

GHS Classification Guidance  
for the Japanese Government  
2<sup>nd</sup> edition

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Edited by

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## Part1 Introduction

### 1-1. Regarding "GHS Classification Guidance"

The “Globally Harmonized System of Classification and Labelling of Chemicals (GHS)” (hereinafter, abbreviated as UN GHS) was discussed in the UN for many years, and the Economic and Social Council adopted a resolution to promote implementation of GHS worldwide, and individual countries are establishing systems to introduce GHS. In Japan, the government launched the GHS Inter-ministerial Committee in 2001, which began translating UN GHS-related documents into Japanese, exchanging information to establish GHS-related domestic laws, promoting the classification of substances in Japan, and implementing the GHS classification of substances requiring MSDS under PRTR Law, Industrial Safety and Health Law, Poisonous and Deleterious Substances Control Law, etc. (about 1,500 substances) as references between FY 2006 and FY 2007, and published the classification results.

To facilitate GHS classification within a short period of two years, the committee established the “GHS Classification Manual,” which defines practical methods for data collection and evaluation criteria for data reliability, and the “Technical Guidance on GHS classification,” which defines detailed technical principles and judgment criteria on health hazards.

It has been pointed out that UN GHS documents include several parts for which individual countries can optionally select how to adapt GHS to its own system and to descriptions that are difficult to classify. Therefore, in FY 2007, the ministries and agencies concerned and interested parties decided the Japanese principles for these parts, while taking international harmonization into account (based on the 2007 revised edition of UN GHS), and worked to establish the Japanese Industrial Standard (JIS) for “Classification method of chemicals based on “Globally Harmonized System of Classification and Labelling of Chemicals (GHS)” (hereafter Classification JIS) based on the principles from FY 2008. In this Guidance, the JIS Z 7252-2009, "Classification methods of chemicals based on GHS" is abbreviated as "Classification JIS".

The ministries and agencies concerned decided to begin classifying new chemicals utilizing the manual and technical guidance, however, a manual providing greater accuracy is required. Accordingly, the new and more accurate “GHS classification guidance” for the Japanese Government, which is consistent with the Classification JIS described above and an integrated “GHS Classification Manual” and “Technical Guidance on GHS classification” that offer more convenience were produced.

This guidance is a manual based on Classification JIS, while providing for global

harmonization, to allow GHS classification to be carried out correctly and effectively. It should be noted, however, that UN GHS includes classifications that are not adopted by Classification JIS, and this guidance includes original Japanese judgments and considerations unique to this guidance. (Regarding classifications that have not been adopted by Classification JIS, explanations are given where possible at the related part. Refer to them.)

It should be noted, however, that this guidance is designed for the effective implementation of the GHS classification, and hence requires a detailed investigation (checking original scientific papers, collection of new findings, hearing the views of experts, etc.) to achieve a more reliable classification.

Furthermore, this guidance may be amended, reflecting revisions to UN GHS, and as is considered reasonable, taking classification implementation status and efficiency, etc., into account, and based on a consensus of all parties concerned.

In the present guidance, parts inside the double-lined frames are copies extracted from the Third revised edition of UN GHS.

1st edition on March 2009

2nd edition on March 2010

(URL in this guidance are as of Jan.2011)

## 1-2. Method of describing classification results

### (1) Regarding the description of classification results

In this guidance, the classification results for some substances are expressed as follows.

Phrases used in classification results	Explanation
Classification not possible	In case no data are available for classification after searching various information sources and in house data and the like, or sufficient data for classification are not available.
Not applicable	Substances outside the class since their physical properties do not meet the GHS definition. For example, considering a hazard class of "XX solids, a substance whose normal state is a Liquid or a gas is designated as "Not applicable." When considering chemical structure, a substance not having chemical groups related to the evaluation items (Table 2-1, right columns) is also designated as "Not applicable."
Not classified	Although sufficient information for classifying a substance was available, sufficient evidence to classify it into the lowest hazard category defined by GHS were not found after classification. In cases of a lack of sufficient information, not "Not classified" but "Classification not possible" should be chosen.

Notes : Most classes of physical hazards in GHS are that of United Nations Recommendations on the Transport of Dangerous Goods (UNRTDG). Dangerous goods are to be transported in suitable containers. Risk is expressed for fire or leakage due to accidental damage to the container and the like. As the result, in some classes of TDG, classification into more dangerous classes may be made.

Also, a substance with results outside the class obtained from test methods defined by UNRTDG is designated as "Not classified." For example, in the class of Oxidizing Solids, potassium nitrate tetrahydrate, nickel nitrate, and strontium nitrate (anhydride) are illustrated not to be in division 5.1 in the brochure of TDG test methods, and they are considered to be "Not classified," although they are oxidative materials.

Therefore, it should be noted that substances designated as "Not classified" in GHS Physical Hazards are not "free from hazards," but have "less hazardous."

Furthermore, as stated in "3-3-1 Acute Toxicity", it should be noted that classification standard for GHS 3rd revised edition and JIS Classification are not identical. For example, Acute Toxicity classification 5 in the GHS 3rd revised edition is classified as "Not classified" in the JIS Classification.

(2) Points to remember when describing classification results

- When quoting an evaluation document as supporting evidence, use its abbreviation if available in the List.
- For the description of GHS classification results, the “GHS data input form” (GHS Inter-ministerial Committee, 2006FY) is helpful. Before describing, refer to the “Explanation of GHS hazard sheet.” Both “GHS data input form” and “Explanation of GHS hazard sheet” are available from: National Institute of Technology and Evaluation  
[http://www.safe.nite.go.jp/english/ghs\\_index.html](http://www.safe.nite.go.jp/english/ghs_index.html)  
“Supporting tool for GHS Classification” can be downloaded from the website of the National Institute of Technology and Evaluation

### 1-3. Workflow of GHS classification

Figures 1-1 to 1-3 show the workflow of GHS classification.

Figure 1-1 GHS Classification Workflow(Physical Hazards)

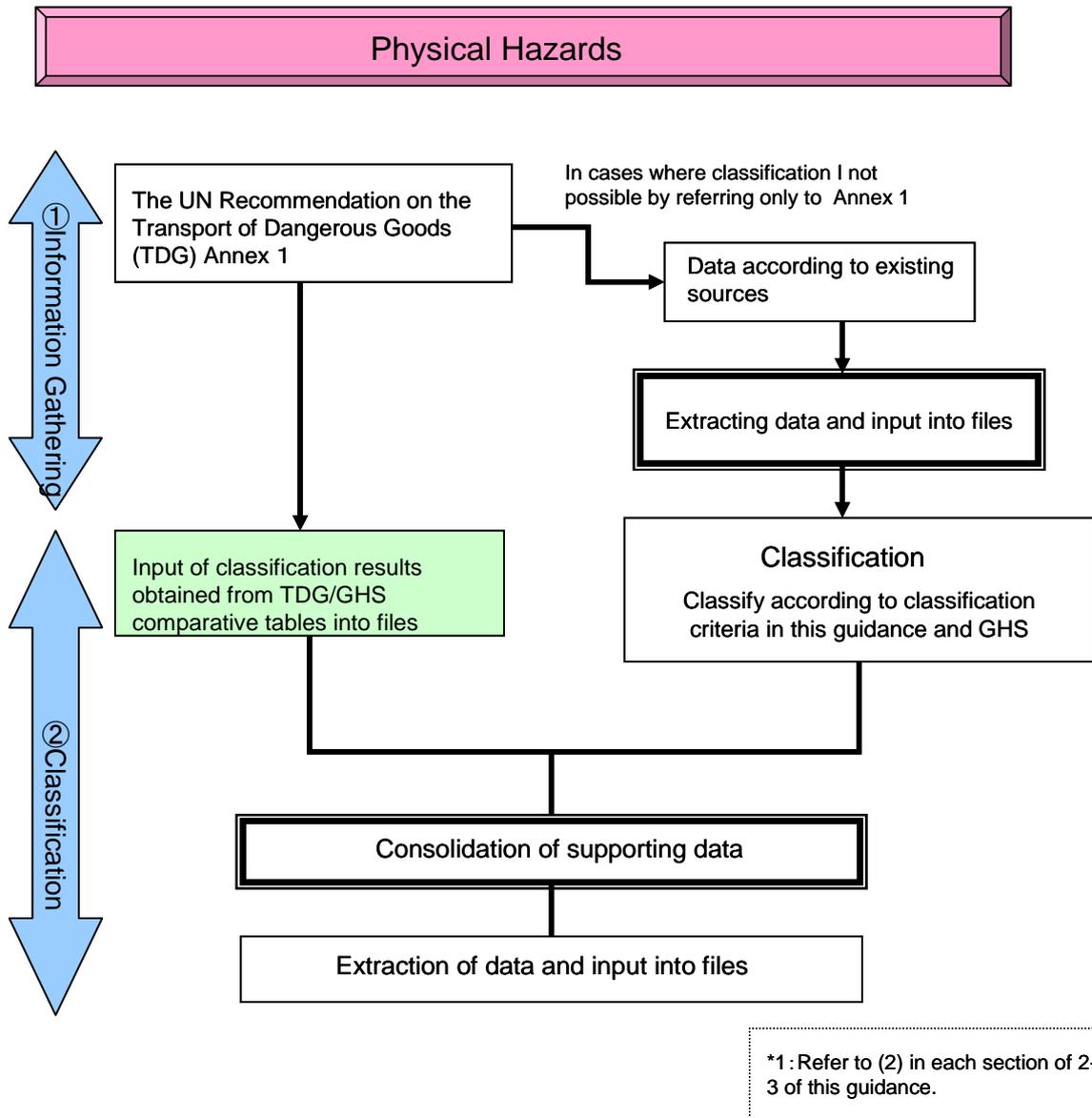


Figure 1-2 GHS Classification workflow(Health Hazards)

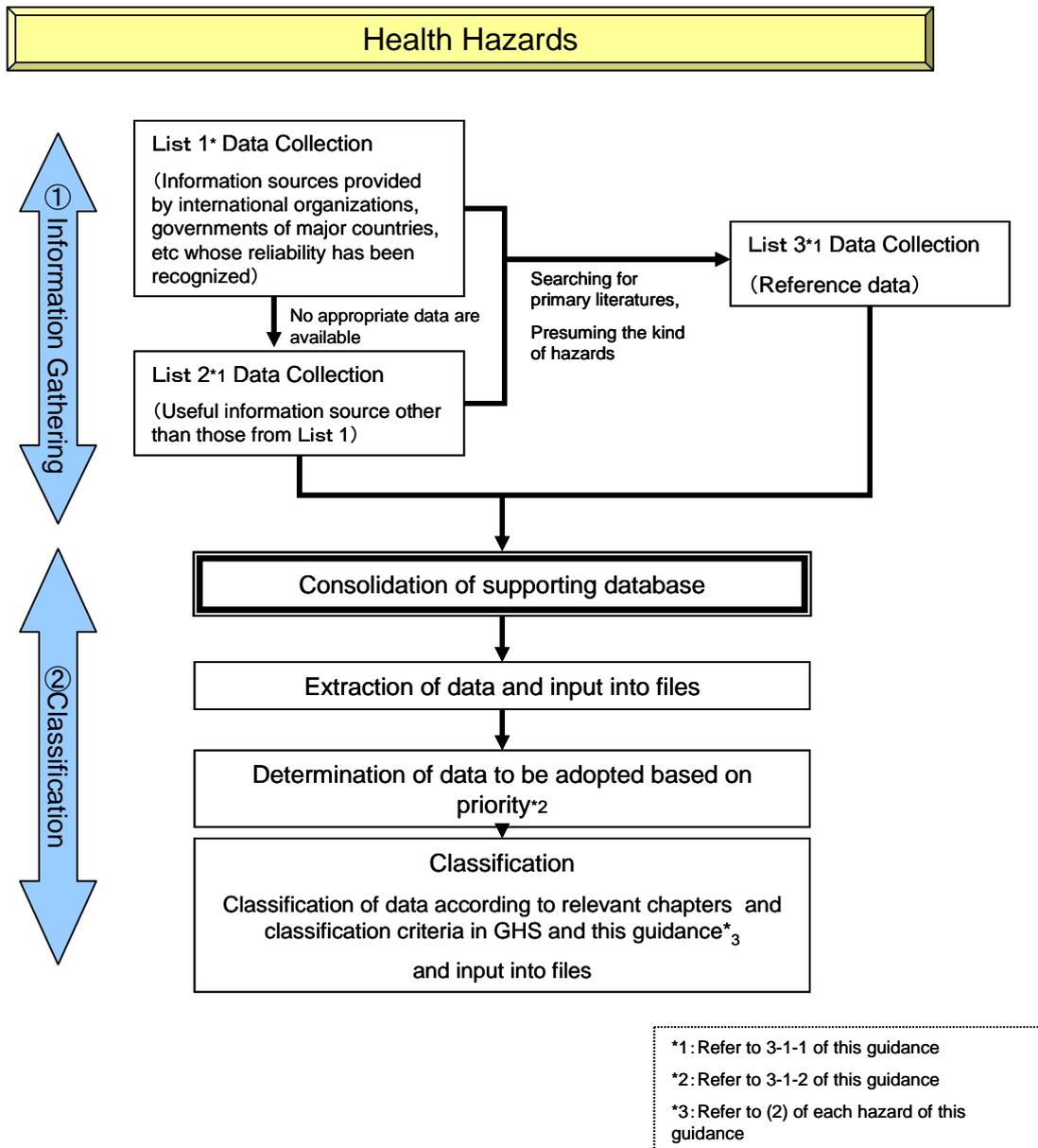
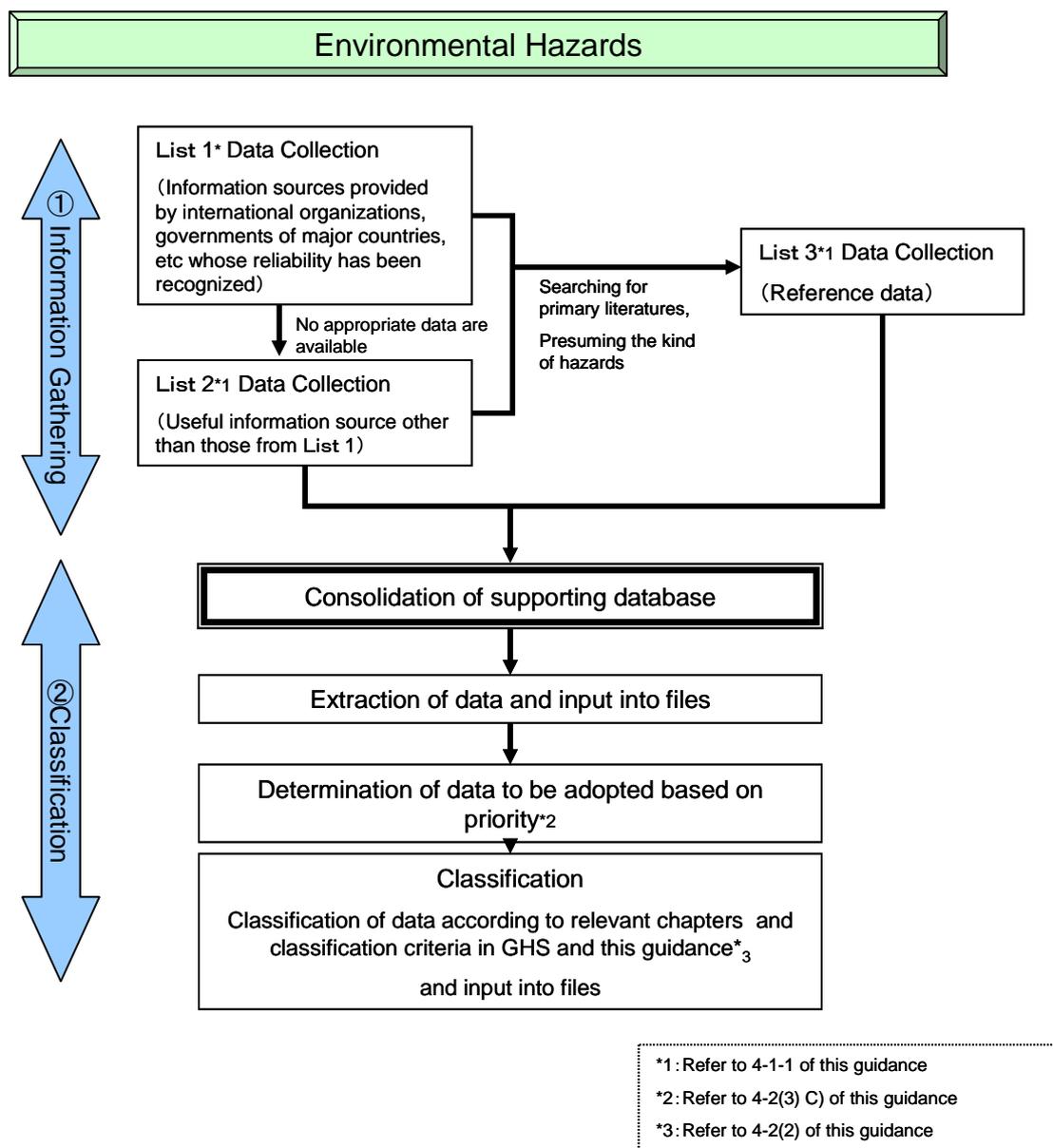


Figure 1-3 GHS Classification workflow(Environmental Hazards)





## Part2. Physical Hazards Guidance

### 2-1. Sources of information available for classification and judgment

The physical properties of substances, particularly the relationship between temperature and physical states, are one of the key factors for GHS classification. Equally important is information regarding physical hazards such as flammability, explosibility, combustion-supporting properties, and explosion limits. What follow are descriptions of literatures concerning the existing systems used as classification criteria and the useful sources of information.

#### 2-1-1 Information directly applicable to GHS classification (Classification according to the United Nations Recommendations on the Transport of Dangerous Goods)

At present, progress is being made to the document that brought together classification results based on GHS. Since, however, the classification of physical hazards in GHS is based on the United Nations Recommendations on the Transport of Dangerous Goods (UNRTDG) (hereinafter abbreviated as TDG classification) that has been utilized under an international consensus, the classification in GHS accords, in principle, with that of TDG. However, as GHS includes dangerous goods whose transportation is prohibited (unstable explosives) and substances not applicable to dangerous goods in TDG classification, their classes and categories could not be found in TDG classification (Table 2-4).

Although the basic procedures of GHS classification are applying the GHS classification to a given substance on the basis of its physicochemical properties and designating its TDG classification and UN number accordingly, due to the above-mentioned fact into account, checking how the substance is classified in TDG is also practically indispensable. For this purpose, recommendations in (1) can be utilized as database, and related literatures (2) and (3) may be used as complement.

#### (1) The United Nations Recommendations on the Transport of Dangerous Goods(UNRTDG)

The recommendations were presented, like the GHS recommendations, by the UN Committee of Experts on the Transport of Dangerous Goods (CETDG), and has complementary contents. Therefore, it is appropriate to use them in GHS classification.

As of March 2010, the latest version is “UN Recommendations on the Transport of Dangerous Goods, Model Regulations, Sixteenth revised edition, 2009”.

[http://www.unece.org/trans/danger/publi/unrec/rev16/16files\\_e.html](http://www.unece.org/trans/danger/publi/unrec/rev16/16files_e.html)

<http://jonai.medwel.cst.nihon-u.ac.jp/uploadfiles/file/pdf/orange1.pdf> (Japanese version of the Fifteenth revised edition, 2007)

A site posting UN numbers and TGD classification results for individual substances is given below (National Institute of Technology and Evaluation). Preferably, the UN numbers and TGD

classification results on the site are to be sufficiently confirmed:

<http://www.safe.nite.go.jp/english/db.html>

## (2) The International Maritime Dangerous Goods Code (IMDG Code)

Regarding maritime transport, the International Maritime Organization (IMO) issues the International Maritime Dangerous Goods Code (IMDGC). As of March 2010, its latest version is for 2008, and its classification agrees with that in (1).

This code is incorporated into the “Regulations for the Carriage and Storage of Dangerous Goods by Ship” of Japan (hereinafter abbreviated as the “Dangerous Goods Regulations”) (the 14th edition by Kaibundo, 2009). The TDG classification is also adopted in the Aviation Law and its enforcement regulations, just like in the Dangerous Goods Regulations.

The site posting the Annex 1 of the Dangerous Goods Regulations: (Note that its content may lag behind that of the UN information)

<http://law.e-gov.go.jp/htmldata/S32/S32F03901000030.html> (Japanese text only)

Although the following literature is not directly related to GHS classification, it is used complementarily.

- EMS GUIDE, Emergency Response Procedures for Ships Carrying Dangerous Goods, EmS (corresponding to the 2002 version of IMDG Code. Its Japanese translation is not available.)

## (3) The Emergency Response Guidebook (ERG)

Guidelines jointly developed by Canada, the U.S., and Mexico for those responding to land transport accidents.

Its Japanese version was first released in 2001(the 3<sup>rd</sup> revised version was released in 2009.)(“Emergency Response Guidebook: Application to the Container Yellow Card labeling system”, the Japan Chemical Industry Association). According to the Guidebook, Japan's yellow cards are to indicate schedule numbers 111-172.

### 2-1-2 Data collection systems of physical properties

As described above, GHS classification starts with searching TDG classification. If none of information regarding TDG classification is obtained, required physicochemical data must be collected from other databases.

Available databases for physical properties that can be used for this purpose are as follows.

For GHS classification of gases and low-temperature boiling liquids, information regarding various physical properties is important. In this section, databases for papers and abstracts that served as standard references for chemical researchers and engineers throughout the 20th century are first given in (1-4). In addition, databases on physical properties are indicated in (5) and (6)

that have been useful especially for chemical engineers. Recent materials on physical properties of organic chemicals, including online databases, are introduced in (7) - (13).

For high-temperature boiling liquids, the information included in the hazard databases described in the next section is often sufficient, because their hazards are less affected by their physical properties.

In cases of solids, their degree of hazard often varies depending on their shape, particle size, surface state, etc., and, in general, each product should be measured and evaluated.

(1) Gmelins Handbuch der Anorganischen Chemie and Gmelin Handbook of Inorganic and Organometallic Chemistry 8th Ed (Gmelin)

They derive from “Handbuch der theoretischen Chemie”, a textbook written by Leopold Gmelin in 1817 for his lecture. The right to edit the textbook was transferred to in the German Chemical Society in 1921, to develop it into a systematic book on inorganic compounds and organometallic compounds.

Publication of its 8th edition started in 1924 (from “zinc,” which had a system number of 32), and it grew into a huge series of about 300 volumes by 1998. The series has been published in English since 1982, and the latest digitized version is available in CD format.

(2) Beilsteins Handbuch der Organischen Chemie and Beilstein Handbook of Organic Chemistry 5th ed. (Beilstein)

These derive from the organic chemistry handbook in two volumes written by K.Beilstein (professor at the Imperial Technical Institute in St. Petersburg) in 1881 and 1882. Its 1st through 3rd editions were published by Beilstein, and, then, the right to edit the book was transferred to the German Chemical Society in 1896.

P. Jacobson and B. Prager jointly started the publication of the 4th edition in 1918. Subsequently, succeeding editors published supplementary volumes to the 4th edition throughout the 20th century.

The book started to be published in English from its 5th enlarged edition, published in 1960. It was digitized and provided in CD format in 1997.

(3) The Merck Index 14th Ed (Merck)

This is a manual for reagents and pharmaceutical materials first published in 1889 by Merck. The latest 14th edition is digitized and provides a search system utilizing the Web.

(4) Chemical Abstracts (CA)

This journal of abstracts has been edited by the American Chemical Society and published by the Chemical Publishing (now Chemical Abstracts Service) since 1907. It covers chemical

literatures and patents worldwide, and includes not only material information but also all relevant information in theoretical chemistry and chemical technology. Every substance listed since 1907 was given a CAS number, retroactively, in September, 2002. It is now utilized primarily online, although its hard copies are still available.

(5) International Critical Tables of Numerical Data, Physics, Chemistry and Technology (ICT)

This database is compiled by the U.S. National Research of Council under the auspices of the International Research Council and the U.S. National Academy of Sciences. A total of 7 volumes were published by McGraw-Hill between 1926 and 1930, and their general index was released in 1933.

(6) Fluid Physical Properties Database for Engineers

This is a revised edition of the "Chemical Substance Constants," which had been published by the Society of Chemical Engineers, Japan until 2003. Instead of providing the physical properties itself, it enables the search for the reference materials which are the source of the physical properties. It now includes a wider range of physical properties to cater for chemical technology and many other fields such as machine technology.

(7) Ullmanns Encyklopaedie der Technischen Chemie and Ullmann's Encyclopedia: Industrial Organic Chemicals (Ullmann)

The 4th edition of Ullmann's Encyclopedia of Industrial Chemistry, which was first published in the 1920s, was published by Verlag Chemie between 1972 and 1984. Volumes 1-7 provide a general introduction, and volumes 8-24, specifics about each substance. Volume 25 is an index. Wiley-VCH published the English version, in eight volumes, in 1999, focusing on organic base raw materials and intermediates.

It covers major chemical reactions, applications, and toxicity, with about 20 pages of description for each group of substances and excellent tables of physical properties.

(8) Handbook of Physical Properties of Organic Chemicals (about 13,000 substances) (Howard)

This database of physical properties was compiled by P.H.Howard and W.M.Meylan (Syracuse Research Corporation) and published by Lewis in 1997. It addresses a total of about 13,000 organic substances, arranged in order of their CAS numbers and contains data for eight parameters: melting point, boiling point (including boiling point under reduced pressure), aqueous solubility, octanol/water distribution coefficient, vapor pressure, dissociation constant, Henry coefficient, and reaction rate constant of hydroxyl radical in atmosphere.

(9) Chapman and Hall Chemical Database (Chapman) (442,257 records as of 1997)

This physicochemical database of organic compounds was originally called "HEILBRON" (a commercial database): <http://library.dialog.com/bluesheets/html/bl0303.html>

(10) CRC Handbook of Chemistry and Physics (CRC)

CRC publishes this handbook of physicochemical properties, and it is now in 84th edition. Information in the book can be searched by CAS number.

(11) HODOC File (Handbook of Data on Organic Compounds) (HODOC)

(25,580 substances as of 2008)

This is a database version of the CRC handbook. In Japan, this database is managed by the Japan Science and Technology Agency:

(12) Sax's Dangerous Properties of Industrial Materials (Sax)

Wiley-VCH Publishing has published this database of dangerous physical properties of industrialized products, and it is now in the 11th edition). Data on reactivity, combustibility and explosibility of more than 20,000 substances are listed. Information of the database can be searched by CAS number.

(13) Hazardous Substances Data Bank (HSDB)

This is a database compiled by the National Library of Medicine (NLM) of the U.S. Department of Health and Human Services, and it contains data on physicochemical properties as well. It is available in CD-ROM and is also searchable online. Search by CAS number is available. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>

(14) eChem Portal (OECD)

This is the portal site of eChem OECD. Physicochemical data can be searched from the CAS number or the name of the substance.

<http://webnet3.oecd.org/echemportal/>

### 2-1-3 Data collections of physicochemical hazard data

Scientific literatures focused on hazards of chemicals began to emerge in the latter half of the 20th century.

They addressed, however, emergency measures and risk management measures rather than listing hazard data, and they were filled with paragraphs on those topics and rating of hazards. They do not serve well in GHS classification especially for physical hazards. Accordingly, GHS classification is going to depend on TDG classification described in 2-1-1 for the time being. As some hazard databases include health hazard data, the ones that predominantly contain the

descriptions of physical hazards are selected in this section.

Note that items (2) and (3), which focus on the reactivity between two substances that are outside the present GHS, are listed only for readers' reference.

(1) Hommel Handbook of Dangerous Goods(Hommel)(1205 substances)

Its Germany version was compiled by Gunter Hommel and published by Springer-Verlag in 1970, undergoing revisions thereafter. The 1987 version was translated into Japanese by Rokuro Arai and published by Springer-Verlag Tokyo.

(2) Bretherick's Handbook of Reactive Chemical Hazards and Bretherick's Handbook of Dangerous Goods (5th edition) (Bretherick)

The first edition was published by Butterworth-Heinemann (U.K.) in 1975, and the 5th edition was published in 1995. It has detailed description on incompatible hazards. Its Japanese version was translated and supervised by Shozo Tamura and published by Maruzen in 1998.

(3) Incompatible Hazard Handbook of Chemicals (Tokyo Fire Department)

The first edition was supervised by Tadao Yoshida and Shozo Tamura and published by Nikkan Kogyo Shinbun in 1980, followed by the second edition in 1997. For each of more than 520 substances, around ten incompatible materials are ranked by the severity.

(4) Hazardous Chemicals Data Book (G. Weiss) and Solvents Safety Handbook (D. J. De Renzo) (Weiss)

The second edition of the former (covering 1,016 substances) was published in 1986 by Noyes Data Corporation (the U.S.), from which the latter (covering 335 solvents) span off.

Data of each substance are given in one page in the former, while the latter provides another page with a table in which 7 properties for example temperature, are compared. Since they are American books, they provide data in Fahrenheit, yards, and pounds.

(5) Dangerous Goods Data Book (Tokyo Fire Department)

The first edition was compiled by the Tokyo Consolidated Fire Prevention Association under the supervision of the Watch Committee of the Tokyo Fire Department and published by Maruzen in 1988, followed by the second edition covering 290 substances in 1993.

(6) Data Sheet of Dangerous Goods in Road Transport (the Research Institute for Safety Engineering)

This data sheet was published by the Research Institute for Safety Engineering in 1991 with the support of the three Public Highway Corporations. Its enlarged edition was published later,

followed by the 1996 edition covering 322 substances.

(7) Chemical Substances Safety Data Book (The Chemical Substances Safety Information Workshop)

This data book, supervised by Yoichi Uehara, was first published by Ohmusha in 1994, followed by the 1997 revised and enlarged edition covering 582 substances.

(8) International Chemical Safety Cards (ICSC)

This database was developed by the International Program on Chemical Safety (IPCS). ILO<sup>1</sup> is responsible for those parts of the database classifying physical hazards such as flashing point, ignition point, and explosion limit, and WHO<sup>2</sup> is responsible for the parts covering health hazards. It is available in 16 different languages including English, Japanese, Chinese, Korean, German, Italian, French, and Russian.

At present, cards for about 1,400 substances are available, each of which can be searched by CAS number.

<http://www.cdc.gov/niosh/ipcs/nicstart.html>

Japanese version : <http://www.nihs.go.jp/ICSC/>

(9) Fire Protection Guide to Hazardous Materials (NFPA)

This Fire Prevention Guide was compiled by NFPA (the U.S. National Fire Protection Association). The 13th edition is now available, listing data on physical hazards such as flashing point, ignition point, and explosion limit, and individual substances can be searched by CAS number.

(10) ISO Standards on Gases (ISO 10156, ISO 5145)

The evaluation of physical hazards of Gases in GHS is based on the following ISO Standards, which are under revision in parallel with the editing of UN GHS. If there should be a conflict between a description in ISO standards and that in the UN GHS, the one in ISO standards has precedence.

- A) ISO 10156 Gases and gas mixtures – Determination of fire potential and oxidizing ability for the selection of cylinder valve outlets. (1996-02-15)
- B) ISO 10156-2 Gas cylinders – Gases and gas mixtures- Part 2: Determination of oxidizing ability of toxic and corrosive gases and gas mixture (2005-08-01)
- C) ISO 5145 Cylinder valve outlets for gases and gas mixtures – Selection and dimensioning. (2004-04-15)

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<sup>1</sup> International Labour Organization

<sup>2</sup> World Health Organization

In B), a new evaluation method for Oxidative Gases is described. Although A) is scheduled to be revised into JIS Z10156-1, the contents regarding Flammable Gases will not be changed. Gas classification in C) is informative.

(11) Matheson Gas Data Book (7th Ed.) (Matheson)

This data book was first published by McGraw-Hill in 1976, and its 7th edition published in 2001 covers physical data of 157 Gases.

(12) Handbook of Compressed Gases (4th Ed.) (Gas Handbook)

The first edition of this handbook was edited by the U.S. Compressed Gas Association and published by Kluwer Academic Publishers. In the 4th edition published in 1999, data of 45 Gases and Mixed Gases are listed.

(13) SIDS Initial Assessment Report

This report is published by OECD and its Japanese version is published by the Japan Chemical Industry Ecology-Toxicology & Information Center. The SIDS report can be downloaded from: <http://www.chem.unep.ch/irptc/sids/OECD/SIDS/sidspub.html>. The Japanese version can also be downloaded from: [http://www.jetoc.or.jp/HP\\_SIDS/SIAPbase.htm](http://www.jetoc.or.jp/HP_SIDS/SIAPbase.htm)

(14) International Uniform Chemical Information Database (IUCLID)

This database is developed by the EU European Chemicals Bureau (ECB), and its CD-ROM version (the updated, Edition 2 - 2000) is also available.

URL : <http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=dat>

#### 2-1-4 Reference materials

The following materials are not directly related to GHS classification and hence should be considered to be only for readers' reference.

(1) Annex I of the EU Council Directive 67/548/EEC (hereinafter abbreviated as "EU DSD classification")

This document is a collection of the label elements for dangerous substances listed in the European Inventory of Existing Commercial Chemical Substances (EINECS), and the label elements based on base-set results of new chemical substances. It contains qualitative descriptions with warning phrases and combined warning phrases.

The classification and categorization adopted in the Annex I of the EU Council Directive 67/548/EEC (After the establishment of CLP Regulations, it was relocated to Table 3-2 Annex VI of the CLP regulations.) is not based on GHS classification criteria, therefore, its results are not

applicable to GHS classification.

The Japanese version of this document was published by JETOC in 2004 as “EU: List of Dangerous Substances (7th edition)”.

The EU Council Directive 67/548/EEC is also referred to as the Dangerous Substances Directive (DSD).

In addition, in EU, GHS classification criteria and labeling regulations were introduced into its regulations on labeling and packaging by the CLP Regulation ("EU Regulation of the European Parliament and of the Council (EC) No. 1272/2008 on classification, labeling, and packaging of substances and mixtures) that entered into force in January 2009. In this guidance, it is referred to as EU CLP classification.

(2) Guidelines for Providing Information on the Safety of Chemical Substances (1993 Notice 1 from the Ministry of Labour, the Ministry of Health and Welfare, and the Ministry of International Trade and Industry)

These guidelines provide definitions of explosive substances, gases under pressure, flammable liquids, flammable solids/gases, pyrophoric substances, substances that emit flammable gases in contact with water, oxidizing substances, self-reactive substances, and corrosive substances. The guidelines can be compared with GHS classification and categorization. They were jointly issued by the Ministry of Labor, the Ministry of Health and Welfare, and the Ministry of International Trade and Industry on March 26, 1993 as Notice 1.

## 2-2. Classification of Physical Hazards based on physical, chemical states and chemical structure

### 2-2-0 Introduction

While there are 16 classes of GHS physical hazards at present, items to be evaluated can be reduced depending on the state of a substance (Gas, Liquid, and Solid). Some items cover substances with particular chemical structures only.

### 2-2-1 Definition of physicochemical state in GHS

In GHS, the state of a substance is defined, in general, under the temperature of 20°C and the atmospheric pressure of 101.3 kPa. Although these conditions are determined as internationally common rules, some substances can not be dealt with under these conditions.

For example, phenol (melting point, 43°C) and 1,6-diaminohexane (melting point, 42°C) are designated as solids according to their GHS definition, but they are normally transported and stored heated in the melted state. The primary reason is that liquids can be more easily weighed and removed from a container to another than solids, and another reason is that they have risk to liquidize and leak during transport under high temperature, when they are contained in a box or a bag for solids.

### 2-2-2 Gases

Gases are defined as (i) substance whose vapor pressure exceeds 300 kPa (absolute) at 50°C or (ii) substance which is completely gaseous at standard atmospheric pressure (101.3 kPa) at 20°C, according to Chapter 1.2 of the third revised version of UN GHS.

If they are combustible when mixed with air, they satisfy the criteria for “flammable gases” (2-3-2). When they contribute to combustion of other substances more than air does, they fall under “oxidizing gases” (2-3-4).

Gases which are contained in a receptacle at pressure of 200 kPa (gauge pressure) or more for the purpose of supply, transport, storage, etc., or which are liquefied or liquefied and refrigerated fall under “gases under pressure” (2-3-5). Gases under pressure do not have chemical hazards inherent to substances but have physical hazards entailed by the conditions of substances.

When flammable gases are used as propellants, aerosols are to be considered for classification as “flammable aerosols” (2-3-3). Each aerosol product sample is tested individually because factors such as the structure of its nozzle affect combustibility/flammability. (When aerosols

contain flammable liquids or flammable solids, their evaluation as “flammable aerosols” is required, even if inflammable gases are used as propellants.)

