol size, border and placement: - ability to identify chemical name - perception of risk - recall of symbol as proxy for attention to symbol - recall of hazard statement as proxy for attention to hazard statement - reported intention to behave - sequence of reading Comparison of whether ranking of hazard to self differs from ranking of hazard to a close relative.

Table A5.1 Comprehensibility Testing: Objectives and Outcomes by Module *(cont'd)*			
Module	**Contents**	**Objectives**	**Outcome**
Module 7	**Pictogram comprehension - Additional testing (Pesticides)**	To test subjects' ability to identify information: - chemical name - health hazards To assess subjects' rating of hazard To test subjects' understanding of pictograms To assess subjects' sequence of reading	Comprehensibility of pictograms: understanding, ranking of hazard, attention, access to key information Comparison of whether ranking of hazard to self differs from ranking of hazard to a close relative.
Module 8	**Comprehensibility of safety data sheets (SDS's) by organisation of data**	To test subjects' ability to identify safety information from an SDS. To test the understanding of hazard information on an SDS. To evaluate what the subject reads on an SDS and the sequence in which subjects report reading the elements of the SDS To assess what information is useful, appropriate and understandable. To assess whether SDS information is related to intention to behave in safe ways. To evaluate the impact of different organisation of SDS information on the above.	Comprehension of SDS hazard information assessed from different aspects: 1) Interpretation of health hazard information; 2) Self-assessment of understandability to others; 3) Scoring of how the subject explains a hazard statement to a third party; 4) Reported intention to behave Agreement between these four measures of understanding will be estimated. The impact of different ways to organise SDS information will be estimated. Subjective assessment of the usefulness and appropriateness of sub-elements to identify areas for further review of SDS development.
Module 9	**Simulation Exercise: Impact of the use of labels and SDS's, and of symbols and signal words on labels on safe chemical practices**	To assess safety practices in relation to a simulated exercise in which a chemical is handled. To evaluate whether safety practices are improved by the presence of the Signal Word 'Danger' and/or by the size of the Hazard Symbol (Skull and Crossbones). To identify whether past experience in relation to chemicals plays a significant role in both safety practices, and in the impact of Signal Words and Symbols on safety practices.	Measures of actual behaviour observed and related to use of labels, SDS's prior to, and during the task. Safety behaviours include use of PPE and other preventive hygiene practices. The impact of varying label elements (with or without 'Danger'; with different size Hazard Symbol) and SDS layout (explicit heath hazard heading versus health hazard data under regulatory information). Relationship between understanding, practice and experimental conditions to be explored.

Table A5.1 Comprehensibility Testing: Objectives and Outcomes by Module *(cont'd)*			
Module	**Contents**	**Objectives**	**Outcome**
Module 10	**Post interview/ Post stimulation interview**	To ascertain past history of contact with chemicals and training. To test the effect of a brief explanation of symbols, signal words, colours and hazard statements on ranking for severity of hazard, and comprehension. To identify chemical information needs from subjects.	Variables derived from training and past experience for stratified analysis of responses to modules 3 to 9. Results will help to indicate whether training should be the subject of more detailed evaluation in the long term. Responses to questions on needs for chemical information can be useful to GHS efforts on chemical safety.
Module 11	**Group exercise - comprehension**	To test whether learning about hazard communication happens differently in a group context than with individuals. To test whether subjects working as a group come up with significantly different answers than when individual subjects are asked a questionnaire.	A quality control assessment on the affect of group versus individual learning. Groups coming up with significantly different responses from individuals indicate that the testing model needs to be revised. Implications for how training should be addressed in future as an element of hazard communication.

A5.3.6 *Consent*: Before conducting any of the modules in this instrument, participants should first give informed consent. To do so, the purpose of the exercises should be explained to them as well as the procedures that will be asked of them. Participants should not be coerced into participating and should know that they have the right to withdraw their participation at any time. The nature of the information provided in the consent procedure is sufficiently generic so as not to give away the explicit hypotheses being tested.

A5.3.7 *Consent procedures* are outlined in the opening sections of modules 1 (focus group), 2 (commencement of interviews) and 10 (simulation exercises). Irrespective of whether the same subjects complete all modules or not, all three consent procedure should be applied when required. The consent procedure for the simulation is by necessity more of an explanation to obviate the obvious bias to be introduced by alerting the subject to the purpose of the exercise.

A5.3.8 *Policy on rewards or compensation to participants:* Each participating respondent in this study is to be given some form of compensation or incentive for participating in the study. Participating respondents should be told in consenting to the testing that at the end of the study some form of compensation will be presented to them. Compensation may vary from country to country depending on what is culturally appropriate and locally available. Some suggestions (based on other studies) are food (lunch), hats/caps, mugs, food (sugar, rice, mealie meal), certificates, etc. It is up to the countries applying the tool to develop an appropriate policy on compensation for participants.

A5.4 Sampling

A5.4.1 *Target populations*

A5.4.1.1 Target populations are outlined in Table A5.2 below. These are largely adult working populations, typical of groups who use, distribute or manage chemicals, either directly or indirectly. Children are another important potential audience. However, although the ability to provide understandable safety messages to children is recognised as critically important, it has not been possible to address this area in this manual because of the specialised methods required for evaluation. Further development at some future point may be able to extend the comprehensibility testing to methods suitable for children.

A5.4.1.2 Proposed methods for attaining representative samples are outlined in the Manual sections for Modules 1 and 2. University students should not be used as they have been extensively used in previous hazard communication studies and are not considered representative of the target populations identified in this study.

A5.4.2 *Focus Groups*

A5.4.2.1 Given the aim of the focus groups to ensure that the instruments used in modules 2 to 11 are sensible across diverse cultures and settings, participants for focus groups should be as far as possible typical of the target groups to be evaluated. Emphasis should be placed on targeting groups of workers and community members from cultures different to the settings in which labels and SDS's have been produced. This will mainly apply to farm workers, non-agricultural workers and community / residents / consumer groups, both literate and non-literate, groups whose cultural and linguistic backgrounds may make hazard communication complex. Categories for focus groups are recommended in the Table A5.2 below.

A5.4.2.2 At least 2 focus groups are recommended per category. However, where results from a focus group in one category (e.g. non-literate farm workers) appear highly similar to an analogous group (e.g. non-literate non-agricultural workers), it may be possible to dispense with further groups. This should only be done if the testers are confident that no different results would be anticipated from additional testing. In general, once findings from different focus groups are consistent, it is recommended to proceed directly to the main evaluation (modules 2 onward). Where findings appear vastly discrepant, or where inadequate information to inform the rest of the instrument has been obtained, it is recommended to continue assembling focus groups until such information is obtained. Under such circumstances, testing until results are consistent or clarity is achieved may require more groups than the 2 per category recommended.

A5.4.2.3 Focus group participants should preferably not be the same workers included in the testing under modules 2 to 11 as some learning will take place through the focus group itself. Groups should aim, wherever possible, to be homogenous for language, inasmuch as all participants should be able to communicate in at least one common language.

A5.5 Questionnaire and experimental design

A5.5.1 Different sub-populations of working and non-working people will have different experiences that influence their comprehension of hazard communication messages. Modules 2 to 8, and module 10 will test comprehension under different experimental conditions. Sample size calculations combined with considerations of logistical ease suggest that the minimum numbers of subjects to be tested are those contained in the Table A5.2 below. Modules 6 (effect of label font and layout on comprehensibility) and 9 (simulation test) include comparisons of different label types (8 and 11 strata respectively). Thus, larger numbers are needed for these modules to generate sufficient cases within each stratum. The other interview modules (3, 4, 5, 7 and 8) have fewer strata (vary from one to four maximum) and thus can be managed with fewer subjects. Users of this instrument may choose to apply all the modules to all participants, in which case the minimum number of participants recommended is as for modules 6 and 9 in Table A5.2. Modules 2 and 10 must be completed by all participants as indicated.

A5.5.2 In view of the length of the full battery of tests (see Table A5.3), it may be necessary for logistic reasons to break up the instrument by having different subjects complete only some of the modules. In this way, more participants are recruiting to the study but they complete only some parts of the evaluation. If this is the case, remember that all subjects must complete modules 2 and 10, irrespective of how many of the other modules they complete. For example, the battery of modules could be sub-divided into sets consisting of a) Modules, 2, 3, 8 and 10; b) Modules 2, 4 and 10; c) Modules 2, 5, 6, 7 and 10; d) Modules 2 and 11; e) Modules 9, 2 and 10. However, it is preferable that, if possible, participants are given the full battery of tests contained in the instrument, and are adequately compensated for their effort.

Table A5.2: Sample Size - recommended numbers					
Category	**Sub-category**		**Focus Group Module 1**	**Interviews: modules 2, 6 and 10; Simulation Module 9**	**Interview modules 3, 4, 5, 7 and 8.**
Target Group 1: Workplace a) Management	**Population 1**: Production Managers, engineering, technical		Optional	30-50*	25
	Population 2: Supervisory Managers in industry, agriculture		Optional	30-50*	25
b) Workers	Population: Farm workers	**3**. Literate	At least one group	100	50
		4. Non-literate	At least one group	100*	50
	Population: Workers other than in agriculture	**5**. Literate	At least one group	100	50
		6. Non-literate	At least one group	100*	50
Target Group 2: Transport	**Population 7**. Transport workers		Optional	30-50	25
Target Group 3: Community Residents/ Consumers/general public	**Population 8**: Literate		At least one group	100	50
	Population 9: Non-literate		At least one group	100*	50
	Population 10: Retailers and distributors		Optional	30-50*	25
Target Group 4: Emergency Responders	**Population 11**: Health Professionals, Technical Extension staff and Emergency Responders		Optional	30-50*	25
Target Group 5: Other	**Population 12**: Enforcement / Regulatory		Optional	30-50*	25

* *Recognising the practical difficulties in organising a simulation test, it is suggested that in these groups simulation testing only be carried out where resources are available and where practically feasible.*

A5.5.3 As far as possible, the selection of sub-groups should be done an as representative a sample as possible, using random selection of the population for participation. This is critical for generalisability of the results. Even where different participants are chosen from the same sub-group to complete different parts of the instrument, for reasons of length of the battery, selection of participants should emphasise representivity. However, it is recognised that random selection may be very difficult to achieve in practice. Nonetheless, it should be borne in mind that whatever, selection is used, it should seek to generate a sample as representative as possible.

A5.5.4 Note that within the modules, randomisation of subjects within the groups is essential and cannot be compromised on. Randomisation is necessary for internal validity of the comparisons and is not the same as random selection of the sample, which is needed for generalisability of the study results.

A5.5.5 *Simulation studies:* Because simulations studies are relatively resource intensive exercises, it is proposed that the simulations only be conducted with limited target populations - workers, both agricultural and non-agricultural, transporters, and consumers. However, where resources permit, these simulations can easily be applied to other strata as desired.

A.5.5.6 *Contamination and Co-intervention*

A5.5.6.1 The testing design requires control circumstances. For this reason, the situation should be avoided where a participant is able to see or be told of the experimental materials of another participant. This will invalidate the comparisons being made where manipulation of the independent variable is key to the evaluation. Such events occurring in an experimental set up are called contamination.

A5.5.6.2 To avoid contamination, participants should avoid contact with each other whilst testing is being conducted. This may require considerable effort on the part of the testing team to ensure that chance meetings of subjects does not occur. Although difficult, every effort should be made to minimise the probability of contamination.

A5.5.6.3 A distinct but related problem is co-intervention, where both experimental groups are subjected to an intervention occurring independent of the experimental situation. This would occur when, for example, every worker in factory received detailed hazard safety training in the week before the testing was done. It may result in a masking of the effect of the different hazard communication elements and may lead to an under-estimation of the effect of different formulations of the label and SDS. Where this is not preventable, note should be taken of the possibility that co-intervention took place.

A5.5.7 *Group Learning*

Module 11 is included to test comprehensibility in the context of group learning. It is applied only to workers (populations 3 to 6 in Table A5.2 above) and will need a sample separate from workers completing Modules 2 to 8. Ten groups should be tested in total including 5 groups of factory workers and 5 groups of farm workers. Groups should aim to be homogenous for literacy level and approximately equal numbers literate and non-literate groups. Each group should not be larger than 10 and not smaller than 6.

A5.5.8 *Context*

A5.5.8.1 The context under which comprehensibility testing is carried out is crucial to the accurate evaluation of meaning and understanding. This is particularly so amongst workers with little formal education who use contextual cues to improve their understanding of hazard messages. For this reason, the bulk of testing in this instrument makes use of complete labels rather than elements of a label or SDS. While well-educated subjects may find it conceptually easier to respond to the isolated elements, the interpretation of such elements may have little bearing to real world learning situations. For this reason, all testing is to be conducted using realistic labels and SDS's.

A5.5.8.2 To maximise realism, an in-site label attached to a container will be used. To attach a different label to each container may pose an unnecessary burden on the tester, so it is proposed that the label be attached to a standard container, and removed after testing. This procedure may require an assistant to the interviewer if overly burdensome for the interviewer. It is important that every visual cue be offered to subjects to maximise their possibilities of comprehension, particularly for workers with low levels of formal education who rely on contextual information to a greater degree. Therefore, the labels should be presented attached to container at all times. A Velcro strip attached to the container may make the procedure relatively simple.

A5.5.8.3 To standardise opportunities for comprehension, the actual chemicals identified in the labels will be spurious chemicals, although made to look as if they could be genuine agents. This aims to retain context, while not disadvantaging those unfamiliar with a particular chemical.

A5.5.8.4 As indicated above, users are encouraged to adapt the test materials within the limits of the experimental design requirements so that the materials appear as authentic as possible to local subjects so as to maximise context.

A5.5.9 *Sample sizes for sub-studies*

Sample sizes for the sub-studies have been calculated based on a two-sided alpha error of 0.1 and a power of 0.8, but have also been tempered by considerations of logistical feasibility. Preliminary piloting of the instrument confirms these estimates. In particular, the simulation exercise has been considered relatively selectively for a smaller number of subjects and target groups, largely because of anticipated logistical constraints.

A5.5.10 *Translations*

A5.5.10.1 Language is key to much hazard communication. Although the instrument seeks to take account as far as possible of language differences, poor and unstandardised translation may introduce considerable error into the testing. For this reason, careful attention needs to be paid to accurate translation. The following procedure should be followed:

- Two persons fluent in English (the language of the current instrument) independently translate the questionnaire into the index language (the language of the target group).
- Both translations are then translated back into English by a further pair of translators independent of each other and of the original translators.

A5.5.10.2 Back-translations should aim to achieve less than 5% errors on first round. Clarification of the errors in the translation should be conducted to correct ambiguities. Where possible, a combined translation should try to include all elements correctly translated and back translated from either questionnaire.

A5.5.10.3 If the latter is not possible, the translation with the lower rate of errors should be taken as the translation of preference. A second round of back translation will be necessary if errors exceed 5%.

A5.5.11 *Timing of Interviews and Focus Groups*

A5.5.11.1 Interviews and focus groups must be set up at a convenient time for both the interviewee and their employer (when this applies). Farm workers should not be requested to attend an interview during a crucial and busy period for farmers (e.g. planting, ploughing, spraying, or harvest). Workers should be interviewed during working time and should not suffer financial loss for their participation. It is not recommended that workers participate in their own time (lunch or after hours) without adequate compensation. If workers agree to participate during lunch break, the time must be adequate and suitable recompense provided (time back, lunch provided, etc).

A5.5.11.2 Table A5.3 gives the estimated time needed for completion of individual modules based on preliminary piloting with two South African factories. Depending on the module and how skilled the administrators of the modules are, total testing time could vary from 20 minutes to 2 hours. Testing times will be prolonged with non-literate workforces.

Table A5.3: Approximate testing times for Hazard Communication Comprehensibility testing

Module	Time (minutes)
1	60 – 120
2	30 – 45
3	45 – 75
4	75 – 105
5	20 – 30
6	20 –30
7	20 –30
8	45 – 75
9	30
10	30 - 45
11	120 – 180

A5.5.12 *Rating and Coding of responses*

A5.5.12.1 Rating of responses to comprehensibility testing requires expert judgement as to the correctness of the response. Previous experience in Zimbabwe has shown that content analysis of open-ended responses may be feasible where observers are carefully standardised in their approach.

A5.5.12.2 This instrument requires the presence of a set of experts to conduct the rating required for comprehension. The panel of experts should be identified before commencing the study in a process outlined below:

(a) Select a panel with a range of experience, including (one or more) employees, employers and practitioners, as well as researchers skilled in the field of coding and rating;

(b) Convene a workshop with the panel to review the nature of potential responses to questions in each of the modules listed. Review the documentation of the GHS process and aim to arrive at consensus as to what responses would constitute the following categories:

- Correct: Meaning is identical, or fully consistent with intention of the GHS construct. This includes responses which are not 100% the same as the GHS meaning but would suffice as the basis for a safety action or precaution;
- Partly correct: Some element of the meaning is correct but it would be insufficient to ensure adequate safety action or precaution;
- Incorrect: Meaning given is either completely wrong, or has very poor relation to the GHS intended meaning;
- Opposite meaning (critical confusions): Meaning given is not only incorrect but indicates an understanding opposite of the intention of the GHS system. Such a critical confusion may result in a dangerous behaviour or action;
- Cannot answer / doesn't know;

(c) Pilot the questionnaire amongst 5 or 10 subjects. Review the results in relation to the criteria selected;

(d) If the results show significant discrepancy, iterate the process above until agreement reached about criteria.

A5.5.12.3 Further coding of responses to questions in the different modules is discussed under each module, where appropriate.

A5.5.13 *Analyses*

Analyses proposed for these modules are simple computations of proportions and means in relation to different strata. More complex analyses may be undertaken and are indicated in the different modules. An overall estimate for comprehensibility may be attempted by combining results from subjects in the different strata, but should be adjusted for weightings by stratum and by other demographic factors known to affect comprehensibility.

A5.5.14 *Feedback and follow up*

All subjects should be offered the opportunity of seeing the results of the comprehensibility evaluations, and to give feedback on the interview and testing procedures.

A5.5.15 *Follow up evaluation*

Subjects participating in these evaluations should be re-interviewed after 1 month and 1 year to assess retention and the medium and long-term benefits of exposure to the GHS hazard messages. Depending on resources and logistics, it may be possible to avoid re-testing on all the modules completed at baseline.

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ANNEX 6

EXAMPLES OF ARRANGEMENTS

OF THE GHS LABEL ELEMENTS

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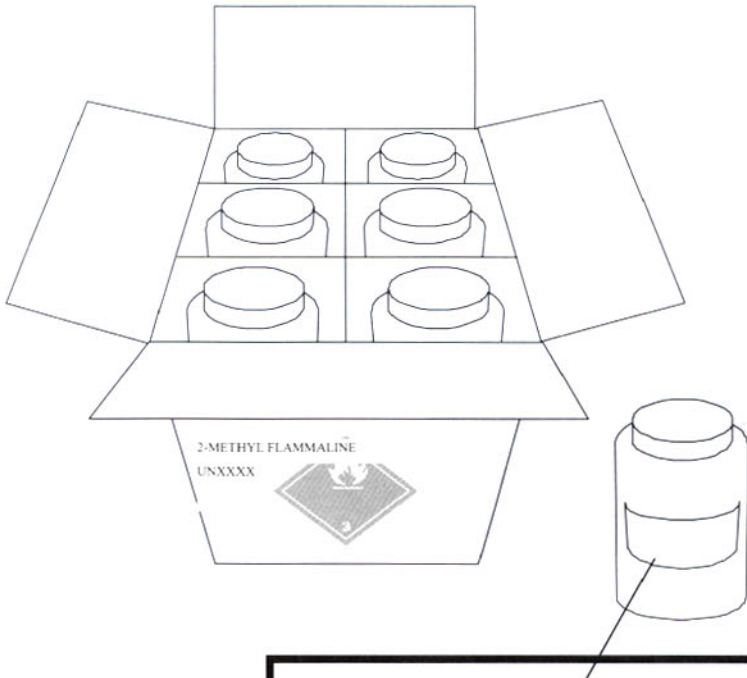
Annex 6

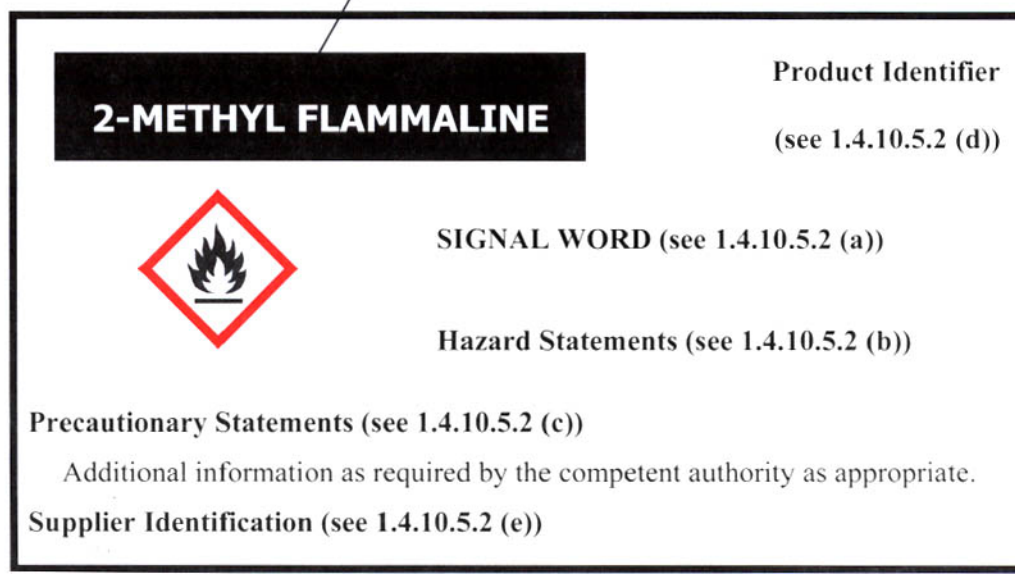
EXAMPLES OF ARRANGEMENTS OF THE GHS LABEL ELEMENTS

The following examples are provided for illustrative purposes and are subject to further discussion and consideration by the GHS Sub-Committee.

Example 1: Combination Packaging for a Category 2 Flammable Liquid

Outer Packaging: Box with a flammable liquid transport label*
Inner Packaging: Plastic bottle with GHS hazard warning label**

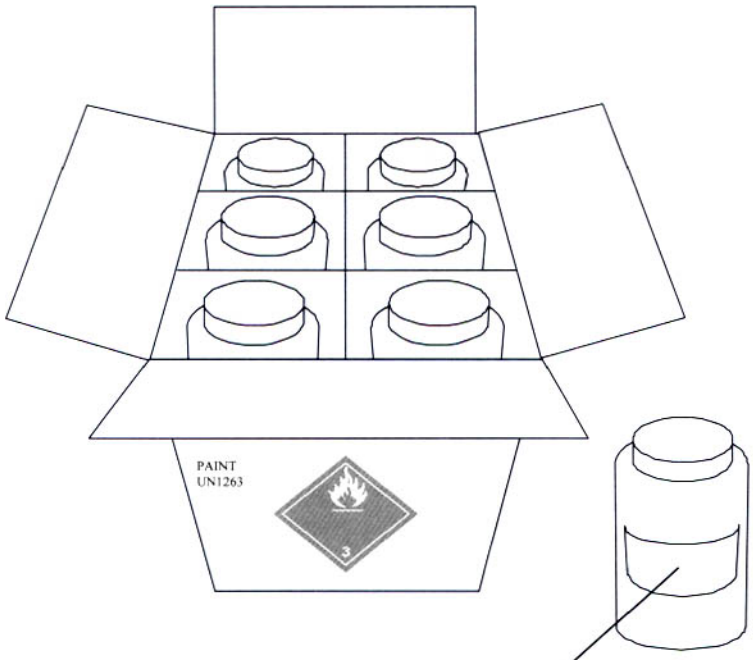




Notes: * *Only the UN transport markings and labels are required for outer packagings.*
** *A flammable liquid pictogram as specified in the "UN Recommendations on the Transport of Dangerous Goods, Model Regulations" may be used in place of the GHS pictogram shown on the inner packaging label.*

Example 2: Combination Packaging for a Category 1 Target Organ/Systemic Toxicant and Category 2 Flammable Liquid

Outer Packaging: Box with a flammable liquid transport label*
Inner Packaging: Plastic bottle with GHS hazard warning label**



PAINT (FLAMMALINE, LEAD CHROMOMIUM)

Product Identifier

(see 1.4.10.5.2 (d))

**

SIGNAL WORD (see 1.4.10.5.2 (a))

Hazard Statements (see 1.4.10.5.2 (b))

Precautionary Statements (see 1.4.10.5.2 (c))

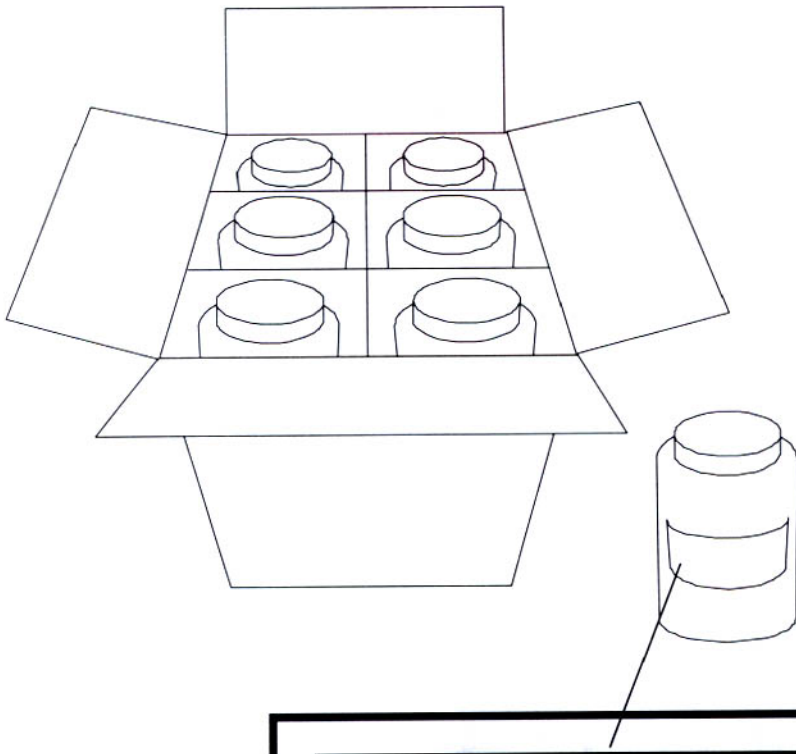
Additional information as required by the competent authority as appropriate.

Supplier Identification (see 1.4.10.5.2 (e))

Notes: * *Only the UN transport markings and labels are required for outer packagings.*
** *A flammable liquid pictogram as specified in the UN Recommendations on the Transport of Dangerous Goods, Model Regulations may be used in place of the GHS pictogram shown on the inner packaging label.*

Example 3: Combination Packaging for a Category 2 Skin Irritant and Category 2A Eye Irritant

Outer Packaging: Box with no label required for transport*
Inner Packaging: Plastic bottle with GHS hazard warning label



BLAHZENE SOLUTION

Product Identifier

(see 1.4.10.5.2 (d))

SIGNAL WORD (see 1.4.10.5.2 (a))

Hazard Statements (see 1.4.10.5.2 (b))

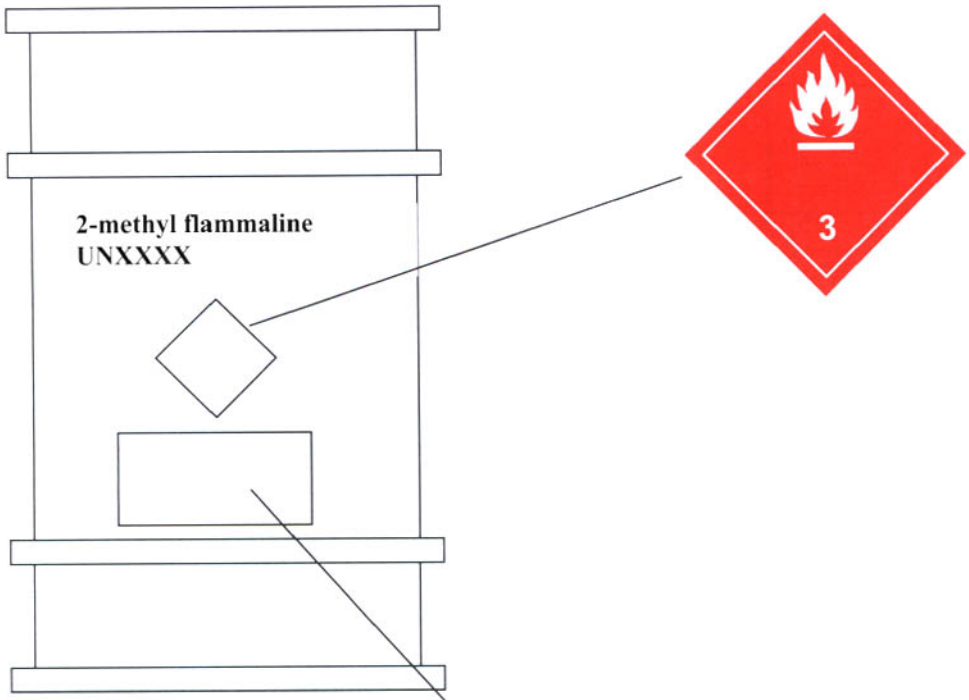
Precautionary Statements (see 1.4.10.5.2 (c))

Additional information as required by the competent authority as appropriate.

Supplier Identification (see 1.4.10.5.2 (e))

Note: * *Some competent authorities may require a GHS label on the outer packaging in the absence of a transport label.*

Example 4: Single Packaging (200 liter drum) for a Category 2 Flammable Liquid



2-METHYL FLAMMALINE

Product Identifier

(see 1.4.10.5.2 (d))

SIGNAL WORD (see 1.4.10.5.2 (a))

Hazard Statements (see 1.4.10.5.2 (b))

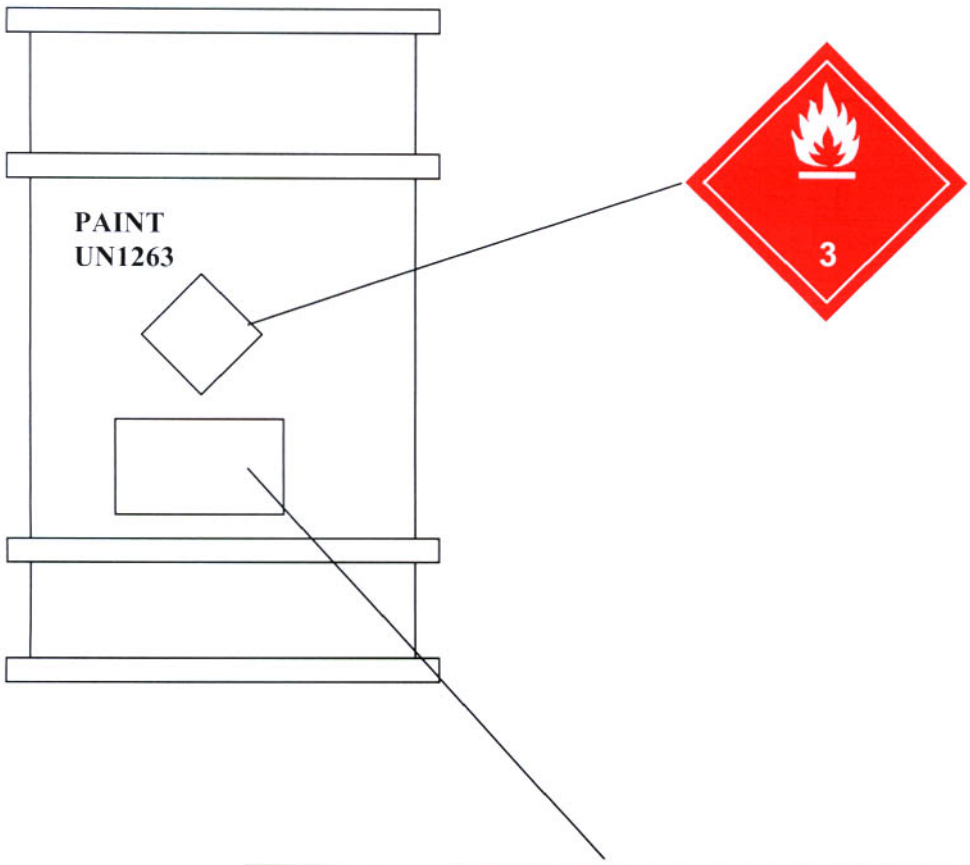
Precautionary Statements (see 1.4.10.5.2 (c))

Additional information as required by the competent authority as appropriate.

Supplier Identification (see 1.4.10.5.2 (e))

Note: *The GHS label and the flammable liquid pictogram and markings required by the "UN Recommendations on the Transport of Dangerous Goods, Model Regulations" may also be presented in a combined format.*

Example 5: Single Packaging for a Category 1 Target Organ/Systemic Toxicant and Category 2 Flammable Liquid



PAINT (METHYL FLAMMALINE, LEAD CHROMOMIUM

Product Identifier

(see 1.4.10.5.2 (d))

SIGNAL WORD (see 1.4.10.5.2 (a))

Hazard Statements (see 1.4.10.5.2 (b))

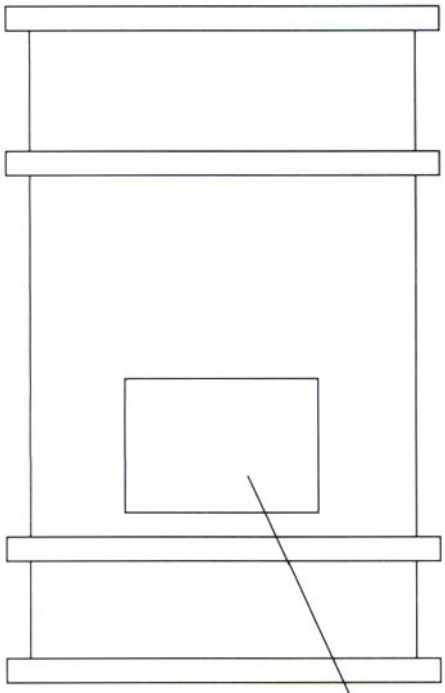
Precautionary Statements (see 1.4.10.5.2 (c))

Additional information as required by the competent authority as appropriate.

Supplier Identification (see 1.4.10.5.2 (e))

***Note**: The GHS label and the flammable liquid pictogram and markings required by the "UN Recommendations on the Transport of Dangerous Goods, Model Regulations" may also be presented in a combined format.*

Example 6: Single Packaging for a Category 2 Skin Irritant and Category 2A Eye Irritant



BLAHZENE SOLUTION

Product Identifier

(see 1.4.10.5.2 (d))

SIGNAL WORD (see 1.4.10.5.2 (a))

Hazard Statements (see 1.4.10.5.2 (b))

Precautionary Statements (see 1.4.10.5.2 (c))

Additional information as required by the competent authority as appropriate.

Supplier Identification (see 1.4.10.5.2 (e))

ANNEX 7

AN EXAMPLE OF CLASSIFICATION IN THE GLOBALLY HARMONIZED SYSTEM

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Annex 7

AN EXAMPLE OF CLASSIFICATION IN THE GLOBALLY HARMONIZED SYSTEM

A7.1 Classification proposal

The following classification proposal draws on the GHS criteria. The document includes both brief statements about the proposal for each health hazard class and details of all the available scientific evidence.

Classification is proposed for both the acute toxicity and the corrosivity of this substance based on standard and non-standard animal studies.

Proposed classification	GHS:	Acute oral toxicity Category 4 Acute dermal (skin) toxicity Category 3 Skin irritation/corrosion Category 1C Eye irritation/serious eye damage Category 1 Flammable liquid Category 4

A7.2 Identification of the substance

1.1 EINECS Name **If not in EINECS** **IUPAC Name**	Globalene Hazexyl Systemol
	CAS No. 999-99-9 EINECS No. 222-222-2
1.2 Synonyms (state ISO name if available)	2-Hazanol Globalethylene
1.3 Molecular formula	$C_xH_yO_z$
1.4 Structural formula	
1.5 Purity (w/w)	
1.6 Significant impurities or additives	
1.7 Known uses	*Industrial:* Solvent for surface coatings and cleaning solutions. Chemical intermediate for Globalexyl UNoxy ILOate. *General public:* Toilet cleaner

A7.3 Physico-chemical characteristics

Classification as a category 4 flammable liquid is proposed for the physico-chemical endpoints.