### 2-2-3 Liquids

“Liquids” are defined as substances which at 50°C has a vapour pressure of not more than 300kPa (3bar), which is not completely gaseous at 20°C and at standard pressure (101.3kPa), and which has a melting point or initial melting point of 20°C or less at standard pressure (101.3kPa), according to 1.2 in the third revised edition of UN GHS. Highly viscous or pasty substances and mixtures, whose melting points cannot be determined, are tested according to ASTM D4359-90. or judged by the penetrometer test for specifying flowability defined by the section 2.3.4 in the Annex of the European Agreement Concerning the International Carriage of Dangerous Goods by Road (ADR).

Liquid substances are assessed to determine if they fall under “flammable liquids” (2-3-6), “pyrophoric liquids” (2-3-9), “self-heating substances and mixtures” (2-3-11), or “corrosive to metals” (2-3-16).

### 2-2-4 Solids

Any substances or mixtures that do not meet the definitions of “liquids” or “gases” are defined as “solids”, according to 1.2 in the third revised edition of UN GHS. Solids can be in various forms: powder, granule, paste, mass, fiber, tablet, etc. The hazards of powdered substance, for instance, may vary depending on their particle size. Therefore, hazards that a substance has in its current form, instead of hazards inherent to the substance, should be assessed.

Solid substances are assessed to determine if they fall under “flammable solids” (2-3-7), “pyrophoric solids” (2-3-10), “self-heating substances and mixtures” (2-3-11), and “corrosive to metals” (2-3-16).

### 2-2-5 Selection of assessment items according to chemical structure

When liquids and solids contain specific chemical groups in their molecules, an assessment should be conducted that takes into account the presence of those groups.

When they contain chemical groups related to explosibility (see 2-2-6), they shall be tested as “explosives” (2-3-1) and “self-reactive substances and mixtures” (2-3-8). When they contain chemical groups related to self-reactivity (see 2-2-7), they shall be tested as “self-reactive substances and mixtures” (2-3-8).

If they contain metals or semimetals (Si, Ge, As, Sb, Bi, etc.) in their molecules, they should be tested as “substances and mixtures which, in contact with water, emit flammable gases” (2-3-12).

If they contain oxygen, fluorine, or chlorine and if any of these elements are bound to elements other than carbon and hydrogen, they should be tested as “oxidizing liquids” (2-3-13) and

“oxidizing solids” (2-3-14).

Organic compounds containing the  $-O-O-$  structure in their molecules, or mixtures containing such compounds, should be tested as “Organic Peroxides” (2-3-15).

The following table summarizes the above.

**Table 2-1 Classification of Physical Hazards based on physical, chemical states and chemical structure**

Section	Hazard Class	Gas	Liquids	Solid	Classifiable chemical structure
2-3-1	Explosives	X	○	○	Substances containing chemical groups related to explosibility in their molecules(see 2-2-6)
2-3-2	Flammable Gases	○	X	X	
2-3-3	Flammable Aerosols	○	○	○	
2-3-4	Oxidizing Gases	△	X	X	
2-3-5	Gases Under Pressure	○	X	X	
2-3-6	Flammable Liquids	X	○	X	
2-3-7	Flammable Solid	X	X	○	(Powdered, granular, or pasty substances are to be assessed.)
2-3-8	Self-reactive Substances and Mixtures	X	○	○	Substances containing chemical groups related to explosivity as well as chemical groups related to self-reactivity in their molecules. (see 2-2-6, 2-2-7)
2-3-9	Pyrophoric Liquids	X	○	X	
2-3-10	Pyrophoric Solids	X	X	○	
2-3-11	Self-heating Substances and Mixtures	X	△	○	
2-3-12	Substances and mixtures which, in contact with water, emit flammable gases	X	○	○	Substances containing metals or semimetals (Si, Ge, As, Sb, Bi, etc.)
2-3-13	Oxidizing Liquids	X	○	X	Substances containing oxygen, fluorine, or chlorine, any of which are bound to elements other than carbon and hydrogen
2-3-14	Oxidizing Solids	X	X	○	
2-3-15	Organic Peroxides	X	○	○	Organic compounds containing –O–O– structure, excluding those whose content of active oxygen (%) meet criteria in 2.15.2.1 (a) and (b) of the third revised edition of UN GHS
2-3-16	Corrosive to Metals	△	○	△	

○ : Classifiable, X : Not classifiable, Δ : Classifiable, but no test method is designated

When a substance does not contain chemical groups mentioned in the column for “classifiable chemical structure” in Table 2-1, the “classification result” should be “not applicable”.

Example : ”Not applicable” in the class of “Organic Peroxides” (The substance in question is an organic compound not containing –O–O– structure.)

When a substance falls under a highly prioritized class of hazards, it is designated as “not applicable”.

#### 2-2-6 Chemical groups related to explosibility

**【GHS 3<sup>rd</sup> revised edition】** (2.1.4.2.2(a))

(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 A 6.1 in Appendix 6 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*;

Examples of the chemical groups are as follows:

Unsaturated C–C bond	Acetylenes, acetylides, 1,2–dienes
C–metals, N–metals	Grignardreagents, organolithium compounds
Neighboring nitrogen atoms	Azides, aliphatic azo compounds, diazonium salts, hydrazines, sulfonyl hydrazides
Neighboring oxygen atoms	Peroxides, ozonides
N–O	Hydroxylamines, nitrate salts, nitrate esters, nitro compounds, nitroso compounds, N–oxides, 1,2–oxazoles
N–halogen	Chloroamines, fluoroamines
O–halogen	Chlorates, perchlorates, iodosyl compounds

(UNRTDG : Manual of Tests and Criteria, Appendix 6, Table A6.19)

#### 2-2-7 Chemical groups related to self-reactivity

**【GHS 3<sup>rd</sup> revised edition】** (2.8.4.2(a))

(a) There are no chemical groups present in the molecule associated with explosive or selfreactive properties; examples of such groups are given in Tables A6.1 and A 6.2 in the A

Appendix 6 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*;

Examples of the functional groups are as follows:

Inter-reacting group	Aminonitriles, haloanilines, organic salts of oxidizing acids
S=O	Halogenated sulfonyl compounds, sulfonyl cyanides, sulfonyl hydrazides
P-O	Phosphites
Strained ring	Epoxides, aziridines
Unsaturated bond	Olefines, oxidized cyanides
N-halogen	Chloroamines, fluoroamines
O-halogen	Chlorates, perchlorates, iodosyl compounds

(UNRTDG : Manual of Tests and Criteria, Appendix 6, Table A6.2)

#### 2-2-8 Guidance for classification and examples of classification results indication

This section schematically explains guidelines for classification and illustrates classification results indication for 16 types of physical hazards. When you are actually engaged in classification, please refer to items on each hazard in sections 2-3.

##### (1) Judgment of Not applicable

A) A substance the state of which is different from the definition for the relevant GHS hazard class or which does not meet the definition in terms of chemical structure, according to Table 2-1, shall be designated as “not applicable” with regard to that class.

B) In case a substance meets conditions for a hazard class with higher priority:

Example: A substance that should be considered as “self-reactive substances and mixtures” contains explosive or self-reacting chemical groups and is classified as “explosives”, “organic peroxides”, “oxidizing liquids”, or “oxidizing solids.”

Example entry : Not applicable (classified as “explosives”)

A substance that should be considered as “self-heating substances and mixtures” is classified as either “pyrophoric liquids” or “pyrophoric solids.”

Example entry : not applicable (classified as “pyrophoric liquids”)

Table 2-2 shows example entries for grounds for classification of substances that are judged to be “not applicable” based on A) or B).

**Table 2-2 Filled examples of "Not applicable"**

Hazard class		Classification result	Classification Grounds and Problems
1	Explosives	Not applicable	Not containing chemical groups related to explosibility
3	Flammable Aerosols	Not applicable	Not an aerosol product
6	Flammable Liquids	Not applicable	"Solids" according to GHS definition
8	Self-reactive Substances and Mixtures	Not applicable	Classified as "explosives"
		Not applicable	Containing neither chemical groups related to explosibility nor those related to self-reactivity
11	Self-heating Substances and Mixtures	Not applicable	Classified as "pyrophoric liquids"
12	Substances and mixtures which, in contact with water, emit flammable gases	Not applicable	Not containing metals or semimetals (B, Si, P, Ge, As, Se, Sn, Sb, Te, Bi, Po, At)
13	Oxidizing Liquids	Not applicable	An inorganic compound that does not contain oxygen or halogen
14	Oxidizing Solids	Not applicable	An organic compound that does not contain fluorine and chlorine but contains oxygen which is not bound to elements other than carbon and hydrogen
15	Organic Peroxides	Not applicable	An organic compound that does not contain -O-O- structure

## (2) Judgment of Not Classified

A substance subject to classification that obviously falls under none of the relevant hazard categories according to definitions of the third revised edition of UN GHS or its well-known scientific properties (for example, "non-combustibility") shall be classified as "not classified". Example entries for the grounds for classification of substances judged as "not classified" are given in Table 2-3.

**Table 2-3 Filled examples of "Not classified"**

Hazard class		Classification result	Grounds and Example Entries
1	Explosives	Not classified	Based on the result of oxygen balance calculation
		Not classified	Desensitized explosives (Title of the review document, year)
6	Flammable Liquids	Not classified	Non-combustibility (based on experience, name of the evaluating organization)

Hazard class		Classification result	Grounds and Example Entries
7	Flammable Solid	Not classified	Non-combustibility (Title of the review document, year)
8	Self-reactive Substances and Mixtures	Not classified	Enter the concrete value ( °C ) of self-accelerating decomposition temperature (SADT). (Title of the review document, year)
9	Pyrophoric Liquids	Not classified	Non-combustibility (Title of the review document, year)
		Not classified	Does not self-ignite upon contact with water of ambient temperature.(Title of the review document, year)
		Not classified	TDG classification is class 3. (UN number)
10	Pyrophoric Solids	Not classified	Non-combustibility (Title of the review document, year)
		Not classified	Do not self-ignite when contacts with water of ambient temperature. (Title of the review document, year)
11	Self-heating Substances and Mixtures	Not classified	Non-combustibility (Title of the review document, year)
12	Substances and mixtures which,in contact with water,emit flammable gases	Not classified	Stable against water(Title of the review document, year)
		Not classified	Stable against water (based on experience, name of the evaluating organization)
13	Oxidizing Liquids	Not classified	Reductive material (Title of the review document, year)
14	Oxidizing Solids	Not classified	Reductive material (Title of the review document, year)
15	Organic Peroxides	Not classified	Active oxygen amount is less than in the definition.
16	Corrosive to Metals	Not classified	Copper and aluminum may be used as container. (Title of the review document, year)

○ Supplement concerning Judgment of "not classified"

■Explosives

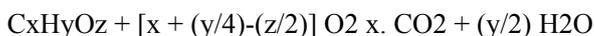
**【GHS 3<sup>rd</sup> revised edition】** (2.1.4.2.2)

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 A 6.1 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:



using the formula:

$$\text{oxygen balance} = -1600 [2x + (y/2) - z] / \text{molecular weight};$$

- (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 to prevent the procedure being applied to a large number of organic materials which are not explosive but which will decompose 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.

#### ■ Self-reactive Substances and Mixtures

**【GHS 3<sup>rd</sup> revised edition】** (2.8.4.2)

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 selfreactive properties; examples of such groups are given in Tables A6.1 and A 6.2 in the Appendix 6 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*; or
- (b) For a single organic substance or a homogeneous mixture of organic substances, the exothermic decomposition energy is less than 300 J/g. The onset temperature and decomposition energy may be estimated using a suitable calorimetric technique (see 20.3.3.3 in Part II of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*).

#### ■ Flammable Liquids or Solids, Pyrophoric Liquids or Solids, Self-heating Substances and Mixtures

In the cases where the substance is confirmed to be noncombustible based on the information of the prescribed review document, enter “Not classified” for “Classification result” and “Non-combustibility” for “Classification Grounds and problems,” with regard to “Flammable Liquids or Solids”, “Pyrophoric Liquids or Solids”, and “Self-heating Substances and Mixtures”, .

Note : Flame-resistant substances are “not classified” either for those hazard classes, but the

boundary between combustibility and flame-resistance is not clearly defined. Accordingly, in this classification, only if a substance is confirmed to be noncombustible based on the prescribed review document, enter "not classified" for "Classification result".

(3) Categorization based on TDG classification

Most of GHS physical hazards test (= UNRTDG test) results, except for certain data such as flashing point and explosion limit, are not published. If physical hazards data are not available from the prescribed review documents according to this guidance, GHS judgment based on TDG classification shall be made. Table 2-4 shows the correspondence between GHS and TDG classifications.

**Table 2-4 Comparison between GHS classification and TDG classifications (UNRTDG)**

GHS classification	GHS Category	UNRTDG(Note : ( ) is a secondary hazard)
1)Explosives	Unstable explosives	Since their transport is prohibited, they have no UN number of dangerous goods transport.
	Division 1.1	1.1
	Division 1.2	1.2
	Division 1.3	1.3
	Division 1.4	1.4
	Division 1.5	1.5
	Division 1.6	1.6
2)Flammable Gases	Category 1	2.1 and 2.3(2.1)
	Category 2*	Although these substances are combustible at 20°C and atmospheric pressure in air, flammable gasses outside the above category are classified as 2.2 or 2.3.
3)Flammable Aerosols	Category 1*	Aerosols are designated as UN1950 (aerosol) and class 2 (Gas).
	Category 2*	
4)Oxidizing Gases	Category 1	2.2(5.1) or 2.3(5.1)
5)Gases Under Pressure	Group Compressed gas*	UN dangerous goods transport class do not have "high-pressure gas" class, but the definition of UNRTDG 2(Gas) agrees with that of GHS 2.5.1. and GHS treats gases which are contained in a receptacle at a pressure of 200kPa (gauge) or more as "gases under pressure". Definitions of compressed gas, liquefied gas, refrigerated liquid gas, and dissolved gas are identical in both classifications.
	Group Liquefied gas*	
	Group Refrigerated liquefied gas*	
	Group Dissolved gas*	

**Table 2-4 Comparison between GHS  
classification and TDG classifications (UNRTDG)**

GHS classification	GHS Category	UNRTDG(Note : ( ) is a secondary hazard)
6)Flammable Liquids	Category1	3 I
	Category2	3 II
	Category3	3 III
	Category4*	Since they are not dangerous goods, they have no UN number.
7)Flammable Solid	Category1	4.1 II
	Category2	4.1 III
8)Self-reactive Substances and Mixtures	TypeA*	Since their transport is prohibited, they have no UN number of dangerous goods transport.
	TypeB	UNRTDG4.1、 UN3221, 3222, 3231, 3232
	TypeC	UNRTDG4.1、 UN3223, 3224, 3233, 3234
	TypeD	UNRTDG4.1、 UN3225, 3226, 3235, 3236
	TypeE	UNRTDG4.1、 UN3227, 3228, 3237, 3238
	TypeF	UNRTDG4.1、 UN3229, 3230, 3239, 3240
	TypeG	Since they are not dangerous goods, they have no UN number.
9)Pyrophoric Liquids	Category1	4.2 I(Liquids)
10)Pyrophoric Solids	Category1	4.2 I(Solid)
11)Self-heating Substances and Mixtures	Category1	4.2 II
	Category2	4.2 III
12)Substances and mixtures which,in contact with water,emit flammable gases	Category1	4.3 I, 4.2(4.3)
	Category2	4.3 II
	Category3	4.3 III
13)Oxidizing Liquids	Category1	5.1 I
	Category2	5.1 II
	Category3	5.1 III
14)Oxidizing Solids	Category1	5.1 I
	Category2	5.1 II
	Category3	5.1 III
15)Organic Peroxides	TypeA*	Since their transport is prohibited, they have no UN number of dangerous goods transport.
	TypeB	UNRTDG5.2、 UN3101, 3102, 3111, 3112
	TypeC	UNRTDG5.2、 UN3103, 3104, 3113, 3114
	TypeD	UNRTDG5.2、 UN3105, 3106, 3115, 3116
	TypeE	UNRTDG5.2、 UN3107, 3108, 3117, 3118
	TypeF	UNRTDG5.2、 UN3109, 3110, 3119, 3120
	TypeG*	Since they are not dangerous goods, they have no UN number.
16)Corrosive to Metals	Category1*	The UN dangerous goods transport class 8 includes Skin Corrosion.

\* Categories for which GHS classification does not agree with UN transport classification

TDG Classification was achieved after continued discussion for many years under the leadership of the International Maritime Organization (IMO) and is considered to have no big omission in evaluation of classified substances. However, the classification of N.O.S (not otherwise specified: a generic term for unspecifiable substances, for example, "all other Explosives") substances is left to the judgment by the consignor. Since such classification is not guaranteed to be based on all properties, classification based on UN numbers with N.O.S. shall not be conducted in principle. However, categorization may be performed if it can be confirmed on the basis of information from prescribed review documents and in light of legal regulations in Japan.

○ Precedence in TDG Classification

In TDG classification, when a substance (or mixture) meets the criteria for inclusion in more than one class, its class is determined in accordance with the order of precedence based on risks. Accordingly, only a part of risks of a substance may be reflected on the TDG classification. Since, in GHS classification, classification must be carried out based on all risks, care should be taken not to classify the "neglected risks" as "Not classified" based on the TDG classification.

In this guidance, the judgment is made by utilizing the tables below.

- UNRTDG Sixteenth revised edition(2009) 2.0.3 Precedence of hazard characteristics (P.53-54),
- IMDGC 2006Ed. 2.0.3 Precedence of hazard characteristic (P.37-38), or
- the "Dangerous Goods Regulations, Annex 1, Recital 3"(see next page)

However, for Toxic Substances (Class 6) and Corrosives (Class 8), in general, GHS classification shall not be based on TDG classification. The following descriptions are based on the table of the Dangerous Goods Regulations.

As shown in the "Dangerous Goods Regulations, Annex 1, Recital 3", Explosives, Self-reactive Substances and Mixtures, Pyrophoric Substances, and Organic Peroxides have the highest precedence. Substances belonging to these classes shall be labeled "Classification not possible" if they do not fall under "Not applicable" in regard to other hazards(Flammable Substances, Self-heating Substances and Mixtures, Substances and mixtures which, in contact with water, emit flammable gases, and Oxidizing Substances) and if they can not be classified from their chemical structures, etc.

Regarding classes other than those with the highest precedence, the order of precedence shall be judged according to the table of the Dangerous Goods Regulations, Annex 1, Recital 3.

The “Dangerous Goods Regulations, Annex 1, Recital 3”

If a substance is judged to meet the criteria for more than one class or category, its class or category shall be determined as stipulated below.

- (1) If a substance is judged to meet the criteria for any of the following classes or categories, the class or category in question shall take precedence, and other classes or categories shall be deemed subsidiary.
  - (i) Explosives,
  - (ii) Gases Under Pressure,
  - (iii) Combustible Substances (only when a substance is judged to meet the criteria of the Recital 2 (4) (ii) for Self-reactive substances)
  - (iv) Pyrophoric Substances,
  - (v) Organic Peroxides,
  - (vi) Toxic Substances (only when the substance is judged to meet the criteria for Toxic substances of the Recital 2 (6) (i) of Packing Groups by inhalation toxicity of vaporizing substances)
- (2) In cases other than (1), the following class or category shall take precedence, and other class or category shall be subsidiary.
- (3) If a substance is judged to meet the criteria for both of Flammable Gases Under Pressure and Toxic Gases Under Pressure), Toxic Gases Under Pressure shall take precedence, and Flammable Gases Under Pressure shall be subsidiary.
- (4) The Packing Group shall be the one with the lowest numbering among Packing Groups.

Notes for the table in the next page are given below:

Note 1: The numbers in the table denote the following classes or categories.

- 3 Flammable Liquids
- 4.1 Combustible Substances
- 4.2 Pyrophoric Substances
- 4.3 Substances and mixtures which, in contact with water, emit flammable gases
- 5.1 Oxidizing Substances
- 6.1 Toxic Substances
- 8 Corrosives

Note 2: "I", "II" or "III" in the table each indicates the case where the Packing Group is judged to be I, II, or III, respectively.

Note 3: "Dermal", "oral", or "inhalation" in the table each indicates the case where the judging criteria is the Recital 2 (6) (i).

Note 4: "\*" in the table indicates that the value in question shall be "6.1" for pesticides and

bactericides.

Note 5: "-" in the table indicates the absence of a given combination.

Note 6. The next Table is based on the "UN Recommendations on the Transport of Dangerous Goods, Model Regulations, Sixteenth revised edition, 2009". Note that the latest Table of the Dangerous Goods Regulations, Annex 1, Recital 3 has empty columns.

	4.2	4.3	5.1(I)	5.1(II)	5.1(III)	6.1(I, Dermal)	6.1(I, Oral)	6.1(II)	6.1(III)	8.( I, Liquid)	8.(I, Solid)	8.( II, Liquid)	8.(II, Solid)	8.( III, Liquid)	8.( III, Solid)
3(I)		4.3				3	3	3	3	3	—	3	—	3	—
3(II)		4.3				3	3	3	3	8	—	3	—	3	—
3(III)		4.3				6.1	6.1	6.1	3*	8	—	8	—	3	—
4.1(II)	4.2	4.3	5.1	4.1	4.1	6.1	6.1	4.1	4.1	—	8	—	4.1	—	4.1
4.1(III)	4.2	4.3	5.1	4.1	4.1	6.1	6.1	6.1	4.1	—	8	—	8	—	4.1
4.2(II)		4.3	5.1	4.2	4.2	6.1	6.1	4.2	4.2	8	8	4.2	4.2	4.2	4.2
4.2(III)		4.3	5.1	5.1	4.2	6.1	6.1	6.1	4.2	8	8	8	8	4.2	4.2
4.3(I)			5.1	4.3	4.3	6.1	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3
4.3(II)			5.1	4.3	4.3	6.1	4.3	4.3	4.3	8	8	4.3	4.3	4.3	4.3
4.3(III)			5.1	5.1	4.3	6.1	6.1	6.1	4.3	8	8	8	8	4.3	4.3
5.1(I)						5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1
5.1(II)						6.1	5.1	5.1	5.1	8	8	5.1	5.1	5.1	5.1
5.1(III)						6.1	6.1	6.1	5.1	8	8	8	8	5.1	5.1
6.1(I, Dermal)										8	6.1	6.1	6.1	6.1	6.1
6.1(I, Oral)										8	6.1	6.1	6.1	6.1	6.1
6.1(II, inhalation)										8	6.1	6.1	6.1	6.1	6.1
6.1(II, Dermal)										8	6.1	8	6.1	6.1	6.1
6.1(II, Oral)										8	8	8	6.1	6.1	6.1
6.1(III)										8	8	8	8	8	8

This Table is based on the "UN Recommendations on the Transport of Dangerous Goods, Model Regulations, Sixteenth revised edition, 2009". Note that the latest Table of the Dangerous Goods Regulations, Annex 1, Recital 3 has empty columns.

For example, paraformaldehyde (UN—3242\*Class 4.1, Packing Group II) shall be flammable solids • Category 2 in GHS classification. Since it is not classified in the higher precedence class 4.2、 4.3, it shall be labeled "Not classified" with regard to pyrophoric substances and substances and mixtures which emit flammable gases upon contact with water. For oxidizing solids(Division 5.1), since Packing Group I takes precedence, it is not relevant. Since, however, Packing Group II and III have lower precedence, test results in TDG classification can not be estimated. Accordingly, based on TDG classification alone, it shall fall under “Classification not possible” with regard to oxidizing solids.(In light of its chemical structure, oxygen binds to carbon and hydrogen only, and so it shall be “not applicable”.)

In case of zirconium nitrate(UN—2728 • Division 5.1, Packing Group III), all of Class 4 takes precedence, its GHS classification shall be “Not classified” for Flammable Solids, Self-heating Substances and Mixtures, and Substances and mixtures which,in contact with water,emit flammable gases.

○ Utilization of subsidiary hazards

If a TDG classification includes a subsidiary class, classification may be performed by utilizing the table of the Dangerous Goods Regulations, Annex 1, Recital 3. Care must be taken, however, because the Packing Group does not indicate the level of subsidiary hazard.

For example, ethyl chloroacetate(UN—1181 • Class 6.1, Subsidiary Class 3, Packing Group II )is estimated to be GHS Category 3 for Flammable Liquids.(If its Category were 1 or 2, it would be classified as Packing Group I or II and would take precedence over Toxic Substances. It would hence be classified as Class 3 and Subsidiary Class 6.1. If it were GHS Category 4, it would be classified as “not a Dangerous Good in transport”.)

On the other hand, in case of morpholine(UN-2054 • Class 8、 Subsidiary Class 3, Packing Group I ), since, if its GHS Category is 2 or 3, it takes precedence over Flammable Liquids, it can not be classified based on TDG classification alone.

(Depending on its flashing point of 37°C, it shall be Category 3.)

(4) Judgment of “Classification not possible”

As described above, a substance which is classified as neither “Not applicable” nor “Not classified” based on its state, chemical composition, chemical properties, etc., and can not be classified based on literature data and TDG classification shall be designated as “Classification not possible” since there is no data that should serve as the grounds for classification. Table 2-5 shows example entries for the grounds for classifying a substance as “Classification not possible”.

**Table 2-5 Filled examples of “Classification not possible”**

Hazard class		Classification result	Grounds for Classification and Example Entries
6	Flammable Liquids	Classification not possible	No data
7	Flammable Solid	Classification not possible	No data
8	Self-reactive Substances and Mixtures	Classification not possible	No data
9	Pyrophoric Liquids	Classification not possible	No data
11	Self-heating Substances and Mixtures	Classification not possible	No data available or no established test method suitable for liquid substances.
16	Corrosive to metal	Classification not possible	No data available or no established test method suitable for gaseous substances.
		Classification not possible	No data available or no established test method suitable for solid substances.

## 2-3. Classification and details of physical hazards

### 2-3-1 Explosives

#### (1) Definitions

Definitions of explosives in UN GHS are as follows, and they are adopted in this guidance.

<p><b>【GHS 3<sup>rd</sup> revised edition】 (2.1.1)</b></p> <p>2.1.1.1 An <i>explosive substance (or mixture)</i> 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.</p> <p>A <i>pyrotechnic substance (or mixture)</i> 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 nondetonative self-sustaining exothermic chemical reactions.</p> <p>An <i>explosive article</i> is an article containing one or more explosive substances or mixtures.</p> <p>A <i>pyrotechnic article</i> is an article containing one or more pyrotechnic substances or mixtures.</p> <p>2.1.1.2 The class of explosives comprises:</p> <ul style="list-style-type: none"><li>(a) Explosive substances and mixtures;</li><li>(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 shall not cause any effect external to the device either by projection, fire, smoke, heat or loud noise; and</li><li>(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.</li></ul>
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#### (2) Classification criteria in GHS

<p><b>【GHS 3<sup>rd</sup> revised edition】 (2.1.2)</b></p> <p>2.1.2.1 Substances, mixtures and articles of this class, which are not classified as an unstable explosive, are assigned to one of the following six divisions depending on the type of hazard they present:</p> <ul style="list-style-type: none"><li>(a) Division 1.1 Substances, mixtures and articles which have a mass explosion hazard (a mass explosion is one which affects almost the entire quantity present virtually instantaneously);</li><li>(b) Division 1.2 Substances, mixtures and articles which have a projection hazard but not a mass explosion hazard;</li><li>(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</li></ul>
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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.

### (3) Guidance for Classification

#### A) Judgment of Not applicable

- 1) If a substance falls under Gases, its “Classification result” shall be “Not applicable”, and indicate “a gas according to GHS definition” for “Classification Grounds and Problems”.
- 2) If a substance does not contain chemical groups related to explosibility, it shall be “Not applicable”, and indicate “It does not contain chemical groups related to explosibility” for “Classification Grounds and Problems”.

#### B) Judgment of Not classified

For substances having explosive chemical groups including oxygen and falling under the provisions of the UN GHS the third revised edition 2.1.4.2.2(b)-(d)(based on calculation result of oxygen balance, exothermic decomposition energy, and content of inorganic compounds), “Classification result” shall be “Not classified”, and “based on calculation result (calculated value: XX)” shall be indicated for “Classification Grounds”.

#### C) Classification based on TDG Classification

- 1) Substances cited in (7) shall be classified according to the TDG Classification.
- 2) Based on results of test series for TDG Classification, “Desensitized Explosives” do not fall under Classes 1.1-1.6, and accordingly, not in “Explosives” in GHS either. For substances falling under “Desensitized Explosives”, regarding “Explosives”,

“Classification result” shall be “Classification not possible”, and “Test method not determined” shall be indicated for “Classification Grounds”.

Test data under the “Explosives Control Law” or the “Fire Defense Law, Class 5 Dangerous Goods” both of which adopted test methods of the UN (although partially), may be used for classification after comparison with GHS test methods and close examination.

(4) Data availability

The performance of explosives depends on their composition, and data regarding explosive performance of each substance are limited.

(5) Comparison with conventional classification systems

Divisions 1.1-1.6 described above follow the definition of Divisions of UNRTDG 2.1.1.4.

(6) Sources of information for classification results under conventional systems

The UNRTDG list of dangerous goods (adopted into Annex 1: Dangerous Goods Regulations) includes the following substance.

- Unstable explosives: explosive substances and articles, whose transportation is prohibited.

The following explosives shown in 1979, the Ministry of Transportation Notice No. 549, “Notice to settle Transportation Standards and the like of Dangerous Goods by Ship”, Article 5 (1), are deemed as unstable explosives.

- (a) AMMONIUM BROMATE
- (b) AMMONIUM BROMATE SOLUTION
- (c) AMMONIUM CHLORATE
- (d) AMMONIUM CHLORATE SOLUTION
- (e) AMMONIUM CHLORITE
- (f) AMMONIUM NITRATE (excluding those listed in Annex 1)
- (g) AMMONIUM NITRITE
- (h) Mixture of INORGANIC NITROUS ACID and AMMONIUM SALT
- (i) SILVER PICRATE, WETTED with not less than 30% water, by mass
- (j) CYCLOTTRIMETHYLENETRINITRAMINE (CYCLONITE, RDX), WETTED with less than 15% water, by mass
- (k) DIAZODINITROPHENOL, WETTED with less than 40% water, or mixture of alcohol and water, by mass
- (l) DIETHYLENEGLYCOL DINITRATE, DESENSITIZED with less than 25% non-volatile, water-insoluble phlegmatizer, by mass
- (m) GUANYLNITROSAMINO GUANYLIDENE HYDRAZINE, WETTED with less than 30%

- water, by mass
- (n)GUANYLNITROSAMINO GUANYLTETRAZENE, WETTED with less than 30% water, or mixture of alcohol and water, by mass
- (o)LEAD AZIDE, WETTED with less than 20% water, or mixture of alcohol and water, by mass
- (p)LEAD STYPHNATE, WETTED with less than 20% water, or mixture of alcohol and water, by mass
- (q)MANNITOL HEXANITRATE, WETTED with less than 40% water, or mixture of alcohol and water, by mass
- (r)MERCURY FULMINATE, WETTED with less than 20% water, or mixture of alcohol and water, by mass
- (s)NITROGLYCERIN, DESENSITIZED with less than 40% non-volatile water-insoluble phlegmatizer, by mass
- (t)PENTAERYTHRITETETRANITRATE, WETTED with less than 25% water, by mass, DESENSITIZED with less than 15% phlegmatizer, by mass
- (u)POWDER CAKE, WETTED with less than 17% alcohol, less than 25% water, by mass
- (v)CYCLOTETRAMETHYLENETETRANITRAMINE, WETTED with less than 15% water, by mass
- (w)CYCLOTRIMETHYLENETRINITRAMINE AND CYCLOTETRAMETHYLENETETRANITRAMINE MIXTURE, WETTED with less than 15% water, by mass

Division 1.1 =UNRTDG1.1

UNNo.	Substance name
0004	AMMONIUM PICRATE dry or wetted with less than 10% water, by mass
0028	BLACK POWDER (GUNPOWDER), COMPRESSED or BLACK POWDER(GUNPOWDER), IN PELLETS
0072	CYCLOTRIMETHYLENETRINITRAMINE(CYCLONITE; HEXOGEN; RDX), WETTED with not less than 15% water, by mass
0074	DIAZODINITROPHENOL, WETTED with not less than 40% water, or mixture of alcohol and water, by mass
0075	DIETHYLENEGLYCOL DINITRATE, DESENSITIZED with not less than 25% non-volatile, water-insoluble phlegmatizer, by mass
0076	DINITROPHENOL, dry or wetted with less than 15% water, by mass
0077	DINITROPHENOLATES, alkali metals, dry or wetted with less than 15% water, by mass
0078	DINITRORESORCINOL, dry or wetted with less than 15% water, by mass
0079	HEXANITRODIPHENYLAMINE (DIPICRYLAMINE; HEXYL)

- 0113 GUANYL-NITROSAMINO GUANYLIDENE HYDRAZINE, WETTED with not less than 30% water, by mass
- 0114 GUANYL-NITROSAMINO GUANYLTETRAZENE(TETRAZENE), WETTED with not less than 30% water, or mixture of alcohol and water, by mass
- 0118 HEXOLITE (HEXOTOL), dry or wetted with less than 15% water, by mass
- 0129 LEAD AZIDE, WETTED with not less than 20% water, or mixture of alcohol and water, by mass
- 0130 LEAD STYPHNATE (LEAD TRINITRORESORCINATE), WETTED with not less than 20% water, or mixture of alcohol and water, by mass
- 0133 MANNITOL HEXANITRATE (NITROMANNITE), WETTED with not less than 40% water, or mixture of alcohol and water, by mass
- 0143 NITROGLYCERIN, DESENSITIZED with not less than 40% non-volatile waterinsoluble phlegmatizer, by mass
- 0146 NITROSTARCH, dry or wetted with less than 20% water, by mass
- 0147 NITRO UREA
- 0150 PENTAERYTHRITOL TETRANITRATE(PENTAERYTHRITOL TETRANITRATE; PETN), wetted with not less than 25% water, by mass, or desensitized with not less than 15% phlegmatizer, by mass
- 0151 PENTOLITE, dry or wetted with less than 15% water, by mass
- 0153 TRINITROANILINE (PICRAMIDE)
- 0154 TRINITROPHENOL (PICRIC ACID), dry or wetted with less than 30% water, by mass
- 0155 TRINITROCHLOROBENZENE(PICRYL CHLORIDE)
- 0207 TETRANITROANILINE
- 0208 TRINITROPHENYLMETHYLNITRAMINE(TETRYL)
- 0209 TRINITROTOLUENE (TNT), dry or wetted with less than 30% water, by mass
- 0213 TRINITROANISOLE
- 0214 TRINITROBENZENE, dry or wetted with less than 30% water, by mass
- 0215 TRINITROBENZOIC ACID, dry or wetted with less than 30% water, by mass
- 0216 TRINITRO-m-CRESOL
- 0217 TRINITRONAPHTHALENE
- 0218 TRINITROPHENETOLE
- 0219 TRINITRORESORCINOL (STYPHNICACID), dry or wetted with less than 20% water, or mixture of alcohol and water, by mass
- 0220 UREA NITRATE, dry or wetted with less than 20% water, by mass
- 0222 AMMONIUM NITRATE with more than 0.2% combustible substances, including any organic substance calculated as carbon, to the exclusion of any other added

	substance
0224	BARIUM AZIDE, dry or wetted with less than 50% water, by mass
0226	CYCLOTETRAMETHYLENETETRANITRAMINE(HMX; OCTOGEN),WETTED with not less than 15% water,by mass
0266	OCTOLITE (OCTOL), dry or wetted with less than 15% water, by mass
0282	NITROGUANIDINE (PICRITE), dry or wetted with less than 20% water, by mass
0340	NITROCELLULOSE, dry or wetted with less than 25% water (or alcohol), by mass
0341	NITROCELLULOSE, unmodified or plasticized with less than 18% plasticizing substance, by mass
0385	5-NITROBENZOTRIAZOL
0386	TRINITROBENZENESULPHONIC ACID
0387	TRINITROFLUORENONE
0390	TRITONAL
0392	HEXANITROSTILBENE
0393	HEXOTONAL
0394	TRINITRORESORCINOL (STYPHNICACID), WETTED with not less than 20% water, or mixture of alcohol and water, by mass
0402	AMMONIUM PERCHLORATE
0483	CYCLOTRIMETHYLENETRINITRAMINE(CYCLONITE; HEXOGEN;RDX), DESENSITIZED
0484	CYCLOTETRAMETHYLENETETRANITRAMINE(HMX; OCTOGEN), DESENSITIZED
0489	DINITROGLYCOLURIL (DINGU)
0490	NITROTRIAZOLONE (NTO)
0496	OCTONAL
0504	1H-TETRAZOLE

Division 1.2 =UNRTDG1.2

At present, only articles have UN numbers, but substances may be included in accordance with the definition.