2.1	**Physical form**	Liquid
2.2	**Molecular weight**	146.2
2.3	**Melting point/range (°C)**	-45
2.4	**Initial Boiling point/ boiling range (°C)**	208.3
2.5	**Decomposition temperature**	
2.6	**Vapour pressure (Pa(°C))**	7
2.7	**Relative density (g/cm3)**	0.887 - 0.890
2.8	**Vapour density (air = 1)**	5.04
2.9	**Fat solubility (mg/kg, °C)**	
2.10	**Water solubility (mg/kg, °C)**	Slightly soluble (0.99% w/w)
2.11	**Partition coefficient (log Pow)**	
2.12	**Flammability** **flash point (°C)** **explosivity limits (%,v/v)** **auto-flammability temp. (°C)**	**closed cup:** 81.7 **open cup:** 90.6 **lower limit:** 1.2 **upper limit:** 8.4
2.13	**Explosivity**	No data available
2.14	**Oxidising properties**	
2.15	**Other physico-chemical properties**	

A7.4 Health and environmental characteristics

A7.4.1 *Acute toxicity*

A7.4.1.1 *Oral*

Classification under GHS Category 4 (300-2000 mg/kg) are justified.

Species	LD_{50} (mg/kg)	Observations and remarks	Ref.
Rat	1480	No further details were available.	2
Rat	1500 (males) 740 (females)	The LD_{50} values in mg/kg were calculated from ml/kg using the known density for EGHE of 0.89 g/cm^3.	8

A7.4.1.2 *Inhalation*

There were no deaths or signs of overt toxicity in animals exposed to the saturated vapour concentration of approximately 0.5 mg/L and therefore, the available data do not support classification.

Species	LC_{50} (mg/l)	Exposure time (h)	Observations and remarks	Ref.
Rat	> 83 ppm. (approx equal to 0.5 mg/l).	4	No deaths, clinical signs or gross lesions occurred at 83 ppm (85 ppm is stated to be the saturated vapour concentration at room temperature).	3
Rat	Not stated	6	The animals were exposed to the saturated vapour concentration at room temperature (assumed to be 85 ppm). No deaths occurred and no signs of gross pathology were observed.	8
Rat	Not stated	8	No deaths occurred with exposure to the "saturated vapour concentration" at room temperature (assumed to be 85 ppm).	2

A7.4.1.3 *Skin*

Classification under GHS Category 3 (200-1000 mg/kg) is justified.

Species	LD_{50} (mg/kg)	Observations and remarks	Ref.
Rat	790	No further details were available.	2
Rabbit (5/sex/ group)	720 (males) 830 (females)	Animals were exposed to up to 3560 mg/kg for 24 hours. All but 2 of the animals that died did so during the application period. Following the exposure period, local toxicity (erythema, oedema, necrosis and ecchymoses) was reported in an unstated number of animals, and persisted throughout the 14 day post-application observation period. Ulceration was also noted in an unstated number of animals at the end of the observation period.	8

A7.4.2 *Skin irritation/corrosion*

There are conflicting reports concerning the irritant nature of this substance. In a dedicated skin irritation study reported in the same paper as the acute dermal study, the author states that "necrosis" was observed in 3 of 6 treated rabbits which was still present on the last day of observation (day 7), along with mild to moderate erythema. Mild to marked oedema was also observed during the course of the study but had resolved within the 7-day observation period. Given that one animal showed no evidence of any skin response in this study and that only slight to moderate skin irritation was observed in the other animals the observation of "necrosis" in three of the animals is somewhat surprising. An acute dermal (skin) toxicity study in rabbits also reported signs of skin irritation including the description 'necrosis' and ulceration but did not quantify the number of animals affected. In contrast to these findings, an old and briefly reported study indicated that there was little or no indication of skin irritation in rabbits.

Similarly mixed skin irritation findings have been observed with a closely related substance, for which both necrosis and no skin irritation has been reported. In addition a secondary source indicates that some other similar substances cause 'moderate' skin irritation, and that prolonged exposure to these group of substances may cause burns. However, much shorter chain similar substances are not considered to be skin irritants.

It was considered that the reported necrosis in both the acute dermal and skin irritation studies cannot be dismissed and, taken together with the findings seen with structurally similar substances, this justifies classification. There are 3 Categories under the GHS for classification as corrosive. The data do not match the criteria readily, but Category 1C would be appropriate since the necrotic lesions observed occurred after an exposure period of 4 hours. There is no evidence to suggest that significantly shorter exposures would produce skin corrosion.

Species	No. of animals	Exposure time (h)	Conc. (w/w)	Dressing: (occlusive, semi-occlusive, open)	Observations and remarks (specify degree and nature of irritation and reversibility)	Ref.
Rabbit	6	4	0.5 ml of 100%	Occlusive	No signs of irritation was observed in one animal, and only slight erythema (grade 1) in another on day 1, which had resolved by day 7. Four animals showed a mild to moderate erythema (grade 1-2) and a mild to marked oedema (grade 1-3) after removal of the dressing. The oedema had resolved by day 7 post-exposure. "Necrosis" at the application site was reported in 3/6 rabbits from day 1 until the end of the observation period on day 7. Desquamation was observed in 4/6 rabbits on day 7.	8
Rabbit (albino)	5	24	100% (volume not stated)	Not stated	Little or no signs of skin irritation were found in this poorly reported study.	2

A7.4.3 *Serious damage to eyes/eye irritation*

The only available study involved exposure of rabbits to considerably lower amounts of the test substance than the standard protocols for this endpoint recommend. Relatively severe (eg. conjunctival redness grade 3) but reversible effects were seen. It is predictable that under standard test conditions, the effects on the eye would be very severe and consequently GHS Category 1 (irreversible effects on the eye) would be justified.

Species	No. of animals	Conc. (w/w)	Observations and remarks (specify degree and nature if irritation, any serious lesions, reversibility)	Ref.
Rabbit	6	0.005 ml of 100%	One hour post-instillation conjunctival redness (grade 3) and discharge (grade 2.8) observed. The mean scores for the 24, 48 and 72 hour readings for corneal opacity, iris, conjunctival redness, chemosis and discharge were all approx 0.5. All lesions had resolved by day 7.	8
Rabbit	60	1 and 5%	A report in the secondary literature of severe eye injury observed in rabbits associated with instillation of an unstated amount of 5%, could not be substantiated as the information was not found in the reference stated.	1

A7.4.4 *Skin and respiratory sensitization*

No data are available. There are no additional grounds for concern (eg. structure activity relationships) and no classification proposed.

A7.4.5 *Target organ/systemic toxicity following single or repeated exposure*

A7.4.5.1 *Toxicity following single exposure*

There is no reliable information available about the potential of this substance to produce specific, non-lethal target organ/systemic toxicity arising from a single exposure. Therefore, under GHS, no classification for target organ/systemic toxicity (TOST) single exposure is proposed.

A7.4.5.2 *Toxicity following repeated exposure*

A7.4.5.2.1 Oral

No oral repeat dose studies or human evidence are available and therefore no classification is proposed.

A7.4.5.2.2 Inhalation

There was no evidence of adverse toxicity in a 13-week rat inhalation study at 0.43 mg/l (approx. 72 ppm), an exposure level close to the saturated vapour concentration. No classification is justified according to GHS criteria.

Species	**conc. mg/l**	**Exposure time (h)**	**Duration of treatment**	**Observations and remarks (specify group size, NOEL, effects of major toxicological significance)**	**Ref.**
Rat (F344) 20/sex / group (plus 10/ sex/group - 4 week recovery groups)	0.12, 0.24 and 0.425	6	5 d/wk for 13 weeks	No deaths occurred. Decreased weight gain was observed in high dose animals of both sexes and medium dose females. There were no toxicologically significant changes in haematological or urinalysis parameters. High dose females showed an increase in alkaline phosphatase. High and medium dose males showed a statistically significant increase in absolute and relative kidney weight. A small increase in absolute liver weight (12%) was observed in high dose females. However, there were no gross or histopathological changes in any organs examined.	3

A7.4.5.2.3 Dermal

Unquantified haematological changes were reported in rabbits exposed to 444 mg/kg dermally for 11 days. However, due to the limited information provided, no conclusions can be drawn from this study and no classification is proposed.

Species	Dose mg/kg	Exposure time (h)	Duration of treatment	Observations and remarks (specify group size, NOEL, effects of major toxicological significance)	Ref.
Rabbit	0, 44, 222 and 444	6	9 doses applied over 11 days	This is an unpublished study reported in the secondary literature. Unquantified decreases in haematological parameters were noted in top dose animals. No description of local effects was provided.	1

A7.4.6 *Carcinogenicity (including chronic toxicity studies)*

No data available – no classification proposed.

A7.4.7 *Mutation in germ cells*

Negative results have been reported *in vitro* from Ames, cytogenetics, and gene mutation tests reported in the secondary literature. There are no *in vivo* data available. These data do not support classification.

***In vitro* studies**

Test	Cell type	Conc. range	Observations and remarks	Ref.
Ames	Salmonella (strains unstated)	0.3-15 mg/plate	**Negative**, in the presence and absence of metabolic activation. This is an unpublished study described in a secondary source and no further information is available.	5
IVC	CHO	0.1-0.8 mg/ml (-S9), 0.08-0.4 mg/ml (+S9)	**Negative**, in the presence and absence of metabolic activation. This is an unpublished study described in a secondary source and no further information is available.	6
Gene mutation	CHO	Not stated	**Negative**. This is an unpublished study described in a secondary source and no further information is available.	7
SCE	CHO	Not stated	**Negative**. This is an unpublished study described in a secondary source and no further information is available.	7

A7.4.8 *Reproductive toxicity-Fertility*

No data available – no classification proposed.

A7.4.9 *Reproductive toxicity-developmental toxicity*

There was no evidence of developmental toxicity in rats or rabbits following inhalation exposure to levels inducing slight maternal toxicity. It is noted that although shorter chain related substances are classified for developmental toxicity, this toxicity decreases with increasing chain length such that there is no evidence of this hazard. No classification is proposed.

Species	Route	Dose	Exposure	Observations and remarks	Ref.
Rat	Inhalation	21, 41 and 80 ppm (0.12, 0.24 and 0.48 mg/L)	days 6-15 of gestation	The substance was tested up to approximately the saturated vapour concentration. Decreases in dam body weight gain, associated with decreases in food consumption, were observed in the medium and high dose groups during the exposure period. There was no evidence of developmental toxicity.	4
Rabbit	Inhalation	21, 41 and 80 ppm (0.12, 0.24 and 0.48 mg/L)	days 6-18 of gestation	The substance was tested up to approximately the saturated vapour concentration. Decrease in absolute body weight during the exposure period was observed in the high dose animals. There was no evidence of developmental toxicity.	4

A7.5 References

1. Patty, F. (Ed.) (1994). Industrial Hygiene and Toxicology. 4th Ed. pxxxx-xx New York: Wiley-Interscience.

2. Smyth, H.F., Carpenter, C.P., Weil, C.S. and Pozzani, U.S. (1954). Range finding toxicity data. *Arch. Ind. Hyg. Occup. Med.*

3. Fasey, Headrick, Silk and Sundquist (1987). Acute, 9-day, and 13-week vapour inhalation studies on Globalene Hazexyl Systemol. *Fundamental and Applied Toxicology.*

4. Wyeth, Gregor, Pratt and Obadia (1989). Evaluation of the developmental toxicity of Globalene Hazexyl Systemol in Fischer 344 rats and New Zealand White rabbits. *Fundamental and Applied Toxicology.*

5. Etc.

ANNEX 8

GUIDANCE ON HAZARDS TO THE

AQUATIC ENVIRONMENT

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Annex 8

GUIDANCE ON HAZARDS TO THE AQUATIC ENVIRONMENT

CONTENTS

		Page
A8.1	**Introduction**	345
A8.2	**The harmonized classification scheme**	349
	A8.2.1 Scope	349
	A8.2.2 Classification categories and criteria	349
	A8.2.3 Rationale	349
	A8.2.4 Application	350
	A8.2.5 Data availability	351
	A8.2.6 Data quality	351
A8.3	**Aquatic toxicity**	353
	A8.3.1 Introduction	353
	A8.3.2 Description of tests	353
	A8.3.3 Aquatic toxicity concepts	355
	A8.3.4 Weight of evidence	357
	A8.3.5 Difficult to test substances	357
	A8.3.6 Interpreting data quality	363
A8.4	**Degradation**	364
	A8.4.1 Introduction	364
	A8.4.2 Interpretation of degradability data	364
	A8.4.3 General interpretation problems	369
	A8.4.4 Decision scheme	371
A8.5	**Bioaccumulation**	373
	A8.5.1 Introduction	373
	A8.5.2 Interpretation of bioconcentration data	373
	A8.5.3 Chemical classes that need special attention with respect to BCF and L_{ow} values	377
	A8.5.4 Conflicting data and lack of data	379
	A8.5.5 Decision scheme	379
A8.6	**Use of QSAR**	381
	A8.6.1 History	381
	A8.6.2 Experimental artifacts causing underestimation of hazard	381
	A8.6.3 QSAR modelling issues	382
	A8.6.4 Use of QSARs in aquatic classification	383
A8.7	**Classification of metals and metal compounds**	387
	A8.7.1 Introduction	387
	A8.7.2 Application of aquatic toxicity data and solubility data for classification	388
	A8.7.3 Assessment of environmental transformation	390
	A8.7.4 Bioaccumulation	390
	A8.7.5 Application of classification criteria to metals and metal compounds	391
Appendix I	**Determination of degradability of organic substances**	397
Appendix II	**Factors influencing degradability in the aquatic environment**	403
Appendix III	**Basic principles of the experimental and estimation methods for determination of BCF and K_{ow} of organic substances**	407
Appendix IV	**Influence of external and internal factors on the bioconcentration potential of organic substances**	413
Appendix V	**Test guidelines**	415
Appendix VI	**References**	421

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Annex 8

GUIDANCE ON HAZARDS TO THE AQUATIC ENVIRONMENT *

A8.1 Introduction

A8.1.1 In developing the set of criteria for identifying substances hazardous to the aquatic environment, it was agreed that the detail needed to properly define the hazard to the environment resulted in a complex system for which some suitable guidance would be necessary. Therefore, the purpose of this document is twofold:

- to provide a description of and guidance to how the system will work;
- to provide a guidance to the interpretation of data for use in applying the classification criteria.

A8.1.2 The hazard classification scheme has been developed with the object of identifying those chemical substances that present, through the intrinsic properties they possess, a danger to the aquatic environment. In this context, the aquatic environment is taken as the aquatic ecosystem in freshwater and marine, and the organisms that live in it. For most substances, the majority of data available addresses this environmental compartment. The definition is limited in scope in that it does not, as yet, include aquatic sediments, nor higher organisms at the top end of the aquatic food-chain, although these may to some extent be covered by the criteria selected.

A8.1.3 Although limited in scope, it is widely accepted that this compartment is both vulnerable, in that it is the final receiving environment for many harmful substances, and the organisms that live there are sensitive. It is also complex since any system that seeks to identify hazards to the environment must seek to define those effects in terms of wider effects on ecosystems rather than on individuals within a species or population. As will be described in detail in the subsequent chapters, a limited set of specific properties of chemical substances have been selected through which the hazard can be best described: aquatic toxicity; lack of degradability; and potential or actual bioaccumulation. The rationale for the selection of these data as the means to define the aquatic hazard will be described in more detail in Chapter A8.2.

A8.1.4 The application of the criteria is also limited, at this stage, to chemical substances. The term substances covers a wide range of chemicals, many of which pose difficult challenges to a classification system based on rigid criteria. The following chapters will thus provide some guidance as to how these challenges can be dealt with based both on experience in use and clear scientific rationale. While the harmonised criteria apply most easily to the classification of individual substances of defined structure (see definition in 1.2), some materials that fall under this category are frequently referred to as "complex mixtures". In most cases they can be characterised as a homologous series of substances with a certain range of carbon chain length/number or degree of substitution. Special methodologies have been developed for testing which provides data for evaluating the intrinsic hazard to aquatic organisms, bioaccumulation and degradation. More specific guidance is provided in the separate chapters on these properties. For the purpose of this Guidance Document, these materials will be referred to as "complex substances" or "multi-component substances".

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* *OECD Environment, Health and Safety Publications, Series on Testing and Assessment, No 27, Environment Directorate, Organization for economic Co-operation and Development, April 2001.*

A8.1.5 Each of these properties (i.e. aquatic toxicity, degradability, bioaccumulation) can present a complex interpretational problem, even for experts. While internationally agreed testing guidelines exist and should be used for any and all new data produced, many data usable in classification will not have been generated according to such standard tests. Even where standard tests have been used, some substances, such as complex substances, hydrolytically unstable substances, polymers etc, present difficult interpretational problems when the results have to be used within the classification scheme. Thus data are available for a wide variety of both standard and non-standard test organisms, both marine and freshwater, of varying duration and utilising a variety of endpoints. Degradation data may be biotic or abiotic and can vary in environmental relevance. The potential to bioaccumulate can, for many organic chemicals, be indicated by the octanol-water partition coefficient. It can however be affected by many other factors and these will also need to be taken into account.

A8.1.6 It is clearly the objective of a globally harmonised system that, having agreed on a common set of criteria, a common data-set should also be used so that once classified, the classification is globally accepted. For this to occur, there must first be a common understanding of the type of data that can be used in applying the criteria, both in type and quality, and subsequently a common interpretation of the data when measured against the criteria. For that reason, it has been felt necessary to develop a transparent guidance document that would seek to expand and explain the criteria in such a way that a common understanding of their rationale and a common approach to data interpretation may be achieved. This is of particular importance since any harmonised system applied to the "universe of chemicals" will rely heavily on self-classification by manufacturers and suppliers, classifications that must be accepted across national boundaries without always receiving regulatory scrutiny. This guidance document, therefore, seeks to inform the reader, in a number of key areas, and as a result lead to classification in a consistent manner, thus ensuring a truly harmonised and self-operating system.

A8.1.7 Firstly, it will provide a detailed description of the criteria, a rationale for the criteria selected, and an overview of how the scheme will work in practice (Chapter A8.2). This chapter will address the common sources of data, the need to apply quality criteria, how to classify when the data-set is incomplete or when a large data-set leads to an ambiguous classification, and other commonly encountered classification problems.

A8.1.8 Secondly, the guidance will provide detailed expert advice on the interpretation of data derived from the available databases, including how to use non-standard data, and specific quality criteria that may apply for individual properties. The problems of data interpretation for "difficult substances", those substances for which standard testing methods either do not apply or give difficult interpretational problems, will be described and advice provided on suitable solutions. The emphasis will be on data interpretation rather than testing since the system will, as far as possible, rely on the best available existing data and data required for regulatory purposes. The three core properties, aquatic toxicity (Chapter A8.3), degradability (ChapterA8.4) and bioaccumulation (ChapterA8.5) are treated separately.

A8.1.9 The range of interpretational problems can be extensive and as a result such interpretation will always rely on the ability and expertise of the individuals responsible for classification. However, it is possible to identify some commonly occurring difficulties and provide guidance that distils accepted expert judgement that can act as an aid to achieving a reliable and consistent result. Such difficulties can fall into a number of overlapping issues:

(a) The difficulty in applying the current test procedures to a number of types of substance;
(b) The difficulty in interpreting the data derived both from these "difficult to test" substances and from other substances;
(c) The difficulty in interpretation of diverse data-sets derived from a wide variety of sources.

A8.1.10 For many organic substances, the testing and interpretation of data present no problems when applying both the relevant OECD Guideline and the classification criteria. There are a number of typical interpretational problems, however, that can be characterised by the type of substance being studied. These are commonly called "difficult substances":

- poorly soluble substances: these substances are difficult to test because they present problems in solution preparation, and in concentration maintenance and verification during aquatic toxicity testing. In addition, many available data for such substances have been produced using "solutions" in excess of the water solubility resulting in major interpretational problems in defining the true $L(E)C_{50}$ for the purposes of classification. Interpretation of the partitioning behaviour can also be problematic where the poor solubility in water and octanol may be compounded by insufficient sensitivity in the analytical method. Water solubility may be difficult to determine and is frequently recorded as simply being less than the detection limit, creating problems in interpreting both aquatic toxicity and bioaccumulation studies. In biodegradation studies, poor solubility may result in low bioavailability and thus lower than expected biodegradation rates. The specific test method or the choice of procedures used can thus be of key importance.

- unstable substances: substance that degrade (or react) rapidly in the test system again present both testing and interpretational problems. It will be necessary to determine whether the correct methodology has been used, whether it is the substance or the degradation/reaction product that has been tested, and whether the data produced is relevant to the classification of the parent substance.

- volatile substances: such substances that can clearly present testing problems when used in open systems should be evaluated to ensure adequate maintenance of exposure concentrations. Loss of test material during biodegradation testing is inevitable in certain methods and will lead to misinterpretation of the results.

- complex or multi-component substances: such substances, for example, hydrocarbon mixtures, frequently cannot be dissolved into a homogeneous solution, and the multiple components make monitoring impossible. Consideration therefore needs to be given to using the data derived from the testing of water accommodated fractions (WAFs) for aquatic toxicity, and the utilisation of such data in the classification scheme. Biodegradation, bioaccumulation, partitioning behaviour and water solubility all present problems of interpretation, where each component of the mixture may behave differently.

- polymers: such substances frequently have a wide range of molecular masses, with only a fraction being water soluble. Special methods are available to determine the water soluble fraction and these data will need to be used in interpreting the test data against the classification criteria.

- inorganic compounds and metals: such substances, which can interact with the media, can produce a range of aquatic toxicities dependant on such factors as pH, water hardness etc. Difficult interpretational problems also arise from the testing of essential elements that are beneficial at certain levels. For metals and inorganic metal compounds, the concept of degradability as applied to organic compounds has limited or no meaning. Equally the use of bioaccumulation data should be treated with care.

- surface active substances: such substances can form emulsions in which the bioavailablity is difficult to ascertain, even with careful solution preparation. Micelle formation can result in an overestimation of the bioavailable fraction even when "solutions" are apparently formed. This presents significant problems of interpretation in each of the water solubility, partition coefficient, bioaccumulation and aquatic toxicity studies.

- ionizable substances: such substances can change the extent of ionization according to the level of counter ions in the media. Acids and bases, for example, will show radically different partitioning behaviour depending on the pH.

- coloured substances: such substance can cause problems in the algal/aquatic plant testing because of the blocking of incident light.

- impurities: some substances can contain impurities that can change in % and in chemical nature between production batches. Interpretational problems can arise where either or both the toxicity and water solubility of the impurities are greater than the parent substance, thus potentially influencing the toxicity data in a significant way.

A8.1.11 These represent some of the problems encountered in establishing the adequacy of data, interpreting the data and applying that data to the classification scheme. Detailed guidance on how to deal with these problems, as well as other issues related will be presented in the following Chapters. The interpretation of data on aquatic toxicity will be covered in Chapter A8.3. This chapter will deal with the specific interpretational problems encountered for the above "difficult substances", including providing some advice on when and how such data can be used within the classification scheme. Also covered will be a general description of the test data used and the testing methodologies suitable for producing such data.

A8.1.12 A wide range of degradation data are available that must be interpreted according to the criteria for rapid degradability. Guidance is thus needed on how to use these data obtained by employing non-standard test methods, including the use of half-lives where these are available, of primary degradation, of soil degradation rates and their suitability for extrapolation to aquatic degradation and of environmental degradation rates. A short description of estimation techniques for evaluating degradability in relation to the classification criteria is also included. This guidance will be provided in Chapter A8.4.

A8.1.13 Methods by which the potential to bioaccumulate can be determined will be described in Chapter 5. This chapter will describe the relationship between the partition coefficient criteria and the bioconcentration factor (BCF), provide guidance on the interpretation of existing data, how to estimate the partition coefficient by the use of QSARs when no experimental data are available and in particular deal with the specific problems identified above for difficult substances. The problems encountered when dealing with substances of high molecular mass will also be covered.

A8.1.14 A chapter is also included which covers general issues concerning the use of QSARs within the system, when and how they may be used, for each of the three properties of concern. As a general approach, it is widely accepted that experimental data should be used rather than QSAR data when such data are available. The use of QSARs will thus be limited to such times when no reliable data are available. Not all substances are suitable for the application of QSAR estimations, however, and the guidance in Chapter A8.6 will address this issue.

A8.1.15 Finally, a chapter is devoted to the special problems associated with the classification of metals and their compounds. Clearly, for these compounds, a number of the specific criteria such as biodegradability and octanol-water partition coefficient cannot be applied although the principle of lack of destruction via degradation, and bioaccumulation remain important concepts. Thus it is necessary to adopt a different approach. Metals and metal compounds can undergo interactions with the media which affect the solubility of the metal ion, partitioning from the water column, and the species of metal ion that exists in the water column. In the water column, it is generally the dissolved metal ions which are of concern for toxicity. The interaction of the substance with the media may either increase or decrease the level of ions and hence toxicity. It is thus necessary to consider whether metal ions are likely to be formed from the substance and dissolve in the water, and if so whether they are formed rapidly enough to cause concern. A scheme for interpreting the results from this type of study is presented in Chapter A8.7.

A8.1.16 While the Guidance Document provides useful advice on how to apply the criteria to a wide variety of situations, it remains a guidance only. It cannot hope to cover all situations that arise in classification. It should therefore be seen as a living document that in part describes the fundamental principles of the system, e.g. hazard based rather than risk based, and the fixed criteria. It must also, in part, be a repository for the accumulated experience in using the scheme to include the interpretations which allow the apparently fixed criteria to be applied in a wide variety of non-standard situations.

A8.2 The harmonized classification scheme

A8.2.1 *Scope*

The criteria were developed taking into account existing systems for hazard classification, such as EU- Supply and Use System, the Canadian and US Pesticide systems, GESAMP hazard evaluation procedure, IMO Scheme for Marine Pollutant, the European Road and Rail Transport Scheme (RID/ADR), and the US Land Transport. These systems include supply and subsequent use of chemicals, the sea transport of chemical substances as well as transport of chemical substances by road and rail. The harmonised criteria are therefore intended to identify hazardous chemicals in a common way for use throughout all these systems. To address the needs for all different sectors (transport and supply and use) it was necessary to create two different classification categories, one acute category, consisting of three classes and one chronic category, consisting of 4 classes. The acute classification category makes provision for two acute hazard classes (acute II and III) not normally used when considering packaged goods. For substances transported in bulk, there are a number of regulatory decisions that can uniquely arise because of the bulk quantities being considered. For these situations, for example where decisions are required on the ship type to be used, consideration of all acute classification classes as well as the chronic classification classes are considered important. The following paragraphs describe in detail the criteria to be used in defining each of these hazard classes.

A8.2.2 *Classification categories and criteria*

The hazard classes for acute and chronic aquatic toxicity and their related criteria are set out in Chapter 3.10, para. 3.10.2.2 and Figure 3.10.1.

A8.2.3 *Rationale*

A8.2.3.1 The harmonised system for classification recognises that the intrinsic hazard to aquatic organisms is represented by both the acute and chronic or longer-term toxicity of a substance, the relative importance of which is determined by the specific regulatory regimes in operation. Distinction can be made between the acute hazard and the chronic hazard and therefore hazard classes are defined for both properties representing a gradation in the level of hazard identified. Clearly the hazard identified by Chronic I is more severe than Chronic II. Since the acute hazard and chronic hazard represent distinct types of hazard, they are not comparable in terms of their relative severity. Both hazard classed should be applied independently for the classification of substances to establish a basis for all regulatory systems.

A8.2.3.2 The principal hazard bands defined by the criteria relate largely to the potential for chronic hazard. This reflects the overriding concern with respect to chemicals in the environment, namely that the effects caused are usually sub-lethal, e.g. effects on reproduction, and caused by longer-term exposure. While recognising that the chronic hazard represents the principal concern, particularly for packaged goods where environmental release would be limited in scope, it must also be recognised that chronic toxicity data are expensive to generate and generally not readily available for most substances. On the other hand, acute toxicity data are frequently readily available, or can be generated to highly standardised protocols. It is this acute toxicity which has therefore been used as the core property in defining both the acute and the chronic hazard. Nevertheless, it has been recognised that, where chronic toxicity data are available, it should be possible to use these in defining the appropriate hazard band. The development of specific criteria using such data is thus a high priority in the future development of the scheme.

A8.2.3.3 While recognising that acute toxicity itself is not a sufficiently accurate predictor of chronic toxicity to be used solely and directly for establishing hazard, it is considered that, in combination with either a potential to bioaccumulate (i.e. a log K_{ow} ≥ 4 unless BCF <500) or potential longer-term exposure (i.e. lack of rapid degradation) it can be used as a suitable surrogate for classification purposes. Substances that show acute toxicity and also bioaccumulate to a significant degree will normally show chronic toxicity at a significantly lower concentration. Precise acute: chronic ratios are difficult to predict and thus the surrogate data are generally precautionary. Equally substances that do not rapidly degrade have a higher potential for

giving rise to longer term exposures which again may result in long-term toxicity being realised. Thus, for example, Category Chronic I should be assigned if either of the following criteria are met:

(i) $L(E)C_{50}$ for any appropriate aquatic species ≤1 mg/l and a potential to bioaccumulate (log K_{ow} ≥4 unless BCF <500)

(ii) $L(E)C_{50}$ for any appropriate aquatic species ≤1 mg/l and a lack of rapid degradation.

A8.2.3.4 The precise definitions of acute toxicity of an appropriate species, lack of rapid degradation and potential to bioaccumulate are detailed in Chapters A8.3, A8.4 and A8.5 respectively.

A8.2.3.5 For some poorly soluble substances, which are normally considered as those having a water solubility < 1 mg/l, no acute toxicity is expressed in toxicity tests performed at the solubility limit. If for such a substance, however, the BCF ≥ 500, or if absent, the log K_{ow} ≥ 4 (indicating a bioaccumulating potential) and the substance is also not rapidly degradable, a safety net classification is applied, Chronic Class IV. For these types of substance the exposure duration in short term tests may well be too short for a steady state concentration of the substance to be reached in the test organisms. Thus, even though no acute toxicity has been measured in a short term (acute) test, it remains a real possibility that such non-rapidly degradable and bioaccumulative substances may exert chronic effects, particularly since such low degradability may lead to an extended exposure period in the aquatic environment.

A8.2.3.6 In defining acute aquatic toxicity, it is not possible to test all species present in an aquatic ecosystem. Representative species are therefore chosen which cover a range of trophic levels and taxonomic groupings. The taxa chosen, fish, crustacea and aquatic plants that represent the "base-set" in most hazard profiles, represent a minimum data-set for a fully valid description of hazard. The lowest of the available toxicity values will normally be used to define the hazard category. Given the wide range of species in the environment, the three tested can only be a poor surrogate and the lowest value is therefore taken for cautious reasons to define the hazard band. In doing so, it is recognised that the distribution of species sensitivity can be several orders of magnitude wide and that there will thus be both more and less sensitive species in the environment. Thus, when data are limited, the use of the most sensitive species tested gives a cautious but acceptable definition of the hazard. There are some circumstances where it may not be appropriate to use the lowest toxicity value as the basis for classification. This will usually only arise where it is possible to define the sensitivity distribution with more accuracy than would normally be possible, such as when large data-sets are available. Such large data-sets should be evaluated with due caution.

A8.2.4 *Application*

A8.2.4.1 Generally speaking, in deciding whether a substance should be classified, a search of appropriate databases and other sources of data should be made for the following data elements:

- water solubility
- octanol/water partition coefficient (log K_{ow})
- fish bioconcentration factor (BCF)
- acute aquatic toxicity (L(E)C50s)
- chronic aquatic toxicity (NOECs)
- available degradation (and specifically evidence of ready biodegradability)
- stability data, in water.

The water solubility and stability data, although not used directly in the criteria, are nevertheless important since they are a valuable help in the data interpretation of the other properties (see para. A8.1.11)

A8.2.4.2 To classify, a review should first be made of the available aquatic toxicity data. It will be necessary to consider all the available data and select those which meet the necessary quality criteria for classification. If there are no data available that meet the quality criteria required by the internationally standardised methods, it will be necessary to examine any available data to determine whether a classification can be made. If the data indicate that the acute aquatic toxicity $L(E)C_{50}$ >100 mg/l for soluble

substances, then the substance is not classified as hazardous. There are a number of cases where no effects are observed in the test and the aquatic toxicity is thus recorded as a >water solubility value, i.e. there is no acute toxicity within the range of the water solubility in the test media. Where this is the case, and the water solubility in the test media is ≥1 mg/l, again, no classification need be applied.

A8.2.4.3 Where the lowest aquatic toxicity data are below 100 mg/l, it is necessary to first decide which hazard band the toxicity falls in, and then to determine whether the chronic and/or the acute class should be applied. This can simply be achieved by examining the available data on the partition coefficient, log K_{ow} and the available data on degradation. If either the log $K_{ow} \geq 4$ or the substance cannot be considered as rapidly degradable, then the appropriate chronic hazard class and the corresponding acute class are applied independently. It should be noted that, although the log K_{ow} is the most readily available indication of a potential to bioaccumulate, an experimentally derived BCF is preferred. Where this is available, this should be used rather than the partition coefficient. In these circumstances, a BCF ≥500 would indicate bioaccumulation sufficient to classify in the appropriate chronic hazard class. If the substance is both rapidly degradable and has a low potential to bioaccumulate (BCF <500 or, if absent log K_{ow} <4) then it should not be assigned to a chronic hazard band, only the acute hazard bands need be applied (see A8.2.1).

A8.2.4.4 For poorly soluble substances, generally speaking, those with a water solubility in the test media of <1 mg/l, for which no aquatic toxicity has been found, should be further examined to determine whether chronic class IV need be applied. Thus, if the substance is both not rapidly degradable and has a potential to bioaccumulate (BCF ≥500 or, if absent log $K_{ow} \geq 4$), the chronic class IV should be applied.

A8.2.5 *Data availability*

The data used to classify a substance can be drawn from data required for regulatory purposes as well as the relevant literature, although a number of internationally recognised data-bases exist which can act as a good starting point. Such databases vary widely in quality and comprehensiveness and it is unlikely that any one database will hold all he information necessary for classification to be made. Some databases specialise in aquatic toxicity and others in environmental fate. There is an obligation on the chemical supplier to make the necessary searches and checks to determine the extent and quality of the data available and to use it in assigning the appropriate hazard band.

A8.2.6 *Data quality*

A8.2.6.1 The precise use of the available data will be described in the relevant chapter but, as a general rule, data generated to standard international guidelines and to GLP is to be preferred over other types of data. Equally, however, it is important to appreciate that classification can be made based on the best available data. Thus if no data is available which conforms to the quality standard detailed above, classification can still be made provided the data used is not considered invalid. To assist this process, a quality scoring guide has been developed and used extensively in a number of fora and generally conforms to the following categories:

(a) Data derived from official data sources that have been validated by regulatoryauthorities, such as EU Water Quality Monographs, USEPA Water Quality Criteria. These data can be considered as valid for classification purposes. No assumption should be made that these are the only data available, however, and due regard should be given to the date of the relevant report. Newly available data may not have been considered;

(b) Data derived from recognised international guidelines (e.g. OECD Guidelines) or national guidelines of equivalent quality. Subject to the data interpretation issues raised in the following chapters, these data can be used for classification;

(c) Data derived from testing which, while not strictly according to a guideline detailed above, follows accepted scientific principles and procedures and/or has been peer reviewed prior to publication. For such data, where all the experimental detail is not

recorded, some judgement may be required to determine validity. Normally, such data may be used within the classification scheme;

(d) Data derived from testing procedures which deviate significantly from standard guidelines and are considered as unreliable, should not be used in classification;

(e) QSAR data. The circumstances of use and validity of QSAR data are discussed in the relevant chapters;

(f) Data derived from secondary sources such as handbooks, reviews, citation, etc. where the data quality cannot be directly evaluated. Such data should be examined where data from quality 1, 2 and 3 are not available, to determine whether it can be used. Such data should have sufficient detail to allow quality to be assessed. In determining the acceptability of these data for the purposes of classification, due regard should be given to the difficulties in testing that may have affected data quality and the significance of the reported result in terms of the level of hazard identified (see A8.3.6.2.3).

A8.2.6.2 Classification may also be made on incomplete toxicity data-sets, e.g. where data are not available on all three trophic levels. In these cases, the classification may be considered as 'provisional' and subject to further information becoming available. In general, all the data available will need to be considered prior to assigning a classification. Where good quality data are not available, lower quality data will need to be considered. In these circumstances, a judgement will need to be made regarding the true level of hazard. For example, where good quality data are available for a particular species or taxa, this should be used in preference to any lower quality data which might also be available for that species or taxa. However, good quality data may not always be available for all the basic data set trophic levels. It will be necessary to consider data of lower quality for those trophic levels for which good quality data are not available. Consideration of such data, however, will also need to consider the difficulties that may have affected the likelihood of achieving a valid result. For example, the test details and experimental design may be critical to the assessment of the usability of some data, such as that from hydrolytically unstable chemicals, while less so for other chemicals. Such difficulties are described further in Chapter A8.3.

A8.2.6.3 Normally, the identification of hazard, and hence the classification will be based on information directly obtained from testing of the substance being considered. There are occasions, however, where this can create difficulties in the testing or the outcomes do not conform to common sense. For example, some chemicals, although stable in the bottle, will react rapidly (or slowly) in water giving rise to degradation products that may have different properties. Where such degradation is rapid, the available test data will frequently define the hazard of the degradation products since it will be these that have been tested. These data may be used to classify the parent substance in the normal way. However, where degradation is slower, it may be possible to test the parent substance and thus generate hazard data in the normal manner. The subsequent degradation may then be considered in determining whether an acute or chronic hazard class should apply. There may be occasions, however, when a substance so tested may degrade to give rise to a more hazardous product. In these circumstances, the classification of the parent should take due account of the hazard of the degradation product, and the rate at which it can be formed under normal environmental conditions.

A8.3 Aquatic toxicity

A8.3.1 *Introduction*

The basis for the identification of hazard to the aquatic environment for a substance is the aquatic toxicity of that substance. Classification is predicated on having toxicity data for fish, crustacea, and algae/aquatic plant available. These taxa are generally accepted as representative of aquatic fauna and flora for hazard identification. Data on these particular taxa are more likely to be found because of this general acceptance by regulatory authorities and the chemical industry. Other information on the degradation and bioaccumulation behaviour is used to better delineate the aquatic hazard. This chapter describes the appropriate tests for ecotoxicity, provides some basic concepts in evaluating the data and using combinations of testing results for classification, summarises approaches for dealing with difficulty substances, and includes a brief discussion on interpretation of data quality.

A8.3.2 *Description of tests*

A8.3.2.1 For classifying substances in the harmonized system, freshwater and marine species toxicity data can be considered as equivalent data. It should be noted that some types of substances, e.g. ionizable organic chemicals or organometallic substances may express different toxicities in freshwater and marine environments. Since the purpose of classification is to characterise hazard in the aquatic environment, the result showing the highest toxicity should be chosen.

A8.3.2.2 The GHS criteria for determining health and environmental hazards should be test method neutral, allowing different approaches as long as they are scientifically sound and validated according to international procedures and criteria already referred to in existing systems for the endpoints of concern and produce mutually acceptable data. According to the proposed system (OECD 1998):

> *"Acute toxicity would normally be determined using a fish 96 hour LC50 (OECD Test Guideline 203 or equivalent), a crustacea species 48 hour EC50 (OECD Test Guideline 202 or equivalent) and/or an algal species 72 or 96 hour EC50 (OECD Test Guideline 201 or equivalent). These species are considered as surrogate for all aquatic organisms and data on other species such as the duckweed Lemna may also be considered if the test methodology is suitable. "*

Chronic testing involves an exposure that is lingering or continues for a longer time; the term can signify periods from days to a year, or more depending on the reproductive cycle of the aquatic organism. Chronic tests can be done to assess certain endpoints relating to growth, survival, reproduction and development.

> *"Chronic toxicity data are less available than acute data and the range of testing procedures less standardised. Data generated according to the OECD Test Guidelines 210 (Fish Early Life Stage), 202 Part 2 or 211 (Daphnia Reproduction) and 201 (Algal Growth Inhibition) can be accepted. Other validated and internationally accepted tests could also be used. The NOECs or other equivalent L(E)Cx should be used."*

A8.3.2.3 It should be noted that several of the OECD guidelines cited as examples for classification are being revised or are being planned for updating. Such revisions may lead to minor modifications of test conditions. Therefore, the expert group that developed the harmonized criteria for classification intended some flexibility in test duration or even species used.

A8.3.2.4 Guidelines for conducting acceptable tests with fish, crustacea, and algae can be found in many sources (OECD, 1999; EPA, 1996; ASTM, 1999; ISO EU). The OECD monograph No.11, Detailed Review Paper on Aquatic Toxicity Testing for Industrial Chemicals and Pesticides, is a good compilation of pelagic test methods and sources of testing guidance. This document is also a source of appropriate test methodologies.

A8.3.2.5 *Fish Tests*

A8.3.2.5.1 Acute testing

Acute tests are generally performed with young juveniles 0.1 - 5 g in size for a period of 96 hours. The observational endpoint in these tests is mortality. Fish larger than this range and/or durations shorter than 96 hours are generally less sensitive. However, for classification, they could be used if no acceptable data with the smaller fish for 96 hours are available or the results of these tests with different size fish or test durations would influence a more hazardous classification band. Tests consistent with OECD Test Guideline 203 (Fish 96 hour LC50) or equivalent should be used for classification.

A8.3.2.5.2 Chronic testing

Chronic or long term tests with fish can be initiated with fertilised eggs, embryos, juveniles, or reproductively active adults. Tests consistent with OECD Test Guideline 210 (Fish Early Life Stage), the fish life-cycle test (US EPA 850.1500), or equivalent can be used in the classification scheme. Durations can vary widely depending on the test purpose (anywhere from 7 days to over 200 days). Observational endpoints can include hatching success, growth (length and weight changes), spawning success, and survival. Technically, the OECD 210 Guideline (Fish Early Life Stage) is not a "chronic" test, but a sub-chronic test on sensitive life stages. It is widely accepted as a predictor of chronic toxicity and is used as such for purposes of classification in the harmonized system. Fish early life stage toxicity data are much more available than fish life cycle or reproduction studies.

A8.3.2.6 *Crustacea Tests*

A8.3.2.6.1 Acute testing

Acute tests with crustacea generally begin with first instar juveniles. For daphnids, a test duration of 48 hours is used. For other crustacea, such as mysids or others, a duration of 96 hours is typical. The observational endpoint is mortality or immobilisation as a surrogate to mortality. Immobilisation is defined as unresponsive to gentle prodding. Tests consistent with OECD Test Guideline 202 Part 1 (Daphnia acute) or USA-EPA OPPTS 850.1035 (Mysid acute toxicity) or their equivalents should be used for classification.

A8.3.2.6.2 Chronic testing

Chronic tests with crustacea also generally begin with first instar juveniles and continue through maturation and reproduction. For daphnids, 21 days is sufficient for maturation and the production of 3 broods. For mysids, 28 days is necessary. Observational endpoints include time to first brood, number of offspring produced per female, growth, and survival. It is recommended that tests consistent with OECD Test Guideline 202 Part 2 (Daphnia reproduction) or US-EPA 850.1350 (Mysid chronic) or their equivalents be used in the classification scheme.

A8.3.2.7 *Algae/Plant Tests*

A8.3.2.7.1 Tests in algae

Algae are cultured and exposed to the test substance in a nutrient-enriched medium. Tests consistent with OECD Test Guideline 201 (Algal growth inhibition) should be used. Standard test methods employ a cell density in the inoculum in order to ensure exponential growth through the test, usually 3 to 4 days duration.

The algal test is a short-term test and, although it provides both acute and chronic endpoints, only the acute EC50 is used for classification in the harmonized system. The preferred observational endpoint in this study is algal growth rate inhibition because it is not dependent on the test design, whereas biomass depends both on growth rate of the test species as well as test duration and other elements of test design. If the endpoint is

reported only as reduction in biomass or is not specified, then this value may be interpreted as an equivalent endpoint.

A8.3.2.7.2 Tests in aquatic macrophytes

The most commonly used vascular plants for aquatic toxicity tests are duckweeds (*Lemna gibba* and *Lemna minor*). The Lemna test is a short-term test and, although it provides both acute and sub-chronic endpoints, only the acute EC50 is used for classification in the harmonized system. The tests last for up to 14 days and are performed in nutrient enriched media similar to that used for algae, but may be increased in strength. The observational endpoint is based on change in the number of fronds produced. Tests consistent with OECD Test Guideline on Lemna (in preparation) and US-EPA 850.4400 (aquatic plant toxicity, Lemna) should be used.

A8.3.3 ***Aquatic toxicity concepts***

This section addresses the use of acute and chronic toxicity data in classification, and special considerations for exposure regimes, algal toxicity testing, and use of QSARs. For a more detailed discussion of aquatic toxicity concepts, one can refer to Rand (1996).

A8.3.3.1 *Acute toxicity*

A8.3.3.1.1 Acute toxicity for purposes of classification refers to the intrinsic property of a substance to be injurious to an organism in a short-term exposure to that substance. Acute toxicity is generally expressed in terms of a concentration which is lethal to 50% of the test organisms (LC50), causes a measurable adverse effect to 50% of the test organisms (e.g. immobilisation of daphnids), or leads to a 50% reduction in test (treated) organism responses from control (untreated) organism responses (e.g. growth rate in algae).

A8.3.3.1.2 Substances with an acute toxicity determined to be less than one part per million (1 mg/l) are generally recognised as being very toxic. The handling, use, or discharge into the environment of these substances poses a high degree of hazard and they are classified in chronic and/or acute band I. Decimal bands are accepted for categorising acute toxicity above this band. Substances with an acute toxicity measured from one to ten parts per million (1 - 10 mg/l) are classified in Class II for acute toxicity, from ten to one hundred parts per million (10 - 100 mg/l) are classified in Class III for acute toxicity, and those over one hundred parts per million are regarded as practically non-toxic.

A8.3.3.2 *Chronic toxicity*

A8.3.3.2.1 Chronic toxicity, for purposes of classification, refers to the potential or actual properties of a substance to cause adverse effects to aquatic organisms during exposures which are determined in relation to the life-cycle of the organism. Such chronic effects usually include a range of sublethal endpoints and are generally expressed in terms of a No Observable Effect Concentration (NOEC), or an equivalent ECx. Observable endpoints typically include survival, growth and/or reproduction. Chronic toxicity exposure durations can vary widely depending on test endpoint measured and test species used.

A8.3.3.2.2 Since chronic toxicity data are less common in certain sectors than acute data, for classification schemes, the potential for chronic toxicity is identified by appropriate combinations of acute toxicity, lack of degradability, and/or the potential or actual bioaccumulation. Where such data exist and show long-term NOECs > 1 mg/l, this can be taken into account when deciding whether the classification based on the acute data should be applied. In this context, the following general approach should be used. In order to remove a chronic classification, it must be demonstrated that the NOEC used would be suitable in removing the concern for all taxa which resulted in classification. This can often be achieved by showing a long-term NOEC >1 mg/l for the most sensitive species identified by the acute toxicity. Thus, if a classification has been applied based on a fish acute LC50, it would generally not be possible to remove this classification using a long-term NOEC from an invertebrate toxicity test. In this case, the NOEC would normally need to be derived from a long-term fish test of the same species or one of equivalent or greater sensitivity. Equally, if classification has resulted from the acute toxicity to more than one taxa, it is likely that NOECs > 1 mg/l from each taxa will need to be

demonstrated. In case of classification of a substance as chronic class IV, it is sufficient to demonstrate that NOECs are greater than the water solubility of the substances under consideration.

A8.3.3.2.3 Testing with algae/Lemna cannot be used for de-classifying chemicals because (1) the algae and Lemna tests are not long-term studies, (2) the acute to chronic ratio is generally narrow and (3) the endpoints are more consistent with the end points for other organisms.

However where classification is applied solely due to the acute toxicity ($L(E)C_{50}$) observed in single algae/aquatic plant tests, but there is evidence from a range of other algae tests that the chronic toxicity (NOECs) for this taxonomic group is above 1mg/l, this evidence could be used to consider declassification. At present this approach cannot be applied to aquatic plants since no standardised chronic toxicity tests have been developed.

A8.3.3.2.4 The GHS is intended to contain a specific value of chronic toxicity below which substances would be classified as chronically toxic, but the criteria are not yet set.

A8.3.3.3 *Exposure regimes*

Four types of exposure conditions are employed in both acute and chronic tests and in both freshwater and saltwater media: static, static-renewal (semi-static), recirculation, and flow-through. The choice for which test type to use usually depends on test substance characteristics, test duration, test species, and regulatory requirements.

A8.3.3.4 *Test media for algae*

Algal tests are performed in nutrient-enriched media and use of one common constituent, EDTA, or other chelators, should be considered carefully. When testing the toxicity of organic chemicals, trace amounts of a chelator like EDTA are needed to complex micronutrients in the culture medium; if omitted, algal growth can be significantly reduced and compromise test utility. However, chelators can reduce the observed toxicity of metal test substances. Therefore, for metal compounds, it is desirable that data from tests with high concentration of chelators and/or tests with stoichiometrical excess of chelator relative to iron be critically evaluated. Free chelator may mask heavy metal toxicity considerably, in particular with strong chelators like EDTA. However, in the absence of available iron in the medium the growth of algae can become iron limited, and consequently data from tests with no or with reduced iron and EDTA should be treated with caution.

A8.3.3.5 *Use of QSARs*

For purpose of classification, and in the absence of experimental data, QSARs can be relied upon to provide predictions of acute toxicity for fish, daphnia, and algae for non-electrolyte, non-electrophilic, and otherwise non-reactive substances (See Chapter A8.6 on Use of QSAR). Problems remain for substances such as organophosphates which operate by means of special mechanisms such as functional groups which interact with biological receptors, or which can form sulfhydryl bonds with cellular proteins. Reliable QSARs have been derived for chemicals acting by a basic narcosis mechanism. These chemicals are nonelectrolytes of low reactivity such as hydrocarbons, alcohols, ketones and certain aliphatic chlorinated hydrocarbons which produce their biological effects as a function of their partition coefficients. Every organic chemical can produce narcosis. However, if the chemical is an electrolyte or contains specific functional groups leading to non-narcotic mechanisms as well, any calculations of toxicity based on partition coefficient alone would severely underestimate the toxicity. QSARs for acute aquatic toxicity of parent compounds cannot be used to predict the effects of toxic metabolites or degradates, when these arise after a longer time period than the duration of acute tests.

A8.3.4 *Weight of evidence*

A8.3.4.1 The best quality data should be used as the fundamental basis for classification. Classification should preferably be based on primary data sources. It is essential that test conditions be clearly and completely articulated.

A8.3.4.2 Where multiple studies for a taxonomic group are available, a decision on what is the most sensitive and highest quality must be made. A judgement has to be made on a case by case basis whether a non-GLP study with a more sensitive observation is used in lieu of a GLP study. It would appear that results that indicate high toxicity from tests performed according to non-standard or non-GLP guidelines should be able to be used for classification, whereas studies, which demonstrate negligible toxicity, would require more careful consideration. Substances, which are difficult to test, may yield apparent results that are more or less severe than the true toxicity. Expert judgement would also be needed for classification in these cases.

A8.3.4.3 Where more than one acceptable test is available for the same taxonomic group, the most sensitive (the one with the lowest L(E)C50 or NOEC) is generally used for classification. However, this must be dealt with on a case-by-case basis. When larger data sets (4 or more values) are available for the same species, the geometric mean of toxicity values may be used as the representative toxicity value for that species. In estimating a mean value, it is not advisable to combine tests of different species within a taxa group or in different life stages or tested under different conditions or duration.

A8.3.5 *Difficult to test substances*

A8.3.5.1 Valid aquatic toxicity tests require the dissolution of the test substance in the water media under the test conditions recommended by the guideline. In addition, a bioavailable exposure concentration should be maintained for the duration of the test. Some chemical substances are difficult to test in aquatic systems and guidance has been developed to assist in testing these materials (DoE 1996; ECETOC 1996; and US EPA 1996). OECD is in the process of finalising a Guidance Document on Aquatic Toxicity testing of Difficult Substances and Mixtures (OECD, 2000). This latter document is a good source of information on the types of substances that are difficult to test and the steps needed to ensure valid conclusions from tests with these materials.

A8.3.5.2 Nevertheless, much test data exist that may have used testing methodologies which, while not in conformity with what might be considered best practice today, can still yield information suitable for application of the classification criteria. Such data require special guidance on interpretation, although ultimately, expert judgement must be used in determining data validity. Such difficult to test substances may be poorly soluble, volatile, or subject to rapid degradation due to such processes as phototransformation, hydrolysis, oxidation, or biotic degradation. When testing algae, coloured materials may interfere with the test endpoint by attenuating the light needed for cell growth. In a similar manner, substances tested as cloudy dispersions above solubility may give rise to false toxicity measurements. Loading of the water column with test material can be an issue for particulates or solids such as metals. Petroleum distillate fractions can also pose loading problems, as well as difficult interpretational problems when deciding on the appropriate concentrations for determining $L(E)C_{50}$ values. The draft Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures describes the more common properties of many types of substances which are likely to pose testing difficulties.

> Stability: If test chemical concentrations are expected to fall below 80% of nominal, testing, in order to be valid, may require exposure regimes which provide for renewal of the test material. Semi-static or flow-through conditions are preferred. Special problems arise, therefore, with respect to testing on algae, where the standard guidelines generally include static tests to be conducted. While alternative exposure regimes are possible for crustacea and fish, these tests are frequently conducted on static conditions as included in the internationally agreed guidelines. In these tests, a certain level of degradation as well as other relevant factors has to be tolerated and appropriate account must be taken in calculations of toxic concentrations. Some approaches on how this can be dealt with are covered in sub-section A8.3.5.6. Where degradation occurs, it is also important to consider the influence of the toxicity of the degradation products on the recorded toxicity in the test. Expert judgement will need to be exercised when deciding if the data can be used for classification.

Degradation: When a compound breaks down or degrades under test condition, expert judgement should be used in calculating toxicity for classification, including consideration of known or likely breakdown products. Concentrations of the parent material and all significant toxic degradates are desirable. If degradates are expected to be relatively non-toxic, renewable exposure regimes are desirable in order to ensure that levels of the parent compounds are maintained.

Saturation: For single component substances, classification should be based only on toxic responses observed in the soluble range, and not on total chemical loading above solubility. Frequently, data are available which indicate toxicity at levels in excess of water solubility and, while these data will often be regarded as not valid, some interpretation may be possible. These problems generally apply when testing poorly soluble substances, and guidance on how to interpret such data is included in sub-section A8.3.5.7 (see also the Guidance Document on Aquatic Toxicity testing of Difficult Substances and Mixtures).

Perturbation of test media: Special provisions may be needed to ensure dissolution of difficult to test substances. Such measures should not lead to significant changes in the test media when such changes are likely to lead to an increase or decrease in the apparent toxicity and hence the classification level of the test substance.

Complex substances: Many substances covered by the classification scheme are in fact mixtures, for which measurement of exposure concentrations is difficult, and in some cases impossible. Substances such as petroleum distillate fractions, polymers, substances with significant levels of impurities, etc can pose special problems since the toxic concentration is difficult to define and impossible to verify. Typical testing procedures often rely on the formation of a Water Soluble Fraction (WSF) or Water Accommodated Fraction (WAF) and data are reported in terms of loading rates. These data may be used in applying the classification criteria.

A8.3.5.3 For classification of organic compounds, it is desirable to have stabilised and analytically measured test concentrations. Although measured concentrations are preferred, classification may be based on nominal concentration studies when these are the only valid data available under certain circumstances. If the material is likely to substantially degrade or otherwise be lost from the water column, care must be taken in data interpretation and classification should be done taking the loss of the toxicant during the test into account, if relevant and possible. Additionally, metals present their own set of difficulties and are discussed separately. Table A8.3.1 lists several properties of difficult to test substances and their relevance for classification.

A8.3.5.4 In most difficult to test conditions, the actual test concentration is likely to be less than the nominal or expected test concentration. Where toxicities ($L(E)C_{50}s$) are estimated to be less than 1mg/l for a difficult to test substance, one can be fairly confident the classification in the Acute Class 1 (and Chronic I if appropriate) is warranted. However, if the estimated toxicity is greater than 1 mg/l, the estimated toxicity is likely to under-represent the toxicity. In these circumstances, expert judgement is needed to determine the acceptability of a test with a difficult to test substance for use in classification. Where the nature of the testing difficulty is believed to have a significant influence on the actual test concentration when toxicity is estimated to be greater than 1 mg/l and the test concentration is not measured, then the test should be used with due caution in classification.

A8.3.5.5 The following paragraphs provide some detailed guidance on some of these interpretational problems. In doing so it should be remembered that this is guidance and hard and fast rules cannot be applied. The nature of many of the difficulties mean that expert judgement must always be applied both in determining whether there is sufficient information in a test for a judgement to be made on its validity, and also whether a toxicity level can be determined suitable for use in applying the classification criteria.

A8.3.5.6 *Unstable substances*

A8.3.5.6.1 While testing procedures should ideally have been adopted which minimised the impacts of instability in the test media, in practice, in certain tests, it can be almost impossible to maintain a concentration throughout the test. Common causes of such instability are oxidation, hydrolysis, photodegradation and biodegradation. While the latter forms of degradation can more readily be controlled, such controls are

frequently absent in much existing testing. Nevertheless, for some testing, particularly acute and chronic fish toxicity testing, a choice of exposure regimes is available to help minimise losses due to instability, and this should be taken into account in deciding on the test data validity.

A8.3.5.6.2 Where instability is a factor in determining the level of exposure during the test, an essential prerequisite for data interpretation is the existence of measured exposure concentrations at suitable time points throughout the test. In the absence of analytically measured concentrations at least at the start and end of test, no valid interpretation can be made and the test should be considered as invalid for classification purposes. Where measured data are available, a number of practical rules can be considered by way of guidance in interpretation:

- where measured data are available for the start and end of test (as is normal for the acute Daphnia and algal tests), the $L(E)C_{50}$ for classification purposes, may be calculated based on the geometric mean of the start and end of test concentrations. Where the end of test concentrations are below the analytical detection limit, such concentrations shall be considered to be half that detection limit.

- where measured data are available at the start and end of media renewal periods (as may be available for the semi-static tests), the geometric mean for each renewal period should be calculated, and the mean exposure over the whole exposure period calculated from these data.

- where the toxicity can be attributed to a degradation breakdown product, and the concentrations of this are known, the $L(E)C_{50}$ for classification purposes, may be calculated based on the geometric mean of the degradation product concentration, back calculated to the parent substance.

- similar principles may be applied to measured data in chronic toxicity testing.

A8.3.5.7 *Poorly soluble substances*

A8.3.5.7.1 These substances, usually taken to be those with a solubility in water of <1 mg/l, are frequently difficult to dissolve in the test media, and the dissolved concentrations will often prove difficult to measure at the low concentrations anticipated. For many substances, the true solubility in the test media will be unknown, and will often be recorded as < detection limit in purified water. Nevertheless such substances can show toxicity, and where no toxicity is found, judgement must be applied to whether the result can be considered valid for classification. Judgement should err on the side of caution and should not underestimate the hazard.

A8.3.5.7.2 Ideally, tests using appropriate dissolution techniques and with accurately measured concentrations within the range of water solubility should be used. Where such test data are available, they should be used in preference to other data. It is normal, however, particularly when considering older data, to find such substances with toxicity levels recorded in excess of the water solubility, or where the dissolved levels are below the detection limit of the analytical method. Thus, in both circumstances, it is not possible to verify the actual exposure concentrations using measured data. Where these are the only data available on which to classify, some practical rules can be considered by way of general guidance:

- where the acute toxicity is recorded at levels in excess of the water solubility, the $L(E)C_{50}$ for classification purposes, may be considered to be equal to or below the measured water solubility. In such circumstances it is likely that Chronic I and/or Acute I classes should be applied. In making this decision, due attention should be paid to the possibility that the excess undissolved substance may have given rise to physical effects on the test organisms. Where this is considered the likely cause of the effects observed, the test should be considered as invalid for classification purposes.

- where no acute toxicity is recorded at levels in excess of the water solubility, the $L(E)C_{50}$ for classification purposes may be considered to be greater than the measured water solubility. In such circumstances, consideration should be given to whether the Chronic IV class should

apply. In making a decision that the substance shows no acute toxicity, due account should be taken of the techniques used to achieve the maximum dissolved concentrations. Where these are not considered as adequate, the test should be considered as invalid for classification purposes.

- where the water solubility is below the detection limit of the analytical method for a substance, and acute toxicity is recorded, the $L(E)C_{50}$ for classification purposes, may be considered to be less than the analytical detection limit. Where no toxicity is observed, the $L(E)C_{50}$ for classification purposes, may be considered to be greater than the water solubility. Due consideration should also be given to the quality criteria mentioned above.

- where chronic toxicity data are available, the same general rules should apply. In principle, only data showing no effects at the water solubility limit, or greater than 1 mg/l need be considered. Again, where these data cannot be validated by consideration of measured concentrations, the techniques used to achieve the maximum dissolved concentrations must be considered as appropriate.

A8.3.5.8 *Other factors contributing to concentration loss*

A number of other factors can also contribute to losses of concentration and, while some can be avoided by correct study design, interpretation of data where these factors have contributed may, from time to time, be necessary.

- sedimentation: this can occur during a test for a number of reasons. A common explanation is that the substance has not truly dissolved despite the apparent absence of particulates, and agglomeration occurs during the test leading to precipitation. In these circumstances, the L(E)C50 for classification purposes, may be considered to be based on the end of test concentrations. Equally, precipitation can occur through reaction with the media. This is considered under instability above.

- adsorption: this can occur for substances of high adsorption characteristics such as high log Kow substances. Where this occurs, the loss of concentration is usually rapid and exposure may best be characterised by the end of test concentrations.

- bioaccumulation: losses may occur through the bioaccumulation of a substance into the test organisms. This may be particularly important where the water solubility is low and log K_{ow} correspondingly high. The $L(E)C_{50}$ for classification purposes, may be calculated based on the geometric mean of the start and end of test concentrations.

A8.3.5.9 *Perturbation of the test media*

A8.3.5.9.1 Strong acids and bases may appear toxic because they may alter pH. Generally however changes of the pH in aquatic systems are normally prevented by buffer systems in the test medium. If no data are available on a salt, the salt should generally be classified in the same way as the anion or cation, i.e. as the ion that receives the most stringent classification. If the effect concentration is related to only one of the ions, the classification of the salt should take the molecular weight difference into consideration by correcting the effect concentration by multiplying with the ratio: $MW_{salt}/MW_{ion.}$

A8.3.5.9.2 Polymers are typically not available in aquatic systems. Dispersible polymers and other high molecular mass materials can perturb the test system and interfere with uptake of oxygen, and give rise to mechanical or secondary effects. These factors need to be taken into account when considering data from these substances. Many polymers behave like complex substances, however, having a significant low molecular mass fraction which can leach from the bulk polymer. This is considered further below.

A8.3.5.10 *Complex substances*

A8.3.5.10.1 Complex substances are characterised by a range of chemical structures, frequently in a homologous series, but covering a wide range of water solubilities and other physico-chemical characteristics. On addition to water, an equilibrium will be reached between the dissolved and undissolved fractions which will be characteristic of the loading of the substance. For this reason, such complex substances are usually tested as a WSF or WAF, and the $L(E)C_{50}$ recorded based on the loading or nominal concentrations. Analytical support data are not normally available since the dissolved fraction will itself be a complex mixtures of components. The toxicity parameter is sometimes referred to as LL_{50}, related to the lethal loading level. This loading level from the WSF or WAF may be used directly in the classification criteria.

A8.3.5.10.2 Polymers represent a special kind of complex substance, requiring consideration of the polymer type and their dissolution/dispersal behaviour. Polymers may dissolve as such without change, (true solubility related to particle size), be dispersible, or portions consisting of low molecular weight fractions may go into solution. In the latter case, in effect, the testing of a polymer is a test of the ability of low molecular mass material to leach from the bulk polymer, and whether this leachate is toxic. It can thus be considered in the same way as a complex mixture in that a loading of polymer can best characterise the resultant leachate, and hence the toxicity can be related to this loading.

Table A8.3.1 Classification of difficult test substances

Property	Nature of difficulty	Relevance for Classification
Poorly water soluble	Achieving/maintaining required exposure concentration. Analysing exposure.	When toxic responses are observed above apparent solubility, expert judgement is required to confirm whether effects are due to chemical toxicity or a physical effect; if no effects are observed, it should be demonstrated that full, saturated dissolution has been achieved.
Toxic at low concentrations	Achieving/maintaining required exposure concentration. Analysing exposure.	Classified based on toxicity < 1 mg/l
Volatile	Maintaining and measuring exposure concentration.	Classification should be based on reliable measurement of concentrations.
Photo-degradable	Maintaining exposure concentrations. Toxicity of breakdown products.	Classification requires expert judgement and should be based on measured concentrations. Toxicity of significant breakdown products should be characterised.
Hydrolytically unstable	Maintaining exposure concentrations. Toxicity of breakdown products. Comparison of degradation half-lives to the exposure regimen used in testing.	Classification requires expert judgement, should be based on measured concentrations, and needs to address the toxicity of significant breakdown products.
Oxidizable	Achieving, maintaining and measuring exposure concentration. Toxicity of modified chemical structures or breakdown products. Comparison of degradation half-lives to the exposure regimen used in testing.	Classification requires expert judgement, should be based on measured concentrations, and needs to address the toxicity of significant breakdown products.
Subject to corrosion/ transformation (this refers to metals /metal compounds)	Achieving, maintaining and measuring exposure concentration. Comparison of partitioning from the water column half-lives to the exposure regimen used in testing.	Classification requires expert judgement, should be based on measured concentrations, and needs to address the toxicity of significant breakdown products.
Biodegradable	Maintaining exposure concentrations. Toxicity of breakdown products. Comparison of degradation half-lives to the exposure regimen used in testing.	Classification requires expert judgement, should be based on measured concentrations, and needs to address the toxicity of significant breakdown products.
Adsorbing	Maintaining exposure concentrations. Analysing exposure. Toxicity mitigation due to reduced availability of test substance.	Classification should use measured concentration of available material.
Chelating	Distinguishing chelated and non-chelated fractions in media.	Classification should use measurement of concentration of bioavailable material.
Coloured	Light attenuation (an algal problem).	Classification must distinguish toxic effects from reduced growth due to light attenuation.
Hydrophobic	Maintaining constant exposure concentrations.	Classification should use measured concentration.
Ionised	Maintaining exposure concentrations. Toxicity of breakdown products. Comparison of degradation half-lives to the exposure regime used in testing.	Classification requires expert judgement, should be based on measured concentrations, and needs to address the toxicity of significant breakdown products.
Multi-component	Preparing representative test batches.	Considered same as complex mixture.

A8.3.6 *Interpreting data quality*

A8.3.6.1 *Standardisation*

Many factors can influence the results of toxicity tests with aquatic organisms. These factors include characteristics of the test water, experimental design, chemical characteristics of the test material, and biological characteristics of the test organisms. Therefore, it is important in conducting aquatic toxicity tests to use standardised test procedures to reduce the influence of these sources of extraneous variability. The goal of test standardisation and international harmonisation of these standards is to reduce test variability and improve precision, reproducibility, and consistency of test results.

A8.3.6.2 *Data hierarchies*

A8.3.6.2.1 Classification should be based on primary data of good quality. Preference is given to data conforming to OECD Test Guidelines or equivalent and Good Laboratory Practices (GLP). While data from internationally harmonised test methods performed on standard test species are preferred, results of tests performed using widely recognised international or national methods or their equivalent may also be used, e.g. ISO or ASTM methods. Data from tests that appear to conform to accepted guidelines but which lacks provisions for GLP can be used in the absence of pertinent GLP data.

A8.3.6.2.2 Pedersen et al (1995) provides a data quality-scoring system, which is compatible with many others in current use, including that, used by the US-EPA for its AQUIRE database. See also Mensink et al (1995) for discussions of data quality. The data quality scoring system described in Pedersen *et al.* includes a reliability ranking scheme, which can be a model for use with in classifying under the harmonised scheme. The first three levels of data described by Pedersen are for preferred data.

A8.3.6.2.3 Data for classification under the harmonised scheme should come from primary sources. However, since many nations and regulatory authorities will perform classification using the globally harmonised scheme, classification should allow for use of reviews from national authorities and expert panels as long as the reviews are based on primary sources. Such reviews should include summaries of test conditions, which are sufficiently detailed for weight of evidence and classification decisions to be made. It may be possible to use the reviews, which were made by a well-recognised group such as GESAMP for which the primary data are accessible.

A8.3.6.2.4 In the absence of empirical test data, validated Quantitative Structure Activity Relationships (QSARs) for aquatic toxicity may be used. Test data always take precedence over QSAR predictions, providing the test data are valid.

A8.4 Degradation

A8.4.1 *Introduction*

A8.4.1.1 Degradability is one of the important intrinsic properties of chemical substances that determine their potential environmental hazard. Non-degradable substances will persist in the environment and may consequently have a potential for causing long-term adverse effects on biota. In contrast, degradable substances may be removed in the sewers, in sewage treatment plants or in the environment.

Classification of chemical substances is primarily based on their intrinsic properties. However, the degree of degradation depends not only on the intrinsic recalcitrance of the molecule, but also on the actual conditions in the receiving environmental compartment as e.g. redox potential, pH, presence of suitable micro-organisms, concentration of the substances and occurrence and concentration of other substrates. The interpretation of the degradation properties in an aquatic hazard classification context therefore requires detailed criteria that balance the intrinsic properties of the substance and the prevailing environmental conditions into a concluding statement on the potential for long-term adverse effects. The purpose of the present chapter is to present guidance for interpretation of data on degradability of organic substances. The guidance is based on an analysis of the above mentioned aspects regarding degradation in the aquatic environment. Based on the guidance a detailed decision scheme for use of existing degradation data for classification purposes is proposed. The types of degradation data included in this Guidance Document are ready biodegradability data, simulation data for transformation in water, aquatic sediment and soil, BOD_5/COD-data and techniques for estimation of rapid degradability in the aquatic environment. Also considered are anaerobic degradability, inherent biodegradability, sewage treatment plant simulation test data, abiotic transformation data such as hydrolysis and photolysis, removal process such as volatilisation and finally, data obtained from field investigations and monitoring studies.

A8.4.1.2 The term degradation is defined in Chapter 1.2 as the decomposition of organic molecules to smaller molecules and eventually to carbon dioxide, water and salts. For inorganic compounds and metals, the concept of degradability as applied to organic compounds has limited or no meaning. Rather the substance may be transformed by normal environmental processes to either increase or decrease the bioavailability of the toxic species. Therefore, the present chapter deals only with organic substances and organo-metals. Environmental partitioning from the water column is discussed in Chapter A8.7.

A8.4.1.3 Data on degradation properties of a substance may be available from standardised tests or from other types of investigations, or they may be estimated from the structure of the molecules. The interpretation of such degradation data for classification purposes often requires detailed evaluation of the test data. Guidance is given in the present chapter and more details can be found in two paragraphs describing available methods (Appendix A8.I) and factors influencing degradation in aquatic environments (Appendix A8.II).

A8.4.2 *Interpretation of degradability data*

A8.4.2.1 *Rapid degradability*

Aquatic hazard classification of chemical substances is normally based on existing data on their environmental properties. Only seldom will test data be produced with the main purpose of facilitating a classification. Often a diverse range of test data is available that does not necessarily fits directly with the classification criteria. Consequently, guidance is needed on interpretation of existing test data in the context of the aquatic hazard classification. Based on the harmonised criteria, guidance for interpretation of degradation data is prepared below for the three types of data comprised by the expression "rapid degradation" in the aquatic environment (see A8.1.8, A8.1.9, A8.1.2.3.1 to A8.2.3.3 and the definition in Part 3, para. 3.10.2.10.3 .

A8.4.2.2 *Ready biodegradability*

A8.4.2.2.1 Ready biodegradability is defined in the OECD Test Guidelines No. 301 (OECD 1992). All organic substances that degrade to a level higher than the pass level in a standard OECD ready biodegradability test or in a similar test should be considered readily biodegradable and consequently also rapidly degradable. Many literature test data, however, do not specify all of the conditions that should be evaluated to demonstrate whether or not the test fulfils the requirements of a ready biodegradability test. Expert judgement is therefore needed as regards the validity of the data before use for classification purposes. Before concluding on the ready biodegradability of a test substance, however, at least the following parameters should be considered.

A8.4.2.2.2 Concentration of test substance

Relatively high concentrations of test substance are used in the OECD ready biodegradability tests (2-100 mg/L). Many substances may, however, be toxic to the inocula at such high concentrations causing a low degradation in the tests although the substances might be rapidly degradable at lower non-toxic concentrations. A toxicity test with micro-organisms (as e.g. the OECD Test Guideline 209 "Activated Sludge, Respiration Inhibition Test", the ISO 9509 nitrification inhibition test, or the ISO 11348 luminescent bacteria inhibition test) may demonstrate the toxicity of the test substance. When it is likely that inhibition is the reason for a substance being not readily degradable, results from a test employing lower non-toxic concentrations of the test substance should be used when available. Such test results could on a case by case basis be considered in relation to the classification criteria for rapid degradation, even though surface water degradation test data with environmentally realistic microbial biomass and non toxic realistic low concentration of the test substance in general are preferred, if available.

A8.4.2.2.3 Time window

The harmonised criteria include a general requirement for all of the ready biodegradability tests on achievement of the pass level within 10 days. This is not in line with the OECD Test Guideline 301 in which the 10-days time window applies to the OECD ready biodegradability tests except to the MITI I test (OECD Test Guideline 301C). In the Closed Bottle test (OECD Test Guideline 301D), a 14-days window may be used instead when measurements have not been made after 10 days. Moreover, often only limited information is available in references of biodegradation tests. Thus, as a pragmatic approach the percentage of degradation reached after 28 days may be used directly for assessment of ready biodegradability when no information on the 10-days time window is available. This should, however, only be accepted for existing test data and data from tests where the 10-days window does not apply.