Division 1.3 =UNRTDG1.3

0161	POWDER, SMOKELESS
0234	SODIUM DINITRO-o-CRESOLATE, dry or wetted with less than 15% water, by mass

- 0235 SODIUM PICRAMATE, dry or wetted with less than 20% water, by mass
- 0236 ZIRCONIUM PICRAMATE, dry or wetted with less than 20% water, by mass
- 0342 NITROCELLULOSE, WETTED with not less than 25% alcohol, by mass
- 0343 NITROCELLULOSE, PLASTICIZED with not less than 18% plasticizing substance, by mass
- 0406 DINITROSOBENZENE
- 0411 PENTAERYTHRITOL TETRANITRATE(PENTAERYTHRITOL TETRANITRATE; PETN) with not less than 7% wax, by mass

Division 1.4 =UNRTDG1.4

- 0407 TETRAZOL-1-ACETIC ACID
- 0448 5-MERCAPTOTETRAZOL-1-ACETIC ACID

Division 1.5 =UNRTDG1.5

- 0331 EXPLOSIVE, BLASTING, TYPE B(AGENT, BLASTING, TYPE B)

Division 1.6 =UNRTDG1.6

There is no article with a specific name that fall under this division.

Desensitized explosives (GHS 2.1.2.2 Note 2)

Some explosives which are wetted with water or alcohols, etc. to suppress their explosive properties do not meet the criteria for GHS Explosives. They are included in Class 3 and a part of Class 4.1 in UNRTDG, and they fall under the substance specified in Schedule 113 (Flammable Solids-Toxic substances (wetted/desensitized explosives) in ERG. They are F-E (Flammable Liquids not reacting with water)and S-J(wetted explosives and self-exothermic substances)in EmS.

e.g. UNRTDG4.1\*ERG113

- 1204 NITROGLYCERIN SOLUTION IN ALCOHOL with not more than 1% nitroglycerin
- 2059 NITROCELLULOSE SOLUTION,FLAMMABLE with not more than 12.6% nitrogen, by dry mass, and not more than 55% nitrocellulose

UNRTDG4.1\*ERG113

- 1310 AMMONIUM PICRATE, WETTED with not less than 10% water, by mass (UNRTDG4.1\*EmS:S-J)
- 1320 DINITROPHENOL, WETTED with not less than 15% water, by mass
- 1336 NITROGUANIDINE (PICRITE), WETTED with not less than 20% water, by mass

1337	NITROSTARCH, WETTED with not less than 20% water, by mass
1354	TRINITROBENZENE, WETTED with not less than 30% water, by mass
1355	TRINITROBENZOIC ACID, WETTED with not less than 30% water, by mass
1356	TRINITROTOLUENE, WETTED with not less than 30% water, by mass
1357	UREA NITRATE, WETTED with not less than 20% water, by mass
1571	BARIUM AZIDE, WETTED with not less than 50% water, by mass
2555	NITROCELLULOSE WITH WATER (not less than 25% water, by mass)

(6) Classification of Explosives-related substances in other classes

If substances to be tested are solid, it involves a risk to perform tests with “desensitized explosives” for GHS “Flammable Solids”(the same tests for substances of UNTDG Class 4.1, Packing group II, III). Therefore, if no information is available from prescribed review documents, the “classification result” shall be “Classification not possible”, and “Desensitized Explosives” shall be indicated for “Classification Grounds and Problems” regarding “Flammable Solids”. When, however, they are liquid and their measurement results of flashing point are available, classification for “Flammable Liquids” shall be carried out by utilizing the results.

## 2-3-2 Flammable Gases

### (1) Definitions

Definitions of flammable gases in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (2.2.1)**

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

### (2) Classification criteria in GHS

**【GHS 3<sup>rd</sup> revised edition】 (2.2.2)**

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 when 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.

### (3) Guidance for Classification

#### A) Judgment of Not applicable

A product which does not meet the GHS definition for gases shall be judged as “not applicable”.

#### B) Judgment of Not Classified

Non-combustible and oxidative gases shall be judged as “not classified”.

#### C) Classification based on TDG Classification

Substances cited in (6) based on TDG classification shall be classified according to it.

#### D) Classification based on data from prescribed literatures

Classification shall be performed based on data of combustible range or explosion limit in prescribed review documents according to the UN GHS third revised edition.

#### (4) Data availability

Physical properties of gaseous substances are relatively easy to obtain. All of combustible/flammable gases at ambient temperature and pressure shall be flammable gases. When data of combustible range (what is called explosive limit) are available, it is easy to pass a judgment for classification of a single gas.

#### (5) Comparison with conventional classification systems

The definition of Class 2.1 described in UNRTDG 2.2.2.1 accords with that of GHS Category 1. It corresponds to Schedule F-D in EmS. S-U also includes toxic gases, etc. In ERG, the provisions for flammable gases are divided into Schedules 115, 116, 117, 118, and 119.

In EU DSD classification, gaseous substances with R-Phrase<sup>3</sup>12(hereinafter, abbreviated as R12) meet these criteria (Categories 1 and 2), but no categorization is shown.

#### (6) Sources of information for classification results under conventional systems

Category 1 = UNRTDG 2.1 and 2.3.2(2.1)

Category 2 = Flammable gas which is not included in Category 1

In GHS, “flammable gases” may include gases with ambient pressure because of the omission of the condition of gases under pressure.

##### Example of category 1)

UNRTDG 2.1	1012	BUTYLENE
	1036	ETHYLAMINE
	1049	HYDROGEN, COMPRESSED
	1978	PROPANE
	2203	SILANE
	2454	METHYL FLUORIDE (REFRIGERANT GAS R 41)
	3153	PERFLUORO(METHYL VINYL ETHER)
UNRTDG 2.3(2.1)	1053	HYDROGEN SULPHIDE
	1082	RIFLUOROCHLOROETHYLENE, STABILIZED
	2188	ARSINE
	2204	CARBONYL SULPHIDE
Example of category 2)	1062	METHYL BROMIDE with not more than 2% chloropicrin

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<sup>3</sup> For R-Phrase, see Appendix.

## 2-3-3 Flammable Aerosols

### (1) Definitions

Definitions of flammable of aerosols in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (2.3.1)**

*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) Classification criteria in GHS

**【GHS 3<sup>rd</sup> revised edition】 (2.3.2)**

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 and mixtures 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.

#### (2.3.4.1 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.

The GHS classification criteria are summarized as follows:

- Category 1 :
- aerosols whose content of flammable components is 85% or more and whose heat of combustion is 30 kJ/g or larger, or
  - spray aerosols for which ignition occurs at a distance of 75 cm or more in the

flame distance (ignition distance) test, or

- foam aerosols which have, in the foam test, 20 cm or more of the flame height and 2 seconds or longer of the flame duration or have 4 cm or more of the flame height and 7 seconds or longer of the flame duration,

- Category 2 :
- spray aerosols for which the heat of combustion is 20 kJ/g or larger and either for which ignition occurs at a distance of 15 cm or more in the flame distance (ignition distance) test or for which the time equivalent is 300 second/ m<sup>3</sup> or less, or the deflagration density is 300 g/ m<sup>3</sup> or less, in the enclosed space ignition test,
  - foam aerosols which have, in the foam test, 4 cm or more of the flame height and 2 seconds or longer of the flame duration,

Not classified : aerosols whose content of flammable components is 1% or less and the heat of combustion is smaller than 20 kJ/g.

### (3) Guidance for Classification

#### A) Judgment of “Not applicable”

In classification of a pure substance, regarding “flammable aerosols”, “classification result” shall be “Not applicable”, and “not an aerosol product” shall be indicated for “Classification Grounds and Problems”.

#### B) Judgment of “Not classified”

A product which has no flammable components or whose flammable components is 1% or less and whose heat of combustion smaller than 20 kJ/g shall be “Not classified”.

### (4) Data availability

The composition of an aerosol product is determined by its product designer. The categories of spray solutions and propellant gases should be determined according to the decision logic in GHS 2.3.4.1 with necessary test, if any.

### (5) Comparison with conventional classification systems

A judging method described in the Special provision 63 for UN number 1950 (Aerosols) in UNRTDG 3.2.1 Dangerous Goods List has been adopted to the GHS decision logic.

## 2-3-4 Oxidizing Gases

### (1) Definitions

Definitions of oxidizing gases in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (2.4.1)**

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) Classification criteria in GHS

**【GHS 3<sup>rd</sup> revised edition】 (2.4.2)**

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% oxygen by volume may be regarded as not oxidizing for some regulatory purposes (e.g. transport)

### (3) Guidance for Classification

#### A) Judgment of Not applicable

A product which does not meet the GHS definition of gases shall be judged as “Not applicable”.

#### B) Classification based on TDG Classification etc

The substance to be evaluated that is listed as a dangerous good (a gas product whose division number or for its subsidiary hazard is 5.1) in the Dangerous Goods List based on TDG classification shall belong to “Category 1”.

The following gases described in ISO10156-2 shall also belong to “Category 1”.

Bis-trifluoromethylperoxide	C i = 40 Note) Ci: Oxygen equivalency coefficient
Bromine pentafluoride	C i = 40
Bromine trifluoride	C i = 40
Chlorine	C i = 0.7
Chlorine pentafluoride	C i = 40
Chlorine trifluoride	C i = 40
Fluorine	C i = 40
Iodine pentafluoride	C i = 40
Nitric oxide	C i = 0.6
Nitrogen dioxide	C i = 1

Nitrogen trifluoride	C i = 1.6
Nitrogen trioxide	C i = 40
Oxygen difluoride	C i = 40
Ozone	C i = 40
Tetrafluorohydrazine	C i = 40

For reference : ISO10156-2, describing an international test method on “oxidizing gases” was established in August 2005. Since the description of 2.4.4.1 in the GHS third revised edition is based on that of ISO10156:1996, it is expected to be amended in the future. Because this test requires an immense amount of time and effort and involves risk of explosion, the measurement results for coefficient of oxygen equivalency have been obtained only for a few substances before the establishment of the ISO.

#### C) Judgment of Not Classified

Other (non-oxidizing) gases than described above shall be judged as “Not classified”.

#### (4)Data availability

Calculation should be performed in accordance with ISO-10156-2, based on the composition.

The coefficients of oxygen equivalency of nitrous oxide and oxygen are described in the GHS third revised edition. Toxic/corrosive oxidizing gases are described in the ISO-10156-2.

#### (5)Comparison with conventional classification systems

The UNRTDG definition (UNRTDG2.5.2) for oxidizing substances (Division 5.1) is limited to liquids and solids. In UNRTDG, no classification criteria are available for oxidizing gases, while some gases are assigned with the division number 5.1 for their subsidiary hazard, but the assignment is not comprehensive. Oxidizing gases fall under Schedule 122 in ERG and S-W in EmS, on the basis of which oxidizing gases can be selected.

Nitrogen trifluoride and all gases listed thereafter in the next section are categorized as “all other oxidizing gases”.

#### (6)Sources of information for classification results under conventional systems

Gases classified as Classes 2.2(5.1), 2.3(5.1), and 2.3(5.1, 8) in the third and fourth columns of the UNRTDG Dangerous Goods List fall under this class. In addition, some of gases classified as Classes 2.2 and 2.3 can fall under “oxidizing gases” even if their subsidiary hazards are not specified.

For transport of dangerous goods, only those classified as “Gases Under Pressure” are subject to regulation, while gases with ambient pressure are also included in the GHS class because of the absence of such conditions in GHS.

(Example) UNRTDG2.2 (5.1)

1003 AIR, REFRIGERATED LIQUID  
1014 CARBON DIOXIDE AND OXYGEN MIXTURE, COMPRESSED  
1070 NITROUS OXIDE  
1072 OXYGEN, COMPRESSED  
1073 OXYGEN, REFRIGERATED LIQUID  
2201 NITROUS OXIDE, REFRIGERATED LIQUID  
2451 NITROGEN TRIFLUORIDE

UNRTDG2.3 (5.1、 8)or UNRTDG2.3 (5.1)

1045 FLUORINE, COMPRESSED  
1067 DINITROGEN TETROXIDE(NITROGEN DIOXIDE)  
1660 NITRIC OXIDE, COMPRESSED  
1749 CHLORINE TRIFLUORIDE  
1975 NITRIC OXIDE AND DINITROGEN TETROXIDE MIXTURE (NITRIC  
OXIDE AND NITROGEN DIOXIDE MIXTURE)  
2190 OXYGEN DIFLUORIDE,COMPRESSED  
2421 NITROGEN TRIOXIDE  
2548 HLORINE PENTAFLUORIDE  
2901 BROMINE CHLORIDE  
3083 PERCHLORYL FLUORIDE

## 2-3-5 Gases Under Pressure

### (1) Definitions

Definitions of gases under pressure in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (2.5.1)**

*Gases under pressure* are gases which are contained in a receptacle at a pressure of 200 kPa (gauge) or more, or which are liquefied or liquefied and refrigerated.

They comprise compressed gases, liquefied gases, dissolved gases and refrigerated liquefied gases.

### (2) Classification criteria in GHS

**【GHS 3<sup>rd</sup> revised edition】 (2.5.2)**

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**

<b>Group</b>	<b>Criteria</b>
<b>Compressed gas</b>	A gas which when packaged under pressure is entirely gaseous at -50 °C; including all gases with a critical temperature $\leq -50$ °C.
<b>Liquefied gas</b>	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.
<b>Refrigerated liquefied gas</b>	A gas which when packaged is made partially liquid because of its low temperature.
<b>Dissolved gas</b>	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.

### (3) Guidance for Classification

A) Judgment of Not applicable

Substances and mixtures that are liquid or solid according to the GHS definition shall be judged as “Not applicable”.

#### B) Classification based on data from prescribed literatures

In GHS classes of gas, “gases under pressure” are conditions made in the pressure vessels by manufacturers depending on their purposes such as transport and use. And other properties (flammable gases, oxidizing gases, acute inhalation toxicity) are based on hazards when these gases exist in air at a standard pressure.

In the new GHS classification, “gases under pressure” are categorized into individual groups depending on critical temperatures obtained, in principle, from prescribed review documents and conditions assumed during transport.

If the gas under pressure is a single substance, categories of refrigerated liquefied gas and dissolved gas are not applied.

#### (4) Data availability

The data required are vapor pressure at 50 °C physical properties at 20 °C and atmospheric pressure, and critical temperature (GHS2.5.4.2). All of them can be obtained relatively easily. Physical conditions, pressure, and the like, when compressed in cylinders, depend on the design of manufacturers.

#### (5) Comparison with conventional classification systems

The definition of Class 2 (gas) set out in UNRTDG2.2.1.2 accords with that of gas in GHS: “a substance that at 50 °C has a vapor pressure greater than 300 kPa (absolute pressure); or is completely gaseous at 20 °C at a standard pressure of 101.3 kPa”. On the other hand, UNRTDG does not provide the definition of “gases under pressure”, which are newly defined by GHS as “gases with vapor pressure of 200 kPa or more”.

#### (6) Sources of information for classification results under conventional systems

These depend on the design selected by the manufacturers. Categorization of Gases Under Pressure is performed by using external data as complement.

## 2-3-6 Flammable Liquids

### (1) Definitions

Definitions of flammable liquids in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (2.6.1)**

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

### (2) Classification criteria in GHS

**【GHS 3<sup>rd</sup> revised edition】 (2.6.2)**

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 Part III, section 32 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.

### (3) Guidance for Classification

#### A) Judgment of Not applicable

Substances and mixtures that are gases and solids shall be judged as “Not applicable”.

#### B) Judgment of Not Classified

Non-combustible Liquids shall be judged as “Not classified”. (Dangerous goods in the Class 4, animal oils and plant oils, and Liquids of specified combustible substances shall also be deemed as “Not classified”). Furthermore, flame-resistant substances are considered as “Not classified” with regard to these classes, but the boundary between combustibility and

flame-resistance is not clearly defined. Accordingly, in this classification, only if the substance is confirmed to be noncombustible based on the prescribed review documents, “Not classified” is to be indicated in the “Classification result” column. (see p.22)

#### C) Classification based on data from prescribed literatures

Regarding GHS classification of flammable liquids, categories based on flash points obtained from the prescribed review documents shall take precedence, and classification based on TDG shall be adopted only when flash points data are not available.

Since Category 4 of flammable liquids in GHS classification does not fall under Dangerous Goods in TDG classification, as for Category 4, UNRTDG classification results can not be used for GHS classification.

#### (4)Data availability

Since such measurements are obligatory under the Fire Defense Law, data can be obtained relatively easily even for articles. However, the law requires the “open-cup method” for the measurement of high flash points, which poses a problem around the upper limit of Category 4.

#### **【Classification based on test results of Class 4 Dangerous Goods in the Fire Defense Law】**

For Class 4 dangerous goods of the Fire Defense Law, data such as flash points and initial boiling points (or boiling points) are available, and they may be utilized. When the measured flash points are 80°C or higher, the flash points are not directly utilized in GHS classification, since the data according to the Fire Defense Law are obtained with open-cup method.

Note : Although measurement of flash point is fundamentally performed with “closed-cup test method”, “open-cup tests” are admitted in special cases.(the UN GHS third revised edition 2.6.4.2.4)In Japan, where data according to the Fire Defense Law have been accumulated, this provision may be utilized. Since flash points obtained with “open-cup tests” are considered to be higher by several °C than that with “closed-cup test method”, when flash points are about 110°C or higher, the substances shall be deemed “Not classified” regardless of the test method. However, when the measurement results with “open-cup tests” are 90-110°C, the substances can be “Not classified” or otherwise in accordance with the measuring method based on GHS. If data with “closed-cup test method” are not available, the substances shall fall under “Classification not possible”.

#### (5)Comparison with conventional classification systems

In general, Categories 1-3 accords with Class 3 of UNRTDG.

Category 1 =UNRTDG3 I (No upper limits are provided for flash points, but no combustible substance with an initial boiling point of 35°C and lower and a flash point of 23°C or higher has been reported.)

Category 2 =UNRTDG3 II

Category 3 =UNRTDG3 III

Category 4 =They are non-dangerous articles in UNRTDG.

The categories of EU DSD classification differ from that of GHS (R12, 11, and 10 only serve as reference).

(6)Sources of information for classification results under conventional systems

Relevant Laws and regulations according to the suitable UNRTDG, such as the Dangerous Goods Regulations (Japan), can be applied to Categories 1, 2, and 3, through the procedures described in the previous section.

(Example of category 1)UNRTDG3 I

1093 ACRYLONITRILE, STABILISED

1131 CARBON DISULPHIDE

2481 ETHYL ISOCYANATE

(Example of category 2)UNRTDG3 II

1090 ACETONE

1154 DIETHYLAMINE

1717 ACETYL CHLORIDE

1230 METHANOL

(Example of category 3)UNRTDG3 III

1157 DIISOBUTYL KETONE

2260 TRIPROPYLAMINE

2529 ISOBUTYRIC ACID

(Example of category 4)DIVINYLBENZENE

N-ETHYLANILINE

ETHYLENE CYANOHYDRIN

NITROBENZENE

## 2-3-7 Flammable Solids

### (1) Definitions

Definitions of flammable solids in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (2.7.1)**

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) Classification criteria in GHS

**【GHS 3<sup>rd</sup> revised edition】 (2.7.2)**

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 s 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 min 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 Part II I, sub-section 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 s or burning rate >2.2 mm/s Metal powders: burning time ≤5 min
2	Burning rate test: Substances or mixtures other than metal powders: (a) wetted zone stops the fire for at least 4 min; and (b) burning time <45 s or burning rate >2.2 mm/s Metal powders: burning time >5 min and ≤10 min

*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.*

(3) Guidance for Classification

A) Judgment of Not applicable

Substances and mixtures that are gases and liquids shall be judged as “Not applicable”.

B) Judgment of Not Classified

Solids known to be non-combustible or flame-resistant by literatures shall be “Not classified”.

C) Classification based on TDG Classification

If the name of a substance is included in TDG classification, the substance shall be classified according to it. If not, “Classification not possible” is applied to it in principle.

(4) Data availability

Few result values of the rate-of-burning tests have been published.

(5) Comparison with conventional classification systems

Flammable solids accord with Class 4.1 of UNRTDG.

Category 4.1 also includes 2-3-8 “Self-reactive Substances and Mixtures” and 2-3-1 “Explosives”. Therefore, ERG should be also considered.

Related ERG Schedules are as follows:

133 Flammable Solid

133 Flammable Solid – toxic/corrosive

170 Metal (powder, dust, shavings, drilling chips, lathe chips, swarf, etc.)

In EmS, “Flammable Solid” is included in Schedule S-G along with “Self-reactive Substances”.

These classification criteria are also applied to the solids of R11 in EU DSD classification.

(6) Sources of information for classification results under conventional systems

Those categories below of UNRTDG (or Dangerous Goods Regulation of Japan) can be applied.

Category 1 =UNRTDG • 4.1 II\* ERG133, 134, 170

Category 2 =UNRTDG • 4.1 III\* ERG133, 134, 170

(Example of category 1)

4.1 II*133	1345	RUBBER SCRAP or RUBBER SHODDY, powdered or granulated, not exceeding 840 microns and rubber content exceeding 45%
	2989	LEAD PHOSPHITE, DIBASIC
4.1 II*134	1868	DECABORANE
4.1 II*170	1309	ALUMINIUM POWDER, COATED
	1323	FERROCERIUM
	1871	TITANIUM HYDRIDE

(Example of category 2)

4.1 III*133	1312	BORNEOL
	1328	HEXAMETHYLENETETRAMINE
	2213	PARAFORMALDEHYDE
	3241	2-BROMO-2-NITROPROPANE-1,3-DIOL
	3251	ISOSORBIDE-5-MONONITRATE
4.1 III*134		There is no article with a specific name that fall under this division.
4.1 III*170	1346	SILICON POWDER, AMORPHOUS
	2878	TITANIUM SPONGE GRANULES or TITANIUM SPONGE POWDERS

## 2-3-8 Self-reactive Substances and Mixtures

### (1) Definitions

Definitions of self-reactive substances and mixtures in UN GHS are as follows, and they are adopted in this guidance.

#### 【GHS 3<sup>rd</sup> revised edition】 (2.8.1)

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) Classification criteria in GHS

#### 【GHS 3<sup>rd</sup> revised edition】 (2.8.2)

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 criteria of Chapters 2.13 or 2.14, except that mixtures of oxidizing substances which contain 5% or more of combustible organic substances shall be classified as self-reactive substances according to the procedure defined in the note below;
- (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.

**NOTE:** *Mixtures of oxidizing substances, meeting the criteria for classification as oxidizing substances, which contain 5.0% or more of combustible organic substances and which do not meet the criteria mentioned in (a), (c), (d) or (e) above, shall be subjected to the self-reactive substances classification procedure;*

*Such a mixture showing the properties of a self-reactive substance type B to F (see 2.8.2.2) shall be classified as a self-reactive substance.*

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 greater than or equal to 150°C is used for desensitization 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 desensitization, 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.

### 2.8.2.3 *Criteria for temperature control*

Self-reactive substances need to be subjected to temperature control if their self-accelerating decomposition temperature (SADT) is less than or equal to 55°C. Test methods for determining the SADT as well as the derivation of control and emergency temperatures are given in the *UN Recommendations for the Transport of Dangerous Goods, Manual of Tests and Criteria, Part II*, section 28. The test selected shall be conducted in a manner which is representative, both in size and material, of the package.

#### (3) Guidance for Classification

##### A) Judgment of Not applicable

- 1) Gas, explosives, organic peroxides, and liquids and solids classified as oxidizing substances shall be “Not applicable”.
- 2) Substances not containing chemical groups related to explosibility (2-2-6) or self-reactivity (2-2-7) shall be “Not applicable”.

##### B) Judgment of Not Classified

Regarding the substances containing chemical groups related to explosibility or self-reactivity, if data on SADT or exothermic decomposition are obtained from prescribed review documents and the guidance of 2.8.2.1(d)(e) in the UN GHS third revised edition is applicable to the substances, fill in “Classification result” with “Not classified”, and fill in “Classification Grounds and Problems” with “SADT \*\* °C” (\*\* is filled with a specific value).

##### C) Classification based on TDG Classification etc

If the name of a substance is included in TDG classification, the substance shall be classified according to it.

Pure substances of some transport-prohibited substances listed in “Notice to settle Transportation Standards and the like of Dangerous Goods by Ship”, Article 5 (1) to (4), based on the Dangerous Goods Regulations, Article 7 (1), belong to the self-reactive substance TYPE A. However, they shall be classified into those containing a required stabilization agent, not into TYPE A.

Substances that cannot be classified by the procedure mentioned above shall be classified as “Classification not possible”.

#### (4) Data availability

Few measurement data related to the flow chart of UN GHS third revised edition 2.8.4 have been published. Mostly, self-reactive substances are traded and used as prepared chemicals in which diluents and/or stabilizing agents are added to them, rather than as pure substances. Classification into TYPE A to G should be made based on a test for individual prepared

chemicals.

(5) Comparison with conventional classification systems

The flow chart of UN GHS third revised edition GHS2.8.4 is exactly the same as that of UNRTDG (Fig. 2.4.1). In EmS, self-reactive substances not requiring temperature control are classified into Schedule S-G along with Flammable Solid, and those requiring are classified into Schedule S-K. In ERG, they are classified in Schedule 149 and 150.

(6) Sources of information for classification results under conventional systems

Chemicals which belong to UNRTDG4.1\*ERG149, 150 in UNRTDG and North-America Emergency Response Guidebook fall under this class.

		The temperature management is unnecessary(149)		Temperature management necessity (150)	
		Liquid	Solid	Liquid	Solid
Type A	=	(Transportation prohibition substance)			
Type B	=	UN 3221,	3222,	3231,	3232
Type C	=	UN 3223,	3224,	3233,	3234
Type D	=	UN 3225,	3226,	3235,	3236
Type E	=	UN 3227,	3228,	3237,	3238
Type F	=	UN 3229,	3230,	3239,	3240
Type G	=	(Non-dangerous articles)			

A typical example is listed in the table of UNRTDG2.5.3.2.4 (or in “Dangerous Goods Regulations, Annex 1, Recital 1(2)”). The following is the example. If an inactivation agent is used, the substance may be classified in a lower TYPE.

(Example of type B)

3221	There is no article with a specific name that fall under this division.
3222	2-DIAZO-1-NAPHTHOL-4(or 5)-SULPHONYLCHLORIDE)
3231	There is no article with a specific name that fall under this division.
3232	AZODICARBONAMIDE FORMULATION TYPE B, TEMPERATURE CONTROLLED

(Example of type C)

3223	There is no article with a specific name that fall under this division.
3224	2,2'-AZODI(ISOBUTYRONITRILE)as a water based paste
3233	There is no article with a specific name that fall under this division.

3234 2,2'-AZODI(ISOBUTYRONITRILE)

(Example of type D)

3225 There is no article with a specific name that fall under this division.

3226 BENZENESULPHONYL HYDRAZIDE

3235 2,2' -AZODI(ETHYL-2-METHYLPROPIONATE)

3236 2,2' -AZODI(2,4-DIMETHYL-4-METHOXYVALERONITRILE)

(Example of type E)

3227 There is no article with a specific name that fall under this division.

3228 4-(DIMETHYLAMINO)-BENZENEDIAZONIUM TRICHLOROZINCATE (-1)

3237 (DIETHYLENEGLYCOL BIS (ALLYL CARBONATE) +  
DIISOPROPYLPEROXYDICARBONATE)

3238 There is no article with a specific name that fall under this division.

(Example of type F)

3229 There is no article with a specific name that fall under this division.

3230 There is no article with a specific name that fall under this division.

3239 There is no article with a specific name that fall under this division.

3240 There is no article with a specific name that fall under this division.

Those substances categorised as Type G are not applied to UNRTDG.

## 2-3-9 Pyrophoric Liquids

### (1) Definitions

Definitions of pyrophoric liquids in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (2.9.1)**

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) Classification criteria in GHS

**【GHS 3<sup>rd</sup> revised edition】 (2.9.2)**

A pyrophoric liquid is classified in a single category for this class using test N.3 in Part III , sub-section 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.

### (3) Guidance for Classification

#### A) Judgment of Not applicable

Substances and mixtures that are gases and solids shall be judged as “Not applicable”.

#### B) Judgment of Not Classified

If it is confirmed based on the information of prescribed review documents that a substance to be assessed does not self-ignite on contact with air of ambient temperature, fill in “Classification result” with “Not classified”, and fill in “Classification Grounds” with “Do not self-ignite in contact with air of ambient temperature”.

Reliable ignition point data can be used as dependable judgment criteria.

Note: If it is confirmed based on the information of prescribed review documents that the ignition point of a substance exceed about 70°C, the substance can be classified as “Not classified”.

Reference: UN GHS third revised edition 2.9.4.2 and 2.10.4.2

#### C) Classification based on TDG Classification

If the name of a substance is included in TDG classification, the substance shall be classified according to it. If not, it falls under “Classification not possible” in principle. However, if it is confirmed that a substance to be assessed does not self-ignite on contact

with air of ambient temperature, the substance can be classified as “Not classified”.

(4)Data availability

Few data have been published.

(5)Comparison with conventional classification systems

The definition of Pyrophoric Liquids in UN GHS third revised edition GHS2.9.1 is identical with that of UNRTDG2.4.3.2.2. In addition, as stated in 2.4.3.3.1, the Packing Group for it is defined as “T”.

In EmS, Pyrophoric Liquids, along with Solid described in 2-3-10, are classified into Schedule S-M (Pyrophoric Hazards) or S-L (Pyrophoric substances and water-reactive substances).

In ERG, they are included in Schedule 135 and 136 (Pyrophoric substances), but are not distinguished from Self-heating Substances and Mixtures described in 2-3-11.

(6)Sources of information for classification results under conventional systems

It is judged that Class 1 is identical with UNRTDG4.2 I (Liquids). These substances may also have the property of “Substances and mixtures which, in contact with water, emit flammable gasesZ” mentioned in 2-3-12.

(Example)UNRTDG4.2 I	1366	DIETHYLZINC
	1370	DIMETHYLZINC
	1380	PENTABORANE
	2445	LITHIUM ALKYL 4.2 4.3
	2870	ALUMINIUM BOROXYDRIDE ALUMINIUM BOROXYDRIDE IN DEVICES
	3053	MAGNESIUM ALKYL
	3076	ALUMINIUM ALKYL HYDRIDES
	3254	TRIBUTYLPHOSPHANE
	3255	tert-BUTYL HYPOCHLORITE

## 2-3-10 Pyrophoric Solids

### (1) Definitions

Definitions of pyrophoric solids in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (2.10.1)**

*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) Classification criteria in GHS

**【GHS 3<sup>rd</sup> revised edition】 (2.10.2)**

A pyrophoric solid is classified in a single category for this class using test N.2 in Part III, sub-section 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 min 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.*

### (3) Guidance for Classification

#### A) Judgment of Not applicable

Substances and mixtures that are gas and liquids shall be “Not applicable”.

#### B) Judgment of Not Classified

If it is confirmed based on the information of prescribed review documents or is judged based on experiences that a substance to be assessed does not self-ignite on contact with air of ambient temperature, fill in “Classification result” with “Not classified”, and fill in “Classification Grounds” with “Do not self-ignite on contact with air of ambient temperature”.

Fill-in example: In the class of “Pyrophoric Solids”, “Not classified” (Do not self-ignite on contact with air of ambient temperature.)

Reliable ignition point data can be used as dependable judgment criteria.

Note: If it is confirmed based on the information of prescribed review documents that the ignition point of a substance exceed about 70°C, the substance can be classified as “Not

classified”.

Reference: UN GHS third revised edition 2.9.4.2 and 2.10.4.2

C) Classification based on TDG Classification

If the name of a substance is included in TDG classification, the substance shall be classified according to it. If not, it falls under “Classification not possible” in principle. However, if it is confirmed that a substance to be assessed does not self-ignite on contact with air of ambient temperature, the substance can be classified as “Not classified”.

(4) Data availability

Few data have been published.

(5) Comparison with conventional classification systems

The definition of Pyrophoric Solids in GHS 2.10.1 is identical with that of UNRTDG 2.4.3.2.1. In addition, as stated in 2.4.3.3.1, the Packing Group for it is defined as “I”.

In EmS, Pyrophoric Solids, along with Liquids described in 2-3-9, are classified into Schedule S-M (Pyrophoric Hazards) or S-L (Pyrophoric substances and water-reactive substances).

In ERG, they are included in Schedule 135 and 136 (Pyrophoric substances), but are not distinguished from Self-heating Substances and Mixtures described in 2-3-11.

(6) Sources of information for classification results under conventional systems

It is judged that Class 1 is identical with UNRTDG 4.2 I (Solid). These substances may also have the property of “Substances and mixtures which, in contact with water, emit flammable gases” mentioned in 2-3-12.

(Example) UNRTDG 4.2 I	1854	BARIUM ALLOYS, PYROPHORIC
	1855	CALCIUM, PYROPHORIC or CALCIUM ALLOYS, PYROPHORIC
	2005	MAGNESIUM DIPHENYL
	2008	ZIRCONIUM POWDER, DRY
	2441	TITANIUM TRICHLORIDE, PYROPHORIC or TITANIUM TRICHLORIDE MIXTURE, PYROPHORIC
	2545	HAFNIUM POWDER, DRY
	2546	TITANIUM POWDER, DRY

## 2-3-11 Self-heating Substances and Mixtures

### (1) Definitions

Definitions of self-heating substances and mixtures in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (2.11.1)**

A *self-heating substance or mixture* is a solid or liquid 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) Classification criteria in GHS

**【GHS 3<sup>rd</sup> revised edition】 (2.11.2)**

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<sup>3</sup>;
- (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 Part III , sub-section 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 <u>and</u> the substance or mixture is to be packed in packages with a volume of more than 3 m <sup>3</sup> ;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 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, <u>and</u> 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 27 m<sup>3</sup>. Substances and mixtures with a temperature of spontaneous combustion higher than 50 °C for a volume of 27 m<sup>3</sup> 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.

(3) Guidance for Classification

A) Judgment of Not applicable

- 1) Substances and mixtures that are gases shall be judged as “Not applicable”.
- 2) Pyrophoric liquids and solids shall be judged as “Not applicable”.

B) Judgment of Not Classified

Non-flammable liquids and solids shall be judged as “Not classified”.

C) Classification based on TDG Classification

If the name of a substance is included in TDG classification, the substance shall be classified according to it. If not, it falls under “Classification not possible” in principle.

D) Classification based on data from prescribed literatures

If the data of screening test described in the UN GHS third revised edition 2.11.4.2 are obtained for a substance from prescribed review documents, and the data show that it is not a self-heating substance, it shall be classified as “Not classified”, and “Classification Grounds and Problems” shall be filled in with the result of the test.

As to the substances for which the classification result on Pyrophoric Liquids is “Classification 1”, or liquid substances to be assessed other than those for which the classification result on “Self-heating Substances and Mixtures” is “Not classified” based on “inflammable” information, fill in “Classification result” of “Self-heating Substances and Mixtures” with “Classification not possible“, and fill in “Classification Grounds” with “No established test method suitable for liquid substances”.

For reference: The test for “Self-heating Substances and Mixtures” defined in TDG classification and also adopted in GHS classification, in which a specimen is kept in a stainless-steel mesh cage in a thermostatic chamber for 24 hours, cannot be applied to liquids (and solid with a melting point of 140 °C or lower). Thus, liquids and solid with a melting point of 140 °C or lower shall be classified as “Classification not possible“.

#### (4)Data availability

Few data for each substance has been published.

#### (5)Comparison with conventional classification systems

In Classification 4.2 described in UNRTDG2.4.3.2.3, the definition of Self-heating Substances accords with the classification criteria of GHS2.11.2. Packing Group II corresponds to GHS Classification 1, and Packing Group III corresponds to Classification 2. Classification 4.2 also includes Pyrophoric Solids (2.4.3.2.1) and Pyrophoric Liquids)(2.4.3.2.2).

In ERG, self-heating substances and mixtures are included in Schedule135 and 136 (Self-heating Substances).

In EmS, they are included in Schedule S-J (wetted explosives and self-heating substances). The former one belongs to UNRTDG Classification 4.1, as described in 2-3-1.

#### (6)Sources of information for classification results under conventional systems

Substances classified into UNRTDG4.2\*EmS: S-J fall under this class.

(Example of category 1) UNRTDG4.2 II\*EmS: S-J

1369	p-NITROSODIMETHYLANILINE
1382	POTASSIUM SULPHIDE, ANHYDROUS or POTASSIUM SULPHIDE with less than 30% water of crystallization
1384	SODIUM DITHIONITE (SODIUM HYDROSULPHITE)
1385	SODIUM SULPHIDE, ANHYDROUS or SODIUM SULPHIDE with less

	than 30% water of crystallization
1923	CALCIUM DITHIONITE (CALCIUM HYDROSULPHITE)
1929	POTASSIUM DITHIONITE (POTASSIUM HYDROSULPHITE)
2318	SODIUM HYDROSULPHIDE with less than 25% water of crystallization
2940	9-PHOSPHABICYCLONANES (CYCLOOCTADIENE PHOSPHINES)
3341	THIOUREA DIOXIDE
(Example of category 2) UNRTDG4.2 III*EmS: S-J	
1362	CARBON, ACTIVATED
1363	COPRA
1364	COTTON WASTE, OILY
1365	COTTON, WET
1379	PAPER, UNSATURATED OIL TREATED, incompletely dried (including carbon paper)
1387	WOOL WASTE, WET
1386	SEED CAKE with more than 1.5% oil and not more than 11% moisture
1857	TEXTILE WASTE, WET
2002	CELLULOID, SCRAP
2793	FERROUS METAL BORINGS, SHAVINGS, TURNINGS or CUTTINGS in a form liable to self-heating
3174	TITANIUM DISULPHIDE

## 2-3-12 Substances and mixtures which, in contact with water, emit flammable gases

### (1) Definitions

Definitions of substances and mixtures which in contact with water, emit flammable gases in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (2.12.1)**

*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) Classification criteria in GHS

**【GHS 3<sup>rd</sup> revised edition】 (2.12.2)**

A substance or mixture which, in contact with water, emits flammable gases is classified in one of the three categories for this class, using test N.5 in Part III, sub-section 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.*

### (3) Guidance for Classification

#### A) Judgment of Not applicable

- 1) Substances for gases shall be judged as “Not applicable”.
- 2) Substances not containing metals or metalloids in their chemical structure shall be judged as “Not applicable”.