A8.4.2.3 *BOD_5/COD*

Information on the 5-day biochemical oxygen demand (BOD_5) will be used for classification purposes only when no other measured degradability data are available. Thus, priority is given to data from ready biodegradability tests and from simulation studies regarding degradability in the aquatic environment. The BOD_5 test is a traditional biodegradation test that is now replaced by the ready biodegradability tests. Therefore, this test should not be performed today for assessment of the ready biodegradability of substances. Older test data may, however, be used when no other degradability data are available. For substances where the chemical structure is known, the theoretical oxygen demand (ThOD) can be calculated and this value should be used instead of the chemical oxygen demand (COD).

A8.4.2.4 *Other convincing scientific evidence*

A8.4.2.4.1 Rapid degradation in the aquatic environment may be demonstrated by other data than referred to in Chapter 3.10, para. 3.10.2.10.3, items (a) and (b). These may be data on biotic and/or abiotic degradation. Data on primary degradation can only be used where it is demonstrated that the degradation products shall not be classified as hazardous to the aquatic environment, i.e. that they do not fulfil the classification criteria.

A8.4.2.4.2 The fulfilment of criterion (c) of Chapter 3.10, para. 3.10.2.10.3, requires that the substance is degraded in the aquatic environment to a level of >70% within a 28-day period. If first-order kinetics are assumed, which is reasonable at the low substance concentrations prevailing in most aquatic environments, the degradation rate will be relatively constant for the 28-day period. Thus, the degradation requirement will be fulfilled with an average degradation rate constant, $k > -(\ln 0.3 - \ln 1)/28 = 0.043$ day^{-1}. This corresponds to a degradation half-life, $t_{½} < \ln 2/0.043 = 16$ days.

A8.4.2.4.3 Moreover, as degradation processes are temperature dependent, this parameter should also be taken into account when assessing degradation in the environment. Data from studies employing environmentally realistic temperatures should be used for the evaluation. When data from studies performed at different temperatures need to be compared, the traditional Q10 approach could be used, i.e. that the degradation rate is halved when the temperature decreases by 10 °C.

A8.4.2.4.4 The evaluation of data on fulfilment of this criterion should be conducted on a case by case basis by expert judgement. However, guidance on the interpretation of various types of data that may be used for demonstrating a rapid degradation in the aquatic environment is given below. In general, only data from aquatic biodegradation simulation tests are considered directly applicable. However simulation test data from other environmental compartments could be considered as well, but such data require in general more scientific judgement before use.

A8.4.2.4.5 Aquatic simulation tests

Aquatic simulation tests are tests conducted in laboratory, but simulating environmental conditions and employing natural samples as inoculum. Results of aquatic simulation tests may be used directly for classification purposes, when realistic environmental conditions in surface waters are simulated, i.e.:

- substance concentration that is realistic for the general aquatic environment (often in the low µg/L range);
- inoculum from a relevant aquatic environment;
- realistic concentration of inoculum (10^3-10^6 cells/mL);
- realistic temperature (e.g. 5 °C to 25 °C); and
- ultimate degradation is determined (i.e. determination of the mineralisation rate or the individual degradation rates of the total biodegradation pathway).

Substances that under these conditions are degraded at least 70% within 28 days, i.e. with a half-life < 16 days, are considered rapidly degradable.

A8.4.2.4.6 Field investigations

Parallels to laboratory simulation tests are field investigations or mesocosm experiments. In such studies, fate and/or effects of chemicals in environments or environmental enclosures may be investigated. Fate data from such experiments might be used for assessing the potential for a rapid degradation. This may, however, often be difficult, as it requires that an ultimate degradation can be demonstrated. This may be documented by preparing mass balances showing that no non-degradable intermediates are formed, and which take the fractions into account that are removed from the aqueous system due to other processes such as sorption to sediment or volatilisation from the aquatic environment.

A8.4.2.4.7 Monitoring data

Monitoring data may demonstrate the removal of contaminants from the aquatic environment. Such data are, however, very difficult to use for classification purposes. The following aspects should be considered before use:

- Is the removal a result of degradation, or is it a result of other processes such as dilution or distribution between compartments (sorption, volatilisation)?

- Is formation of non-degradable intermediates excluded?

Only when it can be demonstrated that removal as a result of ultimate degradation fulfils the criteria for rapid degradability, such data be considered for use for classification purposes. In general, monitoring data should only be used as supporting evidence for demonstration of either persistence in the aquatic environment or a rapid degradation.

A8.4.2.4.8 Inherent biodegradability tests

Substances that are degraded more than 70% in tests for inherent biodegradability (OECD Test Guidelines 302) have the potential for ultimate biodegradation. However, because of the optimum conditions in these tests, the rapid biodegradability of inherently biodegradable substances in the environment cannot be assumed. The optimum conditions in inherent biodegradability tests stimulate adaptation of the micro-organisms thus increasing the biodegradation potential, compared to natural environments. Therefore, positive results in general should not be interpreted as evidence for rapid degradation in the environment*.

A8.4.2.4.9 Sewage treatment plant simulation tests

Results from tests simulating the conditions in a sewage treatment plant (STP) (e.g. the OECD Test Guideline 303) cannot be used for assessing the degradation in the aquatic environment. The main reasons for this are that the microbial biomass in a STP is significantly different from the biomass in the environment, that there is a considerably different composition of substrates, and that the presence of rapidly mineralised organic matter in waste water facilitates degradation of the test substance by co-metabolism.

A8.4.2.4.10 Soil and sediment degradation data

It has been argued that for many non-sorptive (non-lipophilic) substances more or less the same degradation rates are found in soil and in surface water. For lipophilic substances, a lower degradation rate may generally be expected in soil than in water due to partial immobilisation caused by sorption. Thus, when a substance has been shown to be degraded rapidly in a soil simulation study, it is most likely also rapidly degradable in the aquatic environment. It is therefore proposed that an experimentally determined rapid degradation in soil is sufficient documentation for a rapid degradation in surface waters when:

- no pre-exposure (pre-adaptation) of the soil micro-organisms has taken place, and
- an environmentally realistic concentration of substance is tested, and
- the substance is ultimately degraded within 28 days with a half-life <16 days corresponding to a degradation rate >0.043 day^{-1}.

The same argumentation is considered valid for data on degradation in sediment under aerobic conditions.

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* *In relation to interpretation of degradation data equivalent with the harmonised OECD criteria for chronic class IV, the standing EU working group for environmental hazard classification of substances is discussing whether certain types of data from inherent biodegradability tests may be*
used in a case by case evaluation as a basis for not classifying substances otherwise fulfilling this classification criterion:
The inherent biodegradability tests concerned are the Zahn Wellens test (OECD TG 302 B) and the MITI II test (OECD TG 302 C). The conditions for use in this regard are:

(b) The methods must not employ pre-exposed (pre-adapted) micro-organisms;

(a) The time for adaptation within each test should be limited, the test endpoint should refer to the mineralisation only and the pass level and time for reaching these should be, respectively:

- *MITI II pass level > 60 % within 14 days*
- *Zahn Wellens Test > 70 % within 7 days.*

A8.4.2.4.11 Anaerobic degradation data

Data regarding anaerobic degradation cannot be used in relation to deciding whether a substance should be regarded as rapidly degradable, because the aquatic environment is generally regarded as the aerobic compartment where the aquatic organisms, such as those employed for aquatic hazard classification, live.

A8.4.2.4.12 Hydrolysis

Data on hydrolysis (e.g. OECD Test Guideline 111) might be considered for classification purposes only when the longest half-life $t_{½}$ determined within the pH range 4-9 is shorter than 16 days. However, hydrolysis is not an ultimate degradation and various intermediate degradation products may be formed, some of which may be only slowly degradable. Only when it can be satisfactorily demonstrated that the hydrolysis products formed do not fulfil the criteria for classification as hazardous for the aquatic environment, data from hydrolysis studies could be considered.

When a substance is quickly hydrolysed (e.g. with $t_{½}$ < a few days), this process is a part of the degradation determined in biodegradation tests. Hydrolysis may be the initial transformation process in biodegradation.

A8.4.2.4.13 Photochemical degradation

Information on photochemical degradation (e.g. OECD, 1997) is difficult to use for classification purposes. The actual degree of photochemical degradation in the aquatic environment depends on local conditions (e.g. water depth, suspended solids, turbidity) and the hazard of the degradation products is usually not known. Probably only seldom will enough information be available for a thorough evaluation based on photochemical degradation.

A8.4.2.4.14 Estimation of degradation

A8.4.2.4.14.1 Certain QSARs have been developed for prediction of an approximate hydrolysis half-life, which should only be considered when no experimental data are available. However, a hydrolysis half-life can only be used in relation to classification with great care, because hydrolysis does not concern ultimate degradability (see "Hydrolysis" of this Section). Furthermore the QSARs developed until now have a rather limited applicability and are only able to predict the potential for hydrolysis on a limited number of chemical classes. The QSAR program HYDROWIN (version 1.67, Syracuse Research Corporation) is for example only able to predict the potential for hydrolysis on less than $1/5^{th}$ of the existing EU substances which have a defined (precise) molecular structure (Niemelä, 2000).

A8.4.2.4.14.2 In general, no quantitative estimation method (QSAR) for estimating the degree of biodegradability of organic substances is yet sufficiently accurate to predict rapid degradation. However, results from such methods may be used to predict that a substance is not rapidly degradable. For example, when in the Biodegradation Probability Program (e.g. BIOWIN version 3.67, Syracuse Research Corporation) the probability is < 0.5 estimated by the linear or non-linear methods, the substances should be regarded as not rapidly degradable (OECD, 1994; Pedersen *et al.*, 1995 & Langenberg *et al.*, 1996). Also other (Q)SAR methods may be used as well as expert judgement, for example, when degradation data for structurally analogue compounds are available, but such judgement should be conducted with great care. In general, a QSAR prediction that a substance is not rapidly degradable is considered a better documentation for a classification than application of a default classification, when no useful degradation data are available.

A8.4.2.4.15 Volatilisation

Chemicals may be removed from some aquatic environments by volatilisation. The intrinsic potential for volatilisation is determined by the Henry's Law constant (H) of the substance. Volatilisation from the aquatic environment is highly dependent on the environmental conditions of the specific water body in question, such as the water depth, the gas exchange coefficients (depending on wind speed and water

flow) and stratification of the water body. Because volatilisation only represents removal of a chemical from water phase, the Henry's Law constant can not be used for assessment of degradation in relation to aquatic hazard classification of substances. Substances that are gases at ambient temperature may however for example be considered further in this regard (see also Pedersen *et al.*, 1995).

A8.4.2.5 *No degradation data available*

When no useful data on degradability are available - either experimentally determined or estimated data - the substance should be regarded as not rapidly degradable.

A8.4.3 *General interpretation problems*

A8.4.3.1 *Complex substances*

The harmonised criteria for classification of chemicals as hazardous for the aquatic environment focus on single substances. A certain type of intrinsically complex substance are multi-component substances. They are typically of natural origin and need occasionally to be considered. This may be the case for chemicals that are produced or extracted from mineral oil or plant material. Such complex chemicals are normally considered as single substances in a regulatory context. In most cases they are defined as a homologous series of substances within a certain range of carbon chain length and/or degree of substitution. When this is the case, no major difference in degradability is foreseen and the degree of degradability can be established from tests of the complex chemical. One exception would be when a borderline degradation is found because in this case some of the individual substances may be rapidly degradable and other may be not rapidly degradable. This requires a more detailed assessment of the degradability of the individual components in the complex substance. When not-rapidly-degradable components constitute a significant part of the complex substance (e.g. more than 20%, or for a hazardous component, an even lower content), the substance should be regarded as not rapidly degradable.

A8.4.3.2 *Availability of the substance*

A8.4.3.2.1 Degradation of organic substances in the environment takes place mostly in the aquatic compartments or in aquatic phases in soil or sediment. Hydrolysis, of course, requires the presence of water. The activity of micro-organisms depends on the presence of water. Moreover, biodegradation requires that the micro-organisms are directly in contact with the substance. Dissolution of the substance in the water phase that surrounds the micro-organisms is therefore the most direct way for contact between the bacteria and fungi and the substrate.

A8.4.3.2.2 The present standard methods for investigating degradability of chemical substances are developed for readily soluble test compounds. However, many organic substances are only slightly soluble in water. As the standard tests require 2-100 mg/L of the test substance, sufficient availability may not be reached for substances with a low water solubility. Tests with continuous mixing and/or an increased exposure time, or tests with a special design where concentrations of the test substance lower than the water solubility have been employed, may be available on slightly soluble compounds.

A8.4.3.3 *Test duration less than 28 days*

A8.4.3.3.1 Sometimes degradation is reported for tests terminated before the 28 day period specified in the standards (e.g. the MITI, 1992). These data are of course directly applicable when a degradation greater than or equal to the pass level is obtained. When a lower degradation level is reached, the results need to be interpreted with caution. One possibility is that the duration of the test was too short and that the chemical structure would probably have been degraded in a 28-day biodegradability test. If substantial degradation occurs within a short time period, the situation may be compared with the criterion $BOD_5/COD \geq 0.5$ or with the requirements on degradation within the 10-days time window. In these cases, a substance may be considered readily degradable (and hence rapidly degradable), if:

- the ultimate biodegradability exceeds 50% within 5 days; or

- the ultimate degradation rate constant in this period is greater than 0.1 day^{-1} corresponding to a half-life of 7 days.

A8.4.3.3.2 These criteria are proposed in order to ensure that rapid mineralisation did occur, although the test was ended before 28 days and before the pass level was attained. Interpretation of test data that do not comply with the prescribed pass levels must be made with great caution. It is mandatory to consider whether a biodegradability below the pass level was due to a partial degradation of the substance and not a complete mineralisation. If partial degradation is the probable explanation for the observed biodegradability, the substance should be considered not readily biodegradable.

A8.4.3.4 *Primary biodegradation*

In some tests, only the disappearance of the parent compound (i.e. primary degradation) is determined for example by following the degradation by specific or group specific chemical analyses of the test substance. Data on primary biodegradability may be used for demonstrating rapid degradability only when it can be satisfactorily demonstrated that the degradation products formed do not fulfil the criteria for classification as hazardous to the aquatic environment.

A8.4.3.5 *Conflicting results from screening tests*

A8.4.3.5.1 The situation where more degradation data are available for the same substance introduces the possibility of conflicting results. In general, conflicting results for a substance which has been tested several times with an appropriate biodegradability test could be interpreted by a "weight of evidence approach". This implies that if both positive (i.e. higher degradation than the pass level) and negative results have been obtained for a substance in ready biodegradability tests, then the data of the highest quality and the best documentation should be used for determining the ready biodegradability of the substance. However, positive results in ready biodegradability tests could be considered valid, irrespective of negative results, when the scientific quality is good and the test conditions are well documented, i.e. guideline criteria are fulfilled, including the use of non-pre-exposed (non-adapted) inoculum. None of the various screening tests are suitable for the testing of all types of substances, and results obtained by the use of a test procedure which is not suitable for the specific substance should be evaluated carefully before a decision on the use is taken.

A8.4.3.5.2 Thus, there are a number of factors that may explain conflicting biodegradability data from screening tests:

- inoculum;
- toxicity of test substance;
- test conditions;
- solubility of the test substance; and
- volatilisation of the test substance.

A8.4.3.5.3 The suitability of the inoculum for degrading the test substance depends on the presence and amount of competent degraders. When the inoculum is obtained from an environment that has previously been exposed to the test substance, the inoculum may be adapted as evidenced by a degradation capacity, which is greater than that of an inoculum from a non-exposed environment. As far as possible the inoculum must be sampled from an unexposed environment, but for substances that are used ubiquitously in high volumes and released widespread or more or less continuously, this may be difficult or impossible. When conflicting results are obtained, the origin of the inoculum should be checked in order to clarify whether or not differences in the adaptation of the microbial community may be the reason.

A8.4.3.5.4 As mentioned above, many substances may be toxic or inhibitory to the inoculum at the relatively high concentrations tested in ready biodegradability tests. Especially in the Modified MITI (I) test (OECD Test Guideline 301C) and the Manometric Respirometry test (OECD Test Guideline 301F) high concentrations (100 mg/L) are prescribed. The lowest test substance concentrations are prescribed in the Closed Bottle test (OECD Test Guideline 301D) where 2-10 mg/L is used. The possibility of toxic effects

may be evaluated by including a toxicity control in the ready biodegradability test or by comparing the test concentration with toxicity test data on micro-organisms, e.g. the respiration inhibition tests (OECD Test Guideline 209), the nitrification inhibition test (ISO 9509) or, if other microbial toxicity tests are not available, the bioluminescence inhibition test (ISO 11348). When conflicting results are found, this may becaused by toxicity of the test substance. If the substance is not inhibitory at environmentally realistic concentrations, the greatest degradation measured in screening tests may be used as a basis for classification. If simulation test data are available in such cases, consideration of these data may be especially important, because a low non inhibitory concentration of the substance may have been employed, thus giving a more reliable indication of the biodegradation half-life of the substance under environmentally realistic conditions.

A8.4.3.5.5 When the solubility of the test substance is lower than the concentrations employed in a test, this parameter may be the limiting factor for the actual degradation measured. In these cases, results from tests employing the lowest concentrations of test substance should prevail, i.e. often the Closed Bottle test (OECD Test Guideline 301D). In general, the DOC Die-Away test (OECD Test Guideline 301A) and the Modified OECD Screening test (OECD Test Guideline 301E) are not suitable for testing the biodegradability of poorly soluble substances (e.g. OECD Test Guideline 301).

A8.4.3.5.6 Volatile substances should only be tested in closed systems as the Closed Bottle test (OECD Test Guideline 301D), the MITI I test (OECD Test Guideline 301C) and the Manometric Respirometry test (OECD Test Guideline 301F). Results from other tests should be evaluated carefully and only considered if it can be demonstrated, e.g. by mass balance estimates, that the removal of the test substance is not a result of volatilisation.

A8.4.3.6 *Variation in simulation test data*

A number of simulation test data may be available for certain high priority chemicals. Often such data provide a range of half lives in environmental media such as soil, sediment and/or surface water. The observed differences in half-lives from simulation tests performed on the same substance may reflect differences in test conditions, all of which may be environmentally relevant. A suitable half life in the higher end of the observed range of half lives from such investigations should be selected for classification by employing a weight of evidence approach and taking the realism and relevance of the employed tests into account in relation to environmental conditions. In general, simulation test data of surface water are preferred relative to aquatic sediment or soil simulation test data in relation to the evaluation of rapid degradability in the aquatic environment.

A8.4.4 *Decision scheme*

The following decision scheme may be used as a general guidance to facilitate decisions in relation to rapid degradability in the aquatic environment and classification of chemicals hazardous to the aquatic environment.

A substance is considered to be not rapidly degradable unless at least one of the following is fulfilled:

(a) the substance is demonstrated to be readily biodegradable in a 28-day test for ready biodegradability. The pass level of the test (70% DOC removal or 60% theoretical oxygen demand) must be achieved within 10 days from the onset of biodegradation, if it is possible to evaluate this according to the available test data. If this is not possible, then the pass level should be evaluated within a 14 days time window if possible, or after the end of the test; or

(b) the substance is demonstrated to be ultimately degraded in a surface water simulation test* with a half-life of <16 days (corresponding to a degradation of >70% within 28 days); or

(c) the substance is demonstrated to be primarily degraded (biotically or abiotically) in the aquatic environment with a half-life <16 days (corresponding to a degradation of >70% within 28 days) and it can be demonstrated that the degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment.

When these data are not available rapid degradation may be demonstrated if either of the following criteria are justified:

(d) the substance is demonstrated to be ultimately degraded in an aquatic sediment or soil simulation test *with a half-life of < 16 days (corresponding to a degradation of > 70% within 28 days); or

(e) in those cases where only BOD_5 and COD data are available, the ratio of BOD_5/COD is greater than or equal to 0.5. The same criterion applies to ready biodegradability tests of a shorter duration than 28 days, if the half-life furthermore is < 7 days.

If none of the above types of data are available then the substance is considered as not rapidly degradable. This decision may be supported by fulfilment of at least one of the following criteria:

(i) the substance is not inherently degradable in an inherent biodegradability test; or

(ii) the substances is predicted to be slowly biodegradable by scientifically valid QSARs, e.g. for the Biodegradation Probability Program, the score for rapid degradation (linear or non-linear model) < 0.5; or

(iii) the substance is considered to be not rapidly degradable based on indirect evidence, as e.g. knowledge from structurally similar substances; or

(iv) no other data regarding degradability are available.

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* *Simulations tests should reflect realistic environmental conditions such as low concentration of the chemical, realistic temperature and employment of ambient microbial biomass not pre-exposed to the chemical.*

A8.5 Bioaccumulation

A.8.5.1 *Introduction*

A8.5.1.1 Bioaccumulation is one of the important intrinsic properties of chemical substances that determine the potential environmental hazard. Bioaccumulation of a substance into an organism is not a hazard in itself, but bioconcentration and bioaccumulation will result in a body burden, which may or may not lead to toxic effects. In the harmonised integrated hazard classification system for human health and environmental effects of chemical substances (OECD, 1998), the wording "potential for bioaccumulation" is given. A distinction should, however, be drawn between bioconcentration and bioaccumulation. Here bioconcentration is defined as the net result of uptake, transformation, and elimination of a substance in an organism due to waterborne exposure, whereas bioaccumulation includes all routes of exposure (i.e. via air, water, sediment/soil, and food). Finally, biomagnification is defined as accumulation and transfer of substances via the food chain, resulting in an increase of internal concentrations in organisms on higher levels of the trophic chain (European Commission, 1996). For most organic chemicals uptake from water (bioconcentration) is believed to be the predominant route of uptake. Only for very hydrophobic substances does uptake from food becomes important. Also, the harmonised classification criteria use the bioconcentration factor (or the octanol/water partition coefficient) as the measure of the potential for bioaccumulation. For these reasons, the present guidance document only considers bioconcentration and does not discuss uptake via food or other routes.

A8.5.1.2 Classification of a chemical substance is primarily based on its intrinsic properties. However, the degree of bioconcentration also depends on factors such as the degree of bioavailability, the physiology of test organism, maintenance of constant exposure concentration, exposure duration, metabolism inside the body of the target organism and excretion from the body. The interpretation of the bioconcentration potential in a chemical classification context therefore requires an evaluation of the intrinsic properties of the substance, as well as of the experimental conditions under which bioconcentration factor (BCF) has been determined. Based on the guide, a decision scheme for application of bioconcentration data or log K_{ow} data for classification purposes has been developed. The emphasis of the present chapter is organic substances and organo-metals. Bioaccumulation of metals is also discussed in Chapter A8.7.

A8.5.1.3 Data on bioconcentration properties of a substance may be available from standardised tests or may be estimated from the structure of the molecule. The interpretation of such bioconcentration data for classification purposes often requires detailed evaluation of test data. In order to facilitate this evaluation two additional appendixes are enclosed. These appendixes describe available methods (Appendix III of Annex 8) and factors influencing the bioconcentration potential (Appendix IV of Annex 8). Finally, a list of standardised experimental methods for determination of bioconcentration and K_{ow} are attached (Appendix V of Annex 8) together with a list of references (Appendix VI of Annex 8).

A8.5.2 *Interpretation of bioconcentration data*

A8.5.2.1 Environmental hazard classification of a chemical substance is normally based on existing data on its environmental properties. Test data will only seldom be produced with the main purpose of facilitating a classification. Often a diverse range of test data is available which does not necessarily match the classification criteria. Consequently, guidance is needed on interpretation of existing test data in the context of hazard classification.

A8.5.2.2 Bioconcentration of an organic substance can be experimentally determined in bioconcentration experiments, during which BCF is measured as the concentration in the organism relative to the concentration in water under steady-state conditions and/or estimated from the uptake rate constant (k_1) and the elimination rate constant (k_2) (OECD 305, 1996). In general, the potential of an organic substance to bioconcentrate is primarily related to the lipophilicity of the substance. A measure of lipophilicity is the n-octanol-water partition coefficient (K_{ow}) which, for lipophilic non-ionic organic substances, undergoing minimal metabolism or biotransformation within the organism, is correlated with the bioconcentration factor. Therefore, K_{ow} is often used for estimating the bioconcentration of organic substances, based on the empirical relationship between log BCF and log K_{ow}. For most organic substances, estimation methods are

available for calculating the K_{ow}. Data on the bioconcentration properties of a substance may thus be (i) experimentally determined, (ii) estimated from experimentally determined K_{ow}, or (iii) estimated from K_{ow} values derived by use of Quantitative Structure Activity Relationships (QSARs). Guidance for interpretation of such data is given below together with guidance on assessment of chemical classes, which need special attention.

A8.5.2.3 *Bioconcentration factor (BCF)*

A8.5.2.3.1 The bioconcentration factor is defined as the ratio on a weight basis between the concentration of the chemical in biota and the concentration in the surrounding medium, here water, at steady state. BCF can thus be experimentally derived under steady-state conditions, on the basis of measured concentrations. However, BCF can also be calculated as the ratio between the first-order uptake and elimination rate constants; a method which does not require equilibrium conditions.

A8.5.2.3.2 Different test guidelines for the experimental determination of bioconcentration in fish have been documented and adopted, the most generally applied being the OECD test guideline (OECD 305, 1996).

A8.5.2.3.3 Experimentally derived BCF values of high quality are ultimately preferred for classification purposes as such data override surrogate data, e.g. K_{ow}.

A8.5.2.3.4 High quality data are defined as data where the validity criteria for the test method applied are fulfilled and described, e.g. maintenance of constant exposure concentration; oxygen and temperature variations, and documentation that steady-state conditions have been reached, etc. The experiment will be regarded as a high-quality study, if a proper description is provided (e.g. by Good Laboratory Practice (GLP)) allowing verification that validity criteria are fulfilled. In addition, an appropriate analytical method must be used to quantify the chemical and its toxic metabolites in the water and fish tissue (see section 1, Appendix III for further details).

A8.5.2.3.5 BCF values of low or uncertain quality may give a false and too low BCF value; e.g. application of measured concentrations of the test substance in fish and water, but measured after a too short exposure period in which steady-state conditions have not been reached (cf. OECD 306, 1996, regarding estimation of time to equilibrium). Therefore, such data should be carefully evaluated before use and consideration should be given to using K_{ow} instead.

A8.5.2.3.6 If there is no BCF value for fish species, high-quality data on the BCF value for other species may be used (e.g. BCF determined on blue mussel, oyster, scallop (ASTM E 1022-94)). Reported BCFs for microalgae should be used with caution.

A8.5.2.3.7 For highly lipophilic substances, e.g. with log K_{ow} above 6, experimentally derived BCF values tend to decrease with increasing log K_{ow}. Conceptual explanations of this non-linearity mainly refer to either reduced membrane permeation kinetics or reduced biotic lipid solubility for large molecules. A low bioavailability and uptake of these substances in the organism will thus occur. Other factors comprise experimental artefacts, such as equilibrium not being reached, reduced bioavailability due to sorption to organic matter in the aqueous phase, and analytical errors. Special care should thus be taken when evaluating experimental data on BCF for highly lipophilic substances as these data will have a much higher level of uncertainty than BCF values determined for less lipophilic substances.

A8.5.2.3.8 BCF in different test species

A8.5.2.3.8.1 BCF values used for classification are based on whole body measurements. As stated previously, the optimal data for classification are BCF values derived using the OECD 305 test method or internationally equivalent methods, which uses small fish. Due to the higher gill surface to weight ratio for smaller organisms than larger organisms, steady-state conditions will be reached sooner in smaller organisms than in larger ones. The size of the organisms (fish) used in bioconcentration studies is thus of considerable importance in relation to the time used in the uptake phase, when the reported BCF value is based solely on

measured concentrations in fish and water at steady-state. Thus, if large fish, e.g. adult salmon, have been used in bioconcentration studies, it should be evaluated whether the uptake period was sufficiently long for steady state to be reached or to allow for a kinetic uptake rate constant to be determined precisely.

A8.5.2.3.8.2 Furthermore, when using existing data for classification, it is possible that the BCF values could be derived from several different fish or other aquatic species (e.g. clams) and for different organs in the fish. Thus, to compare these data to each other and to the criteria, some common basis or normalisation will be required. It has been noted that there is a close relationship between the lipid content of a fish or an aquatic organism and the observed BCF value. Therefore, when comparing BCF values across different fish species or when converting BCF values for specific organs to whole body BCFs, the common approach is to express the BCF values on a common lipid content. If e.g. whole body BCF values or BCF values for specific organs are found in the literature, the first step is to calculate the BCF on a % lipid basis using the relative content of fat in the fish (cf. literature/test guideline for typical fat content of the test species) or the organ. In the second step the BCF for the whole body for a typical aquatic organism (i.e. small fish) is calculated assuming a common default lipid content. A default value of 5% is most commonly used (Pedersen *et al.*, 1995) as this represents the average lipid content of the small fish used in OECD 305 (1996).

A8.5.2.3.8.3 Generally, the highest valid BCF value expressed on this common lipid basis is used to determine the wet weight based BCF-value in relation to the cut off value for BCF of 500 of the harmonised classification criteria (see Chapter 3.10, Figure 3.10.1).

A8.5.2.3.9 Use of radiolabelled substances

A8.5.2.3.9.1 The use of radiolabelled test substances can facilitate the analysis of water and fish samples. However, unless combined with a specific analytical method, the total radioactivity measurements potentially reflect the presence of the parent substance as well as possible metabolite(s) and possible metabolised carbon, which have been incorporated in the fish tissue in organic molecules. BCF values determined by use of radiolabelled test substances are therefore normally overestimated.

A8.5.2.3.9.2 When using radiolabelled substances, the labelling is most often placed in the stable part of the molecule, for which reason the measured BCF value includes the BCF of the metabolites. For some substances it is the metabolite which is the most toxic and which has the highest bioconcentration potential. Measurements of the parent substance as well as the metabolites may thus be important for the interpretation of the aquatic hazard (including the bioconcentration potential) of such substances.

A8.5.2.3.9.3 In experiments where radiolabelled substances have been used, high radiolabel concentrations are often found in the gall bladder of fish. This is interpreted to be caused by biotransformation in the liver and subsequently by excretion of metabolites in the gall bladder (Comotto *et al.*, 1979; Wakabayashi *et al.*, 1987; Goodrich *et al.*, 1991; Toshima *et al.*, 1992). When fish do not eat, the content of the gall bladder is not emptied into the gut, and high concentrations of metabolites may build up in the gall bladder. The feeding regime may thus have a pronounced effect on the measured BCF. In the literature many studies are found where radiolabelled compounds are used, and where the fish are not fed. As a result high concentrations of radioactive material are found in the gall bladder. In these studies the bioconcentration may in most cases have been overestimated. Thus when evaluating experiments, in which radiolabelled compounds are used, it is essential to evaluate the feeding regime as well.

A8.5.2.3.9.4 If the BCF in terms of radiolabelled residues is documented to be $\geq$ 1000, identification and quantification of degradation products, representing $\geq$ 10% of total residues in fish tissues at steady-state, are for e.g. pesticides strongly recommended in the OECD guideline No. 305 (1996). If no identification and quantification of metabolites are available, the assessment of bioconcentration should be based on the measured radiolabelled BCF value. If, for highly bioaccumulative substances (BCF $\geq$ 500), only BCFs based on the parent compound and on radiolabelled measurements are available, the latter should thus be used in relation to classification.

A8.5.2.4 *Octanol-water-partitioning coefficient (K_{ow})*

A8.5.2.4.1 For organic substances experimentally derived high-quality K_{ow} values, or values which are evaluated in reviews and assigned as the "recommended values", are preferred over other determinations of Kow. When no experimental data of high quality are available, validated Quantitative Structure Activity Relationships (QSARs) for log K_{ow} may be used in the classification process. Such validated QSARs may be used without modification to the agreed criteria if they are restricted to chemicals for which their applicability is well characterised. For substances like strong acids and bases, substances which react with the eluent, or surface-active substances, a QSAR estimated value of K_{ow} or an estimate based on individual *n*-octanol and water solubilities should be provided instead of an analytical determination of K_{ow} (EEC A.8., 1992; OECD 117, 1989). Measurements should be taken on ionizable substances in their non-ionised form (free acid or free base) only by using an appropriate buffer with pH below pK for free acid or above the pK for free base.

A8.5.2.4.2 Experimental determination of K_{ow}

For experimental determination of K_{ow} values, several different methods, Shake-flask, and HPLC, are described in standard guidelines, e.g. OECD Test Guideline 107 (1995); OECD Test Guideline 117 (1989); EEC A.8. (1992); EPA-OTS (1982); EPA-FIFRA (1982); ASTM (1993); the pH-metric method (OECD Test Guideline in preparation). The shake-flask method is recommended when the log K_{ow} value falls within the range from –2 to 4. The shake-flask method applies only to essential pure substances soluble in water and *n*-octanol. For highly lipophilic substances, which slowly dissolve in water, data obtained by employing a slow-stirring method are generally more reliable. Furthermore, the experimental difficulties, associated with the formation of microdroplets during the shake-flask experiment, can to some degree be overcome by a slow-stirring method where water, octanol, and test compound are equilibrated in a gently stirred reactor. With the slow-stirring method (OECD Test Guideline in preparation) a precise and accurate determination of K_{ow} of compounds with log K_{ow} of up to 8.2 is allowed (OECD draft Guideline, 1998). As for the shake-flask method, the slow-stirring method applies only to essentially pure substances soluble in water and *n*-octanol. The HPLC method, which is performed on analytical columns, is recommended when the log K_{ow} value falls within the range 0 to 6. The HPLC method is less sensitive to the presence of impurities in the test compound compared to the shake-flask method. Another technique for measuring log K_{ow} is the generator column method (USEPA 1985).

As an experimental determination of the K_{ow} is not always possible, e.g. for very water-soluble substances, very lipophilic substances, and surfactants, a QSAR-derived K_{ow} may be used.

A8.5.2.4.3 Use of QSARs for determination of log K_{ow}

When an estimated K_{ow} value is found, the estimation method has to be taken into account. Numerous QSARs have been and continue to be developed for the estimation of K_{ow}. Four commercially available PC programmes (CLOGP, LOGKOW (KOWWIN), AUTOLOGP, SPARC) are frequently used for risk assessment if no experimentally derived data are available. CLOGP, LOGKOW and AUTOLOGP are based upon the addition of group contributions, while SPARC is based upon a more fundamental chemical structure algorithm. Only SPARC can be employed in a general way for inorganic or organometallic compounds. Special methods are needed for estimating log K_{ow} for surface-active compounds, chelating compounds and mixtures. CLOGP is recommended in the US EPA/EC joint project on validation of QSAR estimation methods (US EPA/EC 1993). Pedersen *et al.* (1995) recommended the CLOGP and the LOGKOW programmes for classification purposes because of their reliability, commercial availability, and convenience of use. The following estimation methods are recommended for classification purposes (Table A8.5.1).

Table A8.5.1 Recommended QSARs for estimation of K_{ow}

Model	log K_{ow} range	Substance utility
CLOGP	from log K_{ow} <0 – tolog K_{ow} > 9 [1]	The program calculates log K_{ow} for organic compounds containing C, H, N, O, Hal, P, and/or S.
LOGKOW (KOWWIN)	-4 < log K_{ow} < 8 [2]	The program calculates log K_{ow} for organic compounds containing C, H, N, O, Hal, Si, P, Se, Li, Na, K, and/or Hg. Some surfactants (e.g. alcohol ethoxylates, dyestuffs, and dissociated substances may be predicted by the program as well.
AUTOLOGP	log K_{ow} > 5	The programme calculates log K_{ow} for organic compounds containing C, H, N, O, Hal, P and S. Improvements are in progress in order to extend the applicability of AUTOLOGP.
SPARC	Provides improved results over KOWWIN and CLOGP for compounds with log K_{ow} > 5	SPARC is a mechanistic model based on chemical thermodynamic principles rather than a deterministic model rooted in knowledge obtained from observational data. Therefore, SPARC differs from models that use QSARs (i.e. KOWWIN, CLOGP, AUTOLOGP) in that no measured log K_{ow} data are needed for a training set of chemicals. Only SPARC can be employed in a general way for inorganic or organometallic compounds.

1 *A validation study performed by Niemelä, who compared experimental determined log K_{ow} values with estimated values, showed that the program precisely predicts the log K_{ow} for a great number of organic chemicals in the log K_{ow} range from below 0 to above 9 (n = 501, r^2 = 0.967) (TemaNord 1995: 581).*

2 *Based on a scatter plot of estimated vs. experimental log K_{ow} (Syracuse Research Corporation, 1999), where 13058 compound have been tested, the LOGKOW is evaluated being valid for compounds with a log K_{ow} in the interval -4 - 8.*

A8.5.3 *Chemical classes that need special attention with respect to BCF and K_{ow} values*

A8.5.3.1 There are certain physico-chemical properties, which can make the determination of BCF or its measurement difficult. These may be substances, which do not bioconcentrate in a manner consistent with their other physico-chemical properties, e.g. steric hindrance or substances which make the use of descriptors inappropriate, e.g. surface activity, which makes both the measurement and use of log K_{ow} inappropriate.

A8.5.3.2 *Difficult substances*

A8.5.3.2.1 Some chemical substances are difficult to test in aquatic systems and guidance has been developed to assist in testing these materials (DoE, 1996; ECETOC 1996; and US EPA 1996). OECD is in the process of finalising a guidance document for the aquatic testing of difficult substances (OECD, 2000). This latter document is a good source of information, also for bioconcentration studies, on the types of substances that are difficult to test and the steps needed to ensure valid conclusions from tests with these substances. Difficult to test substances may be poorly soluble, volatile, or subject to rapid degradation due to such processes as phototransformation, hydrolysis, oxidation, or biotic degradation.

A8.5.3.2.2 To bioconcentrate organic compounds, a substance needs to be soluble in lipids, present in the water, and available for transfer across the fish gills. Properties which alter this availability will thus change the actual bioconcentration of a substance, when compared with the prediction. For example, readily biodegradable substances may only be present in the aquatic compartment for short periods of time. Similarly, volatility, and hydrolysis will reduce the concentration and the time during which a substance is available for bioconcentration. A further important parameter, which may reduce the actual exposure concentration of a substance, is adsorption, either to particulate matter or to surfaces in general. There are a number of substances, which have shown to be rapidly transformed in the organism, thus leading to a lower BCF value than expected. Substances that form micelles or aggregates may bioconcentrate to a lower extent

than would be predicted from simple physico-chemical properties. This is also the case for hydrophobic substances that are contained in micelles formed as a consequence of the use of dispersants. Therefore, the use of dispersants in bioaccumulation tests is discouraged.

A8.5.3.2.3 In general, for difficult to test substances, measured BCF and K_{ow} values – based on the parent substance – are a prerequisite for the determination of the bioconcentration potential. Furthermore, proper documentation of the test concentration is a prerequisite for the validation of the given BCF value.

A8.5.3.3 *Poorly soluble and complex substances*

Special attention should be paid to poorly soluble substances. Frequently the solubility of these substances is recorded as less than the detection limit, which creates problems in interpreting the bioconcentration potential. For such substances the bioconcentration potential should be based on experimental determination of log K_{ow} or QSAR estimations of log K_{ow}.

When a multi-component substance is not fully soluble in water, it is important to attempt to identify the components of the mixture as far as practically possible and to examine the possibility of determining its bioaccumulation potential using available information on its components. When bioaccumulating components constitute a significant part of the complex substance (e.g. more than 20% or for hazardous components an even lower content), the complex substance should be regarded as being bioaccumulating.

A8.5.3.4 *High molecular weight substances*

Above certain molecular dimensions, the potential of a substance to bioconcentrate decreases.. This is possibly due to steric hindrance of the passage of the substance through gill membranes. It has been proposed that a cut-off limit of 700 for the molecular weight could be applied (e.g. European Commission, 1996). However, this cut-off has been subject to criticism and an alternative cut-off of 1000 has been proposed in relation to exclusion of consideration of substances with possible indirect aquatic effects (CSTEE, 1999). In general, bioconcentration of possible metabolites or environmental degradation products of large molecules should be considered. Data on bioconcentration of molecules with a high molecular weight should therefore be carefully evaluated and only be used if such data are considered to be fully valid in respect to both the parent compound and its possible metabolites and environmental degradation products.

A8.5.3.5 *Surface-active agents*

A8.5.3.5.1 Surfactants consist of a lipophilic (most often an alkyl chain) and a hydrophilic part (the polar headgroup). According to the charge of the headgroup, surfactants are subdivided into classes of anionic, cationic, non-ionic, or amphoteric surfactants. Due to the variety of different headgroups, surfactants are a structurally diverse class of compounds, which is defined by surface activity rather than by chemical structure. The bioaccumulation potential of surfactants should thus be considered in relation to the different subclasses (anionic, cationic, non-ionic, or amphoteric) instead of to the group as a whole. Surface-active substances may form emulsions, in which the bioavailability is difficult to ascertain. Micelle formation can result in a change of the bioavailable fraction even when the solutions are apparently formed, thus giving problems in interpretation of the bioaccumulation potential.

A8.5.3.5.2 Experimentally derived bioconcentration factors

Measured BCF values on surfactants show that BCF may increase with increasing alkyl chain length and be dependant of the site of attachment of the head group, and other structural features.

A8.5.3.5.3 Octanol-water-partition coefficient (K_{ow})

The octanol-water partition coefficient for surfactants can not be determined using the shake-flask or slow stirring method because of the formation of emulsions. In addition, the surfactant molecules will exist in the water phase almost exclusively as ions, whereas they will have to pair with a counter-ion in

order to be dissolved in octanol. Therefore, experimental determination of K_{ow} does not characterise the partition of ionic surfactants (Tolls, 1998). On the other hand, it has been shown that the bioconcentration of anionic and non-ionic surfactants increases with increasing lipophilicity (Tolls, 1998). Tolls (1998) showed that for some surfactants, an estimated log K_{ow} value using LOGKOW could represent the bioaccumulation potential; however, for other surfactants some 'correction' to the estimated log K_{ow} value using the method of Roberts (1989) was required. These results illustrate that the quality of the relationship between log K_{ow} estimates and bioconcentration depends on the class and specific type of surfactants involved. Therefore, the classification of the bioconcentration potential based on log K_{ow} values should be used with caution.

A8.5.4 *Conflicting data and lack of data*

A8.5.4.1 *Conflicting BCF data*

In situations where multiple BCF data are available for the same substance, the possibility of conflicting results might arise. In general, conflicting results for a substance, which has been tested several times with an appropriate bioconcentration test, should be interpreted by a "weight of evidence approach". This implies that if experimental determined BCF data, both ≥ and < 500, have been obtained for a substance the data of the highest quality and with the best documentation should be used for determining the bioconcentration potential of the substance. If differences still remain, if e.g. high-quality BCF values for different fish species are available, generally the highest valid value should be used as the basis for classification.

When larger data sets (4 or more values) are available for the same species and life stage, the geometric mean of the BCF values may be used as the representative BCF value for that species.

A8.5.4.2 *Conflicting log K_{ow} data*

The situations, where multiple log K_{ow} data are available for the same substance, the possibility of conflicting results might arise. If log K_{ow} data both ≥ and < 4 have been obtained for a substance, then the data of the highest quality and the best documentation should be used for determining the bioconcentration potential of the substance. If differences still exist, generally the highest valid value should take precedence. In such situation, QSAR estimated log K_{ow} could be used as a guidance.

A8.5.4.3 *Expert judgement*

If no experimental BCF or log K_{ow} data or no predicted log K_{ow} data are available, the potential for bioconcentration in the aquatic environment may be assessed by expert judgement. This may be based on a comparison of the structure of the molecule with the structure of other substances for which experimental bioconcentration or log K_{ow} data or predicted K_{ow} are available.

A8.5.5 *Decision scheme*

A8.5.5.1 Based on the above discussions and conclusions, a decision scheme has been elaborated which may facilitate decisions as to whether or not a substance has the potential for bioconcentration in aquatic species.

A8.5.5.2 Experimentally derived BCF values of high quality are ultimately preferred for classification purposes. BCF values of low or uncertain quality should not be used for classification purposes if data on log K_{ow} are available because they may give a false and too low BCF value, e.g. due to a too short exposure period in which steady-state conditions have not been reached. If no BCF is available for fish species, high quality data on the BCF for other species (e.g. mussels) may be used.

A8.5.5.3 For organic substances, experimentally derived high quality K_{ow} values, or values which are evaluated in reviews and assigned as the "recommended values", are preferred. If no experimentally data of high quality are available validated Quantitative Structure Activity Relationships (QSARs) for log K_{ow} may be used in the classification process. Such validated QSARs may be used without modification in relation to

the classification criteria, if restricted to chemicals for which their applicability is well characterised. For substances like strong acids and bases, metal complexes, and surface-active substances a QSAR estimated value of K_{ow} or an estimate based on individual *n*-octanol and water solubilities should be provided instead of an analytical determination of K_{ow}.

A8.5.5.4 If data are available but not validated, expert judgement should be used.

A8.5.5.5 Whether or not a substance has a potential for bioconcentration in aquatic organisms could thus be decided in accordance with the following scheme:

Valid/high quality experimentally determined BCF value → YES:
→BCF ≥ 500: *The substance has a potential for bioconcentration*
→BCF < 500: *The substance does not have a potential for bioconcentration.*

Valid/high quality experimentally determined BCF value → NO:
→ Valid/high quality experimentally determined log K_{ow} value → YES:
→ log K_{ow} ≥ 4: *The substance has a potential for bioconcentration*
→ log K_{ow} < 4: *The substance does not have a potential for bioconcentration.*

Valid/high quality experimentally determined BCF value → NO:
→ Valid/high quality experimentally determined log K_{ow} value → NO:
→ Use of validated QSAR for estimating a log K_{ow} value → YES:
→ log K_{ow} ≥ 4: *The substance has a potential for bioconcentration*
→ log K_{ow} < 4: *The substance does not have a potential for bioconcentration.*

A8.6 Use of QSAR

A8.6.1 *History*

A8.6.1.1 Quantitative Structure-Activity Relationships (QSAR) in aquatic toxicology can be traced to the work of Overton in Zürich (Lipnick, 1986) and Meyer in Marburg (Lipnick, 1989a). They demonstrated that the potency of substances producing narcosis in tadpoles and small fish is in direct proportion to their partition coefficients measured between olive oil and water. Overton postulated in his 1901 monograph "Studien über die Narkose," that this correlation reflects toxicity taking place at a standard molar concentration or molar volume within some molecular site within the organism (Lipnick, 1991a). In addition, he concluded that this corresponds to the same concentration or volume for a various organisms, regardless of whether uptake is from water or via gaseous inhalation. This correlation became known in anaesthesia as the Meyer-Overton theory.

A8.6.1.2 Corwin Hansch and co-workers at Pomona College proposed the use of n-octanol/water as a standard partitioning system, and found that these partition coefficients were an additive, constitutive property that can be directly estimated from chemical structure. In addition, they found that regression analysis could be used to derive QSAR models, providing a statistical analysis of the findings. Using this approach, in 1972 these workers reported 137 QSAR models in the form log (1/C) = A log K_{ow} + B, where K_{ow} is the n-octanol/water partition coefficient, and C is the molar concentration of a chemical yielding a standard biological response for the effect of simple non-electrolyte non-reactive organic compounds on whole animals, organs, cells, or even pure enzymes. Five of these equations, which relate to the toxicity of five simple monohydric alcohols to five species of fish, have almost identical slopes and intercepts that are in fact virtually the same as those found by Könemann in 1981, who appears to have been unaware of Hansch's earlier work. Könemann and others have demonstrated that such simple non-reactive non-electrolytes all act by a narcosis mechanism in an acute fish toxicity test, giving rise to minimum or baseline toxicity (Lipnick, 1989b).

A8.6.2 *Experimental artifacts causing underestimation of hazard*

A8.6.2.1 Other non-electrolytes can be more toxic than predicted by such a QSAR, but not less toxic, except as a result of a testing artefact. Such testing artefacts include data obtained for compounds such as hydrocarbons which tend to volatilise during the experiment, as well as very hydrophobic compounds for which the acute testing duration may be inadequate to achieve steady state equilibrium partitioning between the concentration in the aquatic phase (aquarium test solution), and the internal hydrophobic site of narcosis action. A QSAR plot of log K_{ow} vs log C for such simple non-reactive non-electrolytes exhibits a linear relationship so long as such equilibrium is established within the test duration. Beyond this point, a bilinear relationship is observed, with the most toxic chemical being the one with the highest log K_{ow} value for which such equilibrium is established (Lipnick, 1995).

A8.6.2.2 Another testing problem is posed by water solubility cut-off. If the toxic concentration required to produce the effect is above the compound's water solubility, no effect will be observed even at water saturation. Compounds for which the predicted toxic concentration is close to water solubility will also show no effect if the test duration is insufficient to achieve equilibrium partitioning. A similar cut-off is observed for surfactants if toxicity is predicted at a concentration beyond the critical micelle concentration. Although such compounds may show no toxicity under these conditions when tested alone, their toxic contributions to mixtures are still present. For compounds with the same log K_{ow} value, differences in water solubility reflect differences in enthalpy of fusion related to melting point. Melting point is a reflection of the degree of stability of the crystal lattice and is controlled by intermolecular hydrogen bonding, lack of conformational flexibility, and symmetry. The more highly symmetric a compound, the higher the melting point (Lipnick, 1990).

A8.6.3 *QSAR modelling issues*

A8.6.3.1 Choosing an appropriate QSAR implies that the model will yield a reliable prediction for the toxicity or biological activity of an untested chemical. Generally speaking, reliability decreases with increasing complexity of chemical structure, unless a QSAR has been derived for a narrowly defined set of chemicals similar in structure to the candidate substance. QSAR models derived from narrowly defined classes of chemicals are commonly employed in the development of pharmaceuticals once a new lead compound is identified and there is a need to make minor structural modifications to optimise activity (and decrease toxicity). Overall, the objective is make estimates by interpolation rather than extrapolation.

A8.6.3.2 For example, if 96-h LC50 test data for fathead minnow are available for ethanol, n-butanol, n-hexanol, and n-nonanol, there is some confidence in making a prediction for this endpoint for n-propanol and n-pentanol. In contrast, there is would have less confidence in making such a prediction for methanol, which is an extrapolation, with fewer carbon atoms than any of the tested chemicals. In fact, the behaviour of the first member of such a homologous is typically the most anomalous, and should not be predicted using data from remaining members of the series. Even the toxicity of branched chain alcohols may be an unreasonable extrapolation, depending upon the endpoint in question. Such extrapolation becomes more unreliable to the extent that toxicity is related to production of metabolites for a particular endpoint, as opposed to the properties of the parent compound. Also, if toxicity is mediated by a specific receptor binding mechanism, dramatic effects may be observed with small changes in chemical structure.

A8.6.3.3 What ultimately governs the validity of such predictions is the degree to which the compounds used to derive the QSAR for a specific biological endpoint, are acting by a common molecular mechanism. In many and perhaps most cases, a QSAR does not represent such a mechanistic model, but merely a correlative one. A truly valid mechanistic model must be derived from a series of chemicals all acting by a common molecular mechanism, and fit to an equation using one or more parameters that relate directly to one or more steps of the mechanism in question. Such parameters or properties are more generally known as molecular descriptors. It is also important to keep in mind that many such molecular descriptors in common use may not have a direct physical interpretation. For a correlative model, the statistical fit of the data are likely to be poorer than a mechanistic one given these limitations. Mechanisms are not necessarily completely understood, but enough information may be known to provide confidence in this approach. For correlative models, the predictive reliability increases with the narrowness with which each is defined, e.g. categories of electrophiles, such as acrylates, in which the degree of reactivity may be similar and toxicity can be estimated for a "new" chemical using a model based solely on the log K_{ow} parameter.

A8.6.3.4 As an example, primary and secondary alcohols containing a double or triple bond that is conjugated with the hydroxyl function (i.e. allylic or propargylic) are more toxic than would be predicted for a QSAR for the corresponding saturated compounds. This behaviour has been ascribed to a proelectrophile mechanism involving metabolic activation by the ubiquitous enzyme alcohol dehydrogenase to the corresponding α,β-unsaturated aldehydes and ketones which can act as electrophiles via a Michael-type acceptor mechanism (Veith *et al.*, 1989). In the presence of an alcohol dehydrogenase inhibitor, these compounds behave like other alcohols and do not show excess toxicity, consistent with the mechanistic hypothesis.

A8.6.3.5 The situation quickly becomes more complex once one goes beyond such a homologous series of compounds. Consider, for example, simple benzene derivatives. A series of chlorobenzenes may be viewed as similar to a homologous series. Not much difference is likely in the toxicities of the three isomeric dichlorobenzenes, so that a QSAR for chlorobenzenes based upon test data for one of these isomers is likely to be adequate. What about the substitution of other functional groups on benzene ring? Unlike an aliphatic alcohol, addition of a hydroxyl functionality to a benzene ring produces a phenol which is no longer neutral, but an ionizable acidic compound, due to the resonance stabilisation of the resulting negative charge. For this reason, phenol does not act as a true narcotic agent. With the addition of electron withdrawing substituents to phenol (e.g. chlorine atoms), there is a shift to these compounds acting as uncouplers of oxidative phosphorylation (e.g. the herbicide dinoseb). Substitution of an aldehyde group leads to increased toxicity via an electrophile mechanism for such compounds react with amino groups, such as the lysine ε-amino group to produce a Schiff Base adduct. Similarly, a benzylic chloride acts as an electrophile

to form covalent abducts with sulfhydryl groups. In tackling a prediction for an untested compound, the chemical reactivity of these and many other functional groups and their interaction with one another should be carefully studied, and attempts made to document these from the chemical literature (Lipnick, 1991b).

A8.6.3.6 Given these limitations in using QSARs for making predictions, it is best employed as a means of establishing testing priorities, rather than as a means of substituting for testing, unless some mechanistic information is available on the untested compound itself. In fact, the inability to make a prediction along with known environmental release and exposure may in itself be adequate to trigger testing or the development of a new QSAR for a class of chemicals for which such decisions are needed. A QSAR model can be derived by statistical analysis, e.g. regression analysis, from such a data set. The most commonly employed molecular descriptor, log K_{ow}, may be tried as a first attempt.

A8.6.3.7 By contrast, derivation of a mechanism based QSAR model requires an understanding or working hypothesis of molecular mechanism and what parameter or parameters would appropriately model these actions. It is important to keep in mind that this is different from a hypothesis regarding mode of action, which relates to biological/physiological response, but not molecular mechanism.

A8.6.4 *Use of QSARs in aquatic classification*

A8.6.4.1 The following inherent properties of substances are relevant for classification purposes concerning the aquatic environment:

- partition coefficient n-octanol-water log K_{ow};
- bioconcentration factor BCF;
- degradability - abiotic and biodegradation;
- acute aquatic toxicity for fish, daphnia and algae;
- prolonged toxicity for fish and daphnia.

A8.6.4.2 Test data always take precedence over QSAR predications, providing the test data are valid, with QSARs used for filling data gaps for purposes of classification. Since the available QSARs are of varying reliability and application range, different restrictions apply for the prediction of each of these endpoints. Nevertheless, if a tested compound belongs to a chemical class or structure type (see above) for which there is some confidence in the predictive utility of the QSAR model, it is worthwhile to compare this prediction with the experimental data, as it is not unusual to use this approach to detect some of the experimental artefacts (volatilisation, insufficient test duration to achieve equilibrium, and water solubility cut-off) in the measured data, which would mostly result in classifying substances as lower than actual toxicity.

A8.6.4.3 When two or more QSARs are applicable or appear to be applicable, it is useful to compare the predictions of these various models in the same way that predicted data should be compared with measured (as discussed above). If there is no discrepancy between these models, the result provides encouragement of the validity of the predictions. Of course, it may also mean that the models were all developed using data on similar compounds and statistical methods. On the other hand, if the predictions are quite different, this result needs to be examined further. There is always the possibility that none of the models used provides a valid prediction. As a first step, the structures and properties of the chemicals used to derive each of the predictive models should be examined to determine if any models are based upon chemicals similar in both of these respects to the one for which a prediction is needed. If one data set contains such an appropriate analogue used to derive the model, the measured value in the database for that compound vs model prediction should be tested. If the results fit well with the overall model, it is likely the most reliable one to use. Likewise, if none of the models contain test data for such an analogue, testing of the chemical in question is recommended.

A8.6.4.4 The U.S. EPA has recently posted a draft document on its website "Development of Chemical Categories in the HPV Challenge Program," that proposes the use of chemical categories to "... voluntarily compile a Screening Information Data Set (SIDS) on all chemicals on the US HPV list ... [to provide] basic screening data needed for an initial assessment of the physicochemical properties, environmental fate, and

human and environmental effects of chemicals" (US EPA, 1999). This list consists of "...about 2,800 HPV chemicals which were reported for the Toxic Substances Control Act's 1990 Inventory Update Rule (IUR)".

A8.6.4.5 One approach being proposed "...where this is scientifically justifiable ... is to consider closely related chemicals as a group, or category, rather than test them as individual chemicals. In the category approach, not every chemical needs to be tested for every SIDS endpoint". Such limited testing could be justified providing that the "...final data set must allow one to assess the untested endpoints, ideally by *interpolation* [emphasis added here] between and among the category members." The process for defining such categories and in the development of such data are described in the proposal.

A8.6.4.6 A second potentially less data intensive approach being considered (US EPA, 2000a) is "... applying SAR principles to a single chemical that is closely related to one or more better characterised chemicals ("analogs")." A third approach proposed consists of using "... a combination of the analogue and category approaches ... [for] individual chemicals ... [similar to that] used in ECOSAR (US EPA, 2000b), a SAR-based computer program that generates ecotoxicity values. ". The document also details the history of the use of SARs within the U.S. EPA new chemicals program, and how to go about collecting and analysing data for the sake of such SAR approaches.

A8.6.4.7 The Nordic Council of Ministers issued a report (Pederson *et al.*, 1995) entitled "Environmental Hazard Classification," that includes information on data collection and interpretation, as well as a section (5.2.8) entitled "QSAR estimates of water solubility and acute aquatic toxicity". This section also discusses the estimation of physicochemical properties, including log K_{ow}. For the sake of classification purposes, estimation methods are recommended for prediction of "minimum acute aquatic toxicity," for "...neutral, organic, non-reactive and non-ionizable compounds such as alcohols, ketones, ethers, alkyl, and aryl halides, and can also be used for aromatic hydrocarbons, halogenated aromatic and aliphatic hydrocarbons as well as sulphides and disulphides," as cited in an earlier OECD Guidance Document (OECD, 1995). The Nordic document also includes diskettes for a computerised application of some of these methods.

A8.6.4.8 The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) has published a report entitled "QSARs in the Assessment of the Environmental Fate and Effects of Chemicals," which describes the use of QSARs to "...check the validity of data or to fill data gaps for priority setting, risk assessment and classification" (ECETOC, 1998). QSARs are described for predicting environmental fate and aquatic toxicity. The report notes that "a consistent dataset for [an endpoint] covered ... for a well defined scope of chemical structures ("domain") [is needed] ... from which a training set is developed. The document also discusses the advantage of mechanism based models, the use of statistical analysis in the development of QSARs, and how to assess "outliers".

A8.6.4.9 *Octanol-water-partition coefficient (K_{ow})*

A8.6.4.9.1 Computerised methods such as CLOGP (US EPA, 1999), LOGKOW (US EPA, 2000a) and SPARC (US EPA, 2000b) are available to calculate log K_{ow} directly from chemical structure. CLOGP and LOGKOW are based upon the addition of group contributions, while SPARC is based upon a more fundamental chemical structure algorithm. Caution should be used in using calculated values for compounds that can undergo hydrolysis in water or some other reaction, since these transformations need to be considered in the interpretation of aquatic toxicity test data for such reactive chemicals. Only SPARC can be employed in a general way for inorganic or organometallic compounds. Special methods are needed in making estimates of log K_{ow} or aquatic toxicity for surface-active compounds, chelating compounds, and mixtures.

A8.6.4.9.2 Values of log K_{ow} can be calculated for pentachlorophenol and similar compounds, both for the ionised and unionised (neutral) forms. These values can potentially be calculated for certain reactive molecules (e.g. benzotrichloride), but the reactivity and subsequent hydrolysis also need to be considered. Also, for such ionizable phenols, pKa is a second parameter. Specific models can be used to calculate log K_{ow} values for organometallic compounds, but they need to be applied with caution since some of these compounds really exist in the form of ion pairs in water.

A8.6.4.9.3 For compounds of extremely high lipophilicity, measurements up to about 6 to 6.5 can be made by shake flask, and can be extended up to about log K_{ow} of 8 using the slow stirring approach (Bruijn *et al.*, 1989). Calculations are considered useful even in extrapolating beyond what can be measured by either of these methods. Of course, it should be kept in mind that if the QSAR models for toxicity, etc. are based on chemicals with lower log K_{ow} values, the prediction itself will also be an extrapolation; in fact, it is known that in the case of bioconcentration, the relationship with log K_{ow} becomes non-linear at higher values. For compounds with low log K_{ow} values, the group contribution can also be applied, but this is not very useful for hazard purposes since for such substances, particularly with negative log K_{ow} values, little if any partitioning can take place into lipophilic sites and as Overton reported, these substances produce toxicity through osmotic effects (Lipnick, 1986).

A8.6.4.10 *Bioconcentration factor BCF*

A8.6.4.10.1 If experimentally determined BCF values are available, these values should be used for classification. Bioconcentration measurements must be performed using pure samples at test concentrations within water solubility, and for an adequate test duration to achieve steady state equilibrium between the aqueous concentration and that in the fish tissue. Moreover, with bioconcentration tests of extended duration, the correlation with log K_{ow} levels off and ultimately decreases. Under environmental conditions, bioconcentration of highly lipophilic chemicals takes place by a combination of uptake from food and water, with the switch to food taking place at log $K_{ow} \approx 6$. Otherwise log K_{ow} values can be used with a QSAR model as a predictor of the bioaccumulation potential of organic compounds. Deviations from these QSARs tend to reflect differences in the extent to which the chemicals undergo metabolism in the fish. Thus, some chemicals, such as phthalate, can bioconcentrate significantly less than predicted for this reason. Also, caution should be applied in comparing predicted BCF values with those using radiolabeled compounds, where the tissue concentration thus detected may represent a mix of parent compound and metabolites or even covalently bound parent or metabolite.

A8.6.4.10.2 Experimental log K_{ow} values are to be used preferentially. However, older shake flask values above 5.5 are not reliable and in many cases it is better to use some average of calculated values or to have these remeasured using the slow stirring method (Bruijn *et al.*, 1989). If there is reasonable doubt about the accuracy of the measured data, calculated log K_{ow} values shall be used.

A8.6.4.11 *Degradability - abiotic and biodegradation*

QSARs for abiotic degradation in water phases are narrowly defined linear free energy relationships (LFERs) for specific classes of chemicals and mechanisms. For example, such LFERs are available for hydrolysis of benzylic chlorides with various substituents on the aromatic ring. Such narrowly defined LFER models tend to be very reliable if the needed parameters are available for the Substituent(s) in question. Photo degradation, i.e. reaction with UV produced reactive species, may be extrapolated from estimates for the air compartment. While these abiotic processes do not usually result in complete degradation of organic compounds, they are frequently significant starting points, and may be rate limiting. QSARs for calculating biodegradability are either compound specific (OECD, 1995) or group contribution models like the BIODEG program (Hansch and Leo, 1995; Meylan and Howard 1995; Hilal *et al.*, 1994; Howard *et al.*, 1992; Boethling *et al.*, 1994; Howard and Meylan 1992; Loonen *et al.*, 1999). While validated compound class specific models are very limited in their application range, the application range of group contribution models is potentially much broader, but limited to compounds containing the model substructures. Validation studies have suggested that the biodegradability predictions by currently available group contribution models may be used for prediction of "not ready biodegradability" (Pedersen *et al.*, 1995; Langenberg *et al.*, 1996; USEPA, 1993) – and thus in relation to aquatic hazard classification "not rapid degradability."

A8.6.4.12 *Acute aquatic toxicity for fish, daphnia and algae*

The acute aquatic toxicity of non-reactive, non-electrolyte organic chemicals (baseline toxicity) can be predicted from their log K_{ow} value with a quite high level of confidence, provided the presence of electrophile, proelectrophile, or special mechanism functional groups (see above) were not detected.

Problems remain for such specific toxicants, for which the appropriate QSAR has to be selected in a prospective manner. Since straightforward criteria for the identification of the relevant modes of action are still lacking, empirical expert judgement needs to be applied for selecting a suitable model. Thus, if an inappropriate QSAR is employed, the predictions may be in error by several orders of magnitude, and in the case of baseline toxicity, will be predicted less toxic, rather than more.

A8.6.4.13 *Prolonged toxicity for fish and Daphnia*

Calculated values for chronic toxicity to fish and Daphnia should not be used to overrule classification based on experimental acute toxicity data. Only a few validated models are available for calculating prolonged toxicity for fish and Daphnia. These models are based solely on log K_{ow} correlations and are limited in their application to non-reactive, non-electrolyte organic compounds, and are not suitable for chemicals with specific modes of action under prolonged exposure conditions. The reliable estimation of chronic toxicity values depends on the correct discrimination between non-specific and specific chronic toxicity mechanisms; otherwise, the predicted toxicity can be wrong by orders of magnitude. It should be noted that although for many compounds, excess toxicity* in a chronic test correlates with excess toxicity in an acute test, this is not always the case.

* *Excess toxicity, T_e = (Predicted baseline toxicity) / Observed toxicity.*

A8.7 Classification of metals and metal compounds

A8.7.1 *Introduction*

A8.7.1.1 The harmonised system for classifying chemical substances is a hazard-based system, and the basis of the identification of hazard is the aquatic toxicity of the substances, and information on the degradation and bioaccumulation behaviour (OECD 1998). Since this document deals only with the hazards associated with a given substance when the substance is dissolved in the water column, exposure from this source is limited by the solubility of the substance in water and bioavailability of the substance in species in the aquatic environment. Thus, the hazard classification schemes for metals and metal compounds are limited to the hazards posed by metals and metal compounds when they are available (i.e. exist as dissolved metal ions, for example, as M^+ when present as $M\text{-}NO_3$), and do not take into account exposures to metals and metal compounds that are not dissolved in the water column but may still be bioavailable, such as metals in foods. This chapter does not take into account the non-metallic ion (e.g. CN-) of metal compounds which may be toxic or which may be organic and may pose bioaccumulation or persistence hazards. For such metal compounds the hazards of the non-metallic ions must also be considered.

A8.7.1.2 The level of the metal ion which may be present in solution following the addition of the metal and/or its compounds, will largely be determined by two processes: the extent to which it can be dissolved, i.e. its water solubility, and the extent to which it can react with the media to transform to water soluble forms. The rate and extent at which this latter process, known as "transformation" for the purposes of this guidance, takes place can vary extensively between different compounds and the metal itself, and is an important factor in determining the appropriate hazard class. Where data on transformation are available, they should be taken into account in determining the classification. The Protocol for determining this rate is available in Annex 9.

A8.7.1.3 Generally speaking, the rate at which a substance dissolves is not considered relevant to the determination of its intrinsic toxicity. However, for metals and many poorly soluble inorganic metal compounds, the difficulties in achieving dissolution through normal solubilisation techniques is so severe that the two processes of solubilisation and transformation become indistinguishable. Thus, where the compound is sufficiently poorly soluble that the levels dissolved following normal attempts at solubilisation do not exceed the available $L(E)C_{50}$, it is the rate and extent of transformation, which must be considered. The transformation will be affected by a number of factors, not least of which will be the properties of the media with respect to pH, water hardness, temperature etc. In addition to these properties, other factors such as the size and specific surface area of the particles which have been tested, the length of time over which exposure to the media takes place and, of course the mass or surface area loading of the substance in the media will all play a part in determining the level of dissolved metal ions in the water. Transformation data can generally, therefore, only be considered as reliable for the purposes of classification if conducted according to the standard Protocol in Annex 9.

A8.7.1.4 This Protocol aims at standardising the principal variables such that the level of dissolved ion can be directly related to the loading of the substance added. It is this loading level which yields the level of metal ion equivalent to the available $L(E)C_{50}$ that can then be used to determine the hazard band appropriate for classification. The testing methodology is detailed in Annex 9. The strategy to be adopted in using the data from the testing protocol, and the data requirements needed to make that strategy work, will be described.

A8.7.1.5 In considering the classification of metals and metal compounds, both readily and poorly soluble, recognition has to be paid to a number of factors. As defined in Chapter 3.10, the term "degradation" refers to the decomposition of organic molecules. For inorganic compounds and metals, clearly the concept of degradability, as it has been considered and used for organic substances, has limited or no meaning. Rather, the substance may be transformed by normal environmental processes to either increase or decrease the bioavailability of the toxic species. Equally, the log K_{ow} cannot be considered as a measure of the potential to accumulate. Nevertheless, the concepts that a substance, or a toxic metabolite/reaction product may not be rapidly lost from the environment and/or may bioaccumulate are as applicable to metals and metal compounds as they are to organic substances.

A8.7.1.6 Speciation of the soluble form can be affected by pH, water hardness and other variables, and may yield particular forms of the metal ion which are more or less toxic. In addition, metal ions could be made non-available from the water column by a number of processes (e.g. mineralisation and partitioning). Sometimes these processes can be sufficiently rapid to be analogous to degradation in assessing chronic classification. However, partitioning of the metal ion from the water column to other environmental media does not necessarily mean that it is no longer bioavailable, nor does it mean that the metal has been made permanently unavailable.

A8.7.1.7 Information pertaining to the extent of the partitioning of a metal ion from the water column, or the extent to which a metal has been or can be converted to a form that is less toxic or non-toxic is frequently not available over a sufficiently wide range of environmentally relevant conditions, and thus, a number of assumptions will need to be made as an aid in classification. These assumptions may be modified if available data show otherwise. In the first instance it should be assumed that the metal ions, once in the water, are not rapidly partitioned from the water column and thus these compounds do not meet the criteria. Underlying this is the assumption that, although speciation can occur, the species will remain available under environmentally relevant conditions. This may not always be the case, as described above, and any evidence available that would suggest changes to the bioavailability over the course of 28 days, should be carefully examined. The bioaccumulation of metals and inorganic metal compounds is a complex process and bioaccumulation data should be used with care. The application of bioaccumulation criteria will need to be considered on a case-by-case basis taking due account of all the available data.

A8.7.1.8 A further assumption that can be made, which represents a cautious approach, is that, in the absence of any solubility data for a particular metal compound, either measured or calculated, the substance will be sufficiently soluble to cause toxicity at the level of the $L(E)C_{50}$, and thus may be classified in the same way as other soluble salts. Again, this is clearly not always the case, and it may be wise to generate appropriate solubility data.

A8.7.1.9 This chapter deals with metals and metal compounds. Within the context of this Guidance Document, metals and metal compounds are characterised as follows, and therefore, organo-metals are outside the scope of this chapter:

(a) metals, M^0, in their elemental state are not soluble in water but may transform to yield the available form. This means that a metal in the elemental state may react with water or a dilute aqueous electrolyte to form soluble cationic or anionic products, and in the process the metal will oxidise, or transform, from the neutral or zero oxidation state to a higher one;

(b) in a simple metal compound, such as an oxide or sulphide, the metal already exists in the oxidised state, so that further metal oxidation is unlikely to occur when the compound is introduced into an aqueous medium.

However, while oxidisation may not change, interaction with the media may yield more soluble forms. A sparingly soluble metal compound can be considered as one for which a solubility product can be calculated, and which will yield a small amount of the available form by dissolution. However, it should be recognised that the final solution concentration may be influenced by a number of factors, including the solubility product of some metal compounds precipitated during the transformation/dissolution test, e.g. aluminium hydroxide.

A8.7.2 *Application of aquatic toxicity data and solubility data for classification*

A8.7.2.1 *Interpretation of aquatic toxicity data*

A8.7.2.1.1 Aquatic toxicity studies carried out according to a recognised protocol should normally be acceptable as valid for the purposes of classification. Section A8.3 should also be consulted for generic issues that are common to assessing any aquatic toxicity data point for the purposes of classification.

A8.7.2.1.2 Metal complexation and speciation

A8.7.2.1.2.1 The toxicity of a particular metal in solution, appears to depend primarily on (but is not strictly limited to) the level of dissolved free metal ions. Abiotic factors including alkalinity, ionic strength and pH can influence the toxicity of metals in two ways: (i) by influencing the chemical speciation of the metal in water (and hence affecting the availability) and (ii) by influencing the uptake and binding of available metal by biological tissues.

A8.7.2.1.2.2 Where speciation is important, it may be possible to model the concentrations of the different forms of the metal, including those that are likely to cause toxicity. Analysis methods for quantifying exposure concentrations, which are capable of distinguishing between the complexed and uncomplexed fractions of a test substance, may not always be available or economic.

A8.7.2.1.2.3 Complexation of metals to organic and inorganic ligands in test media and natural environments can be estimated from metal speciation models. Speciation models for metals, including pH, hardness, DOC, and inorganic substances such as MINTEQ (Brown and Allison, 1987), WHAM (Tipping, 1994) and CHESS (Santore and Driscoll, 1995) can be used to calculate the uncomplexed and complexed fractions of the metal ions. Alternatively, the Biotic Ligand Model (BLM), allows for the calculation of the concentration of metal ion responsible for the toxic effect at the level of the organism. The BLM model has at present only been validated for a limited number of metals, organisms, and end-points (Santore and Di Toro, 1999). The models and formula used for the characterisation of metal complexation in the media should always be clearly reported, allowing for their translation back to natural environments (OECD, 2000).