#### B) Judgment of Not Classified

If it is judged based on the information of prescribed review documents that a substance containing metals or metalloids is stable even if it is in contact with water (for example, if it is produced using water or is washed using water or if its aqueous solubility is known from literatures), fill in “Classification result” with “Not classified”, and fill in “Classification Grounds” with “Stable to water”.

Reference: UN GHS third revised edition 2.12.4.2(b)(c)

#### C) Classification based on TDG Classification

If the name of a substance is included in TDG classification, the substance shall be classified according to it. If not, it falls under “Classification not possible” in principle.

### (4) Data availability

Few numerical data on the rate of evolution of gas have been published.

### (5) Comparison with conventional classification systems

Judgment criteria of GHS 2.12.2 completely accord with the definition of UNRTDG Classification 4.3.

Judgment criteria of EU classification accord with those of GHS, but further categorization is not given for the former.

### (6) Sources of information for classification results under conventional systems

Based on the laws and regulations pursuant to the applicable UNRTDG (In Japan, “Dangerous Goods Regulations” correspond to them).

Category 1 = UNRTDG·4.3 I

Category 2 = UNRTDG·4.3 II

Category 3 = UNRTDG·4.3 III

Substances classified into UNRTDG·4.2 (4.3) correspond to GHS Category 1.

Substances classified into EU DSD Classification R15 meet GHS judgment criteria, but they do not correspond to Category 1, 2, and 3.

In ERG, Schedules related to “Substances which, in contact with water, emit flammable gases” of GHS are as follows:

135: Pyrophoric substances

138: Water-reactive substances – emitting flammable gas

138: Water-reactive substances – emitting flammable/toxic gas

Example of substances meeting the judgment criteria:

Category 1

UNRTDG4.3I \* ERG138 : Alkali metals and their alloys, hydrides, amalgams and suspended solids including alkali earth metals

1410 LITHIUM ALUMINIUM HYDRIDE

1426 SODIUM BOROHYDRIDE

1428 SODIUM

UNRTDG4.3 I \* ERG139 : Phosphides and part of silane compounds)

1183 ETHYLDICHLOROSILANE

1360 CALCIUM PHOSPHIDE

1714 ZINC PHOSPHIDE

Category 2

UNRTDG4.3II\*ERG138 : ALKALI EARTH METALS, METAL CARBIDES and SILICIDES

1394 ALUMINIUM CARBIDE

1401 CALCIUM

2624 MAGNESIUM SILICIDE

UNRTDG4.3 II\*ERG139 : PHOSPHIDES and some SILANE COMPOUNDS

1340 PHOSPHORUS PENTASULPHIDE, free from yellow and white phosphorus

1395 ALUMINIUM FERROSILICON POWDER

Category 3

UNRTDG4.3 III\*ERG138 : LIGHT METALS and METAL SILICIDES

1398 ALUMINIUM SILICON POWDER, UNCOATED

1435 ZINC ASHES

UNRTDG4.3 III\*ERG139 : METAL SILICIDES

1408 FERROSILICON with 30% or more but less than 90% silicon

Water-reactive substances failing to meet GHS judgment criteria:

There are substances which, in contact with water, emit an inflammable gas (often toxic or corrosive) or produce heat (and dangerous droplets at the same time). These are not included in GHS classification, but they have a Schedule name including the word “water-reactive” in ERG.

137: Water-reactive substances - corrosive

Example: PHOSPHORUS PENTOXIDE, SULFURIC ACID

144: Oxidant (Water-reactive) SODIUM PEROXIDE

155: Toxic substances/corrosive substances (flammable/water-reactive) ACETONE  
CYANOHYDRIN

156: Toxic substances/corrosive substances (flammable/water-reactive) BENZYL  
CHLORIDE

157: Toxic substances/corrosive substances (inflammable/water-reactive) ANTIMONY  
TRICHLORIDE

166: Radioactive substances – corrosive (URANIUM HEXAFLUORIDE –  
water-reactive)

These should be considered separately from “Water-reactive flammable” in GHS.

#### (7) Discussion on GHS Water-Reactive Flammable Substances and Metalloids

##### A) Description of UN GHS third revised edition 2.12

Section 2.12.4.2 of UN GHS third revised edition 2.12 “Substances and mixtures which, in contact with water, emit flammable gases” includes a description: “The classification procedure for this class need not be applied if the chemical structure of the substance or mixture does not contain metals or metalloids”. For smooth classification according to GHS, the definition of “metalloids” is summarized as follows:

##### B) Metalloid

A metalloid is defined as a substance having an intermediate property between those of metals and nonmetals. The property is related to the electric conduction property of single element solids. In the website of Institute for Molecular Science (Okazaki Institute), National Institute of Nature Sciences, Inter-University Research Institute Corporation, B, C, Si, P, Ge, As, Se, Sn, Sb, Te, Bi, Po, At are listed as metalloids. For example, it is presumed that carbon is classified as metalloid because it has a peculiar conductivity in the form of graphite structure.

##### C) Water-reactive flammable substances

Water-reactive flammable substances are the substances which, on contact with water, deprive it of oxygen and emit flammable gases (hydrogen, hydrocarbon, hydrogen sulfide, etc). Therefore, the category “Water-reactive flammable substances” has no direct causal relation with metalloids, which are defined based on the electric conduction property. Giving a theoretical explanation for the description of UN GHS third revised edition 2.12.4.2(a), requires the application of quite an advanced electron theory.

Most of the substances listed in Class 4.3 in TDG classification, however, are actually metals or metal compounds (hydrides, phosphides, carbides, silicon compounds,

borohydrides, alkyl compounds, etc.), and a few metalloid compounds shown below (excluding N.O.S.) are also included in the list.

- UN-1183 ETHYLDICHLOROSILANE
- UN-1242 METHYLDICHLOROSILANE
- UN-1295 TRICHLOROSILANE
- UN-1340 PHOSPHORUS PENTASULFIDE
- UN-2965 BORON TRIHYDRIDE · DIMETHYL ETHER SOLUTION

As substances included in Class 4.3, the following two carbon compounds (excluding metal alkylates) are listed:

- UN-1394 ALUMINUM CARBIDE
- UN-1402 CALCIUM DICARBIDE

Since these substances contain a metal, they are not excluded from “water-reactive flammable substances” even if carbon is excluded from metalloids.

It is presumed that the description of UN GHS third revised edition 2.12.4.2(a), “The chemical structure of the substance or mixture does not contain metals or metalloids” intends to eliminate the discussion on classification assessment for huge amounts of organic compounds composed of only carbon, hydrogen, nitrogen, oxygen, sulfur, and four halogen elements. The aim will be lost if carbon is included in metalloids.

#### D) Scope of the metalloid

If phosphorus is interpreted to be excluded from “metalloids” defined in UN GHS third revised edition 2.12.4.2(a), phosphorus pentasulfide is excluded. Although compounds composed of selenium, tellurium and nonmetal elements are not considered to be water-reactive, they are included in the substances containing metalloids.

Alternatively, it is easier to understand if the description in 2.12.4.2(a) is rephrased as follows: “The classification procedure for this class need not be applied to a substance composed of carbon, hydrogen, nitrogen, oxygen, sulfur, and one or more of four halogen elements, as well as a mixture (solid or liquid) composed of these elements only”. Nevertheless, the description of UN GHS third revised edition adopting the term “metalloids” shall be followed.

If a substance or mixture falls under the exemption described in 2.12.4.2(a), fill the model classification with “Not applicable”, and fill “Grounds” with “Not containing metal or metalloids (B, Si, P, Ge, As, Se, Sn, Sb, Te, Bi, Po, At)”.

#### E) Assessment of inorganic metal compounds

Substances and mixtures exempted from the assessment, based on UN GHS third revised edition 2.12.4.2(a), are the most part of organic compounds (except for organic metal compounds) and a part of inorganic compounds. Thus, the large majority of inorganic metal compounds remain unmentioned. With regard to them, those known to be stable in water

according to UN GHS third revised edition 2.12.4.2(b) (c) shall be classified as “Not classified”.

For the grounds for judgment, see “water solubility” and “reactivity” fields, which are common in the classification entry forms. If the value of aqueous solubility is indicated there or if descriptions such as “water soluble” or “insoluble” are present, it shall be classified as “Not classified”. If a substance is water-reactive, a statement such as “react vigorously with water” is to be entered in the “reactivity” field.

## 2-3-13 Oxidizing Liquids

### (1) Definitions

Definitions of oxidizing liquids in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (2.13.1)**

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) Classification criteria in GHS

**【GHS 3<sup>rd</sup> revised edition】 (2.13.2)**

An oxidizing liquid is classified in one of the three categories for this class using test O.2 in Part I II, sub-section 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 Categories 1 and 2 are not met.

### (3) Guidance for Classification

#### A) Judgment of Not applicable

- 1) Substances of gases and solids shall be judged as “Not applicable”.
- 2) Organic substances which do not contain oxygen, fluorine, or chlorine or which contain any of these elements that are bound to carbon or hydrogen only shall be judged “Not

applicable”.

3) Inorganic substances not containing oxygen or a halogen element shall be judged “Not applicable”.

B) Judgment of Not Classified

Regarding oxidizing liquids or oxidizing solids, if it is confirmed based on review documents that a substance to be assessed is “reductive material”, fill in “Classification result” with “Not classified”, and fill in “Classification Grounds” with “Reductive material”.

C) Classification based on TDG Classification

If the name of a substance is included in TDG classification, the substance shall be classified according to it. If not, it falls under “Classification not possible” in principle.

(4)Data availability

Few experimental data on oxidative materials have been published.

(5)Comparison with conventional classification systems

The definition in GHS2.13.2 is equivalent to that of UNRTDG Classification 5.1 “Liquids”(UNRTDG2.5.2.3.2). In ERG, oxidative materials (including Solid) are classified into Schedules 140, 141, 142, 143 and 144, but it does not serve as a reference for this GHS classification. In EmS, oxidative materials (including Solid) are classified into Schedule S-Q.

(6)Sources of information for classification results under conventional systems

Category 1 =UNRTDG · 5.1 I (Liquids)

Category 2 =UNRTDG · 5.1 II (Liquids)

Category 3 =UNRTDG · 5.1 III (Liquids)

(Example of category 1)1873 PERCHLORIC ACID with more than 50% but not more than 72% acid, by mass

2495 IODINE PENTAFLUORIDE

(Example of category 2)2014 HYDROGEN PEROXIDE, AQUEOUS SOLUTION with not less than 20% but not more than 60% hydrogen peroxide (stabilized as necessary)

2427 POTASSIUM CHLORATE, AQUEOUS SOLUTION

(Example of category 3)2984 HYDROGEN PEROXIDE, AQUEOUS SOLUTION with not less than 8% but less than 20% hydrogen peroxide (stabilized as necessary)

## 2-1-14 Oxidizing Solids

### (1) Definitions

Definitions of oxidizing solids in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (2.14.1)**

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) Classification criteria in GHS

**【GHS 3<sup>rd</sup> revised edition】 (2.14.2)**

An oxidizing solid is classified in one of the three categories for this class using test O.1 in Part I II, sub-section 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 1:** Some oxidizing solids may also present explosion hazards under certain conditions (e.g. when stored in large quantities). For example, some types of ammonium nitrate may give rise to an explosion hazard under extreme conditions and the “Resistance to detonation test” (BC Code<sup>1</sup>, Annex 3, Test 5) may be used to assess this hazard. Appropriate comments should be made in the Safety Data Sheet.

**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.

(3) Guidance for Classification

A) Judgment of Not applicable

- 1) Gases and liquid substances shall be judged as “Not applicable”.
- 2) Organic substances which do not contain oxygen, fluorine, or chlorine or which contain any of these elements that are bound to carbon or hydrogen only shall be judged “Not applicable”.
- 3) Inorganic substances not containing oxygen or any halogen element shall be judged “Not applicable”.

B) Classification based on TDG Classification

If the name of a substance is included in TDG classification, the substance shall be classified according to it. If not, it falls under “Classification not possible” in principle.

(4) Data availability

Few experimental data on oxidative materials have been published.

(5) Comparison with conventional classification systems

The classification criteria of GHS2.14.2 are equivalent to the definition of UNRTDG Classification 5.1 “Solid“(UNRTDG2.5.2.2.2).

In ERG, oxidative materials (including Liquids) are classified into Schedules 140, 141, 142, 143 and 144, but it does not serve as a reference for this GHS classification. In EmS, oxidative materials (including Liquids) are classified into Schedule S-Q.

(6) Sources of information for classification results under conventional systems

Category 1=UNRTDG • 5.1 I (Solid)

Category 2=UNRTDG • 5.1 II (Solid)

Category 3=UNRTDG • 5.1 III (Solid)

(Example of category 1)	1504	SODIUM PEROXIDE
	2466	POTASSIUM SUPEROXIDE
(Example of category 2)	1439	AMMONIUM DICHROMATE
	1463	CHROMIUM TRIOXIDE, ANHYDROUS
	1493	SILVER NITRATE
	1496	SODIUM CHLORITE
	2719	BARIUM BROMATE

(Example of category 3)2067 AMMONIUM NITRATE BASED FERTILIZER

2469 ZINC BROMATE

2724 MANGANESE NITRATE

2728 ZIRCONIUM NITRATE

## 2-3-15 Organic Peroxides

### (1) Definitions

Definitions of organic peroxides in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (2.15.1)**

2.15.1.1 *Organic peroxides* are liquid or solid organic substances which contain the bivalent -O-O- 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) Classification criteria in GHS

**【GHS 3<sup>rd</sup> revised edition】 (2.15.2)**

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 desensitization, will be defined as **organic peroxide TYPE G**. If the organic peroxide 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.*

#### 2.15.2.3 **Criteria for temperature control**

The following organic peroxides need to be subjected to temperature control:

- (a) Organic peroxide types B and C with an SADT  $\leq 50^{\circ}\text{C}$ ;
- (b) Organic peroxide type D showing a medium effect when heated under confinement<sup>1</sup> with an SADT  $\leq 50^{\circ}\text{C}$  or showing a low or no effect when heated under confinement with an SADT  $\leq 45^{\circ}\text{C}$ ; and
- (c) Organic peroxide types E and F with an SADT  $\leq 45^{\circ}\text{C}$ .

Test methods for determining the SADT as well as the derivation of control and emergency temperatures are given in the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*, Part II, section 28. The test selected shall be conducted in a manner which is representative, both in size and material, of the package.

*1 As determined by test series E as prescribed in the Manual of Tests and Criteria, Part II.*

### (3) Guidance for Classification

#### A) Judgment of Not applicable

Inorganic substances and organic substances except Organic Peroxides are judged “Not applicable”.

#### B) Judgment of Not Classified

If the hydrogen peroxide content and the amount of available oxygen in a Organic Peroxide fall below the values stipulated in UN GHS third revised edition 2.15.2.1, fill in “Classification result” with “Not classified”, and fill in “Classification Ground” with “Active oxygen amount fails to satisfy the definition”.

#### C) Classification based on TDG Classification

If the name of a substance is included in TDG classification (for example, it is listed in the table of IMDGC2.5.3.2.4), the substance shall be classified according to the UN number. If not, it falls under “Classification not possible” in principle.

### (4) Data availability

The available oxygen content can be easily calculated by anyone who has basic knowledge of chemistry. However, in the case of hydrogen peroxide content, chemical analysis is presumably required to determine it, unless hydrogen peroxide is added intentionally, in which case the added amount is known. Few data of measurement experiments related to the flow chart of GHS2.15.4 have been published.

Organic Peroxides are often traded and used as prepared chemicals in which diluents and/or stabilizing agents are added to them, rather than as chemical substances. Classification into TYPE A to G should be made based on a test for individual prepared chemicals.

### (5) Comparison with conventional classification systems

The flow chart of 2.15.2.2 is exactly the same as that of UNRTDG (Fig. 2.5.1).

(6) Sources of information for classification results under conventional systems

Chemicals which belong to UNRTDG 5.2\*ERG147, 148 in UNRTDG and North-America Emergency Response Guidebook fall under this class.

		The temperature management is unnecessary(147)		Temperature management necessity (148)	
		Liquid	Solid	Liquid	Solid
Type A	=	(Transportation prohibition substance)			
Type B	=	UN3101,	3102,	3111,	3112
Type C	=	UN3103,	3104,	3113,	3114
Type D	=	UN3105,	3106,	3115,	3116
Type E	=	UN3107,	3108,	3117,	3118
Type F	=	UN3109,	3110,	3119,	3120
Type G	=	(Non-dangerous articles)			

A typical preparation example and classification is listed in the table of UNRTDG 2.5.3.2.4 (or in “Dangerous Goods Regulations, Annex 1, Recital 1”). The following is the example. If an inactivation agent is used, the substance may be classified in a lower TYPE.

(Example of Type B)

3101	1,1-DI-(tert-BUTYLPEROXY) CYCLOHEXANE 1(>80%-100%) 2,5-DIMETHYL-2,5-DI-(tert-BUTYLPEROXY)HEXYNE-3(>86%-100%)
3120	tert-BUTYL MONOPEROXYMALEATE
3111	DIISOBUTYRYL PEROXIDE(>32-52%, diluentB>48%)
3112	DI-(2-METHYLBENZOYL) PEROXIDE(≤87%, water≥13%)

(Example of Type C)

3103	tert-AMYL PEROXYBENZOATE
3104	DIBENZOYL PEROXIDE(≤77%, water≥23%)
3113	tert-BUTYL PEROXYDIETHYLACETATE
3114	DIDECANOYL PEROXIDE

(Example of Type D)

3105	ACETYL ACETONE PEROXIDE(≤42%, diluentA≥48%, water≥8%)
3106	DILAUROYL PEROXIDE
3115	DIACETYL PEROXIDE(≤27%, diluentB≥73%)
3116	DI-n-NONANOYL PEROXIDE

(Example of Type E)

- 3107 DI-tert-AMYL PEROXIDE
- 3108 DIBENZOYL PEROXIDE( $\leq 52\%$ , paste)
- 3117 DIPROPIONYL PEROXIDE( $\leq 27\%$ , diluent  $\geq 73\%$ )
- 3118 tert-BUTYL PEROXYNEODECANOATE( $\leq 42\%$ , stable frozen-water dispersion element)

(Example of Type F)

- 3109 PEROXYACETIC ACID, TYPE F, stabilized( $\leq 43\%$ )
- 3110 DICUMYL PEROXIDE( $> 52\% \sim 100\%$ )
- 3119 DICETYL PEROXYDICARBONATE( $\leq 42\%$ , (stable water dispersion element))
- 3120 DI-(2- ETHYLHEXYL) PEROXYDICARBONATE ( $\leq 52\%$ , stable frozen-water dispersion element)

## 2-3-16 Corrosive to Metals

### (1) Definitions

Definitions of corrosive to metals in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (2.16.1)**

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

### (2) Classification criteria in GHS

**【GHS 3<sup>rd</sup> revised edition】 (2.16.2)**

A substance or a mixture which is corrosive to metals is classified in a single category for this class, using the test in Part III, sub-section 37.4 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of tests and Criteria*, according to the following table:

**Table 2.16.2: Criteria for substances and mixtures corrosive to metal**

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

**NOTE:** *Where an initial test on either steel or aluminium indicates the substance or mixture being tested is corrosive the follow-up test on the other metal is not required.*

### (3) Guidance for Classification

#### A) Judgment of Not Classified

Regarding “Corrosive to Metals”, if it is confirmed based on prescribed review documents that both steel and aluminum can be used as a container for the substance, fill in “Classification result” with “Not classified”, and fill in “Classification Grounds” with “Steel and aluminum can be used as a container”.

#### B) Judgment for those substances that can not be classified

##### 1) In case the test method is not established

The test method for “Corrosive to Metals” defined in TDG classification and adopted in GHS classification can not be applied to gases. It can not be applied to liquids with a boiling point of 55°C or lower, either. In case of solid, it can be applied to those with a melting point of 55°C or lower. Hence, indicate as follows. In case of gases, fill in “Classification result” with “Classification not possible” regarding “corrosive to metals”, and fill in “Classification Grounds” with “No established test method suitable for Gas substances”. In the case of liquids with a boiling point of 55°C or lower, fill in “Classification result” with “Classification not possible” regarding “Corrosive to Metals”, and fill in “Classification

Grounds” with “No established test method suitable for low-temperature boiling Liquids”. In the case of solid with a melting point of higher than 55°C, fill in “Classification result” with “Classification not possible” regarding “Corrosive to Metals”, and fill in “Classification Grounds” with “No established test method suitable for Solid substances”. For all cases mentioned above, it is also permissible to simply indicate “No data” instead of indicating the Classification Grounds.

2) In case of “Classification not possible” because of lack of data

For hazard items that cannot be classified by the above procedure, fill in “Classification result” with “Classification not possible”, and fill in “Classification Grounds” with “No data”.

(4) Data availability

Few numerical data on metal corrosion rate have been published.

(5) Comparison with conventional classification systems

The definition completely accords with that of the Class 8III “Metal corrosivity” described in UNRTDG 2.8.2.5(c)(ii).

(6) Sources of information for classification results under conventional systems

Since metal corrosivity is classified into UNRTDG Class 8 along with skin corrosivity, whether a substance has metal corrosivity or not cannot be judged from the fact that the substance is classified in Class 8. Metal corrosivity thus cannot be attributed to a substance based on “Dangerous Goods Regulations Annex 1” alone. Therefore, a substance that clearly has metal corrosivity shall be classified into this class. If it is not clear whether a substance has metal corrosivity, indicate “presumed” on the label for the substance.

GHS classification is based on UNRTDG, which was developed in relation to the leakage treatment of substances. It should be noted that even if a substance does not fall under this class, it still has a possibility to give damage to a container or pipe for storage or use.

In the test of metal corrosivity, metal pieces (steel and aluminum) are immersed in a liquid (55°C) for 7 to 28 days, and if the corrosion length exceeds 6.25 mm (annualized value), the liquid is judged corrosive. As mentioned above, this criterion for corrosivity was defined in light of the risk that the leakage of a liquid gives damage to a container of transport equipment or other freights when the leakage is not immediately treated. Thus, a different criterion should be applied when determining whether or not a metal can be used for the container or pipe of the liquid. If a liquid is corrosive, even if to a minimal extent, the use of a metal for its container impairs the liquid. In the definition of metal corrosivity in GHS, such a kind of criterion has not been adopted.

Note:

In GHS, it is defined that if test data for a substance, acquired based on the prescribed test method, cannot be obtained from reliable sources, the substance shall be classified as “Classification not possible”. Therefore, some of gasses which are known to impair metals, such as ammonia gas and hydrogen chloride gas, are fall under “Classification not possible” because the test methods for them have not been defined.

## Part3. Health Hazards Guidance

### 3-1 Information and data available for classification

#### 3-1-1 Sources of Information available for classification

In UN GHS, available data are reviewed for classification.

In this guidance, procedures are shown below to reduce variations in classification results as much as possible, while facilitating classification.

Upon conducting investigations for classification, all of the acquired or accessible assessment documents shown in List 1 shall be reviewed regarding each of hazard shown in 3-2-1 to 3-2-10 and information on the relevant substances shall be looked for. If the selected source provides no or insufficient information needed, other information sources should be searched.

When the required information cannot be obtained from sources in List 1, the process with sources in List 2 shall be repeated.

Information sources in List 3 are integrated databases to search the original literatures or to have an idea of the toxicity, and they are to be utilized where appropriate.

Examples of major information sources containing a general introduction or useful databases are shown below. Information sources listed under each List are similar in reliability, but they may vary in toxicity indexes and substances listed (for example, WHO International Agency for Research on Cancer (IARC) specializes in information related to Carcinogenicity, and The Joint FAO/WHO Meeting on Pesticide Residues (JMPR), in agricultural chemicals). This should not limit the use of reliable and useful information sources other than those listed here.

Some on-line sites shown below revise posted information when appropriate, and acquiring the latest information from them is preferable.

(Note)On management of epidemiological data, refer to “3-1-3(2) Epidemiologic data”(p.99).

#### List 1 :

Information sources provided by international organizations, governments of major countries, etc. , whose reliability has been recognized. Basically, these are assessment documents and books whose primary documents can be traced and whose accuracy can be confirmed whenever needed.

However, when confirmation of reliability for individual pieces of information is needed, the source materials should be checked, and if the materials lack reliability, they should not be used as evidence of classification.

Results of biological tests which were performed according to internationally recognized test guidelines (for example, those of OECD) and GLP and judged to be valid by reviews of experts in national committees, etc., shall be treated in the same way.

1-1)	Organization	National Institute of Technology and Evaluation(NITE)
	Source	Initial Risk Assessment
	URL	<a href="http://www.safe.nite.go.jp/english/risk/initial_risk.html">http://www.safe.nite.go.jp/english/risk/initial_risk.html</a>
	Note	Chemicals Evaluation and Research Institute,Japan (CERI)・National Institute of Technology and Evaluation)(NITE) “Hazard Assessment Report” <a href="http://www.cerij.or.jp/ceri_en/hazard_assessment_report/yugai_indx_en.htm">http://www.cerij.or.jp/ceri_en/hazard_assessment_report/yugai_indx_en.htm</a> <a href="http://www.safe.nite.go.jp/english/sougou/view/SelectingListsList_en.faces">http://www.safe.nite.go.jp/english/sougou/view/SelectingListsList_en.faces</a>
1-2)	Organization	Ministry of Health, Labour and Welfare
	Source	“Report on Toxicity Tests of Chemical Substances”, The Liaison Council on the Promotion of Chemical Substances Examination)
	URL	<a href="http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp">http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp</a>
1-3)	Organization	Ministry of Health, Labour and Welfare
	Source	Public announcement on guidelines in order to prevent the impairment of worker’s health based on Industrial Safety and Health Law Article 28-3
1-4)	Organization	Japan Bioassay Research Center
	source	Ministry of Health, Labour and Welfare (Result from Carcinogenicity Studies)
	URL	<a href="http://www.jaish.gr.jp/user/anzen/kag/ankg02.htm">http://www.jaish.gr.jp/user/anzen/kag/ankg02.htm</a> (Japanese text)
1-5)	Organization	Environmental Risk Assessment Office, Ministry of the Environment
	Source	Environmental Risk Assessment for Chemical Substances (vol.1~vol.6)
	URL	<a href="http://www.env.go.jp/en/chemi/chemicals/profile_erac/index.html#vol7">http://www.env.go.jp/en/chemi/chemicals/profile_erac/index.html#vol7</a>
1-6)	Organization	Japan Society For Occupational Health(JSOH)
	Source	Recommendations for allowable concentrations(published every year)
1-7)	Organization	OECD
	Source	SIDS Report(SIDS)
	URL	<a href="http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html">http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html</a>
	Note	SIAP(SIDS Initial Assessment Report)(Japanese version) Japan Chemical Industry Ecology-Toxicology & Information Center <a href="http://www.jetoc.or.jp/HP_SIDS/SIAPbase.htm">http://www.jetoc.or.jp/HP_SIDS/SIAPbase.htm</a>
1-8)	Organization	WHO/IPCS
	Source	Environmental Health Criteria(EHC)(No.1~No.237, as of Sep. 2008)
	URL	<a href="http://www.who.int/ipcs/publications/ehc/en/index.html">http://www.who.int/ipcs/publications/ehc/en/index.html</a>

		<a href="http://www.inchem.org/pages/ehc.html">http://www.inchem.org/pages/ehc.html</a>
	Note	EHC Japanese version : <a href="http://www.nihs.go.jp/hse/ehc/index.html">http://www.nihs.go.jp/hse/ehc/index.html</a>
1-9)	Organization	WHO/IPCS
	Source	Concise International Chemical Assessment Documents (CICAD)
	URL	<a href="http://www.who.int/ipcs/publications/cicad/pdf/en/">http://www.who.int/ipcs/publications/cicad/pdf/en/</a>
	Note	CICAD Japanese version <a href="http://www.nihs.go.jp/hse/cicad/cicad.html">http://www.nihs.go.jp/hse/cicad/cicad.html</a>
1-10)	Organization	WHO International Agency for Research on Cancer(IARC)
	Source	IARC Monographs Programme on the Evaluation of Carcinogenic Risk to Humans(IARC Monographs)
	URL	<a href="http://monographs.iarc.fr/">http://monographs.iarc.fr/</a> or <a href="http://monographs.iarc.fr/htdig/search.html">http://monographs.iarc.fr/htdig/search.html</a>
	Note	SIDS or WHO Assessment Documents (such as EHC, CICAD, IARC, JMPR) can be searched or read through (1) below. Some hazardous assessment documents of international organization and some major countries (Japan, U.S. etc) are linked to the (2) below. (1) <a href="http://www.inchem.org/">http://www.inchem.org/</a> (2) <a href="http://www.safe.nite.go.jp/english/sougou/view/SelectingListsList_en.faces">http://www.safe.nite.go.jp/english/sougou/view/SelectingListsList_en.faces</a>
1-11)	Organization	FAO/WHO Joint Expert Committee on Food Additives(JECFA)
	Source	FAO/WHO Joint Expert Committee on Food Additives - Monographs(JECFA Monographs)
	URL	<a href="http://www.who.int/ipcs/publications/jecfa/monographs/en/index.html">http://www.who.int/ipcs/publications/jecfa/monographs/en/index.html</a>
1-12)	Organization	FAO/WHO Joint Meeting on Pesticide Residues)(JMPR)
	Source	FAO/WHO Joint Meeting on Pesticide Residues - Monographs of toxicological evaluations(JMPR Monographs)
	URL	<a href="http://www.who.int/ipcs/publications/jmpr/en/">http://www.who.int/ipcs/publications/jmpr/en/</a>
	Note	<a href="http://www.inchem.org/">http://www.inchem.org/</a>
1-13)	Organization	EU European Chemicals Bureau (ECB)
	Source	EU Risk Assessment Report : EU RAR (vol.1~vol. 91, as of Sep. 2008)
	URL	<a href="http://ecb.jrc.ec.europa.eu/documentation/">http://ecb.jrc.ec.europa.eu/documentation/</a> <a href="http://ecb.jrc.ec.europa.eu/home.php?CONTENU=/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/">http://ecb.jrc.ec.europa.eu/home.php?CONTENU=/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/</a>
1-14)	Organization	European Center of Ecotoxicology and Toxicology of Chemicals(ECETOC)
	Source	Technical Report and JACC Report

	URL	<a href="http://www.ecetoc.org/publications">http://www.ecetoc.org/publications</a> (list only)
1-15)	Organization	American conference of Governmental Industrial Hygienists(ACGIH)
	Source	ACGIH Documentation of the threshold limit values for chemical substances (7th edition, 2001) (2008 supplement, 2008)and “TLVs and BEIs”(ACGIH, published every year)
	URL	Not available on web sites. Can be purchased from “TLVs and BEIs” WEB. <a href="http://www.acgih.org/home.htm">http://www.acgih.org/home.htm</a>
1-16)	Organization	EPA(Environmental Protection Agency)
	Source	Integrated Risk Information System(IRIS)
	URL	<a href="http://www.epa.gov/iris/">http://www.epa.gov/iris/</a>
1-17)	Organization	National Toxicology Program(NTP)
	URL	<a href="http://ntp-server.niehs.nih.gov/">http://ntp-server.niehs.nih.gov/</a>
1-17-1)	Source	NTP Database Search Home Page: [For Standard Toxicology & Carcinogenesis Studies, Reproductive Studies, Developmental Studies, Immunology Studies, Genetic Toxicity Studies] or <a href="http://ntp-server.niehs.nih.gov/">http://ntp-server.niehs.nih.gov/</a> → Study Results & Research Projects → Study Data Searches
	URL	<a href="http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm">http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm</a>
1-17-2)	Source	Report on Carcinogens (11th,2005)
	URL	<a href="http://ntp-server.niehs.nih.gov/">http://ntp-server.niehs.nih.gov/</a> → Public Health →Report on Carcinogens →11th RoC (The 11 th RoC contains 246 entries, 58 of which are listed as known to be human carcinogens and with the remaining 188 being listed as reasonably anticipated to be human carcinogens.) or <a href="http://ehp.niehs.nih.gov/roc/toc10.html">http://ehp.niehs.nih.gov/roc/toc10.html</a> or <a href="http://ehp.niehs.nih.gov/ntp/docs/ntp.html">http://ehp.niehs.nih.gov/ntp/docs/ntp.html</a>
1-17-3)	Source	Carcinogenicity Technical Report
	URL	<a href="http://ntp-server.niehs.nih.gov/">http://ntp-server.niehs.nih.gov/</a> → Study Results & Research Projects → NTP Study Reports. Various reports including Carcinogenicity → Long-term →TR1~TR533(Carcinogenicity Report)
1-18)	Organization	Agency for Toxic Substances and Disease Registry(ATSDR)
	Source	Toxicological Profile
	URL	<a href="http://www.atsdr.cdc.gov/toxprofiles/index.asp">http://www.atsdr.cdc.gov/toxprofiles/index.asp</a>
1-19)	Organization	Environment Canada/Health Canada
	Source	Assessment Report Environment Canada : Priority Substance Assessment Reports

	URL	<a href="http://www.ec.gc.ca/substances/ese/eng/psap/final/main.cfm">http://www.ec.gc.ca/substances/ese/eng/psap/final/main.cfm</a> (Abstract only on the web site)
1-20)	Organization	Australia NICNAS
	Source	Priority Existing Chemical Assessment Reports
	URL	<a href="http://www.nicnas.gov.au/publications/car/pec/default.asp">http://www.nicnas.gov.au/publications/car/pec/default.asp</a>
1-21)	Organization	Deutsche Forschungsgemeinschaft (DFG)
	Source	MAK Collection for Occupational Health and Safety, MAK Values Documentations and List of MAK and BAT values(published every year)
	URL	Not available on web site.
	Note	“List of MAK and BAT values” is not an assessment document.
1-22)	Source	Patty’s Toxicology (5th edition, 2001)(Patty)
	Note	E. Bingham, B. Cohrssen, C.H. Powell (Eds), John Wiley & Sons, Inc. (vol.1~vol.9)
1-23)	Organization	United States Environmental Protection Agency (EPA)
	Source	Pesticides “Reregistration Eligibility Decision”
	URL	<a href="http://www.epa.gov/pesticides/reregistration/status.htm">http://www.epa.gov/pesticides/reregistration/status.htm</a>

List 2 :

Useful information sources of other assessment documents than listed in List1.

2-1)	Organization	EU
	Source	Annex I of EU 7th Amendment to Council Directive (Latest edition: 29th Directive adapting to Council Directive) : Classification results in Annex 1
	URL	<a href="http://ecb.jrc.ec.europa.eu/home.php?CONTENU=/DOCUMENTS/Classification-Labeling/DIRECTIVE_67-548-EEC/">http://ecb.jrc.ec.europa.eu/home.php?CONTENU=/DOCUMENTS/Classification-Labeling/DIRECTIVE_67-548-EEC/</a>
2-2)	Organization	EU European Chemicals Bureau (ECB)
	Source	International Uniform Chemical Information Database (IUCLID) IUCLID CD-ROM (Update Edition 2 - 2000)
	URL	<a href="http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=dat">http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=dat</a>
2-3)	Organization	National Library of Medicine(NLM)
	Source	Hazardous Substance Data Bank(HSDB)
	URL	<a href="http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB">http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB</a>
2-4)	Organization	German Chemical Society-Advisory Committee on Existing Chemicals of Environmental Relevance
	Source	BUA Report(BUA)
	URL	<a href="http://www.hirzel.de/bua-report/download.html">http://www.hirzel.de/bua-report/download.html</a>
	Note	Full report can not be available from web site.
2-5)	Source	Dreisbach's Handbook of Poisoning (DHP , 13th edition, 2002)
	Note	B-L. True and H. Dreisbach, The Parthenon Publishing Group
2-6)	Organization	Food and Agricultural Materials Inspection Center, Ministry of Agriculture, Forestry, and Fisheries
	Source	A pesticide abstract and evaluation report
	URL	<a href="http://www.acis.famic.go.jp/syouroku/index.htm">http://www.acis.famic.go.jp/syouroku/index.htm</a> (Japanese text)
2-7)	Organization	Japan Crop Protection Association
	Source	Pesticide safety information(List open for the public)
	URL	<a href="http://www.jcpa.or.jp/safe/info_01.html">http://www.jcpa.or.jp/safe/info_01.html</a> (Japanese text)
2-8)	Organization	Food Safety Commission, Cabinet Office, Government of Japan
	Source	Evaluation of effect for the food safety
	URL	<a href="http://www.fsc.go.jp/english/evaluationreports/additives.html">http://www.fsc.go.jp/english/evaluationreports/additives.html</a> (Evaluation reports in Japanese text)

2-9)	Organization	Ministry of Health, Labour and Welfare
	Source	Research on the revision of the safety of the existing additive
	URL	<a href="http://www.ffcr.or.jp/zaidan/MHWinfo.nsf/0f9d5ee834a5bceff492565a10020b585/01ec065c06a3601f49257328000c3afa?OpenDocument">http://www.ffcr.or.jp/zaidan/MHWinfo.nsf/0f9d5ee834a5bceff492565a10020b585/01ec065c06a3601f49257328000c3afa?OpenDocument</a> (Japanese text)
	Note	Information regarding safety for the food additive

List 3 :

These are databases for searching and accessing primary literatures. In the case where data are available in List 1 or 2, these databases should be referred where appropriate.