A8.7.2.2 *Interpretation of solubility data*

A8.7.2.2.1 When considering the available data on solubility, their validity and applicability to the identification of the hazard of metal compounds should be assessed. In particular, a knowledge of the pH at which the data were generated should be known.

A8.7.2.2.2 Assessment of existing data

Existing data will be in one of three forms. For some well-studied metals, there will be solubility products and/or solubility data for the various inorganic metal compounds. It is also possible that the pH relationship of the solubility will be known. However, for many metals or metal compounds, it is probable that the available information will be descriptive only, e.g. poorly soluble. Unfortunately there appears to be very little (consistent) guidance about the solubility ranges for such descriptive terms. Where these are the only information available it is probable that solubility data will need to be generated using the Transformation/Dissolution Protocol (Annex 9).

A8.7.2.2.3 Screening test for assessing solubility of metal compounds

In the absence of solubility data, a simple "Screening Test" for assessing solubility, based on the high rate of loading for 24 h, can be used for metal compounds as described in the Transformation/Dissolution Protocol (Annex 9). The function of the screening test is to identify those metal compounds which undergo either dissolution or rapid transformation such that they are indistinguishable from soluble forms and hence may be classified based on the dissolved ion concentration. Where data are available from the screening test detailed in the Transformation/Dissolution Protocol, the maximum solubility obtained over the tested pH range should be used. Where data are not available over the full pH range, a check should be made that this maximum solubility has been achieved by reference to suitable thermodynamic speciation models or other suitable methods (see paragraph A8.7.2.1.2.3). It should be noted that this test is only intended to be used for metal compounds.

A8.7.2.2.4 Full test for assessing solubility of metals and metal compounds

The first step in this part of the study is, as with the screening test, an assessment of the pH(s) at which the study should be conducted. Normally, the Full Test should have been carried out at the pH that maximises the concentration of dissolved metal ions in solution. In such cases, the pH may be chosen following the same guidance as given for the screening test.

Based on the data from the Full Test, it is possible to generate a concentration of the metal ions in solution after 7 days for each of the three loadings (i.e. 1 mg/L as "low", 10 mg/L as "medium" and 100mg/L as "high") used in the test. If the purpose of the test is to assess the long-term hazard of the substance, then the test at the low loading may be extended to 28 days, at an appropriate pH.

A8.7.2.3 *Comparison of aquatic toxicity data and solubility data*

A decision whether or not the substance be classified will be made by comparing aquatic toxicity data and solubility data. If the $L(E)C_{50}$ is exceeded, irrespective of whether the toxicity and dissolution data are at the same pH and if this is the only data available then the substance should be classified. If other solubility data are available to show that the dissolution concentration would not exceed the $L(E)C_{50}$ across the entire pH range then the substance should not be classified on its soluble form. This may involve the use of additional data either from ecotoxicological testing or from applicable bioavailability-effect models.

A8.7.3 ***Assessment of environmental transformation***

A8.7.3.1 Environmental transformation of one species of a metal to another species of the same does not constitute degradation as applied to organic compounds and may increase or decrease the availability and bioavailability of the toxic species. However as a result of naturally occurring geochemical processes metal ions can partition from the water column. Data on water column residence time, the processes involved at the water – sediment interface (i.e. deposition and re-mobilisation) are fairly extensive, but have not been integrated into a meaningful database. Nevertheless, using the principles and assumptions discussed above in Section A8.7.1, it may be possible to incorporate this approach into classification.

A8.7.3.2 Such assessments are very difficult to give guidance for and will normally be addressed on a case by case approach. However, the following may be taken into account:

- Changes in speciation if they are to non-available forms, however, the potential for the reverse change to occur must also be considered;
- Changes to a metal compound which is considerably less soluble than that of the metal compound being considered.

Some caution is recommended, see paragraphs A8.7.1.5 and A8.7.1.6.

A8.7.4 ***Bioaccumulation***

A8.7.4.1 While log K_{ow} is a good predictor of BCF for certain types of organic compounds e.g. non-polar organic substances, it is of course irrelevant for inorganic substances such as inorganic metal compounds.

A8.7.4.2 The mechanisms for uptake and depuration rates of metals are very complex and variable and there is at present no general model to describe this. Instead the bioaccumulation of metals according to the classification criteria should be evaluated on a case by case basis using expert judgement.

A8.7.4.3 While BCFs are indicative of the potential for bioaccumulation there may be a number of complications in interpreting measured BCF values for metals and inorganic metal compounds. For some metals and inorganic metal compounds the relationship between water concentration and BCF in some aquatic organisms is inverse, and bioconcentration data should be used with care. This is particularly relevant for metals that are biologically essential. Metals that are biologically essential are actively regulated

in organisms in which the metal is essential. Since nutritional requirement of the organisms can be higher than the environmental concentration, this active regulation can result in high BCFs and an inverse relationship between BCFs and the concentration of the metal in water. When environmental concentrations are low, high BCFs may be expected as a natural consequence of metal uptake to meet nutritional requirements and in these instances can be viewed as a normal phenomenon. Additionally, if internal concentration is regulated by the organism, then measured BCFs may decline as external concentration increases. When external concentrations are so high that they exceed a threshold level or overwhelm the regulatory mechanism, this can cause harm to the organism. Also, while a metal may be essential in a particular organism, it may not be essential in other organisms. Therefore, where the metal is not essential or when the bioconcentration of an essential metal is above nutritional levels special consideration should be given to the potential for bioconcentration and environmental concern.

A8.7.5 *Application of classification criteria to metals and metal compounds*

A8.7.5.1 *Introduction to the classification strategy for metals and metal compounds*

A8.7.5.1.1 The schemes for the classification of metals and metal compounds are described below and summarised diagrammatically in Figure A.8.7.1. There are several stages in these schemes where data are used for decision purposes. It is not the intention of the classification schemes to generate new data. In the absence of valid data, it will be necessary to use all available data and expert judgement.

In the following sections, the reference to the $L(E)C_{50}$ refers to the data point(s) that will be used to select the classification band for the metal or metal compound.

A8.7.5.1.2 When considering $L(E)C_{50}$ data for metal compounds, it is important to ensure that the data point to be used as the justification for the classification is expressed in the weight of the molecule of the metal compound to be classified. This is known as correcting for molecular weight. Thus while most metal data is expressed in, for example, mg/L of the metal, this value will need to be adjusted to the corresponding weight of the metal compound. Thus:

$L(E)C_{50}$ metal compounds = $L(E)C_{50}$ of metal x (Molecular Weight of metal compound/Atomic Weight of metal)

NOEC data may also need to be adjusted to the corresponding weight of the metal compounds.

A8.7.5.2 *Classification Strategy for Metals*

A8.7.5.2.1 Where the $L(E)C_{50}$ for the metal ions of concern is greater than 100mg/L, the metals need not be considered further in the classification scheme.

A8.7.5.2.2 Where the $L(E)C_{50}$ for the metal ions of concern is less than or equal to 100mg/L, consideration must be given to the data available on the rate and extent to which these ions can be generated from the metal. Such data, to be valid and useable should have been generated using the Transformation/Dissolution Protocol (Annex 9).

A8.7.5.2.3 Where such data are unavailable, i.e. there is no clear data of sufficient validity to show that the transformation to metal ions will not occur, the safety net classification (Chronic IV) should be applied since the known classifiable toxicity of these soluble forms is considered to produce sufficient concern.

A8.7.5.2.4 Where data from dissolution protocol are available, then, the results should be used to aid classification according to the following rules:

A8.7.5.2.4.1 7 day Transformation Test

If the dissolved metal ion concentration after a period of 7 days (or earlier) exceeds that of the $L(E)C_{50}$, then the default classification for the metals is replaced by the following classification:

(i) If the dissolved metal ion concentration at the low loading rate is greater than or equal to the $L(E)C_{50}$, then classify Acute Class I. Classify also as Chronic Class I, unless there is evidence of both rapid partitioning from the water column and no bioaccumulation;

(ii) If the dissolved metal ion concentration at the medium loading rate is greater than or equal to the $L(E)C_{50}$, then classify Acute Class II. Classify also as Chronic Class II unless there is evidence of both rapid partitioning from the water column and no bioaccumulation;

(iii) If the dissolved metal ion concentration at the high loading rate is greater than or equal to the $L(E)C_{50}$, then classify Acute Class III. Classify also as Chronic Class III unless there is evidence of both rapid partitioning from the water column and no bioaccumulation.

A8.7.5.2.4.2 28 day Transformation Test

If the process described in paragraph A8.7.5.2.4.1 results in the classification of Chronic I, no further assessment is required, as the metal will be classified irrespective of any further information.

In all other cases, further data may have been generated through the dissolution/transformation test in order to show that the classification may be amended. If for substances classified Chronic II, III or IV, the dissolved metal ion concentration at the low loading rate after a total period of 28 days is less than or equal to the of the long-term NOECs, then the classification is removed.

A8.7.5.3 *Classification strategy for metal compounds*

A8.7.5.3.1 Where the $L(E)C_{50}$ for the metal ions of concern is greater than 100mg/L, the metal compounds need not be considered further in the classification scheme.

A8.7.5.3.2 If solubility $\geq L(E)C_{50}$, classify on the basis of soluble ion.

A8.7.5.3.2.1 All metal compounds with a water solubility (either measured e.g. through 24-hour Dissolution Screening test or estimated e.g. from the solubility product) greater or equal to the $L(E)C_{50}$ of the dissolved metal ion concentration are considered as readily soluble metal compounds. Care should be exercised for compounds whose solubility is close to the acute toxicity value as the conditions under which solubility is measured could differ significantly from those of the acute toxicity test. In these cases the results of the Dissolution Screening Test are preferred.

A8.7.5.3.2.2 Readily soluble metal compounds are classified on the basis of the $L(E)C_{50}$ (corrected where necessary for molecular weight):

(i) If the $L(E)C_{50}$ of the dissolved metal ion is less than or equal to 1 mg/L then classify Acute Class I. Classify also as Chronic I unless there is evidence of both rapid partitioning from the water column and no bioaccumulation;

(ii) If the $L(E)C_{50}$ of the dissolved metal ion is greater than 1 mg/L but less than or equal to 10 mg/L then classify Acute Class II. Classify also as Chronic II unless there is evidence of both rapid partitioning from the water column and no bioaccumulation;

(iii) If the $L(E)C_{50}$ of the dissolved metal ion is greater than 10 mg/L and less than or equal to 100 mg/L then classify Acute Class III, Classify also as Chronic Class III unless there is evidence of both rapid partitioning from the water column and no bioaccumulation.

A8.7.5.3.3 *If solubility <$L(E)C_{50}$, classify default Chronic IV*

A8.7.5.3.3.1 In the context of the classification criteria, poorly soluble compounds of metals are defined as those with a known solubility (either measured e.g. through 24-hour Dissolution Screening test or estimated e.g. from the solubility product) less than the $L(E)C_{50}$ of the soluble metal ion. In those cases when the soluble forms of the metal of poorly soluble metal compounds have a $L(E)C_{50}$ less than or equal to 100 mg/L

and the substance can be considered as poorly soluble the default safety net classification (Chronic IV) should be applied.

A8.7.5.3.3.2 7 day Transformation Test

For poorly soluble metal compounds classified with the default safety net classification further information that may be available from the 7-day transformation/dissolution test can also be used. Such data should include transformation levels at low, medium and high loading levels.

If the dissolved metal ion concentration after a period of 7 days (or earlier) exceeds that of the $L(E)C_{50}$, then the default classification for the metals is replaced by the following classification:

(i) If the dissolved metal ion concentration at the low loading rate is greater than or equal to the $L(E)C_{50}$, then classify Acute Class I. Classify also as Chronic Class I, unless there is evidence of both rapid partitioning from the water column and no bioaccumulation;

(ii) If the dissolved metal ion concentration at the medium loading rate is greater than or equal to the $L(E)C_{50}$, then classify Acute Class II. Classify also as Chronic Class II unless there is evidence of both rapid partitioning from the water column and no bioaccumulation;

(iii) If the dissolved metal ion concentration at the high loading rate is greater than or equal to the $L(E)C_{50}$, then classify Acute Class III. Classify also as Chronic Class III unless there is evidence of both rapid partitioning from the water column and no bioaccumulation.

A8.7.5.3.3.3 28 day Transformation Test

If the process described in paragraph A8.7.5.3.3.2 results in the classification of Chronic I, no further assessment is required as the metal compound will be classified irrespective of any further information.

In all other cases, further data may have been generated through the dissolution/transformation test for 28 days in order to show that the classification may be amended. If for poorly soluble metal compounds classified as Chronic II, III or IV, the dissolved metal ion concentration at the low loading rate after a total period of 28 days is less than or equal to the long-term NOECs, then classification is removed.

A8.7.5.4 *Particle size and surface area*

A8.7.5.4.1 Particle size, or moreover surface area, is a crucial parameter in that any variation in the size or surface area tested may cause a significant change in the levels of metals ions released in a given time-window. Thus, this particle size or surface area is fixed for the purposes of the transformation test, allowing the comparative classifications to be based solely on the loading level. Normally, the classification data generated would have used the smallest particle size marketed to determine the extent of transformation. There may be cases where data generated for a particular metal powder is not considered as suitable for classification of the massive forms. For example, where it can be shown that the tested powder is structurally a different material (e.g. different crystallographic structure) and/or it has been produced by a special process and cannot be generated from the massive metal, classification of the massive can be based on testing of a more representative particle size or surface area, if such data are available. The powder may be classified separately based on the data generated on the powder. However, in normal circumstances it is not anticipated that more than two classification proposals would be made for the same metal.

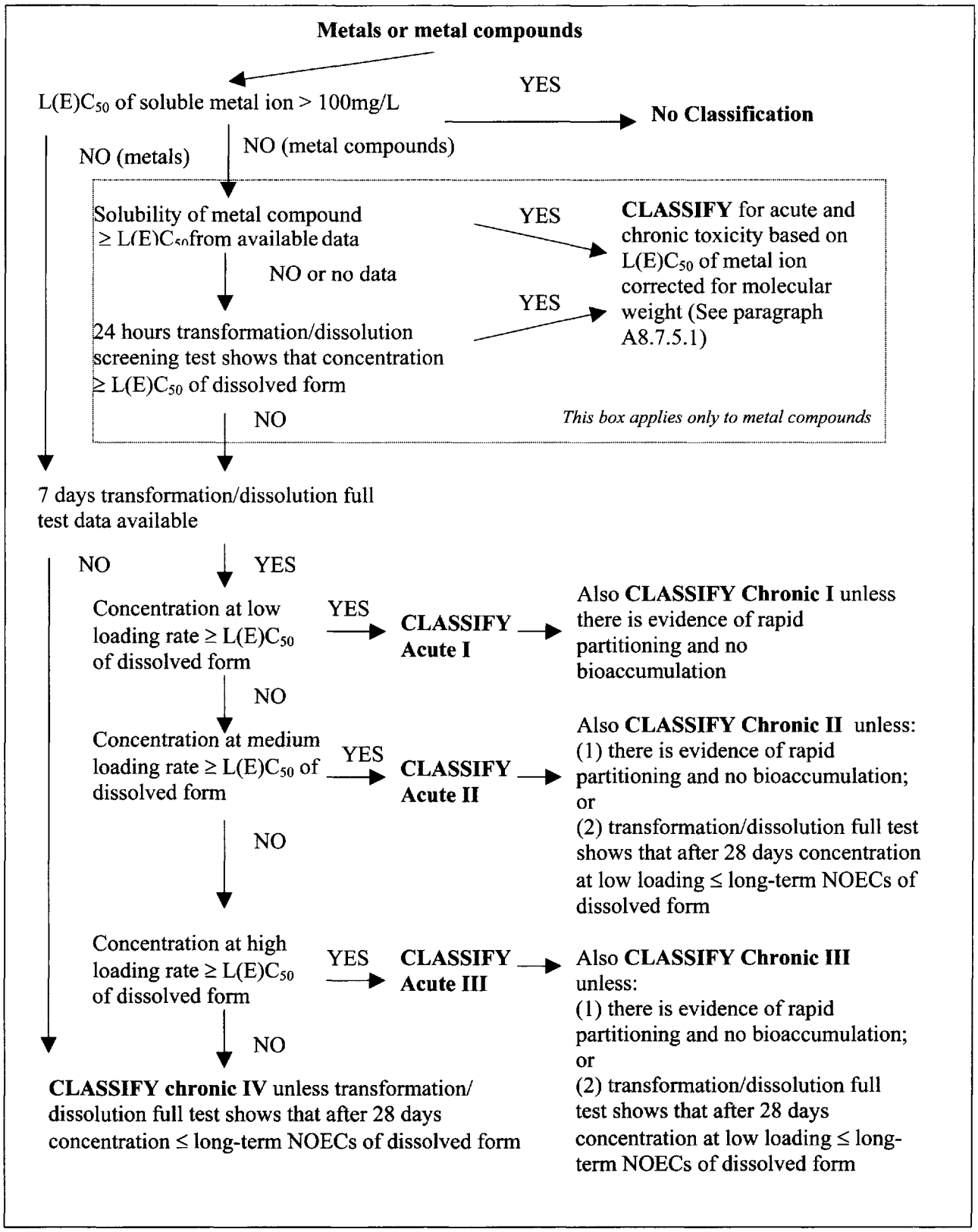
A8.7.5.4.2 Metals with a particle size smaller than the default diameter value of 1 mm can be tested on a case-by-case basis. One example of this is where metal powders are produced by a different production technique or where the powders give rise to a higher dissolution (or reaction) rate than the massive form leading to a more stringent classification.

A8.7.5.4.3 The particle sizes tested depend on the substance being assessed and are shown in the table below:

Type	Particle size	Comments
Metal compounds	Smallest representative size sold	Never larger than 1 mm
Metals – powders	Smallest representative size sold	May need to consider different sources if yielding different crystallographic / morphologic properties
Metals – massive	1 mm	Default value may be altered if sufficient justification

A8.7.5.4.4 For some forms of metals, it may be possible, using the Transformation/Dissolution Protocol (OECD 2001), to obtain a correlation between the concentration of the metal ion after a specified time interval as a function of the surface area loadings of the forms tested. In such cases, it could then be possible to estimate the level of dissolved metal ion concentration of the metal with different particles, using the critical surface area approach as proposed by Skeaff *et. al.* (2000) (See reference in appendix VI, part 5, Metals and metal compounds). That is, from this correlation and a linkage to the appropriate toxicity data, it may be possible to determine a critical surface area of the substance that delivers the $L(E)C_{50}$ to the medium and then to convert the critical surface area to the low, medium and high mass loadings used in hazard identification. While this approach is not normally used for classification it may provide useful information for labelling and downstream decisions.

Figure A8.7.1: Classification Strategy for metals and metal compounds



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Annex 8

APPENDIX I

Determination of degradability of organic substances

1. Organic substances may be degraded by abiotic or biotic processes or by a combination of these. A number of standard procedures or tests for determination of the degradability are available. The general principles of some of these are described below. It is by no way the intention to present a comprehensive review of degradability test methods, but only to place the methods in the context of aquatic hazard classification.

2. Abiotic degradability

2.1 Abiotic degradation comprises chemical transformation and photochemical transformation. Usually abiotic transformations will yield other organic compounds but will not cause a full mineralisation (Schwarzenbach *et al.*, 1993). Chemical transformation is defined as transformation that happens without light and without the mediation of organisms whereas photochemical transformations require light.

2.2 Examples of relevant chemical transformation processes in aqueous environment are hydrolysis, nucleophilic substitution, elimination, oxidation and reduction reactions (Schwarzenbach *et al.*, 1993). Of these, hydrolysis is often considered the most important and it is the only chemical transformation process for which international test guidelines are generally available. The tests for abiotic degradation of chemicals are generally in the form of determination of transformation rates under standardised conditions.

2.3 *Hydrolysis*

2.3.1 Hydrolysis is the reaction of the nucleophiles H_2O or OH^- with a chemical where a (leaving) group of the chemical is exchanged with an OH group. Many compounds, especially acid derivatives, are susceptible to hydrolysis. Hydrolysis can both be abiotic and biotic, but in regard to testing only abiotic hydrolysis is considered. Hydrolysis can take place by different mechanisms at different pHs, neutral, acid- or base-catalysed hydrolysis, and hydrolysis rates may be very dependent on pH.

2.3.2 Currently two guidelines for evaluating abiotic hydrolysis are generally available, the OECD Test Guideline 111 Hydrolysis as a function of pH (corresponding to OPPTS 835.2110) and OPPTS 835.2130 Hydrolysis as a function of pH and temperature. In OECD Test Guideline 111, the overall hydrolysis rate at different pHs in pure buffered water is determined. The test is divided in two, a preliminary test that is performed for chemicals with unknown hydrolysis rates and a more detailed test that is performed for chemicals that are known to be hydrolytically unstable and for chemicals for which the preliminary test shows fast hydrolysis. In the preliminary test the concentration of the chemical in buffered solutions at pHs in the range normally found in the environment (pHs of 4, 7 and 9) at 50°C is measured after 5 days. If the concentration of the chemical has decreased less than 10 % it is considered hydrolytically stable, otherwise the detailed test may be performed. In the detailed test, the overall hydrolysis rate is determined at three pHs (4, 7 and 9) by measuring the concentration of the chemical as a function of time. The hydrolysis rate is determined at different temperatures so that interpolations or extrapolations to environmentally relevant temperatures can be made. The OPPTS 835.2130 test is almost identical in design to the OECD Test Guideline 111, the difference mainly being in the treatment of data.

2.3.3 It should be noted that apart from hydrolysis the hydrolysis rate constants determined by the tests include all other abiotic transformations that may occur without light under the given test conditions. Good agreement has been found between hydrolysis rates in natural and in pure waters (OPPTS 835.2110).

2.4 *Photolysis*

2.4.1 At present, there is no OECD guideline on aqueous photodegradation, but a guidance document, concerning aquatic direct photolysis, is available (OECD, 1997). The Guidance Document is supposed to form the basis for a scheduled guideline. According to the definitions set out in this Guidance Document, phototransformation of compounds in water can be in the form of primary or secondary phototransformation, where the primary phototransformation (photolysis) can be divided further into direct and indirect photolysis. Direct phototransformation (photolysis) is the case where the chemical absorbs light and as a direct result hereof undergoes transformation. Indirect phototransformation is the case where other excited species transfer energy, electrons or H-atoms to the chemical and thereby induces a transformation (sensitised photolysis). Secondary phototransformation is the case where chemical reactions occur between the chemical and reactive short lived species like hydroxy radicals, peroxy radicals or singlet oxygen that are formed in the presence of light by reactions of excited species like excited humic or fulvic acids or nitrate.

2.4.2 The only currently available guidelines on phototransformation of chemicals in water are therefore OPPTS 835.2210 *Direct photolysis rate in water by sunlight* and OPPTS 835.5270 *Indirect photolysis screening test.* The OPPTS 835.2210 test uses a tiered approach. In Tier 1 the maximum direct photolysis rate constant (minimum half-life) is calculated from a measured molar absorptivity. In Tier 2 there are two phases. In Phase 1 the chemical is photolysed with sunlight and an approximate rate constant is obtained. In Phase 2, a more accurate rate constant is determined by using an actinometer that quantifies the intensity of the light that the chemical has actually been exposed to. From the parameters measured, the actual direct photodegradation rate at different temperatures and for different latitudes can be calculated. This degradation rate will only apply to the uppermost layer of a water body, e.g. the first 50 cm or less and only when the water is pure and air saturated which may clearly not be the case in environment. However, the results can be extended over other environmental conditions by the use of a computer programme incorporating attenuation in natural waters and other relevant factors.

2.4.3 The OPPTS 835.5270 screening test concerns indirect photolysis of chemicals in waters that contain humic substances. The principle of the test is that in natural waters exposed to natural sunlight a measured phototransformation rate will include both direct and indirect phototransformation, whereas only direct phototransformation will take place in pure water. Therefore, the difference between the direct photodegradation rate in pure water and the total photodegradation in natural water is the sum of indirect photolysis and secondary photodegradation according to the definitions set out in the Annex 8 Guidance Document. In the practical application of the test, commercial humic substances are used to make up a synthetic humic water, which mimics a natural water. It should be noted that the indirect phototransformation rate determined is only valid for the season and latitude for which it is determined and it is not possible to transfer the results to other latitudes and seasons.

3. Biotic degradability

3.1 Only a brief overview of the test methods is given below. For more information, the comprehensive OECD Detailed Review Paper on Biodegradability Testing (OECD, 1995) should be consulted.

3.2 *Ready biodegradability*

3.2.1 Standard tests for determination of the ready biodegradability of organic substances are developed by a number of organisations including OECD (OECD Test Guidelines 301A-F), EU (C.4 tests), OPPTS (835.3110) and ISO (9408, 9439, 10707).

3.2.2 The ready biodegradability tests are stringent tests, which provide limited opportunity for biodegradation and acclimatisation to occur. The basic test conditions ensuring these specifications are:

- high concentration of test substance (2-100 mg/L);
- the test substance is the sole carbon and energy source;
- low to medium concentration of inoculum (10^4-10^8 cells/mL);
- no pre-adaptation of inoculum is allowed;

- 28 days test period with a 10-days time window (except for the MITI I method (OECD Test Guideline 301C)) for degradation to take place;
- test temperature < 25 °C; and
- pass levels of 70% (DOC removal) or 60% (O_2 demand or CO_2 evolution) demonstrating complete mineralisation (as the remaining carbon of the test substance is assumed to be built into the growing biomass).

3.2.3 It is assumed that a positive result in one of the ready biodegradability tests demonstrates that the substance will degrade rapidly in the environment (OECD Test Guidelines).

3.2.4 Also the traditional BOD_5 tests (e.g. the EU C.5 test) may demonstrate whether a substance is readily biodegradable. In this test, the relative biochemical oxygen demand in a period of 5 days is compared to the theoretical oxygen demand (ThOD) or, when this is not available, the chemical oxygen demand (COD). The test is completed within five days and consequently, the pass level defined in the proposed hazard classification criteria at 50% is lower than in the ready biodegradability tests.

3.2.5 The screening test for biodegradability in seawater (OECD Test Guideline 306) may be seen as seawater parallel to the ready biodegradability tests. Substances that reach the pass level in OECD Test Guideline 306 (i.e. >70% DOC removal or >60 theoretical oxygen demand) may be regarded as readily biodegradable, since the degradation potential is normally lower in seawater than in the freshwater degradation tests.

3.3 *Inherent biodegradability*

3.3.1 Tests for inherent biodegradability are designed to assess whether a substance has any potential for biodegradation. Examples of such tests are the OECD Test Guidelines 302A-C tests, the EU C.9 and C.12 tests, and the ASTM E 1625-94 test.

3.3.2 The basic test conditions favouring an assessment of the inherent biodegradation potential are:

- a prolonged exposure of the test substance to the inoculum allowing adaptation within the test period;
- a high concentration of micro-organisms;
- a favourable substance/biomass ratio

3.3.3 A positive result in an inherent test indicates that the test substance will not persist indefinitely in the environment, however a rapid and complete biodegradation can not be assumed. A result demonstrating more than 70% mineralisation indicates a potential for ultimate biodegradation, a degradation of more than 20% indicates inherent, primary biodegradation, and a result of less than 20% indicates that the substance is persistent. Thus, a negative result means that non-biodegradability (persistence) should be assumed (OECD Test Guidelines).

3.3.4 In many inherent biodegradability tests only the disappearance of the test substance is measured. Such a result only demonstrates a primary biodegradability and not a total mineralisation. Thus, more or less persistent degradation products may have been formed. Primary biodegradation of a substance is no indication of ultimate degradability in the environment.

3.3.5 The OECD inherent biodegradation tests are very different in their approach and especially, the MITI II test (OECD Test Guideline 302C) employs a concentration of inoculum that is only three times higher than in the corresponding MITI I ready biodegradability test (OECD Test Guideline 301C). Also the Zahn-Wellens test (OECD Test Guideline 302B) is a relatively "weak" inherent test. However, although the degradation potential in these tests is not very much stronger than in the ready biodegradability tests, the results can not be extrapolated to conditions in the ready biodegradability tests and in the aquatic environment.

3.4 *Aquatic simulation tests*

3.4.1 A simulation test attempts to simulate biodegradation in a specific aquatic environment. As examples of a standard test for simulation of degradation in the aquatic environment may be mentioned the ISO/DS14592 Shake flask batch test with surface water or surface water/sediment suspensions (Nyholm and Toräng, 1999), the ASTM E 1279-89(95) test on biodegradation by a shake-flask die-away method and the similar OPPTS 835.3170 test. Such test methods are often referred to as river die-away tests.

3.4.2 The features of the tests that ensure simulation of the conditions in the aquatic environment are:

- use of a natural water (and sediment) sample as inoculum; and
- low concentration of test substance (1-100 µg/L) ensuring first-order degradation kinetics.

3.4.3 The use of a radiolabelled test compound is recommended as this facilitates the determination of the ultimate degradation. If only the removal of the test substance by chemical analysis is determined, only the primary degradability is determined. From observation of the degradation kinetics, the rate constant for the degradation can be derived. Due to the low concentration of the test substance, first-order degradation kinetics are assumed to prevail.

3.4.4 The test may also be conducted with natural sediment simulating the conditions in the sediment compartment. Moreover, by sterilising the samples, the abiotic degradation under the test conditions can be determined.

3.5 *STP simulation tests*

Tests are also available for simulating the degradability in a sewage treatment plant (STP), e.g. the OECD Test Guideline 303A Coupled Unit test, ISO 11733 Activated sludge simulation test, and the EU C.10 test. Recently, a new simulation test employing low concentrations of organic pollutants has been proposed (Nyholm et. al., 1996).

3.6 *Anaerobic degradability*

3.6.1 Test methods for anaerobic biodegradability determine the intrinsic potential of the test substance to undergo biodegradation under anaerobic conditions. Examples of such tests are the ISO 11734:1995(E) test, the ASTM E 1196-92 test and the OPPTS 835.3400 test.

3.6.2 The potential for anaerobic degradation is determined during a period of up to eight weeks and with the test conditions indicated below:

- performance of the test in sealed vessels in the absence of O_2 (initially in a pure N_2 atmosphere);
- use of digested sludge;
- a test temperature of 35 °C; and
- determination of head-space gas pressure (CO_2 and CH_4 formation).

3.6.3 The ultimate degradation is determined by determining the gas production. However, also primary degradation may be determined by measuring the remaining parent substance.

3.7 *Degradation in soil and sediment*

3.7.1 Many chemical substances end up in the soil or sediment compartments and an assessment of their degradability in these environments may therefore be of importance. Among standard methods may be mentioned the OECD Test Guideline 304A test on inherent biodegradability in soil, which corresponds to the OPPTS 835.3300 test.

3.7.2 The special test characteristics ensuring the determination of the inherent degradability in soil are:

- natural soil samples are used without additional inoculation;
- radiolabelled test substance is used; and
- evolution of radiolabelled CO_2 is determined.

3.7.3 A standard method for determining the biodegradation in sediment is the OPPTS 835.3180 Sediment/water microcosm biodegradation test. Microcosms containing sediment and water are collected from test sites and test compounds are introduced into the system. Disappearance of the parent compound (i.e. primary biodegradation) and, if feasible, appearance of metabolites or measurements of ultimate biodegradation may be made.

3.7.4 Currently, two new OECD guidelines are being drafted on aerobic and anaerobic transformation in soil (OECD Test Guideline, 1999a) and in aquatic sediment systems (OECD Test Guideline 1999b), respectively. The experiments are performed to determine the rate of transformation of the test substance and the nature and rates of formation and decline of transformation products under environmentally realistic conditions including a realistic concentration of the test substance. Either complete mineralisation or primary degradability may be determined depending on the analytical method employed for determining the transformation of the test substance.

3.8 *Methods for estimating biodegradability*

3.8.1 In recent years, possibilities for estimating environmental properties of chemical substances have been developed and, among these, also methods for predicting the biodegradability potential of organic substances (e.g. the Syracuse Research Corporation's Biodegradability Probability Program, BIOWIN). Reviews of methods have been performed by OECD (1993) and by Langenberg *et al.* (1996). They show that group contribution methods seem to be the most successful methods. Of these, the Biodegradation Probability Program (BIOWIN) seems to have the broadest application. It gives a qualitative estimate of the probability of slow or fast biodegradation in the presence of a mixed population of environmental micro-organisms. The applicability of this program has been evaluated by the US EPA/EC Joint Project on the Evaluation of (Q)SARs (OECD, 1994), and by Pedersen *et al.* (1995). The latter is briefly referred below.

3.8.2 A validation set of experimentally determined biodegradation data was selected among the data from MITI (1992), but excluding substances for which no precise degradation data were available and substances already used for development of the programme. The validation set then consisted of 304 substances. The biodegradability of these substances were estimated by use of the programme's non-linear estimation module (the most reliable) and the results compared with the measured data. 162 substances were predicted to degrade "fast", but only 41 (25%) were actually readily degradable in the MITI I test. 142 substances were predicted to degrade "slowly", which was confirmed by 138 (97%) substances being not readily degradable in the MITI I test. Thus, it was concluded that the programme may be used for classification purposes only when no experimental degradation data can be obtained, and when the programme predicts a substance to be degraded "slowly". In this case, the substance can be regarded as not rapidly degradable.

3.8.3 The same conclusion was reached in the US EPA/EC Joint Project on the Evaluation of (Q)SARs by use of experimental and QSAR data on new substances notified in the EU. The evaluation was based on an analysis of QSAR predictions on 115 new substances also tested experimentally in ready biodegradability tests. Only 9 of the substances included in this analysis were readily biodegradable. The employed QSAR methodology is not fully specified in the final report of the Joint US EPA/EC project (OECD, 1994), but it is likely that the majority of predictions were made by using methods which later have been integrated in the Biodegradation Probability Program.

3.8.4 Also in the EU TGD (EC, 1996) it is recommended that estimated biodegradability by use of the Biodegradation Probability Program is used only in a conservative way, i.e. when the programme predicts fast biodegradation, this result should not be taken into consideration, whereas predictions of slow biodegradation may be considered (EC, 1996).

3.8.5 Thus, the use of results of the Biodegradability Probability Program in a conservative way may fulfil the needs for evaluating biodegradability of some of the large number of substances for which no experimental degradation data are available.

Annex 8

APPENDIX II

Factors influencing degradability in the aquatic environment

1. Introduction

1.1 The OECD classification criteria are considering the hazards to the aquatic environment only. However, the hazard classification is primarily based on data prepared by conduction of tests under laboratory conditions that only seldom are similar to the conditions in the environment. Thus, the interpretation of laboratory test data for prediction of the hazards in the aquatic environment should be considered.

1.2 Interpretation of test results on biodegradability of organic substances has been considered in the OECD Detailed Review Paper on Biodegradability Testing (OECD, 1995).

1.3 The conditions in the environment are typically very different from the conditions in the standardised test systems, which make the extrapolation of degradation data from laboratory tests to the environment difficult. Among the differences, the following have significant influence on the degradability:

- Organism related factors (presence of competent micro-organisms);
- Substrate related factors (concentration of the substance and presence of other substrates); and
- Environment related factors (physico-chemical conditions, presence of nutrients, bioavailability of the substance).

These aspects will be discussed further below.

2. Presence of competent micro-organisms

2.1 Biodegradation in the aquatic environment is dependent on the presence of competent micro-organisms in sufficient numbers. The natural microbial communities consist of a very diverse biomass and when a 'new' substance is introduced in a sufficiently high concentration, the biomass may be adapted to degrade this substance. Frequently, the adaptation of the microbial population is caused by the growth of specific degraders that by nature are competent to degrade the substance. However, also other processes as enzyme induction, exchange of genetic material and development of tolerance to toxicity may be involved.

2.2 Adaptation takes place during a "lag" phase, which is the time period from the onset of the exposure until a significant degradation begins. It seems obvious that the length of the lag phase will depend on the initial presence of competent degraders. This will again depend on the history of the microbial community, i.e. whether the community formerly has been exposed to the substance. This means that when a xenobiotic substance has been used and emitted ubiquitously in a number of years, the likelihood of finding competent degraders will increase. This will especially be the case in environments receiving emissions as e.g. biological wastewater treatment plants. Often more consistent degradation results are found in tests where inocula from polluted waters are used compared to tests with inocula from unpolluted water (OECD, 1995; Nyholm and Ingerslev, 1997).

2.3 A number of factors determine whether the potential for adaptation in the aquatic environment is comparable with the potential in laboratory tests. Among other things adaptation depends on:

- initial number of competent degraders in the biomass (fraction and number);
- presence of surfaces for attachment;
- concentration and availability of substrate; and
- presence of other substrates.