Although hazard information of an individual product is available from existing MSDSs, etc., its direct use for GHS classification should be avoided.

3-1) Database for primary literatures

- Pub-Med/NLM (for original literature)  
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>
- NLM TOXNET (TOXLINE On-line database including original literature)  
<http://toxnet.nlm.nih.gov/index.html>
- JICST (JOIS On-line database)  
<http://pr.jst.go.jp/db/db.html> (Japanese text only)

3-2) General information database on chemical substances

- National Institute of Technology and Evaluation “Chemical Risk Information Platform” (CHRIP) : <http://www.safe.nite.go.jp/english/db.html>
- Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA) “GESTIS-database on hazardous substances” (GESTIS) :  
<http://www.dguv.de/ifa/en/gestis/stoffdb/index.jsp>
- Ministry of the Environment Government “Chemical Substances Fact Sheets” :  
<http://www.env.go.jp/chemi/communication/factsheet.html> (Japanese text only)
- National Institute for Environmental Studies “WebKis-Plus Chemical Substances Database” (WebKis-Plus) : <http://w-chemdb.nies.go.jp/> (Japanese text only)
- National Institute of Advanced Industrial Science and Technology (AIST) “Risk Assessment Documents” : [http://unit.aist.go.jp/riss/crm/mainmenu/e\\_1.html](http://unit.aist.go.jp/riss/crm/mainmenu/e_1.html)
- Chemicals Evaluation and Research Institute, Japan (CERI) “Chemical Substance Hazard Data” : [http://www.cerij.or.jp/ceri\\_en/hazard\\_assessment\\_report/yugai\\_indx\\_en.htm](http://www.cerij.or.jp/ceri_en/hazard_assessment_report/yugai_indx_en.htm)
- Hazardous Substance Fact Sheet (New Jersey Department of Health and Senior Services) :  
<http://web.doh.state.nj.us/rtkhsfs/indexfs.aspx>

- “Sittig’s Handbook of Toxic and Hazardous Chemicals and Carcinogens (4th edition,2002)” (Sittig)
- National Institute for Occupational Safety and Health(NIOSH)“RTECS [Registry of Toxic Effects of Chemical Substances] ” (RTECS) :  
<http://www.cdc.gov/niosh/npg/npgdrtec.html>
- WHO/IPCS “International Chemical Safety Cards” (ICSC) :  
<http://www.cdc.gov/niosh/ipcs/nicstart.html>  
(ICSC Japanese version : <http://www.nihs.go.jp/ICSC/>)

### 3-3) EU classification

- When classification based on Table3-1 Annex VI of EU CLP regulations (hereinafter abbreviated as "EU CLP classification". R-phrase will be referred to as EU DSD classification) together with its evidence information is not available, the substance shall fall under "Classification not possible".
- If EU CLP classification and EU DSD classification together with their evidence information are available and if their classification criteria are different from those of GHS classification, EU CLP classification and EU DSD classification may be used for GHS classification only when the evidence information is scientifically valid.
- If EU CLP classification and EU DSD classification together with their evidence information are available and if their classification criteria accord with that of GHS classification, GHS classification may be performed according to these EU classifications.

Fundamentally, classification shall be performed based on quality, reliability, and consistency of evidence obtained from the information source, with the evidence weighted and experts judgment added where appropriate.

In this guidance, classification based on the Annex VI of EU CLP regulations is abbreviated as EU CLP classification, and R-Phrase is referred to as EU DSD classification. When it is stated as EU classifications unless otherwise specified, it refers to both EU CLP classification and EU DSD classification. Since the classification and categorization adopted in the EU DSD (EU Council Directive 67/548/EEC) is not based on GHS classification criteria, its results are not applicable to GHS classification and categorization.

The Japanese version of this document was published by JETOC in 2004 as “EU: List of Dangerous Substances (7th edition)”.

There are available information sources other than the one stated above. For example, the following information sources were adopted by the expert review meeting for GHS classification

by Ministry of Health, Labour and Welfare (carried out by Japan Industrial Safety and Health Association).

Organization: National Institute for Occupational Safety and Health (NIOSH)

“NIOSH Publications ; Criteria Documents”

[http://www.cdc.gov/niosh/pubs/criteria\\_date\\_desc\\_nopubnumbers.html](http://www.cdc.gov/niosh/pubs/criteria_date_desc_nopubnumbers.html)

“NIOSH Pocket Guide to Chemical Hazards”

<http://www.cdc.gov/niosh/npg/>

### 3-1-2 Order of precedence when multiple data exist

#### (1) Order of Precedence when multiple data exist among information sources in List1

- A) Data obtained from tests which were performed according to internationally recognized test guidelines (for example, those of OECD) and GLP, take precedence.
- B) If there are no data falling under A), data obtained from tests which were performed according to internationally recognized test guidelines (for example, those of OECD) but not clearly according to GLP, take precedence.
- C) When it is difficult to classify according to data based on reliability as shown in A) and B), data considered to have the highest scientific validity shall be adopted after examination of recency of data, dosage selection of the test, selected test animal species, validity of the administration route, etc. If a decision is difficult, it is necessary to seek for judgement by experts.

#### (2) Order of Precedence when conflicting data exist among information sources other than List1

- A) Among data collected from other information sources (for example, information sources shown in List 2), data considered to be reliable (data in accordance with GLP, or data for which supporting data are clearly indicated and evaluated, data considered to have the highest scientific validity after examination of dosage selection of the test, selected test animal species, validity of the administration route, etc.) are adopted. This decision procedure is the same as that in (1).
- B) In this case, the recency of assessment documents and databases or the reliability of cited documents are considered.
- C) For classification, it is required to evaluate and judge the reliability and validity of data comprehensively. When categorization of data based on reliability as shown in A) and B) is not possible, it is necessary to seek for judgement by expert's.

### 3-1-3 Management of information in special cases

Notes on management of analogous compounds and epidemiological information are as follows.

#### (1) Evaluation of analogous compounds

In general, the search, collection, and assessment of hazard data are limited to a substance that can be identified by CAS number and not to its analogous compounds (different molecular species) such as metals, salts, anhydrides, hydrates, and isomers, because they have different solubility, biological absorption, biological activity, etc., and may cause different manifestation of health hazards, even if they are analogous substances.

While sufficient hazard data may not be available for some substance classified substance, they may be available for its analogous substance. In such a case, it shall be written that "On health hazards, refer to ID XXXX, Name of the substance, CAS No. ZZZZ-ZZ-Z" to indicate the existence of another substance to be referred. This phrase may be entered in the column of "classification evidence" for the first item of health hazards, namely, "Acute Toxicity (oral)" in the GHS classification list. Also, as for a chemical (to be identified by CAS number) including plural isomers such as racemic isomers, when a mixture (for example, racemic isomers) has less information but when an isomer has sufficient information, classification is carried out based on the data of the isomer, and "Based on data of XXX isomer" shall be entered in the column for classification evidence.

Regarding carcinogenicity, when an assessment result by IARC is available for "the substance in question and its compounds" even if not for the exact substance in question that can be identified by its CAS number, that carcinogenicity assessment result shall be adopted. In addition, as for analogous compounds, care should be taken because the assessment results may differ for compounds determined as an excluded substance and between its inorganic salt and organic salt (refer to the corresponding examples).

A) If hazard assessment results are definitely different among different states/shapes, they should be listed.

Example : Carcinogenicity of lead : GHS classification Category 1B (inorganic lead)/Not classified (organic lead), According to IARC (2004)

B) If hazard assessment results are not definite among different states/shapes, a comment shall be added to the classification evidence.

Example : Carcinogenicity of cadmium : GHS classification Category 1A, According to IARC (1993), " as cadmium and its compounds"

## (2) Regarding treatment of epidemiological data

In many cases, it is difficult to judge whether a substance should be included based on epidemiological data. However, if the epidemiological data are obtained by searching the information sources shown in this guidance by CAS number, and if assessment is performed for the material group including its analogous compounds but not for the substance that can be identified by its CAS number, such hazard information can be adopted.

Epidemiological data may not be suitable for GHS Categories in which definitions are quantitative, in proportion to the strength of an effect (for example, Acute Toxicity). Management of epidemiological data in CMR (Carcinogenicity, Mutagenicity, and Reproductive Toxicity) is shown below, in which categories are set in accordance with the reliability of evidence.

### ■ Regarding treatment of epidemiological data in CMR

- A) As for human epidemiological data, substances that were evaluated in assessment documents shown in List 1, shall be classified according to the assessment results.
- B) If assessment results based on the same type of epidemiological data differ, or assessment results based on different type of epidemiological data differ, the result of the latest assessment document takes precedence.
- C) When available epidemiological data are limited to that of assessment documents in other than List 1, as well as regarding the treatment of specific epidemiological data, judgement by experts in this fields shall be sought for.

## (3) Conversion table of concentration in diet to dosage per body weight in animal tests

Regarding Specific Target Organ Toxicity (Repeated Exposure) and Reproductive Toxicity, when only the description of the concentration in the diet is available in an animal test report, the dosage per body weight shall be obtained from the concentration in the diet according to the table below (quoted and partially revised from Environmental Health Criteria, No. 104, 1990, p.113). In this case, further conversion is not required in consideration of the body weight of the animal used.

**Table 3-0-1: Relation between concentration in diet (ppm) and dosage per body weight (mg/kg weight /day)**

animal	body weight (kg)	Food consumption per day (g) (except for liquids)	Type of diet	Dosage (mg/kg body weight /day)per concentration in diet of 1ppm	
Mouse	0.02	3	Dry laboratory chow diet	0.15	
				0.1	
Rat(Young)	0.1	10		0.05	
Rat(Matured)	0.4	20		0.04	
Guinea pig	0.75	30		0.03	
Rabbit	2	60		0.025	
Dog	10	250		Moist, semi-solid diet	0.05
Cat	2	100			0.05
Ape	5	250			0.075
Dog	10	750			

Lehman, A.J.(1954) Association of Food and Drug Officials Quarterly Bulletin, 18: 66, partially revised. Values in this table are the average of values obtained from many literatures.

(Example)In cases of rats, what are the values in ppm and mg/kg body weight /day of a substrate which is contained in diet by 0.5%?

(Solution) 0.5% is equal to 5000 ppm. From the table, in cases of matured rat, 1 ppm in the diet is equivalent to 0.050 mg/kg body weight /day. Consequently, 5000 ppm is equivalent to 250 mg/kg body weight /day (5000×0.050).

**Table 3-0-2: Tentative relationship between concentration of drinking water (ppm) and dosage per weight (mg/kg/day)**

animal	body weight (kg)	Water consumption per day (ml)	Dosage (mg/kg body weight /day)per concentration in water of 1ppm
Mouse	0.02	4	0.2
Rat(Young)	0.1	20	0.2
Rat(Matured)	0.4	45	0.125
Guinea pig	0.75	120	0.16
Rabbit	2	140	0.07
Dog	10	300	0.03

"Experimental Zoology Encyclopedia" Kousaku Fujiwara, Asakura shoten, 1989, p.481 (partially revised)

## 3-2 Classification of health hazards

### 3-2-1 Acute Toxicity

#### (1) Definitions

Definitions of Acute Toxicity in UN GHS are as follows, and they are adopted in this guidance. However, nonfatal impact on internal organ of single exposure will be treated as specific target organ toxicity (single exposure), instead of as acute toxicity.

**【GHS 3<sup>rd</sup> revised edition】** (3.1.1)

*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.

#### (2) Classification criteria

A) Classification criteria based on JIS Classification

**Table 3-1: Acute toxicity hazard categories and acute toxicity estimate (ATE) values defining the respective categories**

Exposure route	Category 1	Category 2	Category 3	Category 4
<b>Oral</b> (mg/kg bodyweight)	ATE≤5	5<ATE≤50	50<ATE≤300	300<ATE≤2000
<b>Dermal</b> (mg/kg bodyweight)	ATE≤50	50<ATE≤200	200<ATE≤1000	1000<ATE≤2000
<b>Gases</b> (ppmV)	ATE≤100	100<ATE≤500	500<ATE≤2500	2500<ATE≤20000
<b>Vapours<sup>a)</sup></b> (mg/L)	ATE≤0.5	0.5<ATE≤2.0	2.0<ATE≤10.0	10<ATE≤20
<b>Dusts<sup>b)</sup> and mists<sup>c)</sup></b> (mg/L)	ATE≤0.05	0.05<ATE≤0.5	0.5<ATE≤1.0	1.0<ATE≤5

The ATE for the classification of a substance is derived using any of the following:

- (a) the LD<sub>50</sub> or LC<sub>50</sub> where available,
- (b) the appropriate conversion value from table 3-2 that is related to the results of a range test,  
or
- (c) the appropriate conversion value from table 3-2 that is related to a classification category;

Inhalation ATE values in the table are based on 4 hour testing exposure. Conversion of existing toxicity data which has been generated according to 1 hour exposures should be divided by a factor of 2 for gases and vapours and 4 for dusts and mists.

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), and Category 4 (20000 ppmV).

Note 1: Gas concentrations are expressed in parts per million by volume (ppmV).

Note 2: Generally, dusts are formed through a mechanical process, while mists are formed through condensation of supersaturated vapours or physical shearing of liquids. Dust and mist particles are generally smaller than 1 µm but can range up to about 100 µm.

Note a) Vapours : Gaseous substances or mixtures released from a liquids or solid.

b) Dusts : Solid particles of a substance or a mixture that float in a gas (usually air).

c) Mists : Liquid droplets of a substance or a mixture that float in a gas (usually air).

**Table 3-2 Conversion from experimentally obtained Acute Toxicity range values (or Acute Toxicity hazard categories) to Acute Toxicity point estimates for classification for the respective routes of exposure**

<b>Exposure routes</b>	<b>Classification category or experimentally obtained acute toxicity range estimate (see Note 1)</b>	<b>Converted Acute Toxicity point estimate (see Note 2)</b>
<b><u>Oral</u></b> (mg/kg bodyweight )	0<Category1 ≤5 5<Category2 ≤50 50< Category3 ≤300 300<Category4 ≤2000	0.5 5 100 500
<b><u>Dermal</u></b> (mg/kg bodyweight)	0<Category1 ≤50 50<Category2 ≤200 200<Category3 ≤1000 1000<Category4 ≤2000	5 50 300 1100
<b><u>Gases</u></b> (ppmV )	0< Category1 ≤100 100<Category2 ≤500 500<Category3 ≤2500 2500<Category4 ≤20000	10 100 700 4500
<b><u>Vapours</u></b> (mg/L)	0<Category1 ≤0.5 0.5<Category2 ≤2.0 2.0< Category3 ≤10.0 10.0< Category4 ≤20.0	0.05 0.5 3 11
<b><u>Dust/mist</u></b> (mg/L)	0< Category1 ≤0.05 0.05<Category2 ≤0.5	0.005 0.05

	0.5 < Category 3 ≤ 1.0	0.5
	1.0 < Category 4 ≤ 5.0	1.5

Note 1 Gases concentration are expressed in parts per million per volume (ppmV).

Note 2 These values are designed to be used in the calculation of the Acute Toxicity estimate (ATE) values for classification of a mixture based on its ingredients and do not represent test results. The values are conservatively set at the lower limit of the range of Category 1 and 2, and at a point approximately 1/10<sup>th</sup> from the lower limit of the range for Categories 3-4.

JIS classification assigns acute toxicity of chemical substances from oral, endermatic or inhalation route to one of four toxicity classes. In addition, it is important to note that in oral study of chemical substances with irritant property, the target organ toxicity and manifestation mechanism differ between gavage administration and administration using food or water, and because of this, extrapolation to human may differ completely (for example, observation of erosion or ulcer in anterior stomach can only be seen with gavage administration method and thus cannot be extrapolated to human).

#### B) Classification criteria in GHS (reference information)

In GHS classification, in addition to JIS Classification, Category 5 is set. Explanation of classification criteria by GHS and Category 5 are as follows.

【GHS 3 <sup>rd</sup> revised edition】 (3.1.2)					
Table 3.1.1: Acute toxicity hazard categories and acute toxicity estimate (ATE) values defining the respective categories					
Exposure route	Category 1	Category 2	Category 3	Category 4	Category 5
Oral (mg/kg bodyweight) <i>see: Note (a)</i>	5	50	300	2000	<i>See detailed criteria in Note (f)</i>
Dermal (mg/kg body weight) <i>see: Note (a)</i>	50	200	1000	2000	
Gases (ppmV) <i>see: Note (a)</i> <i>Note (b)</i>	100	500	2500	20000	
Vapours (mg/l) <i>see: Note (a)</i> <i>Note (b)</i>	0.5	2.0	10	20	

Note (c)					
Note (d)					
<b>Dusts and Mists</b> (mg/l) see: Note (a) Note (b) Note (e)	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) The acute toxicity estimate (ATE) for the classification of a substance is derived using the  $LD_{50}/LC_{50}$  where available;
- (b) The acute toxicity estimate (ATE) for a substance in a mixture is derived using:
- (i) the  $LD_{50}/LC_{50}$  where available; otherwise,
  - (ii) the appropriate conversion value from Table 3.1.2 that relates to the results of a range test, or
  - (iii) the appropriate conversion value from Table 3.1.2 that relates to a classification category;
- (c) 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;
- (d) It is recognized 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 Recommendation for the Transport of Dangerous Goods);
- (e) 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 (20000 ppmV)
- The terms “dust”, “mist” and “vapour” are defined as follows;
- (i) Dust: solid particles of a substance or mixture suspended in a gas (usually air);
  - (ii) Mist: liquid droplets of a substance or mixture suspended in a gas (usually air);
  - (iii) Vapour: the gaseous form of a substance or mixture released from its liquid or solid state.
- Dust is generally formed by mechanical processes. Mist is generally formed by condensation of supersaturated vapours or by physical shearing of liquids. Dusts and mists generally have sizes ranging from  $< 1$  to about  $100\mu\text{m}$ ;
- (f) The values for dusts and mists should be reviewed to adapt to any future changes to OECD

*Tes Guidelines with respect to technical limitation in generating, maintaining and measuring dust and mist concentrations in respirable form;*

*(g) 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<sub>50</sub> 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<sub>50</sub> (or LC<sub>50</sub>) 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.*

*Recognizing 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) Items on information sources and data

\* Classification procedure can be referred to "3-1-1 Sources of Information available for classification".

#### A) Data availability

- Classification should be performed based on the toxicity values reported in information available for classification.
- R-Phrase 20, R-Phrase 21, R-Phrase 22, R-Phrase 23, R-Phrase 24, R-Phrase 25, R-Phrase 26, R-Phrase 27 , and R-Phrase 28 (hereinafter abbreviated as "R20"<sup>4</sup>) related to Acute Toxicity in EU classification may be referred.
- Since the information sources mainly consist of review information, the same Acute Toxicity data are often cited in multiple reviews. If the same Acute Toxicity value is found, check the original document and avoid overlapping of the same data.
- OECD test guidelines include the following test methods relating to Acute Toxicity.

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<sup>4</sup> For R-Phrase, see Appendix.

- OECD TG 420 Acute oral toxicity – Fixed dose procedure
- OECD TG 423 Acute oral toxicity – Acute toxic class method
- OECD TG 425 Acute oral toxicity – Up-and-down procedure
- OECD TG 402 Acute dermal toxicity
- OECD TG 403 Acute inhalation toxicity

- EU CLP classification criteria completely accord with that of GHS in JIS classification. In European Commission website, EU harmonized CLP classification results are shown in Table 3-1 Annex VI and Table 3-2 Annex VI, and may be used for reference.  
[http://ec.europa.eu/enterprise/sectors/chemicals/documents/classification/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/chemicals/documents/classification/index_en.htm)
- R-Phrase 20, R-Phrase 21, R-Phrase 22, R-Phrase 23, R-Phrase 24, R-Phrase 25, R-Phrase 26, R-Phrase 27, R-Phrase 28 (hereinafter abbreviated as R20 and so on<sup>5</sup>) regarding Acute toxicity of EU DSD (Dangerous Substances Directive) classification may be used as reference.

B) Order of Precedence where conflicting data exist

Refer to “3-1-2 Order of Precedence where conflicting data exist”.

C) Comparison with conventional classification systems

- EU DSD classification may be referred to as a rough guide but does not accords with GHS completely.
- In EU CLP Regulations Annex VII, conversion to the Acute toxicity of GHS classification is made using the r-phrases and symbol mark of EU DSD classification as shown in the following table.
- UNRTDG Class 6.1 is not sub-categorized by exposure route.

Category		1	2	3	4
Oral (mg/kg)	GHS	5	50	300	2000
	EU CLP classification	H300	H300 T+ ; R28	H301 T ; R25	H302 Xn ; R22
	EU DSD classification	R28	25	R25 200	R22 2000
Dermal (mg/kg)	GHS	50	200	1000	2000
	EU CLP classification	H310 T+ ; R27	H310	H311 T ; R24	H312 Xn ; R21
	EU DSD classification	R27 50	R24	400	R21 2000

<sup>5</sup> For R-Phrase, see Appendix.

Gases (ppmV)	GHS	100	500	2500	20000
	EU CLP classification	H330	H330 T+ ; R26	H331 T ; R23	H332 Xn ; R20
	EU DSD classification	Not defined			
Vapours (mg/l)	GHS	0.5	2	10	20
	EU CLP classification	H330 T+ ; R26	H330 T ; R23	H331	H332 Xn ; R20
	EU DSD classification	R26 0.5	R23 2	R20 20	
Dust/mist (mg/l)	GHS	0.05	0.5	1	5
	EU CLP classification	H330	H330 T+ ; R26	H331 T ; R23	H332 Xn ; R20
	EU DSD classification	R26 0.25	R23 1	R20 5	

(Note) "Oral" and "Dermal" are LD<sub>50</sub> values, and "Vapours" and "Dusts and Mists" are LC<sub>50</sub> values. "Gases" are not defined in the present EU DSD classification.

DSD: Dangerous Substances Directive

#### D) Guidance concerning data

It should be noted that regarding inhalation toxicity, units vary depending on the shape of the inhaled substance. Classification should be performed on the basis of the values for gases (ppmV) if the test atmosphere consists of a gaseous phase including vapour that is substantially a gaseous phase, values for vapours (mg/L) if the test atmosphere consists of a liquid with a relatively low boiling point, and values for mists (mg/L) for other cases.

(Reference) Conversion of ppmV and mg/L units (at 25°C and atmospheric pressure)

$$(\text{ppmV}) = \{ (\text{mg/L}) \times 24.45 \times 10^3 \} / \text{molecular weight}$$

$$(\text{mg/L}) = \{ (\text{ppmV}) \times \text{molecular weight} \times 10^{-3} \} / 24.45$$

#### (4) Guidance for classification and judgment

##### A) Background of this item and points to be noted

As for background of this item, refer to Part 1, Introduction.

As for substances of which only mixture data are available (only mixed or diluted with solvents without toxicity), their GHS classification as chemical substances are performed by appropriately estimating corresponding values from concentrations, and the estimation processes should be described.

##### B) Decision when there are multiple descriptions related to Acute Toxicity

When multiple descriptions related to Acute Toxicity with highly reliable data are available,

and when they fall under multiple categories, in principle, the category is determined according to “3-1-2 Order of Precedence when Conflicting Data Exist”. However, when the substance falls under multiple categories under the above order of precedence, the category under which the greatest number of data fall is adopted.

In addition, if the numbers of data for the categories thus singled out are the same, the category with higher hazard is adopted.

(Methods to classify mixtures by using categorization results include a method using conversion values in Table 3-2 based on the determined category and a method using values considered to be appropriate (the smallest one is adopted) among data shown in the classification reason.)

C) Considerations in the case of assessing the Acute Toxicity LC<sub>50</sub> in inhalation route

- 1) Values for inhalation toxicity are based on a 4-hour animal test. When plural data exist, data should be selected according to the method described in "3-1-2 In case of plural data exist". However, if those data have same reliability, data are adopted based on the following criteria, converted to the 4-hour values, and calculated.
  - a) If 1-hour and 4-hour data are available, only these data are used, and calculation is performed. (1-hour data is converted to a 4-hour equivalent and calculated.)
  - b) If the data satisfying the condition in 1) are not available, data of 30 minutes to 24 hours are used, and calculation is performed.
  - c) If the data satisfying the condition in 1) and 2) are not available, the substance is classified as “Classification not possible”. However, a substance which shows lethal effect by exposure of 4 hours or less (including less than 30 minutes) with the concentration of the criterion value or below for Category 1 (determined by ATE/ LC<sub>50</sub>) is classified as Category 1 (inhalation).

Method for converting LC<sub>50</sub> value B for A hours into LC<sub>50</sub> estimate value D for C hours:

• Gas/vapour :  $D = B\sqrt{A/C}$

• Dust/Mist :  $D = BA/C$

\* When performing GHS classification, enter 4 (hours) for C.

(Regarding conversion) When an experimental value is adopted from the 1-hour exposure test, it shall be converted into a 4-hour equivalent by dividing the 1-hour value by a factor of 2 in the case of gas and vapour and by a factor of 4 in the case of dust and mist. The experimental values other than for 1 hour are not described in the GHS text, but LC<sub>50</sub> in 4 hours necessary for applying the GHS classification shall be obtained by

using the above arithmetic formula.

- 2) In some cases, it is not clear whether the adopted data is from the vapour inhalation test or mist inhalation test. In such cases, the substance shall be determined as “Classification not possible” unless the obvious conclusion can be given based on physical properties such as vapour pressure. The reason why the decision cannot be made shall be clearly described, for example, “If the test condition is vapour, the substance is determined to fall under Category ○○, and, if it is mist, it falls under category △△. But it cannot be determined whether it is vapour or mist based on information obtained, therefore the substance is determined as “Classification not possible”.
- 3) Although a substance is mist, its LC<sub>50</sub> may be described in ppmV, or for gas, its LC<sub>50</sub> may be described in mg/L. In many assessment documents, LC<sub>50</sub> values without test conditions such as temperature are found. If an accurate conversion is not possible, conversion shall be performed according to the following formula.

$$\text{ppmV} \doteq \text{mg/L} \times 1000 \times 24.45 / \text{molecular weight (for conversion at 25}^\circ\text{C and atmospheric pressure)}$$

(Example) Saturated vapour pressure for certain substance is 0.9kPa (25°C). What is the saturated vapour pressure concentration for this substance (ppm)?

(Answer) Saturated vapour pressure concentration = Saturated vapour pressure / atmospheric pressure

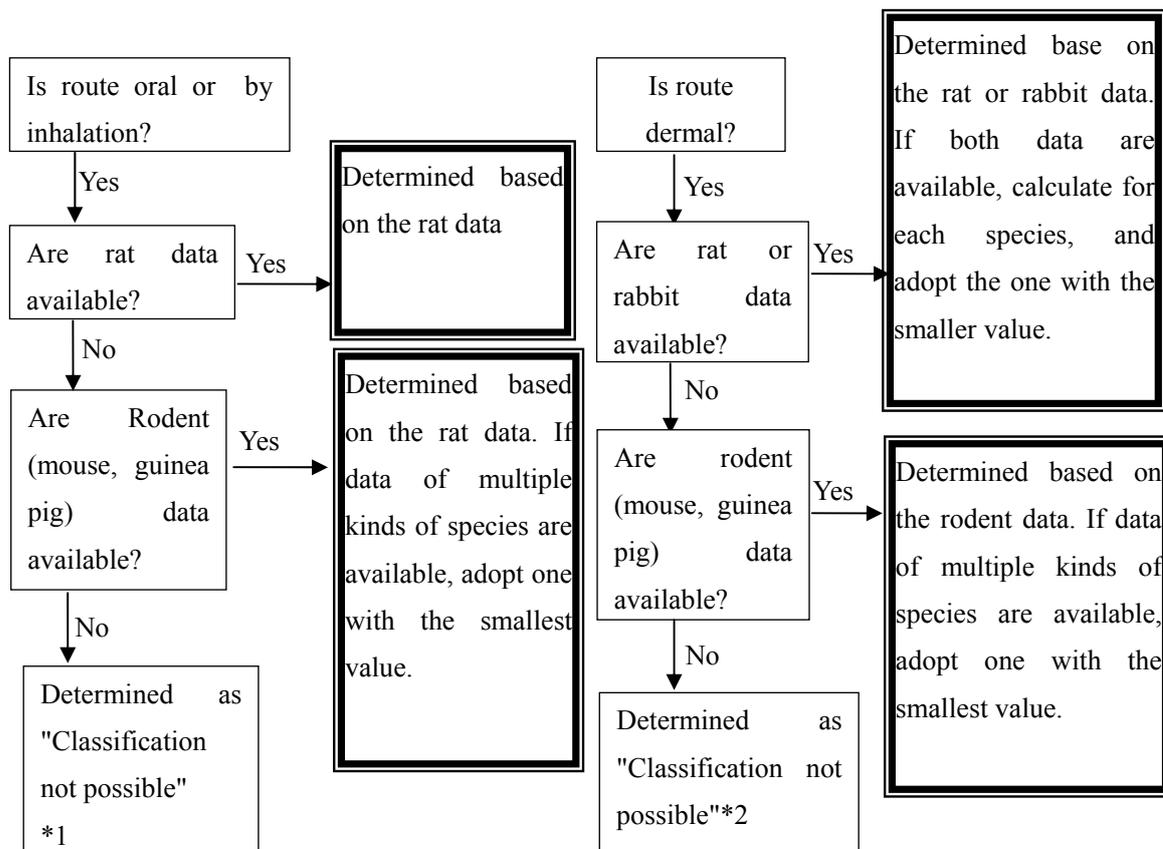
Saturated vapour pressure concentration = 0.9kPa / 101.3kPa

= 0.0088845

= 8885ppm

Therefore, the saturated vapour pressure concentration of a substance that has a saturated vapour pressure of 0.9kPa (25°C) is 8885ppm. When calculating in mmHg, atmospheric pressure should be converted to 760mmHg.

**Fig. 3-1 Handling of animal species difference**



\*1 Data for animals other than rodents are not adopted for classification but are described in the input sheet for future reference.

\*2 Data for animals other than rodents and rabbits are not adopted for classification but are described in the input sheet for future reference.

**D) Reference Value regarding Vapour inhalation in Acute Toxicity classification**

Since, in the classification of Acute Toxicity, the criteria for vapour inhalation are easily misunderstood when one refers only to Table 3.1.1.of the UN GHS third revised edition, it is required for classification to take notice of note (d) of Table 3.1.1.and the text paragraph 3.1.2.6.2 of the same document.

Note (e) attached to the column of “Vapour” in Table 3.1.1 of the UN GHS third revised edition states, “For some substances, 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), and Category 4 (20000 ppmV).”This instructs that, if a test is conducted with vapour that is completely gasified, classification is made with the reference value shown in ppm,

whereas the reference value is set in mg/L in the column of vapour inhalation of the main body of the table since a test described as conducted for “vapour” actually has “inclusion of mist” in some cases, in which cases the concentration cannot be indicated accurately unless indicated in mg/L. The values shown here are the same as the classification reference values of gas. In text 3.1.2.6.2, the same point is repeatedly described.

In accordance with the gist of Note (d) of Table 3.1.1. and the text paragraph 3.1.2.6.2 of the UN GHS third revised edition, classification of acute toxicity in the case of “inhalation” is performed as follows.

- 1) As for gas based on the definition of GHS (defined as “a substance which (i) at 50°C has a vapour pressure greater than 300 kPa (absolute); or (ii) is completely gaseous at 20°C at a standard pressure of 101.3kPa”), the category reference values (ppmV) of gas are applied.
- 2) When an experiment with regard to vapour generated from liquids is performed with concentration exceeding the saturated vapour pressure, the substance is determined as “mists”, and the category reference values of “dusts and mists” are applied.
- 3) When an experiment is performed at the concentration of the saturated vapour pressure or less with the vapour generated from liquids, the substance is handled as “vapours”. When handled as "vapours", since there are cases where mists are estimated to be included and where mist is estimated to be hardly included in accordance with GHS, categorization is performed based on the following a) to d).
  - a) When mists are estimated to be included, categorization is performed based on the reference values in the unit of mg/L shown in the row of “vapours” in the Table.
  - b) When mist is estimated to be hardly included, categorization is performed based on the reference values (the same values as for gases) in the unit of ppmV shown in the Note (e) of UN GHS third revised edition Table 3.1.1.
  - c) When the ATE (LC<sub>50</sub>) value obtained from a test is between the value for the saturated vapour pressure concentration of the substance and a value corresponding to that of the saturated vapour pressure concentration, the substance is determined as “vapour with included mists” with consideration of the possibility of mist inclusion, and 1) is applied. In case of lower concentration, the substance is determined as “vapour with hardly included mist”, and 2) is applied.
  - d) When description in a document is in mg/L, values therein are converted into those in ppmV based on the molecular weight and temperature, and the above method is applied. If the temperature during the inhalation test is not described, the unit conversion is performed by assuming that the temperature is 25°C and the volume of gas of 1 mole is 24.45 L.
- 4) When it is described that a test is conducted definitely for “mists”, the substance tested is treated as mist.

5) Since it is also presumed that vapour generated from solid is inhaled, the vapour which is generated from solid (other than gases/ liquids) is treated as “Vapour” when it is clearly indicated as “vapour” or the inhalation concentration is indicated in unit of ppmV. However, when a concentration is at the value of the saturated vapour pressure concentration or greater, dust may be included. Since GHS has no special definition for this case, specify as follows: “Doubtful description as vapour because the described pressure exceeds the saturated vapour pressure: high possibility of dust inclusion”. When a concentration is at the value that corresponds to the saturated vapour pressure or less, and when the unit is mg/L, and when there is no clear indication of vapour or dust, generally, classification is not possible. In this case, it is desirable to indicate specially, “Category ○○ if it is vapour, Category ○○ if it is dust”.

### 3-2-2 Skin Corrosion/Irritation

#### (1)Definitions

Definitions of Skin Corosion/Irritation in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (3.2.1)**

*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<sup>1</sup>.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<sup>1</sup>.

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

#### (2)Classification criteria

##### A) Classification criteria based on JIS Classification

The categories of corrosion and irritation are calssified into Category 1 Skin Corrosion and Category 2 skin irritation (as will be discussed later, in UN GHS, in addition to JIS classification, Category 3 is set), and Skin Corrosion is sub-categorized based on exposure time and observation period. Criteria are as follows.

**Table 3-3 Skin corrosion category and sub-categories <sup>a)</sup>**

Category 1: Corrosive	Corrosive sub-categories	Corrosive in ≥ 1 of 3 animals	
		Exposure time(T)	Observation period(t)
corrosive	1A	T≤3min	t≤1h
	1B	3min<T≤1h	t≤14days
	1C	1h<T≤4h	t≤14days

Note a) The use of human data is discussed in “Evidence from humans” (the UN GHS the third revised edition 1.3.2.4.7).

**Table 3-4 Categories of skin irritation <sup>a)</sup>**

Category	Criteria
Skin irritation (Category2)	<p>Any one of the below shall serve as the criterion.</p> <p>a) The averaged score values of 2.3 or more and 4.0 or less for erythema/eschar or for edema in at least 2 of 3 tested animal from gradings at 24, 48, and 72 hours after patch removal or, if reactions are delayed, from gradings on 3 consecutive days after the onset of skin responses; or</p> <p>b) Inflammation that persists to the end of the observation period, normally 14 days, in at least 2 animals, particularly taking into account of alopecia (in limited area), hyperkeratosis, hyperplasia, and scaling; or</p> <p>c) In some cases where there is pronounced variability of response among animals and where very definite positive effects that are related to chemical exposure but are less than the criteria above are observed in a single animal.</p>

Note a) The use of human data is discussed in “Evidence from humans” (the UN GHS the third revised edition 1.3.2.4.7).

B) Classification criteria in GHS(Reference Information)

In GHS classification, in addition to JIS Classification, Category 3 is set. Classification criteria of GHS are as follows.

**【GHS 3<sup>rd</sup> revised edition】** (3.2.2)

**Table 3.2.1: Skin corrosion category and sub-categories <sup>a</sup>**

Category 1: Corrosive (applies to authorities not using sub-categories)	Corrosive sub-categories (only applies to some authorities)	Corrosive in 1 of 3 animals	
		Exposure	Observation
corrosive	1A	≤3 min	≤1h
	1B	>3min≤1h	≤14days
	1C	>1h≤4h	≤14days

<sup>a</sup> 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)

**Table 3.2.2 Skin irritation categories <sup>a</sup>**

<b>Categories</b>	<b>Criteria</b>
<b>Irritant (Category 2)</b> (applies to all authorities)	(1) Mean value of $\geq 2.3 \leq 4.0$ 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.
<b>Mild irritant (Category 3)</b> (applies to only some authorities)	Mean value of $1.5 < 2.3$ 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 substance and mixtures” (para.1.3.2.4.7.1)*

(3) Items on information sources and data

\* Classification procedure can be referred to "3-1-1 Sources of Information available for classification".

A) Data availability

- The definitions of the categories are based on irritation test results, but there are few data books that contain detailed Draize scores to which GHS criteria can be applied. Classification of substances into sub-categories (1A, 1B, and 1C) under Category 1 is not possible without detailed data. (OECD has proposed test method guideline 435 (*in vitro* membrane barrier test method) for classification into skin corrosion sub-categories (1A, 1B, and 1C).)
- If an irritation score (averaged score values) based on appropriate irritation data (for example, averaged Draize Score values (for each animal) of erythema/eschar or edema, PII (skin primary irritation index) ) cannot be easily obtained, findings of “Severe”,

“Moderate”, “Mild (Slightly)”<sup>6</sup> and others for Skin Corrosion/Irritation in test reports may be referenced.

- R-Phrases<sup>7</sup> (R34, R35, R38, R36/37, R36/38, R37/38, R36/37/38) in EU DSD classification relating to Skin Corrosion/Irritation may be referred.
- The OECD test guideline includes the following test methods relating to Skin Corrosion/Irritation.

OECD TG 404 Acute dermal irritation / corrosion

OECD TG 430 In vitro skin corrosion: Transcutaneous electrical resistance test

OECD TG 431 In vitro skin corrosion: Human skin model test

OECD TG 435 In vitro membrane barrier test method for skin corrosion

#### B) Order of Precedence when Conflicting Data Exist

Refer to “3-1-2 Order of Precedence when Conflicting Data Exist”.

#### C) Comparison with conventional classification systems

- Substances classified as Corrosive (C) with R34, R35 in EU DSD classification fall under Category 1.
- Substances classified as Irritant (Xi) with R38 and combination of R-Phrases<sup>7</sup> (R36/38, R37/38, R36/37/38) in EU classification fall under Category 2 (in GHS classification). Confirmation with detailed data is required. If evidence information other than EU DSD classification results is not available, the substance shall be judged “Classification not possible”.
- EU CLP classification H314 accords with Category 1, and H315 accords with Category 2.
- Comparison between EU classification and GHS classification is as follows.

##### Skin corrosion

EU DSD classification	C R35	C R34	
EU CLP classification	H314(Note)		
GHS classification	Category 1 A	Category 1 B	Category 1 C

##### Skin irritation

EU DSD classification	Xi R38	
EU CLP classification	H315	
GHS classification	Category2	Category3

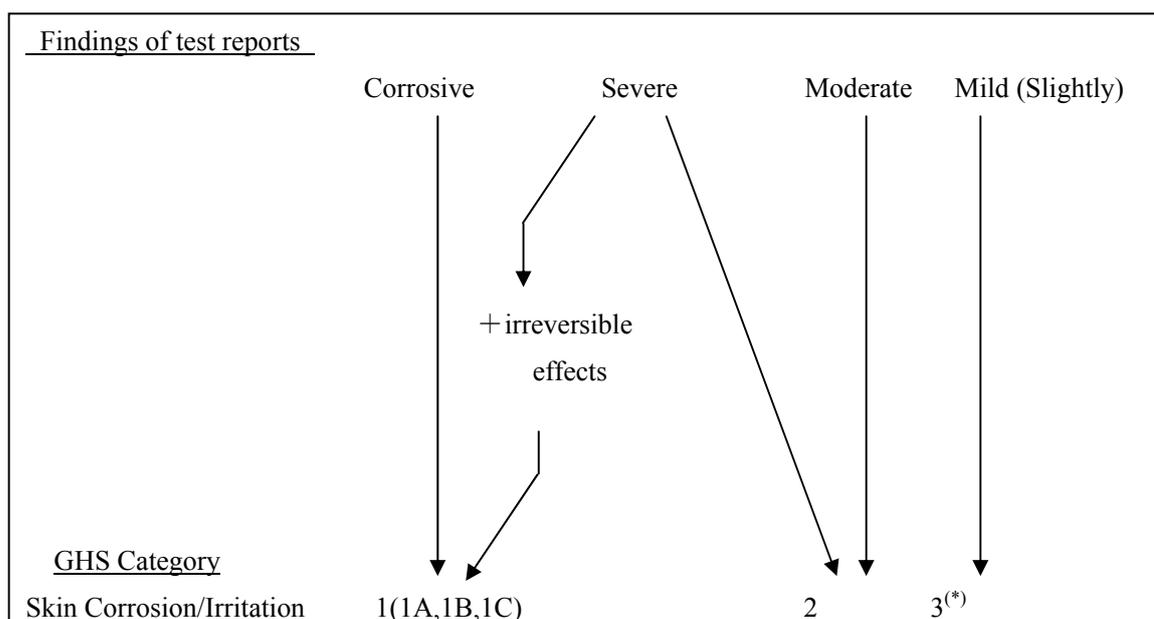
Note: According to the criteria, H314 includes Category 1 B and 1 C. However, in EU CLP Regulations Annex VII, H314 is stated as 1 B.

<sup>6</sup> Some observations distinguish “mild” and “slightly”, but in IUCLD, “slightly” is used instead of “mild”.

<sup>7</sup> For R-Phrase, see Appendix.

#### D) Guidance concerning data

In many cases, findings of test reports are given using the evaluative scale of “severe”, “moderate”, and “mild (slightly<sup>8</sup>)”, and these can be considered to correspond to Categories 1, 2, and 3, respectively. It is preferable to confirm PII (skin primary irritation index) and the like as far as possible, and to classify the substance in question as moderate (corresponding to PII3-5) or severe (corresponding to PII 6-8). Also, the corresponding category should be determined at least upon confirming which classification criteria the given existing classification is based on since substances classified as “moderate” based on different classification criteria may cause different degrees of skin reaction. Category 1 is applied to substances that cause irreversible lesions such as necrosis within observation period of Skin Corrosion/Irritation test. There is an opinion to the effect that “a substance evaluated as “severe” corresponds to Category 2 if no irreversible lesion is observed”. This judgment, however, may be subjective and should be considered only for reference. It is preferable for GHS classification to refer to the original literatures, to examine the validity of data, and to perform classification based on scientific evidence and methods of GHS.



(\*)("Not classified in JIS Classification)

#### E) Decision by physicochemical properties

Substances considered as strong acids ( $\text{pH} \leq 2$ ) or strong alkalis ( $\text{pH} \geq 11.5$ ) based on their physicochemical properties shall be classified as Category 1. However, in this case, as described in the UN GHS the third revised edition, it must be shown that its buffer power

<sup>8</sup> Some observations distinguish “mild” and “slightly”, but in IUCLD, “slightly” is used instead of “mild”.

maintains pH on exposure. In classification, buffering capacity of acids and bases should be taken into account.

#### (4) Guidance for classification and judgment

##### A) Background of this item and points to be noted

Regarding background of this item, refer to Part 1, Introduction.

As for skin corrosion and irritation, classification should be conducted according to the workflow of decision logic 3.2.1, which is the definite decision criteria of UN GHS the third revised edition. In classification, refer to the technical advices such as judging method based on pre-existing test data described below.

Sub-categorization of Corrosion can be performed only when an animal test is conducted that has exposure time and observation period which allow application of the judgment of corrosion in the UN GHS third revised edition (3.2.1). Accordingly, only for such cases, sub-categorization is performed, and for other cases, sub-categorization should not be performed.

In addition, note the following in classification.

\* Unless a description that definitely denies hazards or recognizes extremely low hazards is available in List 1, determination of "Not classified" should be performed carefully. If there is any question, not "Not classified" but "Classification not possible" is preferable, which is based on the absence of sufficient information for judging.

\* When sub-categorization is not possible, the substance shall be classified as "Category 1".

##### B) Judgement by reliable existing revelation course

When a substance has cases to be judged as corrosion (any of sub-categories 1A, 1B, and 1C, or Category 1) or irritation (Category 2) in human or animal results, the substance shall be classified as such. (Example: accidental cases)

##### C) Judgement by existing test data

###### 1) Decision by *in vivo* test result :

###### ■ Corrosion : (any of sub-categories 1A, 1B, and 1C, or Category 1)

In at least 1 of 3 tested animals after exposure for up to 4 hours:

- a) Necrosis into the dermis.
- b) Ulcer, bleeding, or bloody scabs in the applied area.
- c) Blanching of the skin, complete areas of alopecia, and remaining scars are found at the end of the observation period of 14 days.
- d) In the case of erythema/eschar or edema score of 4 or more, the substance is determined as Corrosion (Category 1)(When, however, no irreversible lesion is found, the substance

is determined as Irritation (Category 2)).

■ Irritation (Category 2)

At 24, 48, and 72 hours after application:

- a) Mean value of Draize Score (for each animal) (S) is  $\geq 2.3$  to  $\leq 4.0$  for erythema/eschar or edema in at least 2 of 3 tested animal,
- b) Inflammation and alopecia of limited area, hyperkeratosis, hyperkeratosis, hyperplasia, and scaling persist to the end of 14 days after application in at least 2 of 3 tested animal, or
- c) Definite positive effects are recognized in an animal, but its extent does not satisfy criteria 1) and 2) above. (e.g. when a pronounced variability of response is found among animals, with a definite lesion recognized at the end of the observation period in only 1 of 3 tested animals).

2) Decision by comparison with existing classification :

- The substance classified as Severe or Corrosive is determined as Corrosive (Category 1), and the substance classified as Severe with no irreversible lesion observed is determined as Irritant (Category 2).
- The substance classified as Moderate is determined as Irritation (Category 2).
- It is preferable to confirm PII (skin primary irritation index) and the like as far as possible, and to classify the substance in question as moderate (corresponding to PII 3-5) or severe (corresponding to PII 6-8). Also, it is preferable to determine the corresponding category at least upon confirming which classification criteria the given existing classification is based on since substances classified as “moderate” based on different classification criteria may cause different degrees of skin reaction.

3) Decision by symptom (when no other information is available):

- When described as necrosis, the substance is determined as corrosive (Category 1).

D) Decision by structure-activity relationship or structure-property relationship

In classification, this shall not be considered at all. However, if there is a description to the effect that “the substance is judged to be classed in XX class by the analysis of the structure-activity relationship” in the assessment document of List 1, the substance is classified based on the result.

E) Decision by physicochemical properties

In the case of  $\text{pH} \leq 2$  and  $\text{pH} \geq 11.5$ , the substance is classified as Corrosive (Category 1) (Determination is performed with buffering capacity also taken into account.) (Booman et al (1989) proposed 0.2 meq HCl/g for eye irritation.)

A paper is given below that shows examples that irritation is not determined by pH alone

but affected by composition of acids or alkalis.

“Classification as Corrosive or irritant to Skin of Preparations Containing Acidic or Alkaline Substances, without Testing on Animals”, YOUNG,J.et. al (SDA), Toxicol in vitro VOL.2 NO.1 PAGE 19-26 (1988)

F) Decision by *In vitro* test methods

If data of a test based on OECD TG431 (human skin model, Epiderm), TG430 (skin electric conductivity test) or OECD TG435 (Corrositex®) is available, the substance is classified in accordance with the decision criteria with which each of the test is internationally accepted. Other *in vitro* tests are not considered.

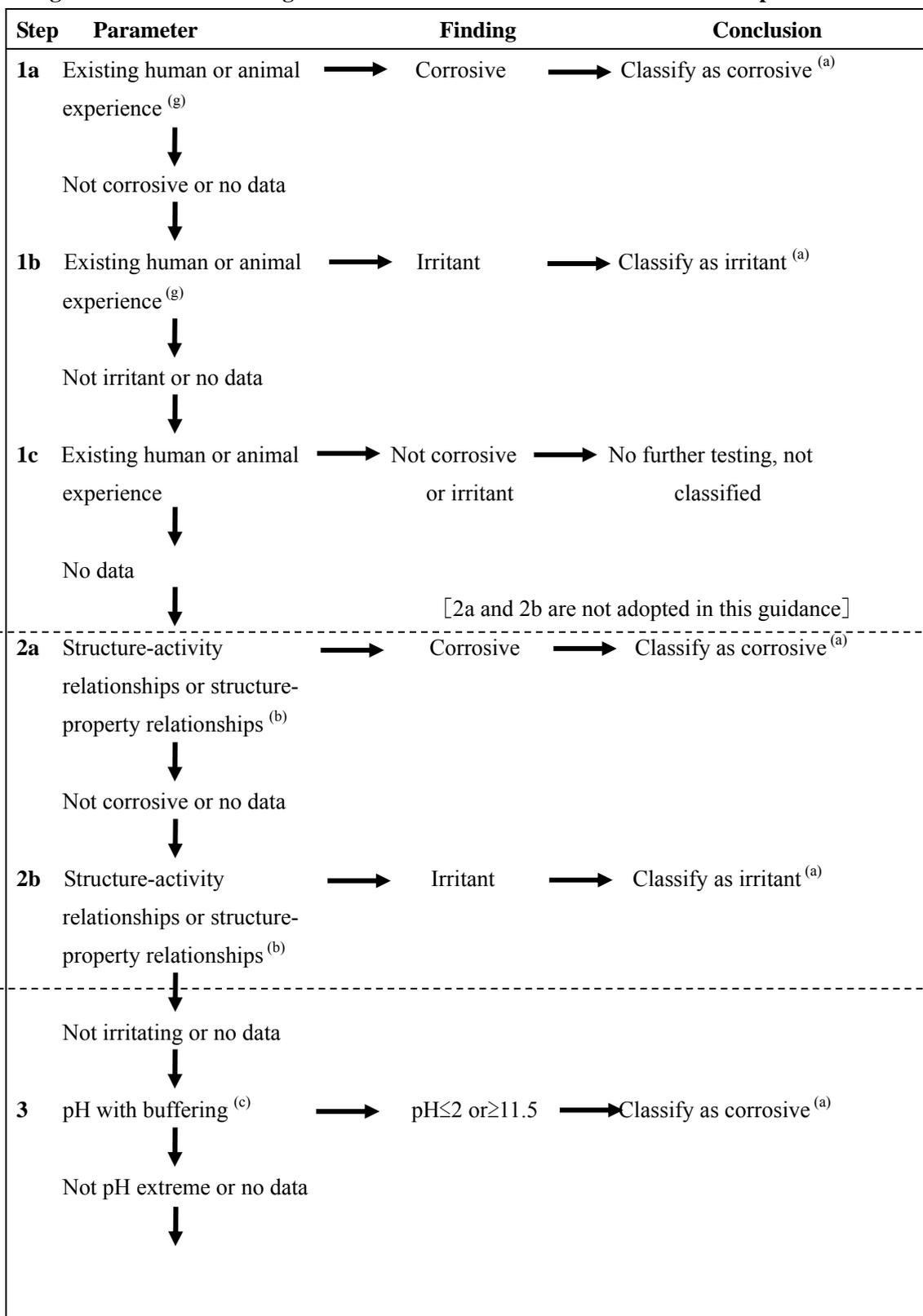
G) Strategy of tiered testing and evaluation for skin corrosion and skin irritation

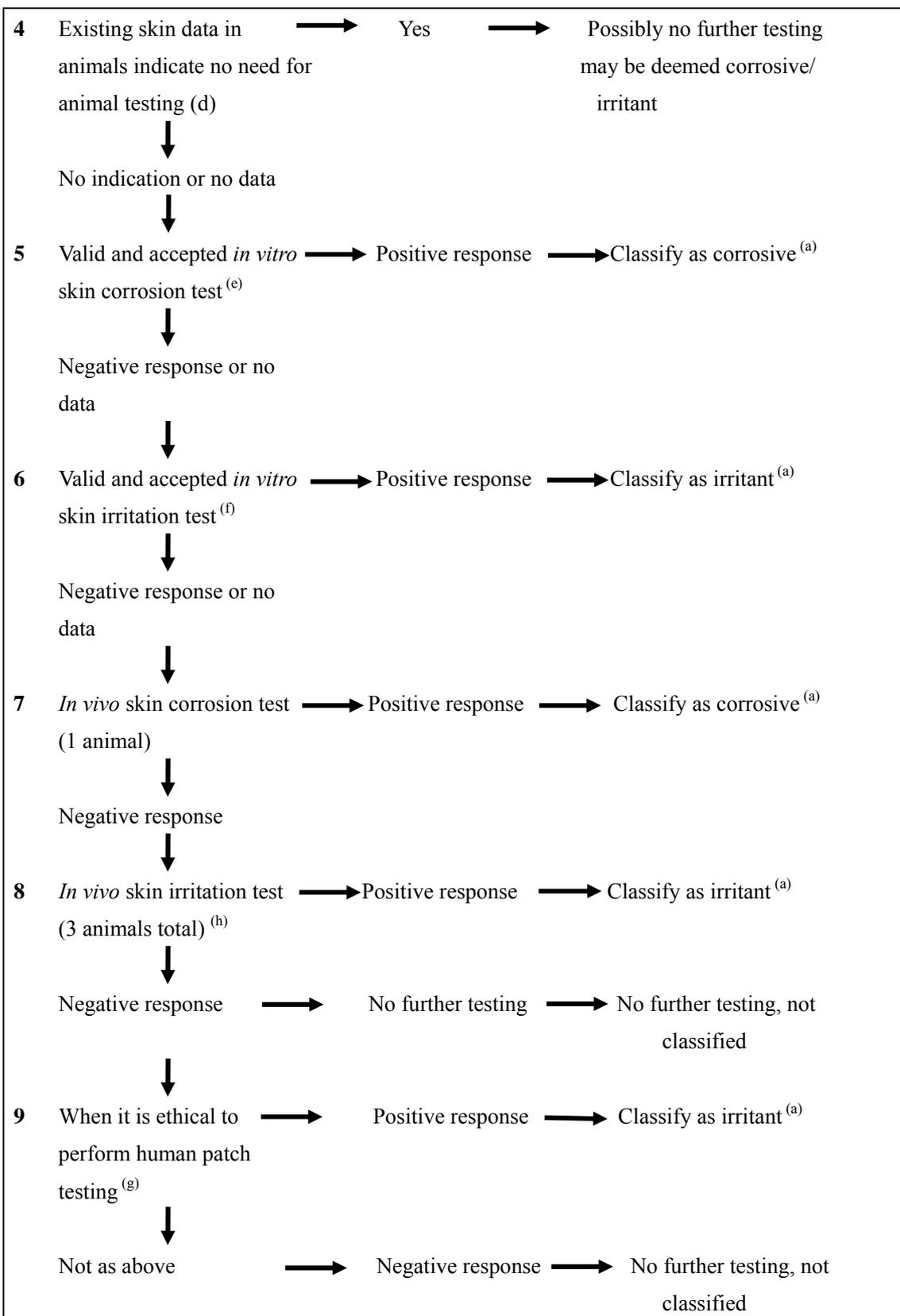
The strategy of tiered testing and evaluation for skin corrosion and skin irritation described in the UN GHS the third revised edition is as follows. As described in D), structure-activity or structure-property relationships (Steps 2a and 2b) is not adopted in this guidance.

There is an argument in “United Nations Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals (UNSCGHS)” to revise this flow diagram. Therefore, this flow diagram should only be used as reference.

【GHS 3<sup>rd</sup> revised edition】

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





[Note for the above figure]

- (a) Classify in categories shown in (2) B).
- (b) Structure-activity and structure-property relationships are presented separately but would be conducted in parallel. However, structure-activity and structure-property relationships are not adopted in this guidance.
- (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.

(Note) The OECD test guidelines defining limit dose and the limit dose is shown below.

OECD test guidelines		Limit dose
No.	Test guideline	
OECD TG404	Acute Dermal Irritation/Corrosion	2000 mg/kg body weight

- (e) Examples of internationally accepted validated *in vitro* test methods for skin corrosion are OECD TG 430, TG 431 and TG 435.(see “F) Decision by *In vitro* test methods”)
- (f) Presently there is 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 TG has been proposed.
- (h) Testing is usually conducted in 3 animals, one coming from the negative corrosion test.

### 3-2-3 Serious Eye Damage/Eye Irritation

#### (1) Definitions

Definitions of Serious Eye Damage/Eye irritation in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (3.3.1)**

*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<sup>1</sup>.

*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<sup>1</sup>.

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

#### (2) Classification criteria

##### A) Classification criteria based on JIS Classification

**Table 3-5 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  $\geq 3$ ; and/or
- iritis  $> 1.5$  ;

calculated as the mean scores following grading at 24, 48, and 72 hours after installation of the test material.

**Table 3-6 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  $\geq 1$ ; and/or
- iritis  $\geq 1$ ; and/or
- conjunctival redness  $\geq 2$ ; and/or
- conjunctival oedema (chemosis)  $\geq 2$

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.

## B) Classification criteria in GHS (reference information)

In classification criteria of JIS Classification and that of GHS, the same categories are adopted.

For detailed descriptions, refer to the UN GHS third revised edition Tables 3.3.1 and 3.3.2.

### (3) Items on information sources and data

\* Classification procedure can be referred to "3-1-1 Sources of Information available for classification".

#### A) Data availability

- The definitions of the categories are based on eye irritation test results, but there are few data books that contain detailed Draize scores to which GHS classification criteria can be applied.
- For skin corrosive materials, tests by installation to animal eyes are not conducted generally. In the case where data of eye irritation test are not available, a skin corrosive material shall be classified as a substance causing serious eye damage (Category 1).
- If data-based irritation score (mean score value) of appropriate irritation data (for example, Draize Score mean values (for each animal), AOI (Acute ocular irritation index)) cannot be easily obtained, reference may be made to findings of "Severe," "Moderate," "Mild (Slightly)<sup>9</sup>," and others for eye damage/eye irritation in test reports. When data in a test report regarding grade of eye irritation reaction (for example, Draize method for rabbit or human findings) is mild and showing full reversibility within 7 days are available, classification may be performed based on them. It is, however, preferable to review the cited original literature, to examine its scientific validity, and then to classify in accordance with the results. Earlier literatures which do not adopt the standardized Draize method may be referred. It is, however, preferable to review the cited original literature, to examine its scientific validity, and then to classify in accordance with the results.
- Reference may be made to R-Phrases<sup>10</sup>(R36, R41, R36/37, R36/38, R37/38, R36/37/38) in EU DSD classification relating to serious eye damage/ eye irritation.
- The OECD test guideline includes the following test method relating to Serious Eye Damage/Eye Irritation.

OECD TG 405 Acute eye irritation / corrosion

#### B) Order of Precedence when Conflicting Data Exist

Refer to "3-1-2 Order of Precedence when Conflicting Data Exist".

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<sup>9</sup> As described in the footnote in 3-2-2 Skin Corrosion/Irritation, some observations distinguish "mild" and "slightly", but in IUCLD, "slightly" is used instead of "mild".

<sup>10</sup> For R-Phrase, see Appendix.

### C) Comparison with conventional classification systems

- Substances classified as R41 in EU DSD classification fall under Category 1.
- Substances classified in R36 and combination of R-Phrases<sup>11</sup> (R36/37, R36/38, R36/37/38) in EU classification fall under Category 2.
- EU CLP classification H318 accords with Category 1, and H319 accords with Category 2.

EU DSD classification	Xi R41	Xi R36	
EU CLP classification	H318	H319	
GHS classification	Category 1	Category 2A	Category 2B

### D) Guidance concerning data

In many cases, findings of test reports are given using the evaluative scale of “severe”, “moderate”, and “mild (slightly)<sup>12</sup>”, and these can be considered to correspond to Categories 1, 2A, and "B, respectively. Depending, however, on the test method used, application conditions of test materials, and criteria for “severe”, “moderate”, and “mild (slightly)”, the extent of eye reactions may differ. It is preferable to confirm the final findings, as well as to review the cited original literature, and to examine the scientific validity of the classification criteria and the data. From the point of view, Category 1 is applied to substances that cause irreversible effects on such as cornea and iris within the observation period of eye damage/ eye irritation test. A substance evaluated as “Severe” including no irreversible effects fall under Category 2A. If there is distinction between “Mild” and “Slightly” in the findings of test report, a substance evaluated as “Slightly” should be classified as “Not classified”.

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<sup>11</sup> For R-Phrase, see Appendix.

<sup>12</sup> As described in the footnote in 3-2-2 Skin Corrosion/Irritation, some observations distinguish “mild” and “slightly”, but in IUCLD, “slightly” is used instead of “mild”. If there is distinction between “Mild” and “Slightly”, a substance evaluated as “Slightly” should be classified as “Not classified”



reversible effects on eye (Category 2) in human or animal results, the substance shall be classified as such. Refer to the UN GHS third revised edition, table 3.3.1 (Example: accidental cases)

C) Judgement by liable existing test data

1) Decision by *in vivo* test(Draize test)result :

a) Decision criteria for serious eye damage(irreversible effects)(Category 1) :

- 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 21 days after installation of the test material.
- At least in 2 of 3 tested animals, the calculated mean scores following grading at 24, 48, and 72 hours after installation of the test material are Corneal opacity  $\geq 3$  and/or iritis  $>1.5$ .

b) Decision criteria for irritation (reversible effects) (Categories 2A, 2B or Category 2) :

- In the Draize test conducted using 3 animals, the calculated mean values of the scores following grading at 24, 48, and 72 hours after installation of the test material are corneal opacity  $\geq 1$  and/or iritis  $\geq 1$  and/or conjunctival redness  $\geq 2$  and/or conjunctival oedema  $\geq 2$ .
- The effects are fully reversed within an observation period of 21 days.
- The substance is classified as mildly irritant to eyes (Category 2B) when the above description applies to the substance and the effects reverse within an observation period of 7 days.

2) Decision by existing classifications :

- A substance which is classified as Severe or Corrosive (corresponding to very strong irritation or corrosiveness corresponding: AOI 80 or more) is classified in Category 1 (When, however, no irreversible lesion is observed, the substance is determined as irritating to eyes (Category 2A)).
- A substance which is classified as moderate (corresponding to strong irritation: AOI 30-80) is classified as Category 2A.
- A substance which is classified as Mild ( $15 \leq \text{AOI} < 30$ ) is classified in Category 2B.
- It is preferable to review the original literature and to confirm irritation to eyes, etc., where possible.

D) Decision by structure-activity relationship or structure-property relationship

In classification, this shall not be considered at all. However, if there is a description that the substance is judged to be classed in a given class by the analysis of the structure-activity relationship in the assessment document of List 1, the substance is classified based on the

result.

E) Decision by physicochemical properties

In the case of  $\text{pH} \leq 2$  or  $\text{pH} \geq 11.5$ , the substance is classified in Category 1 (Determination is performed with buffering capacity also taken into account.) (Booman et al (1989) proposed 0.2 meq HCl/g for eye irritation.)

A paper is given below showing examples that irritation is not determined by pH alone but affected by composition of acids or alkalis.

“Classification as Corrosive or irritant to Skin of Preparations Containing Acidic or Alkaline Substances, without Testing on Animals”, YOUNGJ, et. Al (SDA), Toxicol in vitro VOL.2 NO.1 PAGE 19-26 (1988)

F) Decision by *In vitro* test methods

Examples of internationally accepted validated *in vitro* test methods for eye irritation are OECD TG 437 and TG438.

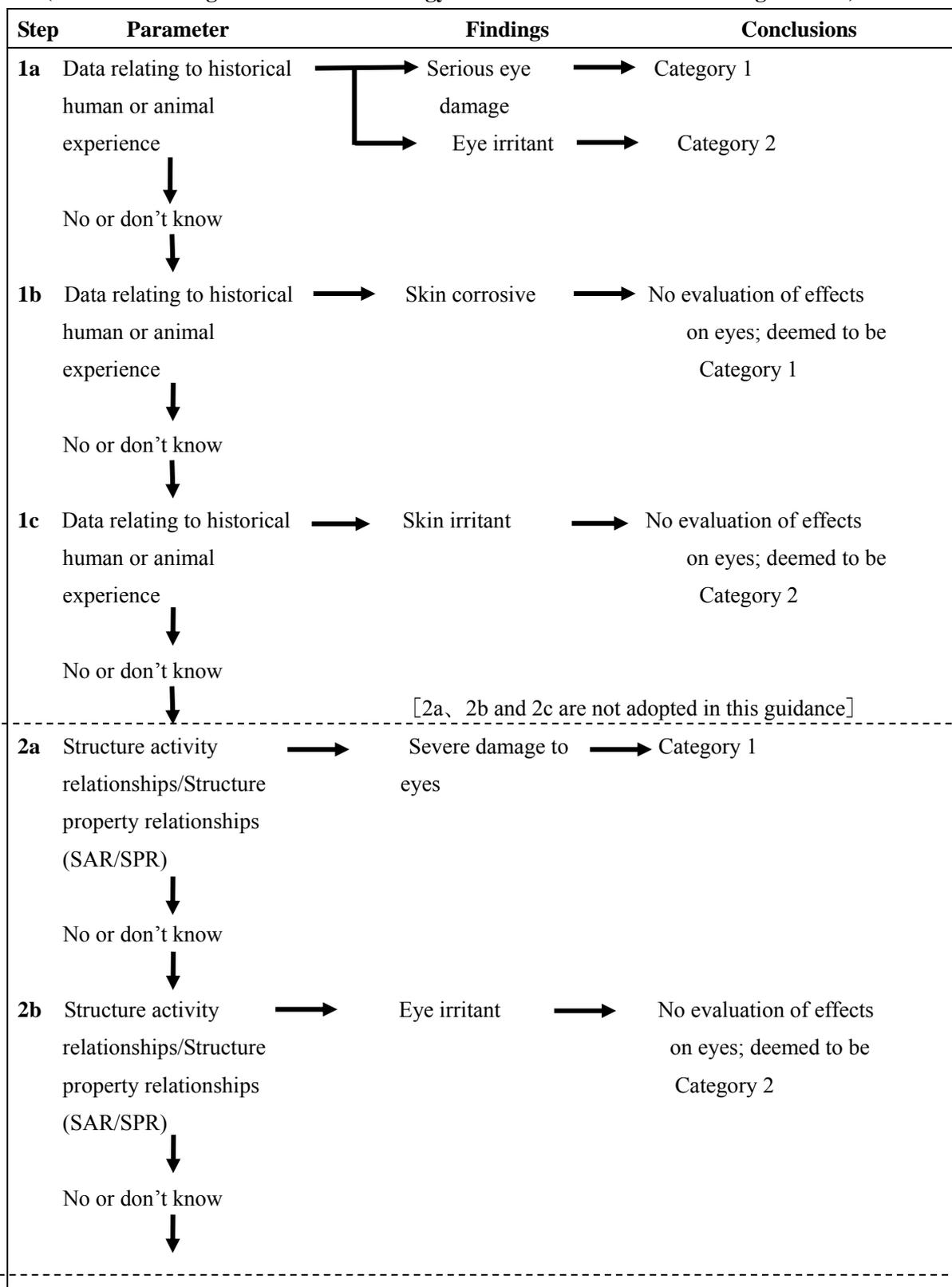
G) Strategy of testing and evaluation for Serious Eye Damage/Eye Irritation

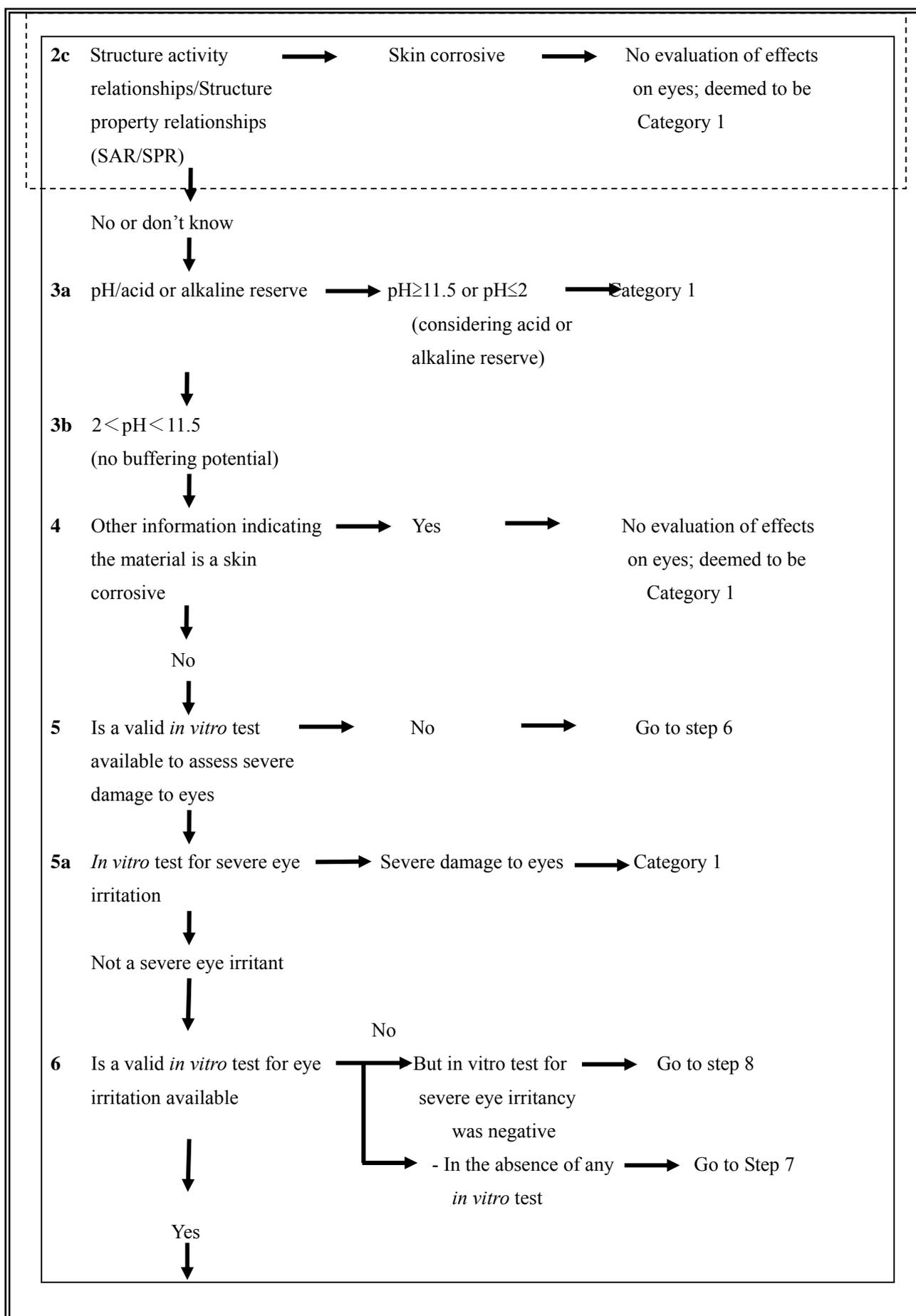
The strategy of tiered testing and evaluation for Serious Eye Damage/Eye Irritation described in the UN GHS the third revised edition, Fig. 3.3.1 is as follows. As described in D), structure-activity relationship or structure-property relationship (Steps 2a, 2b, and 2c) is not adopted in this guidance.