2.4 The length of the lag phase depends on the initial number of competent degraders and, for toxic substances, the survival and recovery of these. In standard ready biodegradability tests, the inoculum is sampled in sewage treatment plants. As the load with pollutants is normally higher than in the environment, both the fraction and the number of competent degraders may be higher than in the less polluted aquatic environment. It is, however, difficult to estimate how much longer the lag phase will be in the aquatic environment than in a laboratory test due to the likely lower initial number of competent degraders.

2.5 Over long periods of time, the initial concentration of competent degraders is not important as they will grow up when a suitable substrate is present in sufficient concentrations. However, if the degradability in a short period of time is of concern, the initial concentration of competent degrading micro-organisms should be considered (Scow, 1982).

2.6 The presence of flocs, aggregates and attached micro-organisms may also enhance adaptation by e.g. development of microbial niches with consortia of micro-organisms. This is of importance when considering the capability of adaptation in the diverse environments in sewage treatment plants or in sediment or soil. However, the total number of micro-organisms in ready biodegradability tests and in the aquatic environment are of the same orders of magnitude (10^4-10^8 cells/mL in ready biodegradability tests and 10^3-10^6 cells/mL or more in surface water (Scow, 1982). Thus, this factor is probably of minor importance.

2.7 When discussing the extrapolation to environmental conditions it may be valuable to discriminate between oligotrophic and eutrophic environments. Micro-organisms thriving under oligotrophic conditions are able to mineralise organic substrates at low concentrations (fractions of mg C/L), and they normally have a greater affinity for the substrate but lower growth rates and higher generation times than eutrophic organisms (OECD, 1995). Moreover, oligotrophs are unable to degrade chemicals in concentrations higher than 1 mg/L and may even be inhibited at high concentrations. Opposite to that, eutrophs require higher substrate concentrations before mineralisation begins and they thrive at higher concentrations than oligotrophs. Thus, the lower threshold limit for degradation in the aquatic environment will depend on whether the microbial population is an oligotroph or an eutroph population. It is, however, not clear whether oligotrophs and eutrophs are different species or whether there is only an oligotrophic and an eutrophic way of life (OECD, 1995). Most pollutants reach the aquatic environment directly through discharge of wastewater and consequently, these recipients are mostly eutrophic.

2.8 From the above discussion it may thus be concluded that the chance of presence of competent degraders is greatest in highly exposed environments, i.e. in environments continuously receiving substances (which more frequently occurs for high production volume chemicals than for low production volume chemicals). These environments are often eutrophic and therefore, the degradation may require relatively high concentrations of substances before onset. On the other hand, in pristine waters competent species may be lacking, especially species capable of degradation of chemicals only occasionally released as low production volume chemicals.

3. Substrate related factors

3.1 *Concentration of test substance*

3.1.1 In most laboratory tests, the test substance is applied in very high concentrations (2-100 mg/L) compared to the concentrations in the lower µg/L range that may be expected in the aquatic environment. In general, growth of micro-organisms is not supported when a substrate is present in concentrations below a threshold level of around 10 µg/L and at lower concentrations, even the energy requirement for maintenance is not met (OECD, 1995). The reason for this lower threshold level is possibly a lack of sufficient stimulus to initiate an enzymatic response (Scow, 1982). This means in general that the concentrations of many substances in the aquatic environment are at a level where they can only hardly be the primary substrate for degrading micro-organisms.

3.1.2 Moreover, the degradation kinetics depends on substance concentration (S_0) compared with the saturation constant (K_s) as described in the Monod equation. The saturation constant is the concentration of

the substrate resulting in a specific growth rate of 50% of the maximum specific growth rate. At substrate concentrations much lower than the saturation constant, which is the normal situation in most of the aquatic environment, the degradation can be described by first order or logistic kinetics (OECD, 1995). When a low density of micro-organisms (lower than 10^3-10^5 cells/mL) prevails (e.g. in oligotrophic waters), the population grows at ever decreasing rates which is typical of logistic kinetics. At a higher density of micro-organisms (e.g. in eutrophic waters), the substrate concentration is not high enough to support growth of the cells and first order kinetics apply, i.e. the degradation rate is proportional with the substance concentration. In practice, it may be impossible to distinguish between the two types of degradation kinetics due to uncertainty of the data (OECD, 1995).

3.1.3 In conclusion, substances in low concentrations (i.e. below 10 µg/L) are probably not degraded as primary substrates in the aquatic environment. At higher concentrations, readily degradable substances will probably be degraded as primary substrates in the environment at a degradation rate more or less proportional with the concentration of the substance. The degradation of substances as secondary substrates is discussed below.

3.2 *Presence of other substrates*

3.2.1 In the standard tests, the test substance is applied as the sole substrate for the micro-organisms while in the environment, a large number of other substrates are present. In natural waters, concentrations of dissolved organic carbon are often found in the range 1-10 mg C/L, i.e. up to a factor 1000 higher than a pollutant. However, much of this organic carbon is relatively persistent with an increasing fraction of persistent matter the longer the distance from the shore.

3.2.2 Bacteria in natural waters are primarily nourishing on exudates from algae. These exudates are mineralised very quickly (within minutes) demonstrating that there is a high degradation potential in the natural micro-organism communities. Thus, as micro-organisms compete for the variety of substrates in natural waters, there is a selection pressure among micro-organisms resulting in growth of opportunistic species capable of nourishing on quickly mineralised substrates, while growth of more specialised species is suppressed. Experiences from isolation of bacteria capable of degrading various xenobiotics have demonstrated that these organisms are often growing relatively slowly and survive on complex carbon sources in competition with more rapidly growing bacteria. When competent micro-organisms are present in the environment, their numbers may increase if the specific xenobiotic substrate is continuously released and reach a concentration in the environment sufficient to support growth. However, most of the organic pollutants in the aquatic environment are present in low concentrations and will only be degraded as secondary substrates not supporting growth.

3.2.3 On the other hand, the presence of quickly mineralised substrates in higher concentrations may facilitate an initial transformation of the xenobiotic molecule by co-metabolism. The co-metabolised substance may then be available for further degradation and mineralisation. Thus, the presence of other substrates may increase the possibilities for a substance to be degraded.

3.2.4 It may then be concluded that the presence of a variety of substrates in natural waters and among them quickly mineralised substrates, may on the one hand cause a selection pressure suppressing growth of micro-organisms competent of degrading micro-pollutants. On the other hand it may facilitate an increased degradation by an initial co-metabolism followed by a further mineralisation. The relative importance of these processes under natural conditions may vary depending on both the environmental conditions and the substance and no generalisation can yet be established.

4. Environment related factors

4.1 The environmental variables control the general microbial activity rather than specific degradation processes. However, the significance of the influence varies between different ecosystems and microbial species (Scow, 1982).

4.2 *Redox potential*

One of the most important environment related factors influencing the degradability is probably the presence of oxygen. The oxygen content and the related redox potential determines the presence of different types of micro-organisms in aquatic environments with aerobic organisms present in the water phase, in the upper layer of sediments and in parts of sewage treatment plants, and anaerobic organisms present in sediments and parts of sewage treatment plants. In most parts of the water phase, aerobic conditions are prevailing and the prediction of the biodegradability should be based on results from aerobic tests. However, in some aquatic environments the oxygen content may be very low in periods of the year due to eutrophication and the following decay of produced organic matter. In these periods, aerobic organisms will not be able to degrade the chemical, but anaerobic processes may take over if the chemical is degradable under anaerobic conditions.

4.3 *Temperature*

Another important parameter is the temperature. Most laboratory tests are performed at 20-25 °C (standard aerobic ready biodegradability tests), but anaerobic tests may be performed at 35 °C as this better mimics the conditions in a sludge reactor. Microbial activity is found in the environment at temperatures ranging from below 0 °C to 100 °C. However, optimum temperatures are probably in the range from 10 °C to 30 °C and roughly, the degradation rate doubles for every 10 °C increase of temperature in this range (de Henau, 1993). Outside this optimum range the activity of the degraders is reduced drastically although some specialised species (termo- and psycrophilic bacteria) may thrive. When extrapolating from laboratory conditions, it should be considered that some aquatic environments are covered by ice in substantial periods of the year and that only minor or even no degradation can be expected during the winter season.

4.4 *pH*

Active micro-organisms are found in the entire pH range found in the environment. However, for bacteria as a group, slightly alkaline conditions favour the activity and the optimum pH range is 6-8. At a pH lower than 5, the metabolic activity in bacteria is significantly decreased. For fungi as a group, slightly acidic conditions favour the activity with an optimum pH range of 5-6 (Scow, 1982). Thus, an optimum for the degrading activity of micro-organisms will probably be within the pH range of 5-8, which is the range most often prevailing in the aquatic environment.

4.5 *Presence of nutrients*

The presence of inorganic nutrients (nitrogen and phosphorus) is often required for microbial growth. However, these are only seldom the activity limiting factors in the aquatic environment where growth of micro-organisms is often substrate limited. However, the presence of nutrient influences the growth of primary producers and then again the availability of readily mineralised exudates.

Annex 8

APPENDIX III

Basic principles of the experimental and estimation methods for determination of BCF and K_{ow} of organic substances

1 Bioconcentration factor (BCF)

1.1 *Definition*

The bioconcentration factor is defined as the ratio between the concentration of the chemical in biota and the concentration in the surrounding medium, here water, at steady state. BCF can be measured experimentally directly under steady-state conditions or calculated by the ratio of the first-order uptake and elimination rate constants, a method that does not require equilibrium conditions.

1.2 *Appropriate methods for experimental determination of BCF*

1.2.1 Different test guidelines for the experimental determination of bioconcentration in fish have been documented and adopted; the most generally applied being the OECD test guideline (OECD 305, 1996) and the ASTM standard guide (ASTM E 1022-94). OECD 305 (1996) was revised and replaced the previous version OECD 305A-E, (1981). Although flow-through test regimes are preferred (OECD 305, 1996), semi-static regimes are allowed (ASTM E 1022-94), provided that the validity criteria on mortality and maintenance of test conditions are fulfilled. For lipophilic substances (log K_{ow} > 3), flow-through methods are preferred.

1.2.2 The principles of the OECD 305 and the ASTM guidelines are similar, but the experimental conditions described are different, especially concerning:

- method of test water supply (static, semi-static or flow through);
- the requirement for carrying out a depuration study;
- the mathematical method for calculating BCF;
- sampling frequency: Number of measurements in water and number of samples of fish;
- requirement for measuring the lipid content of the fish;
- the minimum duration of the uptake phase;

1.2.3 In general, the test consists of two phases: The exposure (uptake) and post-exposure (depuration) phases. During the uptake phase, separate groups of fish of one species are exposed to at least two concentrations of the test substance. A 28-day exposure phase is obligatory unless a steady state has been reached within this period. The time needed for reaching steady-state conditions may be set on the basis of K_{ow} – k_2 correlations (e.g. log k_2 = 1.47 – 0.41 log K_{ow} (Spacie and Hamelink, 1982) or log k_2 = 1.69 – 0.53 log K_{ow} (Gobas *et al.*, 1989)). The expected time (d) for e.g. 95% steady state may thus be calculated by: $-\ln(1-0.95)/k_2$, provided that the bioconcentration follows first order kinetics. During the depuration phase the fish are transferred to a medium free of the test substance. The concentration of the test substance in the fish is followed through both phases of the test. The BCF is expressed as a function of the total wet weight of the fish. As for many organic substances, there is a significant relationship between the potential for bioconcentration and the lipophilicity, and furthermore, there is a corresponding relationship between the lipid content of the test fish and the observed bioconcentration of such substances. Therefore, to reduce this source of variability in the test results for the substances with high lipophilicity, bioconcentration should be expressed in relation to the lipid content in addition to whole body weight (OECD 305 (1996), ECETOC (1995)). The guidelines mentioned are based on the assumption that bioconcentration may be approximated by a first-order process (one-compartment model) and thus that BCF = k_1/k_2 (k_1: first-order uptake rate, k_2: first-order depuration rate, described by a log-linear approximation). If the depuration follows biphasic kinetics, i.e. two distinct depuration rates can be identified, the approximation k_1/k_2 may significantly underestimate BCF. If a second order kinetic has been indicated, BCF may be estimated from the relation: C_{Fish}/C_{Water}, provided that "steady-state" for the fish-water system has been reached.

1.2.4 Together with details of sample preparation and storage, an appropriate analytical method of known accuracy, precision, and sensitivity must be available for the quantification of the substance in the test solution and in the biological material. If these are lacking it is impossible to determine a true BCF. The use of radiolabelled test substance can facilitate the analysis of water and fish samples. However, unless combined with a specific analytical method, the total radioactivity measurements potentially reflect the presence of parent substance, possible metabolite(s), and possible metabolised carbon, which have been incorporated in the fish tissue in organic molecules. For the determination of a true BCF it is essential to clearly discriminate the parent substance from possible metabolites. If radiolabelled materials are used in the test, it is possible to analyse for total radio label (i.e. parent and metabolites) or the samples may be purified so that the parent compound can be analysed separately.

1.2.5 In the log K_{ow} range above 6, the measured BCF data tend to decrease with increasing log K_{ow}. Conceptual explanations of non-linearity mainly refer to either biotransformation, reduced membrane permeation kinetics or reduced biotic lipid solubility for large molecules. Other factors consider experimental artefacts, such as equilibrium not being reached, reduced bioavailability due to sorption to organic matter in the aqueous phase, and analytical errors. Moreover, care should be taken when evaluating experimental data on BCF for substances with log K_{ow} above 6, as these data will have a much higher level of uncertainty than BCF values determined for substances with log K_{ow} below 6.

2. log K_{ow}

2.1 *Definition and general considerations*

2.1.1 The log *n*-octanol-water partition coefficient (log K_{ow}) is a measure of the lipophilicity of a substance. As such, log K_{ow} is a key parameter in the assessment of environmental fate. Many distribution processes are driven by log K_{ow}, e.g. sorption to soil and sediment and bioconcentration in organisms.

2.1.2 The basis for the relationship between bioconcentration and log K_{ow} is the analogy for the partition process between the lipid phase of fish and water and the partition process between n-octanol and water. The reason for using K_{ow} arises from the ability of octanol to act as a satisfactory surrogate for lipids in fish tissue. Highly significant relationships between log K_{ow} and the solubility of substances in cod liver oil and triolin exist (Niimi, 1991). Triolin is one of the most abundant triacylglycerols found in freshwater fish lipids (Henderson and Tocher, 1987).

2.1.3 The determination of the *n*-octanol-water partition coefficient (K_{ow}) is a requirement of the base data set to be submitted for notified new and priority existing substances within the EU. As the experimental determination of the K_{ow} is not always possible, e.g. for very water-soluble and for very lipophilic substances, a QSAR derived K_{ow} may be used. However, extreme caution should be exercised when using QSARs for substances where the experimental determination is not possible (as for e.g. surfactants).

2.2 *Appropriate methods for experimental determination of K_{ow} values*

2.2.1 For experimental determination of K_{ow} values, two different methods, Shake-flask and HPLC, have been described in standard guidelines e.g. OECD 107 (1995); OECD 117 (1983); EEC A.8. (1992); EPA-OTS (1982); EPA-FIFRA (1982); ASTM (1993). Not only data obtained by the employment of the shake-flask or the HPLC method according to standard guidelines are recommended. For highly lipophilic substances, which are slowly soluble in water, data obtained by employing a slow-stirring method are generally more reliable (De Bruijn *et al.*, 1989; Tolls and Sijm, 1993; OECD draft Guideline, 1998). The slow stirring method is currently being ringtested for development of a final OECD guideline.

2.2.2 *Shake-flask method*

The basic principle of the method is to measure the dissolution of the substance in two different phases, water and *n*-octanol. In order to determine the partition coefficient, equilibrium between all interacting components of the system must be achieved after which the concentration of the substances dissolved in the two phases is determined. The shake-flask method is applicable when the log K_{ow} value falls

within the range from -2 to 4 (OECD 107, 1995). The shake-flask method applies only to essential pure substances soluble in water and *n*-octanol and should be performed at a constant temperature (±1°C) in the range 20-25 °C.

2.2.3 *HPLC method*

HPLC is performed on analytical columns packed with a commercially available solid phase containing long hydrocarbon chains (e.g. C_8, C_{18}) chemically bound onto silica. Chemicals injected onto such a column move along at different rates because of the different degrees of partitioning between the mobile aqueous phase and the stationary hydrocarbon phase. The HPLC method is not applicable to strong acids and bases, metals complexes, surface-active materials, or substances that react with the eluent. The HPLC method is applicable when the log K_{ow} value falls within the range 0 to 6 (OECD 117, 1989). The HPLC method is less sensitive to the presence of impurities in the test compound compared to the shake-flask method.

2.2.4 *Slow stirring method*

With the slow-stirring method a precise and accurate determination of K_{ow} of compounds with log K_{ow} up till 8.2 is allowed (De Bruijn *et al.*, 1989). For highly lipophilic compounds the shake-flask method is prone to produce artefacts (formation of microdroplets), and with the HPLC method K_{ow} needs to be extrapolated beyond the calibration range to obtain estimates of K_{ow}.

In order to determine a partition coefficient, water, n-octanol, and test compound are equilibrated with each other after which the concentration of the test compound in the two phases is determined. The experimental difficulties associated with the formation of microdroplets during the shake-flask experiment can to some degree be overcome in the slow-stirring experiment as water, octanol, and the test compound are equilibrated in a gently stirred reactor. The stirring creates a more or less laminar flow between the octanol and the water, and exchange between the phases is enhanced without microdroplets being formed.

2.2.5 *Generator Column Method*

Another very versatile method for measuring log K_{ow} is the generator column method. In this method, a generator column method is used to partition the test substance between the octanol and water phases. The column is packed with a solid support and is saturated with a fixed concentration of the test substance in *n*-octanol. The test substance is eluted from the octanol -saturated generator column with water. The aqueous solution exiting the column represents the equilibrium concentration of the test substance that has partitioned from the octanol phase into the water phase. The primary advantage of the generator column method over the shake flask method is that the former completely avoids the formation of micro-emulsions. Therefore, this method is particularly useful for measuring K_{ow} for substances values over 4.5 (Doucette and Andren, 1987 and 1988; Shiu *et al.*, 1988) as well as for substances having log K_{ow} values less than 4.5. A disadvantage of the generator column method is that it requires sophisticated equipment. A detailed description of the generator column method is presented in the "Toxic Substances Control Act Test Guidelines" (USEPA 1985).

2.3 ***Use of QSARs for determination of log K_{ow}*** *(see also in A8.6, « Use of QSARs »)*

2.3.1 Numerous QSARs have been and continue to be developed for the estimation of K_{ow}. Commonly used methods are based on fragment constants. The fragmental approaches are based on a simple addition of the lipophilicity of the individual molecular fragments of a given molecule. Three commercially available PC programs are recommended in the European Commission's Technical Guidance Document (European Commission, 1996) for risk assessment, part III, if no experimentally derived data are available.

2.3.2 CLOGP (Daylight Chemical Information Systems, 1995) was initially developed for use in drug design. The model is based on the Hansch and Leo calculation procedure (Hansch and Leo, 1979). The program calculates log K_{ow} for organic compounds containing C, H, N, O, Hal, P, and/or S. Log K_{ow} for salts

and for compounds with formal charges cannot be calculated (except for nitro compounds and nitrogen oxides). The calculation results of log K_{ow} for ionizable substances, like phenols, amines, and carboxylic acids, represent the neutral or unionised form and will be pH dependent. In general, the program results in clear estimates in the range of log Kow between 0 and 5 (European Commission, 1996, part III). However a validation study performed by Niemelä (1993), who compared experimental determined log K_{ow} values with estimated values, showed that the program precisely predicts the log K_{ow} for a great number of organic chemicals in the log K_{ow} range from below 0 to above 9 (n=501, r2=0.967). In a similar validation study on more than 7000 substances the results with the CLOGP-program (PC version 3.32, EPA version 1.2) were r2= 0.89, s.d.= 0.58, n= 7221. These validations show that the CLOGP-program may be used for estimating reliable log K_{ow} values when no experimental data are available. For chelating compounds and surfactants the CLOGP program is stated to be of limited reliability (OECD, 1993). However, as regards anionic surfactants (LAS) a correction method for estimating adjusted CLOGP values has been proposed (Roberts, 1989).

2.3.3 LOGKOW or KOWWIN (Syracuse Research Corporation) uses structural fragments and correction factors. The program calculates log K_{ow} for organic compounds containing the following atoms: C, H, N, O, Hal, Si, P, Se, Li, Na, K, and/or Hg. Log K_{ow} for compounds with formal charges (like nitrogenoxides and nitro compounds) can also be calculated. The calculation of log K_{ow} for ionizable substances, like phenols, amines and carboxylic acids, represent the neutral or unionised form, and the values will thus be pH dependent. Some surfactants (e.g. alcohol ethoxylates (Tolls, 1998), dyestuffs, and dissociated substances may be predicted by the LOGKOW program (Pedersen *et al*, 1995). In general, the program gives clear estimates in the range of log K_{ow} between 0 and 9 (TemaNord 1995:581). Like the CLOGP-program, LOGKOW has been validated (Table 2) and is recommended for classification purposes because of its reliability, commercial availability, and convenience of use.

2.3.4 AUTOLOGP (Devillers *et al.*, 1995) has been derived from a heterogeneous data set, comprising 800 organic chemicals collected from literature. The program calculates log K_{ow} values for organic chemicals containing C, H, N, O, Hal, P, and S. The log K_{ow} values of salts cannot be calculated. Also the log K_{ow} of some compounds with formal charges cannot be calculated, with the exception of nitro compounds. The log K_{ow} values of ionizable chemicals like phenols, amines, and corboxylic acids can be calculated although pH-dependencies should be noted. Improvements are in progress in order to extend the applicability of AUTOLOGP. According to the presently available information, AUTOLOGP gives accurate values especially for highly lipophilic substances (log $K_{ow} > 5$) (European Commission, 1996).

2.3.5 SPARC. The SPARC model is still under development by EPA's Environmental Research Laboratory in Athens, Georgia, and is not yet public available. SPARC is a mechanistic model based on chemical thermodynamic principles rather than a deterministic model rooted in knowledge obtained from observational data. Therefore, SPARC differs from models that use QSARs (i.e. KOWWIN, LOGP) in that no measured log K_{ow} data are needed for a training set of chemicals. EPA does occasionally run the model for a list of CAS numbers, if requested. SPARC provides improved results over KOWWIN and CLOGP only for compounds with log K_{ow} values greater than 5. Only SPARC can be employed in a general way for inorganic or organometallic compounds.

In Table 1, this Appendix, an overview of log K_{ow} estimation methods based on fragmentation methodologies is presented. Also other methods for the estimation of log K_{ow} values exist, but they should only be used on a case by case basis and only with appropriate scientific justification.

Table 1 Overview of QSAR methods for estimation of log K_{ow} based on fragmentation methodologies (Howard and Meylan (1997)).

Method	Methodology	Statistics
CLOGP Hansch and Leo (1979), CLOGP Daylight (1995)	Fragments + correction factors	Total n = 8942, r^2= 0,917, sd = 0,482 Validation: n = 501, r^2 = 0,967 Validation: n = 7221, r^2 = 0,89, sd = 0,58
LOGKOW (KOWWIN) Meylan and Howard (1995), SRC	140 fragments 260 correction factors	Calibration: n = 2430, r^2= 0,981, sd = 0,219, me = 0,161 Validation: n = 8855, r^2= 0,95, sd = 0,427, me = 0,327
AUTOLOGP Devillers *et al.* (1995)	66 atomic and group contributions from Rekker and Manhold (1992)	Calibration: n = 800, r^2= 0,96, sd = 0,387
SPARC Under development by EPA, Athens, Georgia.	Based upon fundamental chemical structure algorithm.	No measured log Kow data are needed for a training set of chemicals.
Rekker and De Kort (1979)	Fragments + correction factors	Calibration n = 1054, r^2 = 0,99 Validation: n = 20, r^2 = 0,917, sd = 0,53, me = 0,40
Niemi *et al.* (1992)	MCI	Calibration n = 2039, r^2 = 0,77 Validation: n = 2039, r^2 = 0,49
Klopman *et al* (1994)	98 fragments + correction factors	Calibration n = 1663, r^2 = 0,928, sd = 0,3817
Suzuki and Kudo (1990)	424 fragments	Total: n= 1686, me = 0,35 Validation: n = 221, me = 0,49
Ghose *et al.* (1988) ATOMLOGP	110 fragments	Calibration: n = 830, r^2 = 0,93, sd = 0,47 Validation: n = 125, r^2 = 0,87, sd = 0,52
Bodor and Huang (1992)	Molecule orbital	Calibration: n = 302, r^2 = 0,96, sd = 0,31, me = 0,24 Validation: n = 128, sd = 0,38
Broto *et al.* (1984) ProLogP	110 fragments	Calibration: n = 1868, me= ca. 0,4

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Annex 8

APPENDIX IV

Influence of external and internal factors on the bioconcentration potential of organic substances

1. Factors influencing the uptake

The uptake rate for lipophilic compounds is mainly a function of the size of the organism (Sijm and Linde, 1995). External factors such as the molecular size, factors influencing the bioavailability, and different environmental factors are of great importance to the uptake rate as well.

1.1 *Size of organism*

Since larger fish have a relatively lower gill surface to weight ratio, a lower uptake rate constant (k_1) is to be expected for large fish compared to small fish (Sijm and Linde, 1995; Opperhuizen and Sijm, 1990). The uptake of substances in fish is further controlled by the water flow through the gills; the diffusion through aqueous diffusion layers at the gill epithelium; the permeation through the gill epithelium; the rate of blood flow through the gills, and the binding capacity of blood constituents (ECETOC, 1995).

1.2 *Molecular size*

Ionised substances do not readily penetrate membranes; as aqueous pH can influence the substance uptake. Loss of membrane permeability is expected for substances with a considerable cross-sectional area (Opperhuizen *et al.*, 1985; Anliker *et al.*, 1988) or long chain length (> 4.3 nm) (Opperhuizen, 1986). Loss of membrane permeability due to the size of the molecules will thus result in total loss of uptake. The effect of molecular weight on bioconcentration is due to an influence on the diffusion coefficient of the substance, which reduces the uptake rate constants (Gobas *et al.*, 1986).

1.3 *Availability*

Before a substance is able to bioconcentrate in an organism it needs to be present in water and available for transfer across fish gills. Factors, which affect this availability under both natural and test conditions, will alter the actual bioconcentration in comparison to the estimated value for BCF. As fish are fed during bioconcentration studies, relatively high concentrations of dissolved and particulate organic matter may be expected, thus reducing the fraction of chemical that is actually available for direct uptake via the gills. McCarthy and Jimenez (1985) have shown that adsorption of lipophilic substances to dissolved humic materials reduces the availability of the substance, the more lipophilic the substance the larger reduction in availability (Schrap and Opperhuizen, 1990). Furthermore, adsorption to dissolved or particulate organic matter or surfaces in general may interfere during the measurement of BCF (and other physical-chemical properties) and thus make the determination of BCF or appropriate descriptors difficult. As bioconcentration in fish is directly correlated with the available fraction of the chemical in water, it is necessary for highly lipophilic substances to keep the available concentration of the test chemical within relatively narrow limits during the uptake period.

Substances, which are readily biodegradable, may only be present in the test water for a short period, and bioconcentration of these substances may thus be insignificant. Similarly, volatility and hydrolysis will reduce the concentration and time in which the substance is available for bioconcentration.

1.4 *Environmental factors*

Environmental parameters influencing the physiology of the organism may also affect the uptake of substances. For instance, when the oxygen content of the water is lowered, fish have to pass more water over their gills in order to meet respiratory demands (McKim and Goeden, 1982). However, there may be species dependency as indicated by Opperhuizen and Schrap (1987). It has, furthermore, been shown that

the temperature may have an influence on the uptake rate constant for lipophilic substances (Sijm *et al.* 1993), whereas other authors have not found any consistent effect of temperature changes (Black *et al.* 1991).

2. Factors influencing the elimination rate

The elimination rate is mainly a function of the size of the organism, the lipid content, the biotransformation process of the organism, and the lipophilicity of the test compound.

2.1 *Size of organism*

As for the uptake rate the elimination rate is dependent on the size of the organism. Due to the higher gill surface to weight ratio for small organisms (e.g. fish larvae) than that of large organisms, steady-state and thus "toxic dose equilibrium" has shown to be reached sooner in early life stages than in juvenile/adult stages of fish (Petersen and Kristensen, 1998). As the time needed to reach steady-state conditions is dependent on k_2, the size of fish used in bioconcentration studies has thus an important bearing on the time required for obtaining steady-state conditions.

2.2 *Lipid content*

Due to partitioning relationships, organisms with a high fat content tend to accumulate higher concentrations of lipophilic substances than lean organisms under steady-state conditions. Body burdens are therefore often higher for "fatty" fish such as eel, compared to "lean" fish such as cod. In addition, lipid "pools" may act as storage of highly lipophilic substances. Starvation or other physiological changes may change the lipid balance and release such substances and result in delayed impacts.

2.3 *Metabolism*

2.3.1 In general, metabolism or biotransformation leads to the conversion of the parent compound into more water-soluble metabolites. As a result, the more hydrophilic metabolites may be more easily excreted from the body than the parent compound. When the chemical structure of a compound is altered, many properties of the compound are altered as well. Consequently the metabolites will behave differently within the organism with respect to tissue distribution, bioaccumulation, persistence, and route and rate of excretion. Biotransformation may also alter the toxicity of a compound. This change in toxicity may either be beneficial or harmful to the organism. Biotransformation may prevent the concentration in the organism from becoming so high that a toxic response is expressed (detoxification). However, a metabolite may be formed which is more toxic than the parent compound (bioactivation) as known for e.g. benzo(a)pyrene.

2.3.2 Terrestrial organisms have a developed biotransformation system, which is generally better than that of organisms living in the aquatic environment. The reason for this difference may be the fact that biotransformation of xenobiotics may be of minor importance in gill breathing organisms as they can relatively easily excrete the compound into the water (Van Den Berg *et al.* 1995). Concerning the biotransformation capacity in aquatic organisms the capacity for biotransformation of xenobiotics increases in general as follows: Molluscs < crustaceans < fish (Wofford *et al.*, 1981).

3. Lipophilicity of substance

A negative linear correlation between k_2 (depuration constant) and log K_{ow} (or BCF) has been shown in fish by several authors (e.g. Spacie and Hamelink, 1982; Gobas *et al.*, 1989; Petersen and Kristensen, 1998), whereas k_1 (uptake rate constant) is more or less independent of the lipophilicity of the substance (Connell, 1990). The resultant BCF will thus generally increase with increasing lipophilicity of the substances, i.e. log BCF and log K_{ow} correlate for substances which do not undergo extensive metabolism.

Annex 8

APPENDIX V

Test guidelines

1. Most of the guidelines mentioned are found in compilations from the organisation issuing them. The main references to these are:

- EC guidelines: European Commission (1996). Classification, Packaging and Labelling of Dangerous Substances in the European Union. Part 2 – Testing Methods. European Commission. 1997. ISBN92-828-0076-8. (Homepage: http://ecb.ei.jrc.it/testing-methods/);

- ISO guidelines: Available from the national standardisation organisations or ISO (Homepage: http://www.iso.ch/);

- OECD guidelines for the testing of chemicals. OECD, Paris, 1993 with regular updates (Homepage: http://www.oecd.org/ehs/test/testlist.htm);

- OPPTS guidelines: US-EPA homepage:http://www.epa.gov/opptsfrs/home/guidelin.htm and (http://www.epa.gov/OPPTS_Harmonized/850_Ecological_Effects_Test_Guidelines / Drafts);

- ASTM: ASTM's homepage: http://www.astm.org. Further search via "standards".

2. Test guidelines for aquatic toxicity *

OECD Test Guideline 201 (1984) Alga, Growth Inhibition Test
OECD Test Guideline 202 (1984) Daphnia sp. Acute Immobilisation Test and Reproduction Test
OECD Test Guideline 203 (1992) Fish, Acute Toxicity Test
OECD Test Guideline 204 (1984) Fish, Prolonged Toxicity Test: 14-Day Study
OECD Test Guideline 210 (1992) Fish, Early-Life Stage Toxicity Test
OECD Test Guideline 211 (1998) Daphnia magna Reproduction Test
OECD Test Guideline 212 (1998) Fish, Short-term Toxicity Test on Embryo and Sac-Fry Stages
OECD Test Guideline 215 (2000) Fish, Juvenile Growth Test
OECD Test Guideline 221 (in preparation) *Lemna* sp. Growth inhibition test
EC C.1: Acute Toxicity for Fish (1992)
EC C.2: Acute Toxicity for Daphnia (1992)
EC C.3: Algal Inhibition Test (1992)
EC C.14: Fish Juvenile Growth Test (2001)
EC C.15: Fish, Short-term Toxicity Test on Embryo and Sac-Fry Stages (2001)
EC C.20: Daphnia Magna Reproduction Test (2001)

OPPTS Testing Guidelines for Environmental Effects (850 Series Public Drafts):

850.1000 Special consideration for conducting aquatic laboratory studies (Adobe PDF)
850.1000 Special consideration for conducting aquatic laboratory studies (Text to HTML)
850.1010 Aquatic invertebrate acute toxicity, test, freshwater daphnids (Adobe PDF)

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* *The list below is as of September 2000 and will need to be regularly updated as new guidelines are adopted or draft guidelines are elaborated.*

850.1010 Aquatic invertebrate acute toxicity, test, freshwater daphnids (Text to HTML)
850.1020 Gammarid acute toxicity test (Adobe PDF)
850.1020 Gammarid acute toxicity test (Text to HTML)
850.1035 Mysid acute toxicity test (Adobe PDF)
850.1035 Mysid acute toxicity test (Text to HTML)
850.1045 Penaeid acute toxicity test (Adobe PDF)
850.1045 Penaeid acute toxicity test (Text to HTML)
850.1075 Fish acute toxicity test, freshwater and marine (Adobe PDF)
850.1075 Fish acute toxicity test, freshwater and marine (Text to HTML)
850.1300 Daphnid chronic toxicity test (Adobe PDF)
850.1300 Daphnid chronic toxicity test (Text to HTML)
850.1350 Mysid chronic toxicity test (Adobe PDF)
850.1350 Mysid chronic toxicity test (Text to HTML)
850.1400 Fish early-life stage toxicity test (Adobe PDF)
850.1400 Fish early-life stage toxicity test (Text to HTML)
850.1500 Fish life cycle toxicity (Adobe PDF)
850.1500 Fish life cycle toxicity (Text to HTML)
850.1730 Fish BCF (Adobe PDF)
850.1730 Fish BCF (Text to HTML)
850.4400 Aquatic plant toxicity test using Lemna spp. Tiers I and II (Adobe PDF)
850.4400 Aquatic plant toxicity test using Lemna spp. Tiers I and II (Text to HTML)
850.4450 Aquatic plants field study, Tier III (Adobe PDF)
850.4450 Aquatic plants field study, Tier III (Text to HTML)
850.5400 Algal toxicity, Tiers I and II (Adobe PDF)
850.5400 Algal toxicity, Tiers I and II (Text to HTML)

3. Test guidelines for biotic and abiotic degradation *

ASTM E 1196-92

ASTM E 1279-89(95) Standard test method for biodegradation by a shake-flask die-away method

ASTM E 1625-94 Standard test method for determining biodegradability of organic chemicals in semi-continuous activated sludge (SCAS)

EC C.4. A to F: Determination of ready biodegradability. Directive 67/548/EEC, Annex V. (1992)

EC C.5. Degradation: biochemical oxygen demand. Directive 67/548/EEC, Annex V. (1992)

EC C.7. Degradation: abiotic degradation: hydrolysis as a function of pH. Directive 67/548/EEC, Annex V. (1992)

EC C.9. Biodegradation: Zahn-Wellens test. Directive 67/548/EEC, Annex V. (1988)

EC C.10. Biodegradation: Activated sludge simulation tests. Directive 67/548/EEC, Annex V. (1998)

EC C.11. Biodegradation: Activated sludge respiration inhibition test. Directive 67/548/EEC, AnnexV.(1988)

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* *The list below is as of September 2000 and will need to be regularly updated as new guidelines are adopted or draft guidelines are elaborated.*

EC C.12. Biodegradation: Modified SCAS test. Directive 67/548/EEC, Annex V. (1998)

ISO 9408 (1991). Water quality - Evaluation in an aqueous medium of the "ultimate" biodegradability of organic compounds - Method by determining the oxygen demand in a closed respirometer

ISO 9439 (1990). Water quality - Evaluation in an aqueous medium of the "ultimate" biodegradability of organic compounds - Method by analysis of released carbon dioxide

ISO 9509 (1996). Water quality - Method for assessing the inhibition of nitrification of activated sludge micro-organisms by chemicals and wastewaters

ISO 9887 (1992). Water quality - Evaluation of the aerobic biodegradability of organic compounds in an aqueous medium - Semicontinuous activated sludge method (SCAS)

ISO 9888 (1991). Water quality - Evaluation of the aerobic biodegradability of organic compounds in an aqueous medium - Static test (Zahn-Wellens method)

ISO 10707 (1994). Water quality - Evaluation in an aqueous medium of the "ultimate" biodegradability of organic compounds - Method by analysis of biochemical oxygen demand (closed bottle test)

ISO 11348 (1997). Water quality - Determination of the inhibitory effect of water samples on the light emission of *Vibrio fischeri* (Luminescent bacteria test)

ISO 11733 (1994). Water quality - Evaluation of the elimination and biodegradability of organic compounds in an aqueous medium - Activated sludge simulation test

ISO 11734 (1995). Water quality - Evaluation of the "ultimate" anaerobic biodegradability of organic compounds in digested sludge - Method by measurement of the biogas production

ISO/DIS 14592 .(1999) Water quality - Evaluation of the aerobic biodegradability of organic compounds at low concentrations in water. Part 1: Shake flask batch test with surface water or surface water/sediment suspensions (22.11.1999)

OECD Test Guideline 111 (1981). Hydrolysis as a function of pH. OECD guidelines for testing of chemicals

OECD Test Guideline 209 (1984). Activated sludge, respiration inhibition test. OECD guidelines for testing of chemicals

OECD Test Guideline 301 (1992). Ready biodegradability. OECD guidelines for testing of chemicals

OECD Test Guideline 302A (1981). Inherent biodegradability: Modified SCAS test. OECD guidelines for testing of chemicals

OECD Test Guideline 302B (1992). Zahn-Wellens/EMPA test. OECD guidelines for testing of chemicals

OECD Test Guideline 302C (1981). Inherent biodegradability: Modified MITI test (II). OECD guidelines for testing of chemicals

OECD Test Guideline 303A (1981). Simulation test - aerobic sewage treatment: Coupled units test. OECD guidelines for testing of chemicals. Draft update available 1999

OECD Test Guideline 304A (1981). Inherent biodegradability in soil. OECD guidelines for testing of chemicals

OECD Test Guideline 306 (1992). Biodegradability in seawater. OECD guidelines for testing of chemicals

OECD (1998b). Aerobic and anaerobic transformation in aquatic sediment systems. Draft proposal for a new guideline, December 1999

OECD (1999). Aerobic and anaerobic transformation in soil. Final text of a draft proposal for a new guideline, October. 1999

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Annex 8

APPENDIX VI

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ANNEX 9

GUIDANCE ON TRANSFORMATION/DISSOLUTION OF METALS AND METAL COMPOUNDS IN AQUEOUS MEDIA

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Annex 9

GUIDANCE ON TRANSFORMATION/DISSOLUTION OF METALS AND METAL COMPOUNDS IN AQUEOUS MEDIA*

A9.1 Introduction

A9.1.1 This Test Guidance is designed to determine the rate and extent to which metals and sparingly soluble metal compounds can produce soluble available ionic and other metal-bearing species in aqueous media under a set of standard laboratory conditions representative of those generally occurring in the environment. Once determined, this information can be used to evaluate the short term and long term aquatic toxicity of the metal or sparingly soluble metal compound from which the soluble species came. This Test Guidance is the outcome of an international effort under the OECD to develop an approach for the toxicity testing and data interpretation of metals and sparingly soluble inorganic metal compounds (SSIMs) (reference 1, this annex and section A8.7 of Annex 8). As a result of recent meetings and discussions] held within the OECD and EU, the experimental work on several metals and metal compounds upon which this Test Guidance is based has been conducted and reported (references 5 to 11, this annex).

A9.1.2 The evaluation of the short term and long term aquatic toxicity of metals and sparingly soluble metal compounds is to be accomplished by comparison of (a) the concentration of the metal ion in solution, produced during transformation or dissolution in a standard aqueous medium with (b) appropriate standard ecotoxicity data as determined with the soluble metal salt (acute and chronic values). This document gives guidance for performing the transformation/dissolution tests. The strategy to derive an environmental hazard classification using the results of the dissolution/transformation protocol is not within the scope of this Guidance document and can be found in Annex 8, section A8.7.

A9.1.3 For this Test Guidance, the transformations of metals and sparingly soluble metal compounds are, within the context of the test, defined and characterised as follows:

(a) metals, M^0, in their elemental state are not soluble in water but may transform to yield the available form. This means that a metal in the elemental state may react with the media to form soluble cationic or anionic products, and in the process the metal will oxidise, or transform, from the neutral or zero oxidation state to a higher one;

(b) in a simple metal compound, such as an oxide or sulphide, the metal already exists in an oxidised state, so that further metal oxidation is unlikely to occur when the compound is introduced into an aqueous medium. However, while oxidisation state may not change, interaction with the media may yield more soluble forms. A sparingly soluble metal compound can be considered as one for which a solubility product can be calculated, and which will yield small amount of the available form by dissolution. However, it should be recognised that the final solution concentration may be influenced by a number of factors, including the solubility product of some metal compounds precipitated during the transformation/dissolution test, e.g. aluminium hydroxide.

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* *OECD Environment, Health and Safety Publications, Series on Testing and Assessment, No. 29, Environment Directorate, Organisation for Economic Co-operation and Development, April 2001.*

A9.2 Principles

A9.2.1. This Test Guidance is intended to be a standard laboratory transformation/ dissolution protocol based on a simple experimental procedure of agitating various quantities of the test substance in a pH buffered aqueous medium, and sampling and analysing the solutions at specific time intervals to determine the concentrations of dissolved metal ions in the water. Two different types of tests are described in the text below:

A9.2.2 *Screening transformation/dissolution test – sparingly soluble metal compounds*

A9.2.2.1 For sparingly soluble metal compounds, the maximum concentration of total dissolved metal can be determined by the solubility limit of the metal compound or from a screening transformation/dissolution test. The intent of the screening test, performed at a single loading, is to identify those compounds which undergo either dissolution or rapid transformation such that their ecotoxicity potential is indistinguishable from soluble forms.

A9.2.2.2 Sparingly soluble metal compounds, having the smallest representative particle size on the market are introduced into the aqueous medium at a single loading of 100 mg/L. Such dissolution as will occur is achieved by agitation during a 24 hours period. After 24 hours agitation, the dissolved metal ion concentration is measured.

A9.2.3 *Full transformation/dissolution test - metals and sparingly soluble metal compounds*

A9.2.3.1 The full transformation/dissolution test is intended to determine level of the dissolution or transformation of metals and metal compounds after a certain time period at different loadings of the aqueous phase. Normally massive forms and/or powders are introduced into the aqueous medium at three different loadings: 1, 10 and 100 mg/L. A single loading of 100 mg/L may be used if a significant release of dissolved metal species is not anticipated. Transformation/dissolution is accomplished by standardised agitation, without causing abrasion of the particles. The short term transformation/dissolution endpoints are based on the dissolved metal ion concentrations obtained after a 7 days transformation/dissolution period. The long term transformation/dissolution endpoint is obtained during a 28 days transformation/dissolution test, using a single load of 1 mg/L.

A9.2.3.2 As pH has a significant influence on transformation/dissolution both the screening test and the full test should in principle be carried out at a pH that maximises the concentration of the dissolved metal ions in solution. With reference to the conditions generally found in the environment a pH range of 6 to 8.5 must be used, except for the 28 day full test where the pH range of 5.5 to 8.5 should be used in order to take into consideration possible long term effects on acidic lakes.

A9.2.3.3 As in addition the surface area of the particles in the test sample has an important influence on the rate and extent of transformation/dissolution, powders are tested at the smallest representative particle size as placed on the market, while massives are tested at a particle size representative of normal handling and use. A default diameter value of 1 mm should be used in absence of this information. For massive metals, this default may only be exceeded when sufficiently justified. The specific surface area should be determined in order to characterise and compare similar samples.

A9.3 Applicability of the test

This test applies to all metals and sparingly soluble inorganic metal compounds. Exceptions, such as certain water reactive metals, should be justified.

A9.4 Information on the test substance

Substances as placed on the market should be used in the transformation/dissolution tests. In order to allow for correct interpretation of the test results, it is important to obtain the following information on the test substance(s):

- substance name, formula and use on the market;
- physical-chemical method of preparation;
- identification of the batch used for testing;
- chemical characterisation: overall purity (%) and specific impurities (% or ppm);
- density (g/cm^3) or specific gravity;
- measured specific surface area (m^2/g)- measured by BET N_2 adsorption-desorption or equivalent technique;
- storage, expiration date;
- known solubility data and solubility products;
- hazard identification and safe handling precautions;
- material Safety Data Sheets (MSDS) or equivalent.

A9.5 Description of the test method

A9.5.1 *Apparatus and reagents*

A9.5.1.1 The following apparatus and reagents are necessary for performing tests:

- Pre-cleaned and acid rinsed closed glass sample bottles (paragraph A9.5.1.2);
- transformation /dissolution medium (ISO 6341) (paragraph A9.5.1.3);
- test solution buffering facilities (paragraph A9.5.1.4);
- agitation equipment: orbital shaker, radial impeller, laboratory shaker or equivalent (paragraph A9.5.1.5);
- appropriate filters (e.g.0.2 µm Acrodisc) or centrifuge for solids-liquid separation (paragraph A9.5.1.7);
- means to control the temperature of the reaction vessels to + 2 °C within the temperature range of 20 °C to 25 °C, such as a temperature controlled cabinet or a water bath;
- syringes and/or automatic pipettes;
- pH meter showing acceptable results within + 0.2 pH units;
- dissolved oxygen meter, with temperature reading capability;
- thermometer or thermocouple; and
- analytical equipment for metal analysis (e.g. atomic adsorption spectrometry, inductively coupled axial plasma spectrometry).

A9.5.1.2 All glass test vessels must be carefully cleaned by standard laboratory practices, acid-cleaned (e.g. HCl) and subsequently rinsed with de-ionised water. The test vessel volume and configuration (one- or two-litre reaction kettles) should be sufficient to hold 1 or 2 L of aqueous medium without overflow during the agitation specified. If air buffering is used (tests carried out at pH 8), it is advised to increase the air buffering capacity of the medium by increasing the headspace/liquid ratio (e.g. 1 L medium in 2.8 L flasks).

A9.5.1.3 A reconstituted standard water based on ISO 6341 should be used*, as the standard transformation/dissolution medium. The medium should be sterilised by filtration (0.2 µm) before use in the tests. The chemical composition of the standard transformation/dissolution medium (for tests carried out at pH 8) is as follows:

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* *For hazard classification purposes the results of the dissolution/transformation protocol are compared with existing ecotoxicity data for metals and metal compounds. However, for purposes such as data validation, there might be cases where it may be appropriate to use the aqueous medium from a completed transformation test directly in an OECD 202 and 203 daphnia and fish ecotoxicity test. If the $CaCl_2.2H_2O$ and $MgSO_4.7H_2O$ concentrations of the transformation medium are reduced to one-fifth of the ISO 6341 medium, the completed transformation medium can also be used (upon the addition of micronutrients) in an OECD 201 algae ecotoxicity test.*

$NaHCO_3$:	65.7 mg/L
KCl:	5.75 mg/L
$CaCl_2.2H_2O$:	294 mg/L
$MgSO_4.7H_2O$:	123 mg/L

For tests carried out at lower pH values, adjusted chemical compositions are given in paragraph A9.5.1.7.

A9.5.1.4 The concentration of total organic carbon in the medium should not exceed 2.0mg/L.

A9.5.1.5 In addition to the fresh water medium, the use of a standardised marine test medium may also be considered when the solubility or transformation of the metal compound is expected to be significantly affected by the high chloride content or other unique chemical characteristics of marine waters and when toxicity test data are available on marine species. When marine waters are considered, the chemical composition of the standard marine medium is as follows:

NaF:	3mg/L
$SrCl_2.6H_2O$:	20mg/L
H_3BO_3:	30mg/L
KBr:	100mg/L
KCl:	700mg/L
$CaCl_2.2H2O$:	1.47g/L
Na_2SO_4:	4.0g/L
$MgCl_2.6H2O$:	10.78g/L
NaCl:	23.5g/L
$Na_2SiO_3.9H2O$:	20mg/L
$NaHCO_3$:	200mg/L

The salinity should be 34 $\pm$ 0.5 g/kg and the pH should be 8.0 $\pm$ 0.2. The reconstituted salt water should also be stripped of trace metals (from ASTM E 729-96).

A9.5.1.6 The transformation/dissolution tests are to be carried out at a pH that maximises the concentration of the dissolved metal ions in solution within the prescribed pH range. A pH-range of 6 to 8.5 must be used for the screening test and the 7 day full test, and a range of 5.5 to 8.5 for the 28 day full test (para. A9.2.3.2).

A9.5.1.7 Buffering at pH 8 may be established by equilibrium with air, in which the concentration of CO_2 provides a natural buffering capacity sufficient to maintain the pH within an average of $\pm$ 0.2 pH units over a period of one week (reference 7, Annex 9). An increase in the headspace/liquid ratio can be used to improve the air buffering capacity of the medium.

For pH adjustment and buffering down to pH 7 and 6, Table A9.1 shows the recommended chemical compositions of the media, as well as the CO_2 concentrations in air to be passed through the headspace, and the calculated pH values under these conditions.

Table A9.1: Recommended chemical composition of testing medium

Chemical composition of medium	$NaHCO_3$	6.5 mg/L	12.6 mg/L
	KCl	0.58 mg/L	2.32 mg/L
	$CaCl_2.2H_2O$	29.4 mg/L	117.6 mg/L
	$MgSO_4.7H_2O$	12.3 mg/L	49.2 mg/L
CO_2 concentration (balance is air) in test vessel		0.50%	0.10%
Calculated pH		6.09	7.07

***NOTE**: The pH values were calculated using the FACT (Facility for the Analysis of Chemical Thermodynamics) System (http://www.crct.polymtl.ca/fact/fact.htm).*

A9.5.1.8 Alternative equivalent buffering methods may be used if the influence of the applied buffer on the chemical speciation and transformation rate of the dissolved metal fraction would be minimal.

A9.5.1.9 During the full transformation/dissolution tests, agitation should be used which is sufficient to maintain the flow of aqueous medium over the test substance while maintaining the integrity of the surface of the test substance and of any solid reaction product coatings formed during the test. For 1 L of aqueous medium, this may be accomplished by the use of:

- a radial impeller set at 200 r.p.m., with blades deployed 5 cm from the bottom of a 1 L reaction kettle. The radial impellers consist of two fixed polypropylene blades of dimensions 40 mm width x 15 mm height on a PVC-coated steel rod 8 mm diameter and 350 mm long; or
- a 1.0 to 3.0 L flask capped with a rubber stopper and placed on an orbital or laboratory shaker set at 100 r.p.m.

Other methods of gentle agitation may be used provided they meet the criteria of surface integrity and homogeneous solution.

A9.5.1.10 The choice of solids-liquid separation method depends on whether adsorption of soluble metal ions on filters occurs and whether or not a suspension is generated by the agitation prescribed in A9.5.1.9, which will in turn depend on particle size distributions and particle density. For solids of density greater than approximately 6 g/cm^3 and particle size ranges as low as 50% < 8 μm, experience has shown that the gentle agitation methods prescribed in A9.5.1.9 are unlikely to result in suspensions. Hence, filtration of a sample through e.g. a 25 mm diameter 0.2 μm hydrophilic polyethersulphone membrane syringe filter (as an option, overlain by a 0.8 μm prefilter) will result in a solution essentially free of solids.

However, in the event that suspensions occur, stopping the agitation to allow the suspension to settle for about 5 minutes prior to taking a solution sample may be useful.

A9.5.2 ***Prerequisites***

A9.5.2.1 *Analytical method*

A suitable validated analytical method for the total dissolved metal analysis is essential to the study. The analytical detection limit should be lower than the appropriate chronic or long term value from the exotoxicity tests.

The following analytical validation aspects are at a minimum to be reported:

- detection and quantification limit of the analytical method;
- analytical linearity range within the applicable analytical range;
- a blank run consisting of transformation medium (this can be done during the tests);
- matrix effect of the transformation medium on the measurement of the dissolved metal ion;
- mass balance (%) after completion of the transformation test;
- reproducibility of the analysis;
- adsorptive properties of the soluble metal ions on the filters (if filtration is used for the separation of the soluble from the solid metal ion).

A9.5.2.2 *Determination of the appropriate pH of the dissolution medium*

If no relevant literature data exist, a preliminary screening test may need to be carried out in order to ensure that the test is performed at a pH maximising transformation/dissolution within the pH range described in A9.2.3.2 and A9.5.1.6.

A9.5.2.3 *Reproducibility of transformation data*

A9.5.2.3.1 For a standard set-up of three replicate test vessels and two replicate samples per test vessel at each sampling time, it is reasonable to anticipate that for a constant loading of a substance, tested in a narrow particle size (e.g. 37 - 44 μm) and total surface area range, the within-vessel variation in transformation data should be less than 10% and the between-vessel variation should be less than 20 % (reference 5, this annex).

A9.5.2.3.2 To estimate the reproducibility of the transformation test, some Guidance is given in the following. The results can be used to eventually improve on reproducibility by adjusting the final test set-up through varying the number of replica test vessels and/or replica samples or further screening of the particles. The preliminary tests also allow for a first evaluation of the transformation rate of the tested substance and can be used to establish the sampling frequency.

A9.5.2.3.3 In preparing the transformation/dissolution medium, the pH of the medium should be adjusted to the desired pH (air buffering or CO_2 buffering) by agitation for about half an hour to bring the aqueous medium into equilibrium with the buffering atmosphere. At least three samples (e.g. 10 - 15 ml) are drawn from the test medium prior to addition of the substance, and the dissolved metal concentrations are measured as controls and background.

At least five test vessels, containing the metal or metal compound (e.g.100 mg solid/L medium), are agitated as described in A9.5.1.9 at a temperature $\pm$ 2 °C in the range 20 - 25 °C, and triplicate samples are taken by syringe from each test vessel after 24 hours. The solid and solution are separated by membrane filter as described in A9.5.1.10, the solution is acidified with 1% HNO_3 and analysed for total dissolved metal concentration.

A9.5.2.3.4 The within-test vessel and between-test vessel means and coefficients of variation of the measured dissolved metal concentrations are calculated.

A9.5.3 ***Test performance***

A9.5.3.1 *Dissolution screening test – sparingly soluble metal compounds*

A9.5.3.1.1 After dissolution medium is prepared, add the medium into at least three test vessels (number of test vessels depend on the reproducibility obtained during the preliminary test). After a half-hour of agitation to bring the aqueous medium into equilibrium with the atmosphere or buffering system (paras. A9.5.1.6 to A9.5.1.8), the pH, temperature and dissolved O_2 concentrations of the medium are measured. Then at least two 10 - 15 mL samples are taken from the test medium (prior to addition of the solids) and the dissolved metal concentration measured as controls and background.

A9.5.3.1.2 The metal compound is added to the test vessels at a loading of 100 mg/L and the test vessels are covered and agitated rapidly and vigorously. After the 24 hours agitation, the pH, temperature and dissolved O_2 concentrations are measured in each test vessel, and two to three solution samples are drawn by syringe from each test vessel and the solution is passed through a membrane filter as described in paragraph A9.5.1.10 above, acidified (e.g. 1 % HNO3) and analysed for total dissolved metal concentration.

A9.5.3.2 *Full test - metals and metal compounds*

A9.5.3.2.1 Repeat A9.5.3.1.1

A9.5.3.2.2 For 7 day test, substance loadings of 1, 10 and 100 mg/L, respectively, are added to the test vessels (number of which depends on the reproducibility as established in –sub-section A9.5.2.3), containing the aqueous medium. The test vessels are closed and agitated as described in A9.5.1.9. If a 28 day test is to be conducted, the test with 1 mg/L loading may be extended to 28 days, provided that the same pH value is to be chosen for both 7 day and 28 day tests. However, since 7-day tests are only conducted at pH ranges of 6 and higher, separate 28-day tests are needed to cover the pH range between 5.5 and 6. It may also be useful to include a concurrent control test with no substance loaded (i.e. a blank test solution). At established

time intervals (e.g. 2 hours, 6 hours, 1, 4 and 7 days), the temperature, pH and dissolved O_2 concentrations are measured in each test vessel, and at least two samples (e.g. 10 - 15 mL) are drawn by syringe from each test vessel. The solid and dissolved fractions are separated as per A9.5.1.10 above. The solutions are acidified (e.g. 1 % HNO_3) and analysed for dissolved metal concentration. After the first 24 hours, the solution volumes should be replenished with a volume of fresh dissolution medium equal to that already drawn. Repeat after subsequent samplings. The maximum total volume taken from the test solutions should not exceed 20% of the initial test solution volume. The test can be stopped when three subsequent total dissolved metal concentration data points vary no more than 15%. The maximum duration for the loadings of 10 and 100 mg/L is seven days (the short term test) and 28 days for the loading of 1 mg/L test medium (long term test).

A9.5.4 ***Test Conditions***

A9.5.4.1 The transformation/dissolution tests should be done at a controlled ambient temperature $\pm$ 2 °C in the range 20 – 25 °C.

A9.5.4.2 The transformation/dissolution tests are to be carried out within the pH range described in paragraphs A9.2.3.2 and A9.5.1.6. The test solution pH should be recorded at each solution sampling interval. The pH can be expected to remain constant ($\pm$ 0.2 units) during most tests, although some short-term pH variations have been encountered at 100 mg/L loadings of reactive fine powders (reference 7, this annex), due to the inherent properties of the substance in the finely divided state.

A9.5.4.3 Above the aqueous medium, the head space provided by the reaction vessel should be adequate in most instances to maintain the dissolved oxygen concentration above 70% of its saturation in air, which is about 8.5 mg/L. However, in certain instances, reaction kinetics may be limited not by the availability of molecular oxygen in the head space above the solution but by the transfer of dissolved oxygen to, and removal of reaction product away from, the solid-solution interface. In this case, little can be done, other than await the restoration of equilibrium.

A9.5.4.4 To reduce chemical and biological contamination as well as evaporation, the transformation/dissolution kinetics must be performed in closed vessels and in the dark, whenever possible.

A9.6 Treatment of the results

A9.6.1 ***Screening test***

The mean dissolved metal concentrations at 24 hours are calculated (with confidence intervals).

A9.6.2 ***Full test: Determination of the extent of transformation/dissolution***

A9.6.2.1 *Short term test*

The dissolved metal concentrations, measured during the different short term (7 days) tests, are plotted versus time, and the transformation/dissolution kinetics may be determined, if possible. The following kinetic models could be used to describe the transformation/dissolution curves:

(a) Linear model:

$$C_t = C_0 + kt, \text{ mg/L}$$

where:

C_0 = initial total dissolved metal concentration (mg/L) at time t = 0;
C_t = total dissolved metal concentration (mg/L) at time t;
k = linear rate constant, mg/L-days.

(b) First order model:

$C_t = A(1-e^{(-kt)})$, mg/L

where:

A = limiting dissolved metal concentration (mg/L) at apparent equilibrium = constant;

C_t = total dissolved metal concentration (mg/L) at time t;

k = first order rate constant, 1/days.

(c) Second order model:

$C_t = A(1-e^{(-at)}) + B(1-e^{(-bt)})$, mg/L

where:

C_t = total dissolved metal concentration (mg/L), at time t;

a = first order rate constant, 1/days;

b = second order rate constant, 1/days;

C = A + B = limiting dissolved metal concentration (mg/L).

(d) Reaction kinetic equation:

$C_t = a[1-e^{-bt} - (c/n)\{1 + (b\,e^{-nt} - n\,e^{-bt})/(n - b)\}]$, mg/L

where:

C_t = total dissolved metal concentration (mg/L) at time t;

a = regression coefficient (mg/L);

b,c,d = regression coefficients (1/days);

n = c+d.

Other reaction kinetic equations may also apply (reference7 and 8, this annex).

For each replicate vessel in the transformation test, these model parameters are to be estimated by regression analyses. The approach avoids possible problems of correlation between successive measurements of the same replicate. The mean values of the coefficients can be compared using standard analysis of variance if at least three replicate test vessel were used. The coefficient of determination, r^2, is estimated as a measure of the "goodness of fit" of the model.

A9.6.2.1 *Long term test*

The dissolved metal concentrations, measured from the 1 mg/L loading during the 28 day test, are plotted versus time and the transformation/dissolution kinetics determined, if possible, as described in A9.6.1 and A9.6.2.

A9.7 Test report

The test report should include (but is not limited to) the following information (also see A9.4 and A9.5.2.1):

- identification of the sponsor and testing facility;
- description of the tested substance;
- description of the reconstituted test medium and metal loadings;
- test medium buffering system used and validation of the pH used (as per paras. A9.2.3.2 and A9.5.1.6 to A9.5.1.8) description of the analytical method;
- detailed descriptions of the test apparatus and procedure;
- preparation of the standard metal solution;

- results of the method validation;
- results from the analyses of metal concentrations, pH, temperature, oxygen;
- dates of tests and analyses at the various time intervals;
- mean dissolved metal concentration at different time intervals (with confidence intervals);
- transformation curves (total dissolved metal as a function of time);
- results from transformation/dissolution kinetics, if determined;
- estimated reaction kinetic quation, if determined;
- deviations from the study plan if any and reasons;
- any circumstances that may have affected the results; and
- reference to the records and raw data.

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Annex 9

APPENDIX

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CORRIGENDUM

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GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS

Corrigendum 1

NOTE: Corrigenda to the Globally Harmonized System of Classification and Labelling of Chemicals are also made available via INTERNET on the web site of the United Nations Economic Commission for Europe at the following address: http://www.unece.org/trans/danger/publi/ghs/ghs.html

TABLE OF CONTENTS

Page v In the titles of Chapters 2.8, 2.11 and 2.12, **replace** "substances" **with** "chemicals".

PART 1

Page 8
1.1.3.1.5.3 8th line, **insert** a space between "countries'" and "requirements".
1.1.3.2 4th line, **correct** the acronym to read UNCETDG/GHS.

Page 13 **Replace** the current ISO definition with the following:
"ISO means the "International Organization for Standardization; "

Page 32
1.4.10.5.3.1 (c) **Delete** the word "new".

Page 36 **Replace** the footnote number "4" **with** "1".

Page 37 **Replace** the footnote number "5" **with** "2".

PART 2

Page 49 In the second diamond-shaped box on the left side, **replace** "division 5.1" **with** "the classes of oxidizing substances"; in the last box of the left side of the page, **replace** "division 5.1" **with** "the classes".

Page 71
2.6.4.2.5 **Replace** the first line under "***National standards***" **with**: "*American Society for Testing Materials International, 100 Barr Harbor Drive, PO Box C 700, West Conshohocken, Pennsylvania, USA 19428-2959"*

(PTO)

ST/SG/AC.10/30/Corr.1
ENGLISH ONLY
(Corrigendum 1 applies to the English version only)

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Page 72
2.6.4.2.5 **Replace** *"Deutscher Normenausschuss"* **with**:

" Deutsches Institut für Normung, Burggraffenst 6, D-10787 Berlin".

Pages 77, 85 and 89

In the headings of chapters 2.8, 2.11 and 2.12 respectively, **replace** "substances" **with** "chemicals".

Page 79 In box 10 of decision logic 2.8, **delete** "for transport".

Page 85
2.11.1 In the first line of the definition, after "solid" **insert** "or liquid".

Page 104 In box 10 of decision logic 2.15, **delete** "for transport".

PART 3

Page 111 **Insert** the following missing paragraph:

"3.1.2.6.4 Of particular importance is the use of well articulated values in the high toxicity categories for dusts and mists. Inhaled particles between 1 and 4 microns mean mass aerodynamic diameter (MMAD) will deposit in all regions of the rat respiratory tract. This particle size range corresponds to a maximum dose of about 2 mg/l. In order to achieve applicability of animal experiments to human exposure, dusts and mists would ideally be tested in this range in rats. The cut-off values in the table for dusts and mists allow clear distinctions to be made for materials with a wide range of toxicities measured under varying test conditions. The values for dusts and mists should be reviewed in the future to adapt to any future changes in OECD or other test guidelines with respect to technical limitations in generating, maintaining, and measuring dust and mist concentrations in respirable form."

Page 134 In the brackets of the second box on the left, **replace** "3.2.1.1" **with** "3.2.1."

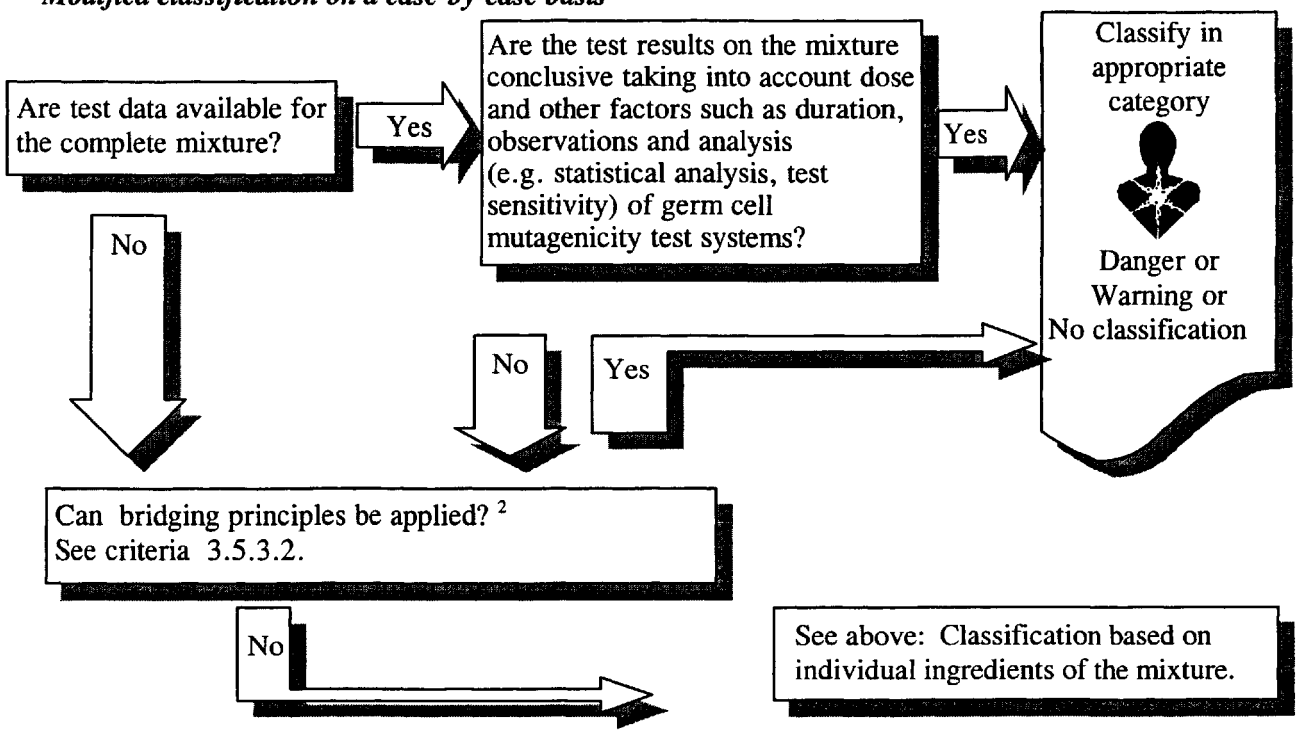
Page 142 In the last brackets of the sentence below Table 3.3.1, **replace** "para..3.2.4.7" **with** "para.1.3.2.4.7".

Page 157
3.4.5.1 In the penultimate box on the left, **replace** "(see 3.4.3.4)" **with** "(see 3.4.3.3)".

Page 158
3.4.5.2 In the penultimate box on the left, **replace** "(see 3.4.3.4)" **with** "(see 3.4.3.3)".

Page 164 **Replace** the decision logic 3.5.2 with the following:

"Modified classification on a case-by-case basis



Page 164 **Correct** the end of footnote 2 of decision logics 3.5.2 to read: ".....in accordance with paragraph 3.5.3.2".

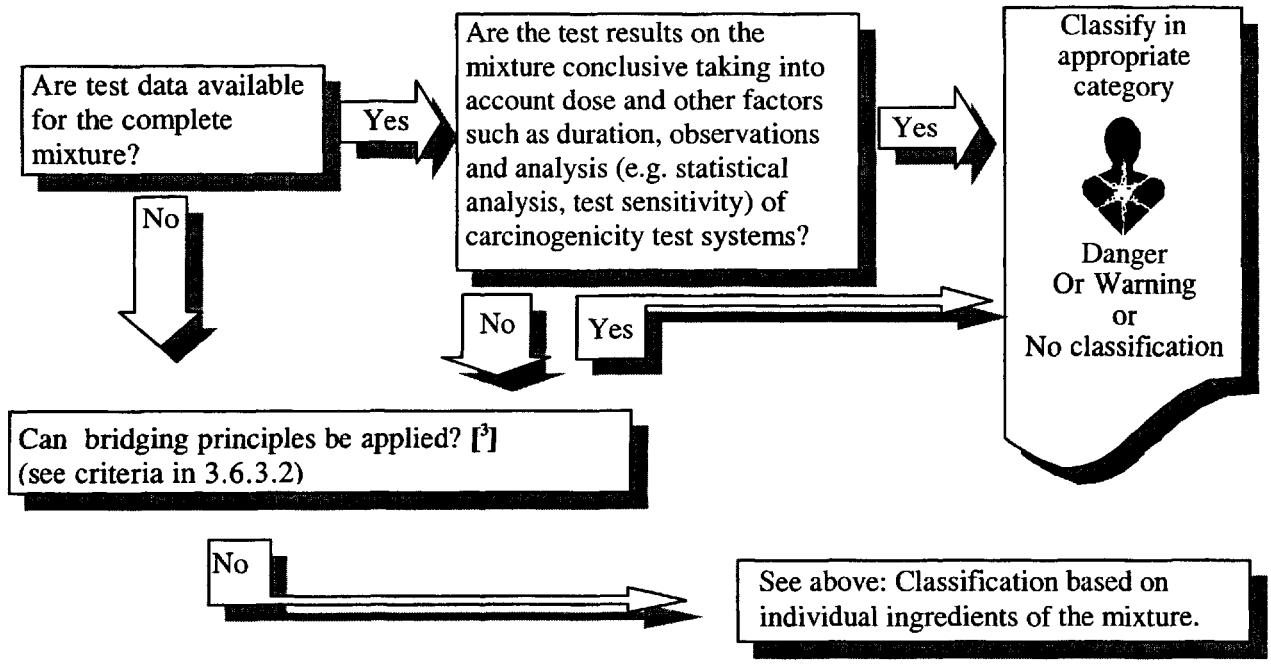
Page 169

3.6.2.7 4th line, **replace** the reference to the proceedings **with** "*WHO/IPCS workshop on the Harmonization of Risk Assessment for Carcinogenicity and Mutagenicity (Germ cells)-A Scoping Meeting (1995, Carshalton, UK)*".

Page 173

3.6.5.2 **Replace** the decision logic 3.6.2 **with** the following:

Modified classification on a case-by-case basis



Page 173 **Add** a footnote 3 to read as follows:

"[3] *If data of another mixture are used in the application of bridging principles, the data on that mixture must be conclusive in accordance with paragraph 3.6.3.1.*".

Page 174
3.6.5.3 In the end of the first sentence, **replace** "3.6.5.2.1 and 3.6.5.2.2" **with** "3.6.5.3.1 and 3.6.5.3.2".

Page 174 **Renumber** footnotes 3 and 4 as footnotes 4 and 5 respectively.

Page 185 **Correct** the end of footnote 6 of decision logics 3.7.2 to read: ".....in accordance with paragraph 3.7.3.2".

Page 211 to 223 Wherever they appear in 3.10.2 to 3.10.4, **replace** the roman numbers designating the aquatic hazard acute and chronic categories (Acute I, II, III; Chronic I, II, III, IV) **with** arabic numbers (Acute 1, 2, 3; Chronic 1, 2, 3, and 4).

ANNEX 1

Page 237 In the title, **replace** "substances" **with** "chemicals".

Page 239 In the title, **replace** "substances" **with** "chemicals".

Page 240 In the title, **replace** "substances" **with** "chemicals".

Page 248 In the Table "Toxic to reproduction", 4th column: **move** the words "effects on or via lactation" into the title of the column to read: "Additional category on effects on or via lactation".

ANNEX 2

Page 261 In the title, **replace** "substances" **with** "chemicals".

Page 263 In the title, **replace** "substances" **with** "chemicals".

Page 264 In the title, **replace** "substances" **with** "chemicals".

Page 282 In Hazard Category 1, in the Hazard Statement, **replace** "through prolonged or repeated exposure" **with** "through single exposure";

In Hazard Category 2, in the Hazard Statement, **replace** "through prolonged or repeated exposure" **with** "through single exposure".

ANNEX 3

Page 297
A3.3.3.3 16th and 17th statements, **after** "lukewarm" **insert** "water".