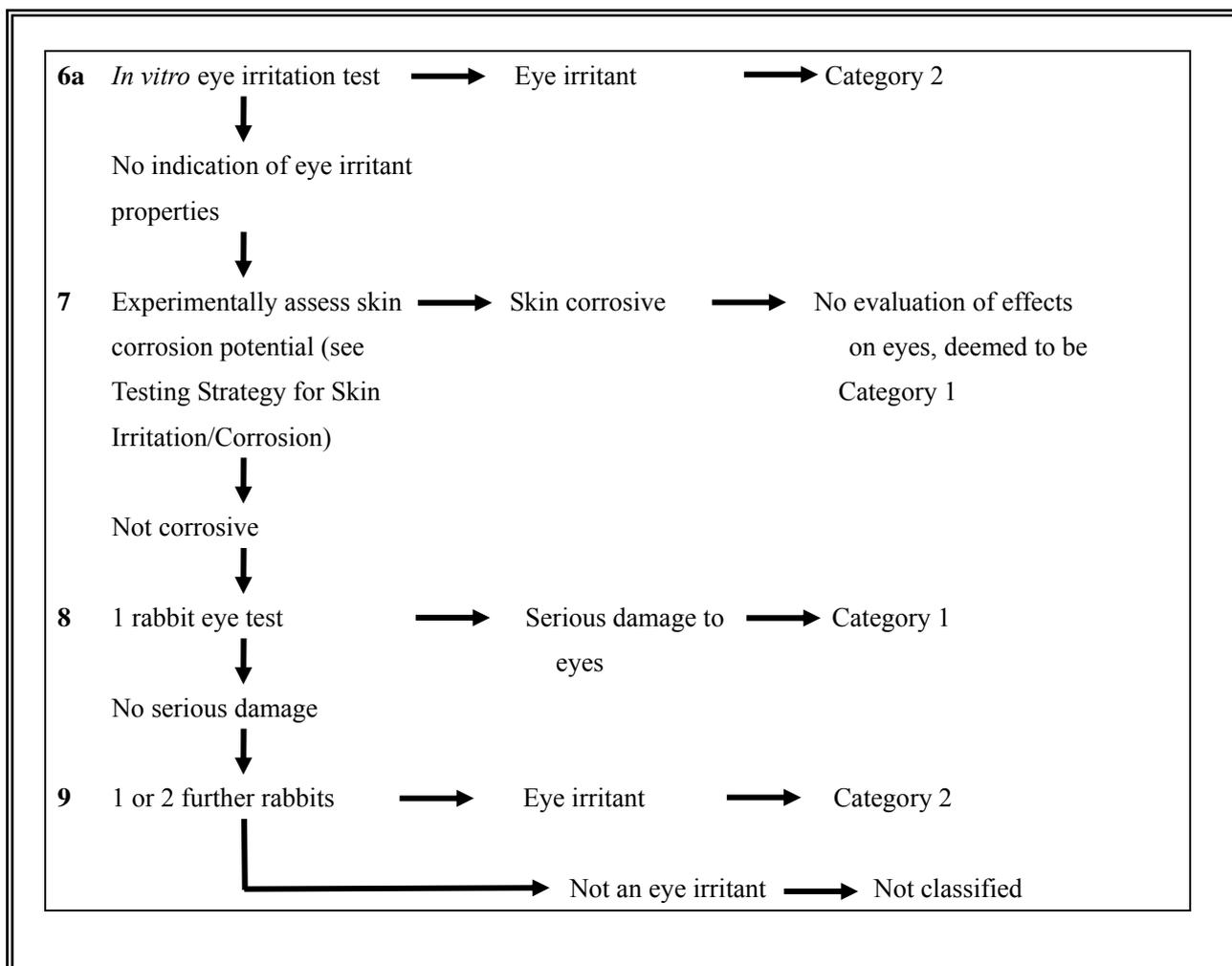
There is an argument in “United Nations Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals (UNSCGHS)” to revise this flow diagram. Therefore, this flow diagram should only be used as reference. (Also, refer to Skin irritation/corrosion test and summary of the results.)

【GHS 3<sup>rd</sup> revised edition】

**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)







**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/c [Not adopted in this guidance]: 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  $\leq 2$  and  $\geq 11.5$  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<sub>50</sub> 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 section 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 recognized 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, section 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.*

## 3-2-4 Respiratory or Skin Sensitization

### (1) Definitions

Definitions of Respiratory or Skin Sensitization in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (3.4.1)**

3.4.1.1 A *respiratory sensitizer* is a substance that will lead to hypersensitivity of the airways following inhalation of the substance<sup>1</sup>.

A *skin sensitizer* is a substance that will lead to an allergic response following skin contact<sup>1</sup>.

3.4.1.2 For the purpose of this chapter, sensitization includes two phases: the first phase is induction of specialized immunological memory in an individual by exposure to an allergen. The second phase is elicitation, i.e. production of a cell-mediated or antibody-mediated allergic response by exposure of a sensitized individual to an allergen.

3.4.1.3 For respiratory sensitization, the pattern of induction followed by elicitation phases is shared in common with skin sensitization. For skin sensitization, an induction phase is required in which the immune system learns to react; clinical symptoms can then arise when subsequent exposure is sufficient to elicit a visible skin reaction (elicitation phase). As a consequence, predictive tests usually follow this pattern in which there is an induction phase, the response to which is measured by a standardized elicitation phase, typically involving a patch test. The local lymph node assay is the exception, directly measuring the induction response. Evidence of skin sensitization in humans normally is assessed by a diagnostic patch test.

3.4.1.4 Usually, for both skin and respiratory sensitization, lower levels are necessary for elicitation than are required for induction. Provisions for alerting sensitized individuals to the presence of a particular sensitizer in a mixture can be found at section 3.4.4.

### (2) Classification criteria

#### A) Classification criteria based on JIS Classification

In JIS Classification, “Substances shall be classified as respiratory sensitizers Category 1 in accordance with the criteria given below:”

- a) If there is evidence in humans that the substance can lead to specific respiratory hypersensitivity and/or
- b) If there are positive results from an appropriate animal test.

Also, “Substances shall be classified as skin sensitizers Category 1 in accordance with the

criteria given below:”

- a) If there is evidence in humans that the substance can lead to sensitization by skin contact in a substantial number(\*) of persons, and/or
- b) If there are positive results from an appropriate animal test.

(\*) “a substantial number” depends on the person responsible for classification. The grounds for judging a given number to be substantial shall be indicated in the reason for judgment.

**B) Classification criteria in GHS (Reference information)**

JIS classification adopts Category 1 pursuant to UN GHS 3rd revised edition. UN GHS 3rd revised edition created following sub-classes (1A, 1B).

【GHS 3<sup>rd</sup> revised edition】

Figure 3.4.1: Hazard category and sub-categories for respiratory sensitizers

CATEGORY 1:	Respiratory sensitizer
	A substance is classified as a respiratory sensitizer (a) if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity and /or (b) if there are positive results from an appropriate animal test.
Sub-category 1A:	Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitization rate in humans based on animal or other tests. Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitization rate in humans based on animal or other tests. Severity of reaction may also be considered.

Figure 3.4.2: Hazard category and sub-categories for skin sensitizers

CATEGORY 1:	Skin sensitizer
	A substance is classified as a skin sensitizer (a) if there is evidence in humans that the substance can lead to sensitization by skin contact in a substantial number of persons, or (b) if there are positive results from an appropriate animal test.
Sub-category 1A:	Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitization in humans. Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitization in humans. Severity of reaction may also be considered.

(3)Items on information sources and data

\* Classification procedure can be referred to "3-1-1 Sources of Information available for classification".

A) Data availability

- Classification is performed based on the weight of evidence for respiratory or skin sensitization. When considering the human evidence, it is necessary for a decision on classification to take into account the size of the population exposed and the extent of exposure.
- A single category each is adopted for classification of respiratory sensitization and skin sensitization, i.e., whether the substance induces sensitization (Category 1) or not (Not classified). Although sensitization occurs depending on the size of population exposed, when proportion is exceedingly small it is difficult to determine. It is desirable to seek the judgments of experts, as it requires consideration of frequency of sensitization and intensity of effects.
- As for skin sensitization, if there are appropriate animal test data showing positive results, classification can be based on these data. Criteria by positive rate and exposure concentration is shown in UN GHS 3rd revised edition.
- Judgement of "Not classified" should be made with caution, since even substances with no clear description of sensitizer in the information sources of this guidance may be sensitizing to human.
- (Reference information 1) The signal word used for skin sensitization Category 1 is "Warning", while the word for respiratory sensitization Category 1 is "Danger", since the latter is considered to produce more serious effects on human health.
- (Reference information 2) For sensitizers in general, the following information is helpful.
  - Frosch et al. Contact Dermatitis 4<sup>th</sup> Ed. Springer (413 substances)
  - "Allergen List" Japanese Society for Contact Dermatitis (25 substances)  
<http://www.fujita-hu.ac.jp/~jsdacd/html/allergen.html> (Website in Japanese text)
- Reference may be made to the following items in each of classification systems below.
  - EU DSD classification: R42 • R43 • R42/43
  - Recommendation of Acceptable Concentration by the Japan Society For Occupational Health: respiratory tract sensitization and skin sensitization
  - TLV table of ACGIH : SEN or Sensitization substances
  - MAK (Germany): Labeling of Sensitization substance (Sa, Sh, Sah)
- OECD test guidelines include the following test methods relating to respiratory or skin sensitization.
  - OECD TG 406 Skin sensitization
  - OECD TG 429 Skin sensitization: Local Lymph Node Assay (LLNA)

## B) Order of Precedence when Conflicting Data Exist

Refer to “3-1-2 Order of Precedence when Conflicting Data Exist” .

## C) Comparison with conventional classification systems

- EU DSD classification categories relating to sensitization are R42, R43, and R42/43.
- The Recommendation of Acceptable Concentration of the Japan Society For Occupational Health includes the list of substances recognized as sensitizers. In the TLV table of ACGIH, SEN mark is assigned to sensitizers, and, in the MAK table of MAK (Germany), Sa · Sh · Sah marks are assigned.
- EU DSD classification · R42 and R42/43, as well as respiratory tract sensitization in the Recommendation of Acceptable Concentration by the Japan Society For Occupational Health, correspond to respiratory sensitization Category 1.
- EU DSD classification · R43 and R42/43, as well as skin sensitization in the Recommendation of Acceptable Concentration of the Japan Society For Occupational Health, corresponds to skin sensitization Category 1.
- EU CLP classification H334 accords with respiratory sensitization Category 1, and H317 accords with skin sensitization Category 1.
- Whether SEN substances in ACGIH is respiratory sensitizers or skin sensitizers must be confirmed by reviewing the ACGIH Documentations.
- When necessary, classification criteria of exposure situation, the size of the population exposed, and the existence of sensitization should be examined by reviewing the quoted original literature.

## D) Guidance concerning data

- Classification should be performed on the basis of any description concerning sensitization found in test reports, reviews, assessment documents, etc.

## (4) Guidance for classification and judgment

### A) Background of this item and points to be noted

Regarding the background of this item, refer to Part 1, Introduction. Also in classification, take the points below into account.

\*Unless description that definitely denies hazards or recognizes extremely low hazards is available in List 1, determination of “Not classified” should be performed carefully. If there is any question, not “Not classified” but “Classification not possible,” which is based on the absence of sufficient information for judging, is preferable.

### B) Classification procedures

1) Respiratory Sensitization :

Substances meeting [Decision Criteria 1] through [Decision Criteria 3] below shall be determined as belonging to Category 1.

[Decision Criteria 1]: In the cases where the substance is concluded to be positive in any assessment document in List 1 (“Is concluded” does not mean “is suggested” or “has the possibility”, but “is definitely stated (to be obviously positive).”).

(Exclusion Rule)

Even if the substance meets Decision Criteria 1, if it is proved that the substance induces asthma in only those who have bronchial hypersensitivity, the substance is determined as “Not classified”.

[Decision Criteria 2]: If there is evidence in humans that the substance can lead to specific respiratory hypersensitivity.

Regarding evidence in humans, refer to the UN GHS third revised edition 3.4.2.1.2.

Evidence refers to the following points.

**【GHS 3<sup>rd</sup> revised edition】** (3.4.2.1.2.3)

(a) clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include:

(i) *in vivo* immunological test (e.g. skin prick test);

(ii) *in vitro* immunological test (e.g. serological analysis);

(iii) studies that may indicate other specific hypersensitivity reactions where immunological mechanisms of action have not been proven, e.g. repeated lowlevel irritation, pharmacologically mediated effects;

(iv) a chemical structure related to substances known to cause respiratory hypersensitivity;

(b) data from positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.

[Decision Criteria 3]: If there are positive results from an appropriate animal test.

(At present, since recognized animal models for the testing of respiratory hypersensitivity are not available(the UN GHS third revised edition 3.4.2.1.3 footnote 2), [Decision Criteria 3] is not adopted in this guidance. When an appropriate animal model is set, this Decision Criteria will be adopted.)

2) Skin Sensitization :

Substances applicable to any of [Decision Criteria 1] through [Decision Criteria 4]

below shall be determined as belonging to Category 1. In classification, take into account the UN GHS third revised edition 3.4.2.2.4. “Specific considerations”.

**【GHS 3<sup>rd</sup> revised edition】**

3.4.2.2.4.1 For classification of a substance, evidence should include any or all of the following using a weight of evidence approach:

- (a) Positive data from patch testing, normally obtained in more than one dermatology clinic;
- (b) 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;
- (c) Positive data from appropriate animal studies;
- (d) Positive data from experimental studies in man (see Chapter 1.3, para. 1.3.2.4.7);
- (e) Well documented episodes of allergic contact dermatitis, normally obtained in more than one dermatology clinic.
- (f) Severity of reaction may also be considered.

[Decision Criteria 1]: In the case where the substance is concluded as positive in any assessment document in List 1.

[Decision Criteria 2]: If there is evidence in humans that can lead to specific symptom by skin contact.

[Decision Criteria 3]: If there is an epidemiological study report showing allergic contact dermatitis caused by the substance, or if there are two or more case reports of allergic contact dermatitis from separate medical institutions, in List 1 or List 2.

[Decision Criteria 4]: If a positive result is obtained in the following animal tests.

○ Decision Criteria for a Positive Result

When using adjuvant: 30% or more of animals react,

When not using adjuvant: 15% or more of animals (guinea pig) react.

\* The ratio of sensitized animal is often not clear. When the ratio is not clear, it is preferable to review the original literature and to examine the content and the ratio carefully. The same applies when skin sensitization based on the test is reported in List 1 and the ratio is not clear. In cases where the substance is

clearly concluded to include skin sensitization in List 1 based on the test, the substance is determined as belonging to Category 1. In all other cases, the substance shall be classified as “Classification not possible”.

\* As for List 2, if an animal test was performed by the test method approved by OECD shown below, if the ratio of sensitized animal is clear, and in the cases where the substance is concluded as positive in skin sensitization, then the substance shall be classified in Category 1. In all other cases, the substance shall be classified as “Classification not possible” even if a test was carried out.

○ Animal tests on skin sensitization approved by OECD

Positive data of animal test cannot be denied by the negative data of skin sensitization in humans. On the other hand, ambiguous positive data on human skin sensitization shall be categorized by referring to clear negative data of animal tests. (The concordance between human data and animal test data are reported in, 1) Magnusson B et. al. 1969: J Investigative Dermatol. 52、 268-276、 2) Robinson MK et. al. 1990: Toxicology 61、 91-107、 3) Schneider K and Akkan Z、 2004: Reg. Toxicol. Pharmacol., etc.)

OECD test Guideline	Test guideline	Animal	Presence of Adjuvant
406	Guinea Pig Maximization Test (Magnusson and Kligman)	Guinea pig	Use
406	Buehler Test	Guinea pig	Non-use
429*	LLNA (Local Lymph Node Assay)	Mouse	Non-use

In above guinea pig tests, decision is performed based on subjective evaluation for erythema and edema, while in LLNA method, incorporation of 3H-methylthymidine is indexed by T-cell formation induced during induction phase of allergic reaction. In LLNA method, Stimulation Index(SI value) of 3 or more is positive.

The following skin sensitization test methods which are not approved in Japanese classification since they are not approved by OECD. The UN GHS third revised edition (which will come into force in July 2009) will provide sub-categories (1A, 1B) based on strength of sensitization, and the animal test methods used for their decision are above 3 test methods approved by OECD.

Test guideline	Animal	Presence of Adjuvant
Adjuvant and Patch Test	Guinea pig	Use
Draize Test	Guinea pig	Non-use
Freund’s Complete Adjuvant Test	Guinea pig	Use

Open Epicutaneous Test	Guinea pig	Non-use
Optimization Test	Guinea pig	Use
Split Adjuvant Test	Guinea pig	Use
Mouse Ear Swelling Test (MEST)	Mouse	Non-use

### 3-2-5 Germ Cell Mutagenicity

#### (1)Definitions

Definitions of Germ Cell Mutagenicity in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (3.5.1)**

3.5.1.1 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.

3.5.1.2 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.

3.5.1.3 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.

3.5.1.4 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.

Reference: Regarding a bacterial reverse mutation test (Ames test)

The Ames test is useful as a screening test for mutagens (especially, carcinogens), but its results alone cannot conclude "mutations in the germ cells of humans that can be transmitted to the progeny"- germ cell mutagenicity.

#### (2)Classification criteria

A) Classification criteria based on JIS Classification

**Table 3-7 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.

The classification is based on 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.

The classification is based on any of the following.

- a) Positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals; or
- b) Positive result(s) from *in vivo* somatic germ 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
- c) 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 human subjects.

Category 2 : Chemicals which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans.

The classification is based on any of the following.

- a) Somatic cell mutagenicity tests *in vivo*, in mammals; or
- b) 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.

#### B) Classification criteria in GHS (Reference information)

In classification criteria of JIS Classification and those of GHS, the same categories are adopted.

#### (3) Items on information sources and data

\*Regarding procedure of classification, refer to “3-1-1 Sources of information available for classification”

##### A) Data availability

- 1) In the UN GHS third revised edition, “mutagenicity tests” and “genotoxicity tests” have different meanings. The mutagenicity tests are tests indexed with gene mutation, structural and numerical abnormality of chromosome, and the genotoxicity tests are tests indexed with other elements, for example, DNA damage and DNA repairing. There exist extremely many kinds of mutagenicity tests and genotoxicity tests, and GHS shows examples of test

methods that provide criteria for classification as heritable mutagens (Note) in humans. In table 3-8, in addition to GHS examples, several test methods are included to provide data that serve as the basis for classification.

(Note) The purport of GHS Categories is to take account of heritable mutagenicity effects in humans. In this guidance, to facilitate understanding, the term “heritable mutagenicity” is used in addition to “germ cell mutagenicity.” The “germ cell mutagenicity” means effects to induce mutagenicity/genotoxicity in germ cells, and “heritable mutagenicity” means effects to induce gene mutation chromosomal abnormality in future generation of the mutagenicity recognized in germ cells. In the UN GHS third revised edition, the term “heritable mutagenicity” is not used, but the corresponding phrase “to induce heritable mutations in germ cells of humans” is used.

- 2) The UN GHS third revised edition 3.5.5.1 “Decision logic 3.5.1 for substances” starts with the question, “Does the substance have data on mutagenicity?”. The phrase “data on mutagenicity” basically means data obtained from *in vivo* mutagenicity/genotoxicity tests that are generally used and normally means a set of data including those obtained from *in vitro* tests. Expert's support is required for making a decision on mutagenicity based on multiple conflicting test results.
- 3) For many chemicals, results from many mutagenicity tests (or genotoxicity tests) are reported including *in vitro* tests, but results from *in vivo* tests using mammalian germ cells are rare. Expert's evaluation and decision are required for passing judgment on mutagenicity to human germ cells based on a large amount of *In vitro* and *in vivo* test reports.
- 4) Although human data are precious, usage of epidemiological data is extremely limited since, in many cases, data obtained from human monitoring exposed with some chemicals (for example, chromosome analysis on human peripheral lymphocytes) show unclear effects by the chemicals, and since the number of subjects is not sufficient to give a generalized conclusion. Epidemiological data may provide conflicting results, but they may be easily used when the validity of the finding (negative or positive) is recognized by assessment documents in List 1.
- 5) Chemicals having dataset from *in vivo* and *in vitro* tests are less in number than chemicals having *in vitro* test data only. In general, it is difficult to determine the existence of heritable mutagenicity based on results of *in vitro* tests only.

- 6) Results from rodent spermshape abnormality test shall not be used in this classification in principle since they may be affected by effects to other than genetic materials
- 7) Data from various kinds of tests using drosophila (sex-linked or recessive lethal test, wing spot test, etc.) are, generally, not used in this classification since biological dynamics and reproduction development process are not the same between insects and mammals. However when other suitable mammalian *in vivo* mutagenicity/genotoxicity test data are not available, and especially when positive results from drosophila sex-linked or recessive lethal test are available, judgement by experts in this fields shall be sought for using the data and GHS classification category.
- 8) There exist many kinds of *in vitro* genotoxicity tests (Comet test in mammalian culture cells, UDS test in mammalian culture cells, DNA (Rec-assay) in *Bacillus subtilis*, umu test in *Salmonella typhimurium*, SOS test in *Escherichia coli*, chromatid aberration with aneuploid test in yeast, etc.) and Host-mediated assay, but results of these tests are, in principle, not used in this classification.
- 9) In *in vivo* mutagenicity/genotoxicity tests, various administration routes are used. Although the common human exposure routes take precedence, test data with any administration route may be utilized unless the inappropriateness of the route is rationally explained.
- 10) Substances that have been concluded by epidemiological studies to induce heritable mutation in human population shall be classified in Category 1A. However, no such substance has been identified to date. Substances which have obtained positive results with many test methods such as *in vivo* mutagenicity tests using germ cells, and should be regarded as if they induce gene mutation or chromosomal abnormality to human germ cells shall be classified in Category 1B. Category 1B includes substances showing positive result(s) in *in vivo* heritable mutagenicity tests in mammalian germ cells (rodent dominant lethal mutation test, mouse heritable translocation assay, mouse specific locus test, etc.), positive result(s) in *in vivo* mutagenicity tests in mammalian somatic cells (mammalian bone marrow chromosome aberration test, mammalian erythrocyte micronucleus test, mouse spot test, etc.) coupled with some evidence that the substances have potential to induce mutation in germ cells (for example, positive results in such as mammalian spermatogonial chromosome aberration test, spermatid micronucleus assay, sister chromatid exchange analysis in spermatogonia, unscheduled DNA synthesis (UDS) test in

testicular cells, or evidence of exposure of germ cells to the active substances or its metabolite(s)), or positive results showing mutagenicity in human germ cells without evidence of transmission to progeny (for example, an increase in the frequency of aneuploidy in sperm cells of exposed human subjects).

11) Substances which have the potential to induce genetic mutations or chromosomal abnormality in human germ cells based on other information shall be classified in Category 2. Category 2 includes substances having positive evidence from *in vivo* somatic cell mutagenicity tests in mammals (mammalian bone marrow chromosomal abnormality test, mammalian erythrocyte micronucleus test, mouse spot test, etc.), or positive results in *in vivo* somatic cell genotoxicity tests (*in vivo* liver unscheduled DNA synthesis (UDS) test, mammalian bone marrow sister chromatid exchange (SCE) test, etc.) and positive results from *in vitro* mutagenicity tests (*in vitro* mammalian chromosomal abnormality test, *in vitro* mammalian cell genetic mutation test, bacterial reverse mutation test, etc.). Substances which have positive results from *in vitro* mammalian mutagenicity tests only but show (strong) structural similarity with known germ cell mutagens (Category 1) shall be classified in Category 2.

12) OECD test guidelines include the following test methods relating to mutagenicity/genotoxicity.

TG 471 Bacterial Reverse Mutation Test (Ames Test)

TG 473 In Vitro Mammalian Chromosome Aberration Test

TG 474 Mammalian Erythrocyte Micronucleus Test

TG 475 Mammalian Bone Marrow Chromosome Aberration Test

TG 476 In Vitro Mammalian Cell Gene Mutation Test

TG 477 Genetic Toxicology: Sex-linked Recessive Lethal Test in *Drosophila*  
*Melanogaster*

TG 478 Genetic Toxicology: Rodent Dominant Lethal Test

TG 479 Genetic Toxicology: In Vitro Sister Chromatid Exchange Assay in Mammalian  
Cells

TG 480 Genetic Toxicology: *Saccharomyces Cerevisiae* Gene Mutation Assay

TG 481 Genetic Toxicology: *Saccharomyces Cerevisiae* Mitotic Recombination Assay

TG 482 Genetic Toxicology: DNA Damage and Repair, Unscheduled DNA Synthesis in  
Mammalian Cells In Vitro

TG 483 Mammalian Spermatogonial Chromosome Aberration Test

TG 484 Genetic Toxicology: Mouse Spot Test

TG 485 Genetic Toxicology: Mouse Heritable Translocation Assay

TG 486 Unscheduled DNA Synthesis (UDS) Test with Mouse Liver Cells In Vitro  
(TG 487 In Vitro Mammalian Cell Micronucleus Test (MNvit), Draft)

Regarding the above mutagenicity tests, the following information source is helpful.

National Institute of Health Sciences, Division of Genetics and Mutagenesis

“5. Genotoxicity tests” in “Explanation of terms” (Japanese)

[http://dgm2alpha.nihs.go.jp/other%20files/genotoxicity%20\(09.1.4\).html](http://dgm2alpha.nihs.go.jp/other%20files/genotoxicity%20(09.1.4).html)

**Table 3-8 Test data as the basis of GHS classification(\* : added to the examples in the GHS)**

<p>(1) Examples of <i>in vivo</i> heritable germ cell mutagenicity tests in mammals</p> <ul style="list-style-type: none"><li>• Rodent dominant lethal test</li><li>• Mouse heritable translocation assay</li><li>• Mouse specific locus test</li></ul> <p>(2) Examples of <i>in vivo</i> mutagenicity tests in germ cell in mammals</p> <ul style="list-style-type: none"><li>• Mammalian spermatogonial chromosomal aberration test</li><li>• Spermatid micronucleus assay</li><li>• Gene mutation tests with transgenic animal models in germ cells*</li><li>• Analysis of aneuploidy in sperm cells of exposed people</li></ul> <p>(3) Examples of <i>in vivo</i> somatic cell mutagenicity tests in mammals</p> <ul style="list-style-type: none"><li>• Mammalian bone marrow chromosome aberration test</li><li>• Mouse spot test</li><li>• Mammalian erythrocyte micronucleus test</li><li>• Metaphase or micronucleus formation analysis of peripheral lymphocytes of exposed people (Human monitoring)*</li><li>• Mammalian peripheral lymphocytes chromosome aberration test*</li><li>• Gene mutation tests with transgenic animal models in somatic cells*</li></ul> <p>(4) Examples of <i>in vivo</i> genotoxicity tests in germ cell in mammals</p> <ul style="list-style-type: none"><li>• Sister chromatid exchange (SCE) analysis in spermatogonia</li><li>• Unscheduled DNA synthesis (UDS) test in testicular cells</li><li>• Assays of (covalent) binding or adduct formation to germ cell DNA*</li><li>• Assays of DNA damage in germ cells (comet assay, alkaline elution assay, etc.)*</li></ul> <p>(5) Examples of <i>in vivo</i> genotoxicity tests in somatic cells in mammals</p> <ul style="list-style-type: none"><li>• Liver UDS test</li><li>• Bone marrow or peripheral lymphocytes SCE analysis</li><li>• Assays of (covalent) binding or adduct formation to somatic cell DNA*</li><li>• Assays of DNA damage in somatic cells (comet assay, alkaline elution assay, etc.)*</li></ul> <p>(6) Examples of <i>in vitro</i> mutagenicity tests</p> <ul style="list-style-type: none"><li>• <i>In vitro</i> mammalian cell chromosome aberration test</li><li>• <i>In vitro</i> mammalian cell micronucleus test*</li><li>• <i>In vitro</i> mammalian cell gene mutation test</li></ul>
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Reference: In addition to the above test methods, there are other test methods as follows. In

principle, these test methods are not required to be used in classification. When using these test methods, it is preferable to seek for an expert's judgement.

- Sperm abnormality test using rodents (See A 6))
- Several drosophila tests sex-linked recessive lethal test, wing spot test, etc. (See A 7) )
- *In vitro* genotoxicity tests(See A 8))
  - comet assay,
  - UDS test using mammalian cultured cells
  - DNA repair test (Rec-assay) in bacteria
  - umu test or SOS test using bacteria
  - aneuploidy test using yeast,etc.
- host-mediated assay in bacterial gene mutation test(See A 8))

#### B) Order of Precedence when Conflicting Data Exist

By referring to “3-1-2 Order of precedence when Conflicting Data Exist”, basically the following data are adopted with precedence. All of appropriate data, however, should be utilized, and classification should be performed based on the overall weight of evidence.

- 1) Classification should be based on tests which were conducted appropriately and validated sufficiently. For example, tests conducted according to internationally recognized test methods such as OECD test guidelines and GLP satisfy this condition.
- 2) Data concerning mutagenicity tests are abundant, but such data are assigned greater evidential weight which shows more appropriately that the tested substances are regarded to induce heritable mutations in human germ cells (*in vivo* tests using germ cells rather than somatic cells, *in vivo* tests rather than *in vitro* tests, *in vitro* tests using human cells rather than mammalian cells).
- 3) As can be seen from the classification criteria described in the UN GHS third revised edition, generally, classification in Category 2 is not based only on positive results from *in vitro* mutagenicity tests. An attention needs to be paid also to results from *in vivo* mutagenicity tests in drosophila. Some test reports may contain multiple negative or positive results, and the classification based on a part of positive results alone is required to be verified of its validity.

#### C) Comparison with conventional classification systems

- The concept of GHS DSD classification for Germ Cell Mutagenicity is fundamentally in accord with that for Mutagen Categories 1, 2, and 3 in EU DSD classification.
- Mutagens classified as Category 1 (R46) in EU classification correspond to substances in Category 1A.(To date, no such substance has been identified.)
- Mutagens classified as Category 2 (R46) in EU DSD classification correspond to

substances in Category 1B.

- Mutagens classified as Category 3 (R68) in EU DSD classification correspond to substances in Category 2.
- EU CLP classification H340 accords with Category 1B, and H341 accords with Category 2.

#### D) Guidance concerning data

Classification should be performed based on data derived from appropriate information sources. (Germ cell) Mutagenicity classification established by EU and classification of German MAK Committee are helpful.

The mutagenicity in EU classification and the germ cell mutagenicity in GHS have the same objective and classification criteria. Accordingly, test methods which can be used in EU classification can also be used in GHS classification. Other test methods, if appropriate, can also be used.

#### (4) Guidance for classification and judgment

##### A) Background of this item and points to be noted

Regarding the background of this item, refer to Part 1, Introduction.

In classification, compare and examine all available data. It is preferable to seek for an expert's judgment about the evaluation of test results as needed. Substances having only *in vitro* mutagenicity data available shall, generally, be classified in "Classification not possible".

- \* Regarding germ cell mutagenicity, refer to the UN GHS third revised edition and this item, and classify substances according to the Workflow in Decision logic 3.5.1, the UN GHS third revised edition.
- \* The workflow for classification of Germ Cell Mutagenicity (Fig.3-2) in this guidance, which is based on the information in UN GHS third revised edition Fig 3-5-1, shows one of the classification procedures which take into account the weight of evidence. In the classification workflow, factors such as quality of the data are taken into account. Data related to human in the UN GHS third revised edition are included as "examples of *in vivo* mutagenicity tests in germ cell in mammals" which is shown in Table 3-8.

##### B) Classification Criteria

Shown below are examples of test results corresponding to each GHS Category and the classification workflow in Fig. 3-2 for helping classification. In the workflow, positive results fundamentally take precedence, but their appropriateness may be examined when needed. "Negative" results may be the result of using only one of many indexes (for example, using a part of strains in bacterial reverse mutation tests) or the result of tests conducted

inappropriately (for example, inappropriate sampling time in bone marrow micronucleus test), and examination of their validity should be performed when needed. On the whole, the validity of each set of data is considered, and the substance is determined based on the weight of evidence.

1) Category 1A : When evidence from epidemiological studies in human germ cells are available:

Substances whose human heritable mutagenicity was recognized by human epidemiological studies shall be classified in Category 1A. However, no such substance has been identified to date.

2) Category 1B : When *in vivo* mutagenicity test data and information suggesting germ cell mutagenicity are available:

Since positive results have been obtained with many test methods such as *in vivo* mutagenicity tests using germ cells, substances which should be regarded as if they induce heritable mutation in humans shall be classified in Category 1B. Specifically, the following cases are applicable :

a) Positive results from heritable mutagenicity tests in mammalian germ cells (rodent dominant lethal mutation test, mouse reciprocal translocation assay, mouse specific locus test, etc.).

b) Positive results from mutagenicity tests in mammalian germ cells (mammalian spermatogonial chromosomal abnormality test, mammalian spermatid micronucleus assay, germ cell gene mutation test using transgenic mouse/rat, etc.).

c) Positive results from mutagenicity tests in mammalian somatic cells (mammalian bone marrow chromosome aberration test, mammalian erythrocyte micronucleus test, mouse spot test, etc.) and some evidence that the substances have potential to induce mutation in germ cells: for example, positive results in *in vivo* genotoxicity tests in germ cells (sister chromosome exchange (SCE) analysis in mammalian spermatogonia, unscheduled DNA synthesis (UDS) test in mammalian testicular cells, etc.) and evidence of exposure of germ cells to the substances or their metabolite(s).

d) Positive results showing mutagenicity in human germ cells even if there is no evidence showing effects to next generation: for example, an increase in the frequency of aneuploidy in sperm cells of exposed human subjects.

3) Category 2 : When *in vivo* mutagenicity/genotoxicity test data are available, but when no direct information suggesting mutation of germ cells is available:

Substances suspected to cause heritable mutagenicity in humans shall be classified in Category 2. For example, the following cases meet this condition :

a) Positive results from mutagenicity tests in mammalian somatic cells (mammalian bone

marrow chromosome aberration test, mammalian erythrocyte micronucleus test, mouse spot test, etc.),

b) Positive results from genotoxicity tests in mammalian somatic cells (unscheduled DNA synthesis (UDS) test in mammalian liver, sister chromosome exchange (SCE) test analysis in mammalian bone marrow, etc.) and positive results from *in vitro* mutagenicity tests (chromosomal abnormality test in mammalian cultured cells, gene mutation test in mammalian cultured cells, bacterial reverse mutation test, etc.).

c) Exceptionally, strong positive results from *in vitro* mutagenicity tests with multiple indexes and (strong) structural similarity with known germ cell mutagens (Category 1, that is heritable mutagens) even in the absence of *in vivo* test data (See 5) 2) and seek for an expert's judgment.) .

4) Not classified : When data on *in vivo* mutagenicity tests are available and the result is negative:

Substances whose data required for classification are available (fundamentally *in vivo* and *in vitro* mutagenicity) and which are not classified in Category 1 or Category 2 shall be classified in "Not classified". For example, substances whose results of inheritable mutagenicity or *in vivo* mutagenicity tests (in somatic cells or germ cells) were negative fall under this category.

5) Classification not possible : When data required for classification are not available:

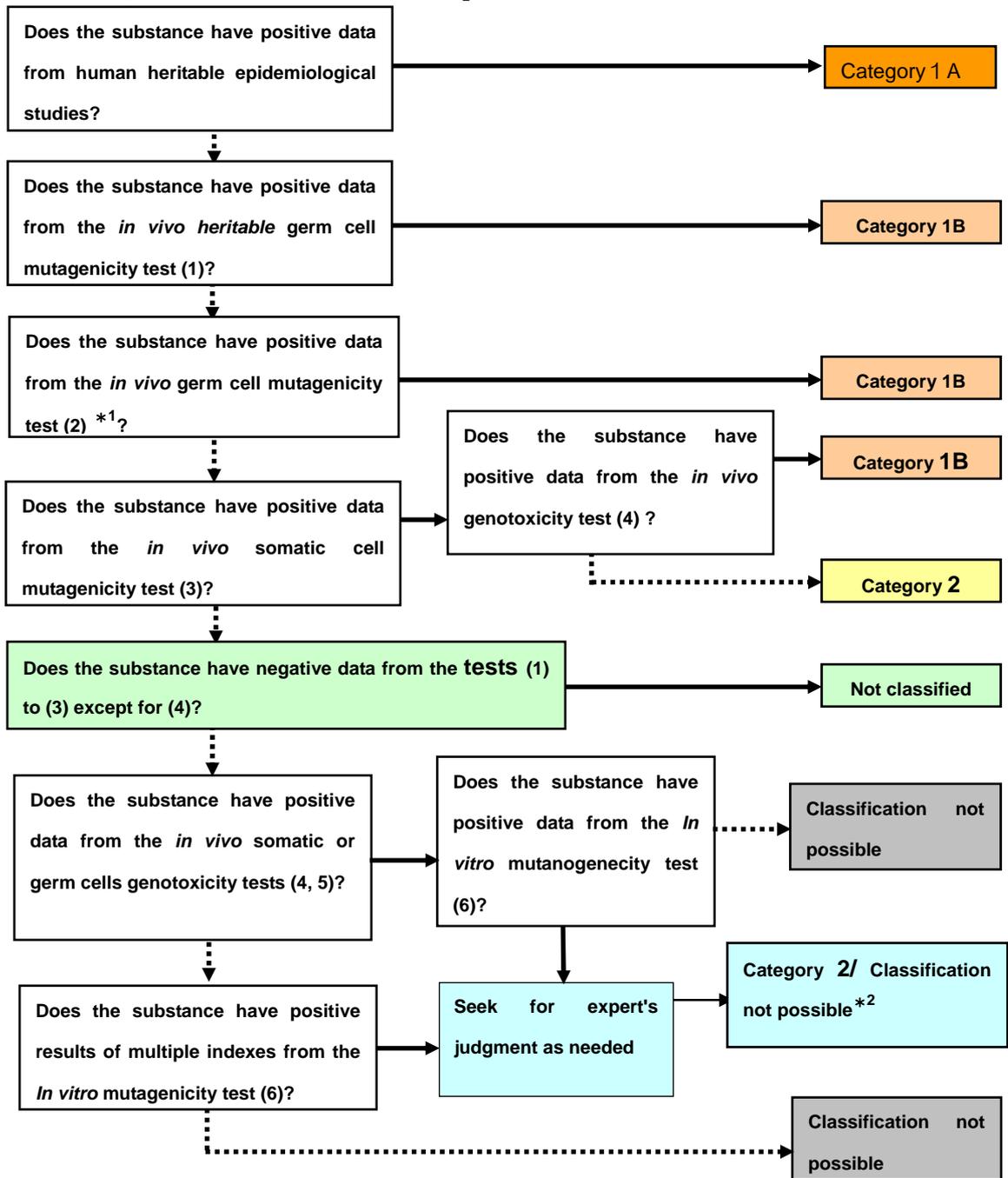
a) It is difficult to estimate human inheritable mutagenicity from results of *in vitro* mutagenicity tests only. Accordingly, in principle, substances whose available data are only from *in vitro* mutagenicity tests shall be classified in "Classification not possible", but an expert's judgment should be sought for as needed.

b) Exceptionally, some substances for which no *in vivo* test data are available but which show strong positive results from *in vitro* mutagenicity tests with multiple indexes (for example, chromosomal abnormality test in mammalian cultured cells and bacterial reverse mutation test) may be appropriately classified into Category 2. Hence, an expert's judgment should be sought for in this case.

c) When a substance has negative results from *in vivo* genotoxicity tests but no negative data from *in vivo* mutagenicity tests, the substance is not judged to have sufficient information for assessing *in vivo* (finally germ cells) mutagenicity even if there is a negative support for *in vitro* mutagenicity.

**Fig. 3-2 Workflow for classification of Germ Cell Mutagenicity in GHS**

(The number for each test corresponds to that of test in Table 3-8.)



→ : Yes      -.-> No

Continuous line boxes show mutagenicity tests and dotted line boxes show genotoxicity tests.

\*1 Even for tests other than those for humans, it is preferable that positive results in “(2) *in vivo* germ cell mutagenicity test” is supported by positive results in “(3) *in vivo* somatic cell mutagenicity test”.

\*2 The substance is determined as “Category 2” or “Classification not possible”

Overall, the validity of each set of data should be considered, and the substance is judged based on the weight of evidence.

### 3-2-6 Carcinogenicity

#### (1) Definitions

Definitions of Carcinogenicity in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (3.6.1)**

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.

#### (2) Classification criteria

##### A) Classification criteria based on JIS Classification

Hazard categories for carcinogens in JIS Classification are shown below.

**Table 3-9 Hazard categories for carcinogens**

Category 1: The placing of a known or presumed human carcinogen in Category 1 is done on the basis of epidemiological and/or animal data. An individual chemical may be further distinguished :

Category 1A: The placing of a chemical known to have carcinogenic potential for humans in Category 1A is largely based on human evidence.

Category 1B: The placing of a chemical presumed to have carcinogenic potential for humans in Category 1B 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 judgment 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

### B) Classification criteria in GHS (Reference information)

In classification criteria of JIS classification and that of GHS, the same categories are adopted.

### (3) Items on information sources and data

\* Classification procedure can be referred to "3-1-1 Sources of Information available for classification".

#### A) Data availability

- Many descriptions on carcinogenicity can be found in hazard-related reviews and databases. Useful rankings of carcinogenicity are reported by many organizations, which can be of reference in classification (WHO International Agency for Research on Cancer (IARC), Classification results of EU classification, the U.S. National Toxicology Program (NTP), carcinogens in "Recommendations for Acceptable Concentrations" by the Japan Society For Occupational Health, Carcinogenicity notes in "TLVs and BEIs" by ACGIH, Integrated Risk Information System (IRIS) by the U.S. EPA, Carcinogenicity notes in "List of MAK and BAT Values" by Germany DFG, etc. See [3-1]).
- OECD Test Guidelines include the following test methods relating to Carcinogenicity.
  - OECD TG 451 Carcinogenicity studies
  - OECD TG 453 Combined chronic toxicity / carcinogenicity studies

#### B) Order of Precedence when Conflicting Data Exist

By referring to "3-1-2 Order of Precedence when Conflicting Data Exist", the following points should be taken into consideration.

Information by IARC and EU represents conclusions by many experts, and takes precedence. Besides, information by the Japan Society For Occupational Health, US—EPA, US—NTP, ACGIH, and the Germany DFG, if any, can be of reference.

#### C) Comparison with conventional classification systems

- The principles of GHS classification for Carcinogenicity accords with those of the IARC Carcinogenicity group classification and the Carcinogenicity category classification of EU classification.
- The GHS classification categories are substantially the same as those in conventional classification systems. If a conventional classification system is to be used, it should correspond to GHS categories as follows.

**Table 3-10 Correspondence table between GHS classification and classifications by other organizations (Carcinogenicity)**

GHS	IARC	JSOH	ACGIH	EPA 1986	EPA 1996	EPA 2005	NTP	EU
1A	1	1	A1	A	K/L	CaH	K	1
1B	2A	2A	A2	B1, B2		L	R	2
2	2B	2B	A3	C		S		3
Classification not possible	3		A4	D	CBD	I		
Not classified	4		A5	E	NL	NL		

\* When Carcinogenicity classification is performed according to the above table, data need not to be input into other items such as toxicity information or epidemiological/ occupational exposure. When EU classification alone is available, however, toxicity information is needed. (Note 1) Since EU classification does not provide the basic hazard information for its classification decisions, review other information sources and confirm their validity. If EU classification alone is available, classify the substance as “Classification not possible”.

(Note 2) Note that the abbreviations of EPA classification change from year to year.

Abbreviations in the 1986 Guideline:

A: Human carcinogen

B1: Probably human carcinogen (Limited human evidence of carcinogenicity in human)

B2: Probably human carcinogen (sufficient animal evidence, but inadequate human evidence for carcinogenicity)

C: Possible human carcinogen (human data are inadequate and animal data demonstrate limited evidence of carcinogenicity)

D: Not classifiable as to human carcinogenicity

E: Evidence of Non-carcinogenicity for human

Abbreviations in the 1996 Guideline (tentative) are as follows:

K: Known human carcinogens

L: Likely to produce cancer in humans

CBD: Cannot be determined

NL: Not likely to be carcinogenic in humans

Abbreviations in the 2005 Guideline are as follows:

CaH: Carcinogenic to humans

L: Likely to be carcinogenic to humans

S: Suggestive evidence of carcinogenic potential

I: Inadequate information to assess carcinogenic potential

NL: Not likely to be carcinogenic to humans

Abbreviations in the Japan Society for Occupational Health classification are as follows:

Group 1: carcinogenic to humans

Group 2A: probably carcinogenic to humans

Group 2B: possibly carcinogenic to humans

Abbreviations in the ACGIH classification are as follows:

A1: Confirmed human carcinogen

A2: Suspected human carcinogen

A3: Confirmed animal carcinogen with unknown relevance to humans

A4: Not classifiable as a human carcinogen

A5: Not suspected as a human carcinogen

Abbreviations in the National Toxicology Program (NTP) classification are as follows:

K: Known

R: Reasonably suspected

#### D) Guidance concerning data

For classification based on carcinogenicity test data, substances known to be carcinogens for humans shall be classified in Category 1A. Substances presumed to be carcinogens for humans largely based on animal evidence shall be classified in Category 1B. Other substances suspected to be human carcinogens shall be classified in Category 2.

#### (4) Guidance for classification and judgment

##### A) Background of this item and points to be noted

As for background of this item, refer to Part 1, Introduction.

In classification, take the following points into account.

- \* Regarding all assessment documents in List 1, be sure to search a description relating to the substance.
- \* If required information for GHS classification of a given substance is not available, do not try to classify it in a Procrustean fashion but classify it in “Classification not possible”.
- \* Unless a description that definitely denies hazards or recognizes extremely low hazards

is available in List 1, the determination of “Not classified” should be performed carefully. If there is any question, a given substance should rather be classified in “Classification not possible” due to insufficient information for judgment.

**B) Substance for which GHS classification is possible without expert's judgment**

For substances classified in accordance with the following procedures, the GHS classification can be adopted without an expert's judgment.

1) Substances already evaluated by the following organizations are subject to GHS classification according to the correspondence table (Table 3-10 Correspondence table of GHS classification and classifications of other organizations (Carcinogenicity)). The evaluation results of IARC take precedence. If multiple assessment documents classified a substance in different categories, the substance is classified in accordance with the latest document in principle. If the latest documents (for example, EPA and NTP) classified the substance in different categories and if GHS classification is not possible, classification shall be properly carried out by referring to previous assessment documents (expert's judgement shall be sought for where necessary).

(Example) If a substance is classified in K/L by the EPA classification(1996), and in 2A by the IARC classification(1997), the substance shall be classified in Category 1B by GHS classification.

(Reference document : “Carcinogenicity assessment of chemical substances and their classification criteria (seventh edition)”, JETOC special document No.218(2007))

- International Agency for Research on Cancer : IARC
- Japan Society For Occupational Health
- American conference of Governmental Industrial Hygienists : ACGIH
- Environmental Protection Agency : EPA (The Guideline draft (1996) and the Guideline (2005) do not use numbers/letters in classification. Therefore, in this guidance, the following abbreviations are used for the sake of convenience.)
- the U.S. National Toxicology Program : NTP

2) When a substance is definitely determined to be classified in “Classification not possible” due to the absence of relevant information in “Table 3-10 Correspondence table of GHS classification and classifications of other organizations (Carcinogenicity)” and insufficiency of other hazard information, it should be classified as such.

3) Data are not available → “Classification not possible”, Positive data are not available (only negative data are available) for a substance → the substance shall be classified in “Not classified” based on an expert's judgment

4) If EU classification together with its evidence information is not available, the substance shall be classified in “Classification not possible”. If EU classification together with its

evidence information is not available but if the criteria for EU classification are different from those for GHS classification, EU classification may be utilized in GHS classification provided that the information on which the former is based is scientifically appropriate. If EU classification together with its evidence information is not available and the criteria for EU classification are the same as those for GHS classification, GHS classification may be performed according to EU classification.

C) Descriptions requiring an expert's judgment

B) As for substances whose classification it is difficult to or impossible to determine in accordance with B) 1) and B) 2) above and those for which human carcinogenicity is strongly presumed to be impossible due to species difference and other factors as the result of a proof or estimation of the mechanism of animal carcinogenicity, all the descriptions regarding carcinogenicity cited in the assessment documents shall be collected and an expert's judgment shall be sought for, as follows.

- 1) Descriptions relating to Carcinogenicity, or descriptions suggesting Carcinogenicity in List 1 (except for assessment documents shown in B) 1))
- 2) Descriptions shown below in List 2 and List 3. This prescription shall not prohibit persons responsible for classification from presenting the documents and descriptions which they judged to be considered in the template.
  - Descriptions given in a section clearly intended for “carcinogenicity”
  - Descriptions which confirmed the occurrence of tumor(s) after conducting histopathological inspection in a long-term administration test with animals (or descriptions clearly referring to the presence or absence of or suggestion of carcinogenicity or tumor)
  - Epidemiological studies in human groups

D) Substances especially requiring an expert's judgment

- 1) The following substances are generally classified as carcinogens and need careful examination. Since some substances induce cancer inherent to animals (with species difference) through the mechanism different from that of humans, such as the different metabolic system, a cautious investigation should be conducted for the judgment based on these categories.
  - a) Aromatic hydrocarbons
  - b) Aromatic amines
  - c) N—nitroso compounds
  - d) Quinoline-derivatives
  - e) Nitrosodifuran-derivatives

- f) Azo compounds
- g) Haloethers and other active halogenides
- h) Metals(arsenic, cadmium, chromium, nickel, etc.)

(Reference: "Toxicology", edited by the Japanese Society of Toxicology, Educational committee, p.143-156 Asakura Shoten (2004))

2) In extrapolation from animals to humans, it is known that the following instances of carcinogenicity may be denied as human carcinogenicity depending on the species difference described above. The denial of carcinogenicity below requires expert's decision.

- a) Kidney Carcinogenicity in rat induced by renal tubular over accumulation of  $\alpha_2$ u-globulin
- b) Rodent liver Carcinogenicity proved to be similar with the carcinogenic mechanism of phenobarbital
- c) Rat thyroid gland Carcinogenicity derived from metabolic stimulation activity of thyroid hormones in liver
- d) Rat testis Carcinogenicity through dopaminergic hypothalamic stimulation
- e) Bladder Carcinogenicity induced by physical stimulation to urinary bladder mucosa by urine metabolites

## 3-2-7 Reproductive Toxicity

### (1) Definitions

Definitions of Reproductive Toxicity in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (3.7.1)**

#### 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 as working definitions in IPCS/EHC Document N° 225 Principles for evaluation health risks to reproduction associated with exposure to chemicals. 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:

- (a) Adverse effects on sexual function and fertility;
- (b) Adverse effects on development of the offspring.

Some reproductive toxic effects cannot be clearly assigned to either impairment of sexual function and fertility or to developmental toxicity. Nonetheless, chemicals with these effects would be classified as reproductive toxicants with a general hazard statement.

#### 3.7.1.2 ***Adverse effects on sexual function and fertility***

Any effect of chemicals that would interfere with sexual function and fertility. 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, pregnancy outcomes, 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 death of the developing organism, structural abnormality, altered growth and functional deficiency.

(2) Classification criteria

A) Classification criteria based on JIS Classification

Hazard categories of Reproductive toxicants and effects on lactation in JIS Classification are presented below.

**Table 3-11 Hazard categories for Reproductive toxicants**

Category 1 : Known or presumed human reproductive toxicant

This category includes substances which are known to have produced an adverse effect on sexual function and fertility 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 human reproductive toxicant

The placing of the substance in this category is largely based on evidence from humans.

Category 1B : presumed human reproductive toxicant

The placing of the chemical substance in this category is largely based on evidence from experimental animals. Data from animal studies should provide clear evidence of an adverse effect on sexual function and fertility 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 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 toxicant

This category includes substances :

- a) for which there is some evidence from humans or experimental animals, positively supplemented with other information, of an adverse effect on sexual function and fertility, or on development, in

- the absence of other toxic effects, or
- b) 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.
- c) 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.

**Table 3-12 Hazard category for effects on or via lactation**

<p>Effects on or via lactation</p> <p>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:</p> <p>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</p> <p>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</p> <p>c) human evidence indicating a hazard to babies during the lactation period.</p>
--

B) Classification criteria in GHS(Reference information)

In classification criteria of JIS classification and that of GHS, the same categories are adopted.

(3)Items on information sources and data

\* Classification procedure can be referred to "3-1-1 Sources of Information available for classification".

A) Data availability

- Assessment concerning reproductive toxicity has been reported in SIDS, EHC, ECETOC, “Chemical Substances Hazard Data” by CERI, etc.
- A large amount of data are available from reports on reproductive toxicity, but experts must check their original literature to see if they meet the requisite criteria.
- OECD Test Guidelines include the following test methods relating to Reproductive Toxicity.

- OECD TG 414 Prenatal development toxicity study
- OECD TG 415 One-generation reproduction toxicity study
- OECD TG 416 Two-generation reproduction toxicity
- OECD TG 421 Reproduction / developmental toxicity screening test
- OECD TG 422 Combined repeated dose toxicity study with the reproduction /  
developmental toxicity screening test

#### B) Order of Precedence when Conflicting Data Exist

Refer to “3-1-2 Order of Precedence when Conflicting Data Exist”.

If appropriate information sources based on data cannot be obtained easily, try to obtain the original EU assessment documents from the EU DSD classification (R60, R61, R62, R63, and R64) corresponding to reproductive toxicity. If the assessment documents are available, classify substances based on them.

#### C) Comparison with conventional classification systems

- The concept of the EU category classification on reproductive toxicity is in accord with that of the GHS category classification.
- Substances classified as Category 1 in EU DSD classification with R60, R61 fall under GHS classification Category 1A.
- Substances classified as Category 2 in EU DSD classification with R60, R61 fall under GHS classification Category 1B.
- Substances classified as Category 3 in EU DSD classification with R62, R63 fall under GHS classification Category 2.
- Since substances in EU classification R64 (May be hazardous for breastfed children) fall under “the additional category for effects on or via lactation”, The hazard statement “May cause harm to breast-fed children.” Is applied to them.
- EU CLP classification H360D and H360F accord with Category 1A or Category 1B, and H361d and H361f accord with Category 2. H360FD, H360Fd and H36Df accord with Category 1A or 1B, and H361fd accords with Category 2.

#### D) Guidance concerning data

When classification is performed based on reproductive toxicity test data, substances known to have reproductive toxicity to humans are classified in Category 1A. Substances presumed to have reproductive toxicity to humans largely based on evidence from experimental animals are classified in Category 1B. Other substances suspected of reproductive toxicity to humans are classified in Category 2.

#### (4) Guidance for classification and judgment

##### A) Background of this item and points to be noted

As for background of this item, refer to Part 1, Introduction.

In classification, take the following points into account.

- \* Regarding all assessment documents in List 1, be sure to search a description relating to the substance.
- \* Unless a description that definitely denies hazards or recognizes extremely low hazards is available in List 1, the determination of “Not classified” should be performed carefully. If there is any question, a given substance should rather be classified in “Classification not possible” due to insufficient information for judgment.

##### B) Key points for classification

- Taking into account that when there is any difference between tested animal and humans regarding administration methods or action mechanisms, the results of the animal tests lose their weight as evidence. For example, if the action mechanism of a substance is different in humans and tested animals and if it is clearly proved that the hazard caused by the substance is not manifested in humans, then the substance should not be classified in this category, even if reproductive toxicities are manifested in the tested animals.
- When a test material indicates toxicity in the bodies of mothers among the tested animal, the test material can sometimes be observed as if it indicated reproductive toxicity. Accordingly, when evidence of reproductive toxicity is secondary non-specific effects caused by other toxic actions, the evidence should not be used for classification. The same shall apply for embryos and fetuses.

##### C) General considerations

###### 1) Reproductive Toxicity

GHS defines reproductive toxicity as toxic effects on sexual function and fertility in adult males and females, as well as on development of offspring.

###### 2) Adverse effects on sexual function and fertility

Any effect by chemicals that could interfere with sexual function and fertility. This includes alterations to the female and male reproductive organs, adverse effects on onset of puberty, gamete reproduction and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, or pregnancy outcomes, premature reproductive senescence, or modifications in other normal reproductive functions.

###### 3) Adverse effects on development of the offspring

In its widest sense, developmental toxicity includes any effects which interferes with normal development of the conceptus, fetus, and born children. However, for the purpose

of classification, the developmental toxicity is limited to adverse effects essentially induced during pregnancy or as a result of parental exposure.

#### D) Decision logic and classification of substances

##### 1) Decision logic for substances

Decision is performed according to the UN GHS third revised edition 3.7.5.1 Decision logic for reproductive toxicity. The possibility that the toxicity for dam animals may be secondary result should be examined sufficiently. (For example, see the UN GHS third revised edition 3.7.2.4)

##### 2) Classification

In principle, information shall be collected according to this guidance, and substances shall be classified in accordance with the collected data.

[Substance to be determined as “Classification not possible”]

A substance is determined to be placed in “Classification not possible” when no data on reproductive toxicity of the substance is available.

[Substance to be classified as]:

Category 1A : Substance known to have adverse effect on human sexual functions, fertility, or development of offspring

(Decision criteria)

A substance which is clearly described as recognized to have reproductive toxicity in humans in information of list 1.

\* When other substances are considered to fall under Category 1A, an expert's decision shall be sought for.

\* When a substance falls under “③ 4) Substance requiring caution on classification” given below and when information sufficiently proving that the substance falls under Category 1A is not obtained as a result of literature survey based on this classification guidance, an expert's decision shall be sought for.

Category 1B : Substance presumed to have adverse effect on human sexual functions, fertility, or development of offspring

(Decision criteria)

Substances which meet the following conditions. Substances corresponding to “Not classified” are excluded, however.

Substances for which it is described in the materials in List 1 that clear reproductive toxicity\* (except for small changes in sperm measurement items, incidence of spontaneous defects in fetus, variant/ossoification retardation, fetal/pup body weight,

and postnatal development indexes) is manifested in animal experiments at a dose at which general toxicity (which is not limited to maternal toxicity but defined as effects other than reproductive toxicity to female and male parental animals; the same shall apply hereinafter) is not manifested in parental animals.

\* The reproductive toxicity here means reproductive toxicity defined in c), that is, effects on parental sexual function, fertility, and development. The same shall apply throughout this guidance.

Category 2 : Substance suspected to have toxicity for human reproduction/development  
(Decision criteria)

Substances which meet any of the following conditions with information in List 1 or List 2. Substances corresponding to “Category 1” and “Not classified” are excluded, however.

a) Substances for which it is described that clear reproductive toxicity (except for small changes in sperm measurement items, incidence of spontaneous defects in fetus, variant/ossoification retardation, fetal/pup body weight, and postnatal development indexes) is manifested in animal tests at a dose at which general toxicity in parental animals is manifested.

It is to be noted, however, that cases are reported that indicate a relationship between serious effects on parental animals (death, significant inhibition of body weight increase, etc.) and effects on fetus (Khera KS 1984: Teratology 29, 411-416, Carny EW et. al. 2004: Toxicol. Sci. 82, 234-249, Fleeman TL et. al. 2005: Birth Defects Research (Part B) 74, 442-449). When there is a definite relationship between them, the substances are not assumed to be classified as Category 2.

b) Substances for which no description on general toxicity for parental animals in animal tests is available but which is described to result in clear manifestation of reproductive toxicity (except for small changes in sperm measurement items, incidence of spontaneous defects in fetus, variant/ossoification retardation, fetal/pup body weight, and postnatal development indexes).

(In general, the dose at which general toxicity is manifested may not be clear in review documents. In such cases, it is preferable to review the original literature and to confirm the dosage.)

(Special case)

A substance for which it is described in the materials in List 2 that clear reproductive toxicity (except for small changes in sperm measurement items, incidence of spontaneous defects in fetus, variant/ossoification retardation, fetal/pup body weight, and postnatal development indexes) is manifested at a dosage at which

general toxicity is not manifested is to be placed in Category 2 in this guidance since there is no sufficient proof (evidence) to classify it in Category 1B.

c) Substance of which reports on human reproductive toxicity are available that can not be considered to be sufficient. (Substance not classified in Category 1A) \*

\* This includes a case where it is described in the materials in List 2 that reproductive toxicity is recognized with humans.

Not classified : Substances which are considered to have no reproductive/developmental toxicity to humans.

(Decision criteria)

If appropriate tests both for reproductive and developmental effects have been conducted and no apparent adverse effect has been detected, then it is reasonable to consider that the tested substance has no reproductive/developmental toxicity and should be determined as 'Not classified'. In addition, when any of the following conditions is applicable, it is not appropriate to apply Category 1 or Category 2 to the tested substance. In the following cases, refer to section 2) in the [3“Points to be noted in classification”] and classification shall be performed accordingly.

- a) In the case when the substance is reported to have adverse effects on reproductive function, fertility, or development, but these effects are induced as non-specific and secondary effects of other toxicity.
- b) In the case when the reproductive toxicity of the substance has been proven to occur through specific mechanisms of action to the animal species tested, or when the reproductive toxicity in animals has been shown not to occur in humans because of the significant toxicokinetic difference.
- c) In the case when the substance induces only non-significant or minimal effects (small changes in sperm parameters or in the incidence of spontaneous defects in the fetus, small changes in the proportion of common fetal variants/retarded ossification, or slight changes in the fetus/pup body weights or in postnatal development measures)..

### 3) Points to be noted in classification

- a) When exposure of reproductive organs to test material is at a unrealistically high level in a test using administration routes such as intravenous injection or intra-abdominal injection, or when local damage is caused to reproductive organs by irritation or other factors, the result of such a test is not used as the basis of classification. Adverse effects on reproduction recognized only at an extremely high dose (for example, a dose that induces prostration, severe inappetence, and high mortality) in an animal test are not

used as the basis of classification, unless information is available of, for example, toxicokinetics indicating that humans are more susceptible than animals, supporting the appropriateness of the classification.

b) A substance for which available information regarding reproductive toxicity is determined as insufficient to make a final decision is to be placed in “Classification not possible” because sufficient information is not available for GHS classification. An expert's judgment shall be sought for when necessary.

c) Effects on or via lactation

When a description regarding effects on or via lactation is found, an expert's judgment shall be sought for. The expert judges whether the substance has "effects on or via lactation" from his/her expertise based on GHS.

d) Substances requiring cautions in classification

Reference 1 cited at the end of this item lists the following substances as human teratogens. Since substances subsumed under these can be classified in “Category 1A”, information about them should be collected with special care in accordance with this guidance.

(Schardein, 2000, Table 1-18)

- Alcohol
- Anticancer agents (Aminopterin, Busulfan, Chlorambucil, Methotrexate, Cytarabine, Cyclophosphamide, Mechlorethamine)
- Androgenic hormones
- Antithyroid drugs, Aminoglycoside antibiotics
- Coumarine anticoagulants
- Diethylstilbestrol
- Methyl mercury
- PCBs
- Thalidomide
- Anticonvulsants (Hydantoin, Primidone, Carbamazepine, Diones, Valproic acid)
- Penicillamine
- Lithium
- Cocaine
- Retinoic acids
- ACE inhibitors
- Toluene, Tetracyclines

Item 1 also contains the list of substances considered to cause male-mediated developmental toxicity (Schardein, 2000, Table 1-9) and the list of example substances having toxicity to development by California Proposition 65 (Schardein, 2000, Table

1-16). The substances shown there should be examined with special care in accordance with this guidance, and information sufficient for decision should be collected.

e) Limit dose

In the UN GHS third revised edition 3.7.2.5.9, it is described that 1000 mg/kg can be adopted as a limit dose. When a dose is more than 1000 mg/kg, do not apply the limit dose mechanically, but judgment by expert's regarding the adoption of the limit dose shall be sought for. OECD test guidelines defining a limit dose and the limit dose defined therein are shown below.

No.	Test guideline	Limit dose
414	Prenatal Development Toxicity Study	1000 mg/kg body weight / day
415	One-Generation Reproduction Toxicity Study	1000 mg/kg body weight
416	Two-Generation Reproduction Toxicity Study	1000 mg/kg body weight / day

Reference1. Schardein JL, Chemically Induced Birth Defects-3<sup>rd</sup> edition, Marcel Dekker, New York, 2000

Reference2. Shepard TH, Lemire RJ, Catalog of Teratogenic Agents, 11th edition, Johns Hopkins Univ Press, Baltimore, 2004

## 3-2-8 Specific Target Organ Toxicity-Single Exposure

### (1) Definitions

Definitions of Specific Target Organ Toxicity-Single Exposure in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (3.8.1)**

3.8.1.1 The purpose of this chapter is to provide a means of classifying substances and mixtures that produce specific, non lethal target organ toxicity arising from a single exposure. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed and not specifically addressed in chapters 3.1 to 3.7 and 3.10 are included (see also para. 3.8.1.6).

3.8.1.2 Classification identifies the substance or mixture as being a specific target organ 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 or mixture 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 recognized that human data will be the primary source of evidence for this hazard class.

3.8.1.4 A assessment should take into consideration not only significant changes in a single organ or biological system but also generalized changes of a less severe nature involving several organs.

3.8.1.5 Specific target organ 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 toxicity following a repeated exposure is classified in the GHS as described in *Specific target organ toxicity – Repeated exposure* (Chapter 3.9) and is therefore excluded from the present chapter. Other specific toxic effects, listed below are assessed separately in the GHS and consequently are not included here:

- (a) acute toxicity (Chapter 3.1);
- (b) skin corrosion/irritation (Chapter 3.2);
- (c) serious eye damage/eye irritation (Chapter 3.3);

- (b) respiratory or skin sensitization (Chapter 3.4);
- (e) germ cell mutagenicity (Chapter 3.5);
- (f) carcinogenicity (Chapter 3.6);
- (g) reproductive toxicity (Chapter 3.7); and
- (h) aspiration toxicity (Chapter 3.10).

3.8.1.7 The classification criteria in this chapter are organized as criteria for substances Categories 1 and 2 (see 3.8.2.1), criteria for substances Category 3 (see 3.8.2.2) and criteria for mixtures (see 3.8.3). See also Figure 3.8.1.

## (2) Classification criteria

### A) Classification criteria based on JIS Classification

Table 3-13 Hazard categories for Specific Target Organ 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 :

- a) reliable and good quality evidence from human cases or epidemiological studies; or
- b) 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 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 in order to help in classification (see Table 3.14). In exceptional cases, human evidence can also be used to place a substance in Category 2.

Category 3 : Transient target organ effects

There are target organ effects for which a substance/mixture may not meet the criteria to be classified in Categories 1 or 2 indicated above. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alternation of structure or function. This category only includes narcotic effects and respiratory tract irritation. Substances/mixtures may be classified

specifically for these effects as discussed in H.4 (Note: classification criteria of mixtures).

For these categories 1 through 3, 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 toxicant. Attempts should be made to determine the primary target organ, organ/system of toxicity, and classify for that purpose, e.g. hepatotoxicants, 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.

**Table 3-14: Guidance value ranges for single-dose exposures**

		Guidance value ranges for:		
Route of exposure	Units	Category 1	Category 2	Category 3
Oral (rat)	mg/kg body weight	$C \leq 300$	$300 < C \leq 2000$	Guidance values do not apply
Dermal (rat or rabbit)	mg/kg body weight	$C \leq 1000$	$1000 < C \leq 2000$	
Inhalation (rat) gas	ppmV/4h	$C \leq 2500$	$2500 < C \leq 20000^*$	
Inhalation (rat) vapour	mg/L/4h	$C \leq 10$	$10 < C \leq 20$	
Inhalation (rat) dust/mist/fume	mg/L/4h	$C \leq 1.0$	$1.0 < C \leq 5.0$	

\*It should be noted that this range was modified to  $2500 < C \leq 20000$  at the 15<sup>th</sup> session of the UN GHS Sub-Committee (ST/SG/AC.10/C.4/30 25 July 2008), and revised to “ $2500 < C \leq 20000$ ” in the UN GHS third revised edition.

#### B) Classification criteria in GHS (Reference information)

The same categories are adopted for classification criteria in JIS Classification and GHS. Their guidance value ranges are also the same. For detailed descriptions, refer to the UN GHS third revised edition 3.8.2 about categories, and the UN GHS third revised edition Table 3.8.1 about guidance values.

The GHS criteria for specific target organ toxicity (single exposure) Category 3 “respiratory tract irritation” are as follows.

##### 【GHS 3<sup>rd</sup> revised edition】 (3.8.2.2.1)

The criteria for respiratory tract irritation as Category 3 are:

- (a) Respiratory irritant effects (characterized by localized redness, edema, pruritis and/or pain) that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included. It is recognized that this evaluation is based primarily on human data;

- (b) Subjective human observations could be supported by objective measurements of clear respiratory tract irritation (RTI ) (e.g. electrophysiological responses, biomarkers of inflammation in nasal or bronchoalveolar lavage fluids;
- (c) The symptoms observed in humans should also be typical of those that would be produced in the exposed population rather than being an isolated idiosyncratic reaction or response triggered only in individuals with hypersensitive airways. Ambiguous reports simply of “irritation” should be excluded as this term is commonly used to describe a wide range of sensations including those such as smell, unpleasant taste, a tickling sensation, and dryness, which are outside the scope of this classification endpoint;
- (d) There are currently no validated animal tests that deal specifically with RTI, however, useful information may be obtained from the single and repeated inhalation toxicity tests. For example, animal studies may provide useful information in terms of clinical signs of toxicity (dyspnoea, rhinitis etc) and histopathology (e.g. hyperemia, edema, minimal inflammation, thickened mucous layer) which are reversible and may be reflective of the characteristic clinical symptoms described above. Such animal studies can be used as part of weight of evidence evaluation;
- (e) This special classification would occur only when more severe organ effects including in the respiratory system are not observed.

The GHS criteria for specific target organ toxicity (single exposure) Category 3 “narcotic effects” are as follows.

**【GHS 3<sup>rd</sup> revised edition】 (3.8.2.2.2)**

The criteria for narcotic effects as Category 3 are:

- (a) Central nervous system depression including narcotic effects in humans such as drowsiness, narcosis, reduced alertness, loss of reflexes, lack of coordination, and vertigo are included. These effects can also be manifested as severe headache or nausea, and can lead to reduced judgment, dizziness, irritability, fatigue, impaired memory function, deficits in perception and coordination, reaction time, or sleepiness;
- (b) Narcotic effects observed in animal studies may include lethargy, lack of coordination righting reflex, narcosis, and ataxia. If these effects are not transient in nature, then they should be considered for classification as Category 1 or 2.

(3) Items on information sources and data

\* Classification procedure can be referred to "3-1-1 Sources of Information available for classification".

A) Data availability

- Sufficient information for classification cannot be obtained from simple descriptions in existing MSDSs. A literature search should be carried out for reliable reviews and primary information relevant to toxic actions.
- Substances with R-Phrases<sup>13</sup>(R39, R68, R37, and R67) in EU DSD classification are feared to possess specific target organ toxicity (single exposure).
- T<sup>+</sup>, R39 and T, R39 correspond to Category 1. R68 corresponds to Category 2. R37 and R67 correspond to Single Exposure Category 3 respiratory tract irritation and narcotic effects, respectively.

#### B) Order of Precedence when Conflicting Data Exist

- 1) Data from evaluation by reliable organizations (for example, data obtained from reference documents shown in List 1).
- 2) If appropriate sources of information based on data cannot be obtained easily, try to obtain the original EU assessment documents for the EU classification (R39, R68, and R67) corresponding to Specific Target Organ Toxicity-Single Exposure. When the assessment documents are obtained, classify on the basis of the documents.
- 3) Report data which can be considered to be reliable (Measurements are according to GLP, or data which are the basis of judgment are clearly shown and evaluated, etc.).
- 4) Data collected from other sources of information (for example, data from references shown in List 2 or 3)

#### C) Comparison with conventional classification systems

Systems in accord with GHS include R-Phrases<sup>14</sup> (R39, R68, R37, and R67) in EU DSD classification.

EU CLP classification H370 accords with Category 1, H371 accords with Category 2, and H335 or H336 accord with Category 3.

#### D) Guidance concerning data

- If information on specific, non lethal, target organ toxicity arising from a single exposure are available, experts should judge whether the toxicity has significant health effects in humans or not.
- The exposure route by which the classified substance has produced damage should be specified.
- Examples are provided below of toxic effects in humans or experimental animals that must be taken into consideration in classification of specific target organ toxicity.

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<sup>13</sup>For R-Phrase, see Appendix.

<sup>14</sup>For R-Phrase, see Appendix.

**【GHS 3<sup>rd</sup> revised edition】 (3.8.2.1.7.3)**

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:

- (a) Morbidity resulting from single exposure;
- (b) Significant functional changes, more than transient in nature, in the respiratory system, central or peripheral nervous systems, other organs or other organ systems, including signs of central nervous system depression and effects on special senses (e.g. sight, hearing and sense of smell);
- (c) Any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters;
- (d) Significant organ damage that may be noted at necropsy and/or subsequently seen or confirmed at microscopic examination;
- (e) Multifocal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;
- (f) Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction;
- (g) Evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

- Hazards listed below are treated separately in the UN GHS third revised edition and hence are not included in specific target organ toxicity.
  - Acute Toxicity (3-2-1)
  - Skin Corrosion/Irritation (3-2-2)
  - Serious Eye Damage/Eye Irritation (3-2-3)
  - Respiratory or Skin Sensitization (3-2-4)
  - Germ Cell Mutagenicity (3-2-5)
  - Carcinogenicity (3-2-6)
  - Reproductive Toxicity (3-2-7)
  - Aspiration Hazard (3-2-10)

(4)Guidance for classification and judgment

A) Background of this item and points to be noted

As for background of this item, refer to Part 1, Introduction.

In classification, take the following points into account.

- \* Unless a description that definitely denies hazards or recognizes extremely low hazards is available in List 1, the determination of “Not classified” should be performed carefully. If there is any question, a given substance should rather be classified in “Classification not possible” due to insufficient information for judgment.
- \* When an affected organ can be identified, indicate the applicable category along with the affected organ in parentheses for “GHS classification.” When such an organ cannot be identified, put “systemic toxicity” in parentheses. (Example entry : Category 1 (liver, kidney, blood), or Category 1 (systemic toxicity))
- \* In a case where a substance can be classified in Category 1 (respiratory organs) or Category 2 (respiratory organs), it shall not be classified in Category 3 (respiratory tract irritation).
- \* In a case where a substance can be classified in Category 1 (central nervous system) or Category 2 (central nervous system), it can be classified in Category 3 (narcotic).
- \* When the same substance is classified into different categories depending on affected organs, indicate the category for each of the affected organs. (Example entry : Category 1 (liver, kidney), Category 2 (blood), Category 3 (respiratory tract irritation))
- \* As for substances of which data are available only for a mixture (provided mixed or diluted with solvents without toxicity), their GHS classification as chemical substances are performed by estimating from concentrations appropriately, and the estimation processes are to be described as a ground for classification.

B) Regarding classification procedure

- 1) Substances meeting [Decision criteria 1a] or [Decision criteria 1b] below are placed in Category 1.

[Decision criteria 1a]: Substances for which evidence of inducing toxic effects in humans are available in List 1.

(Notes)

- a) Effects on organs that are obviously known to be secondary effects shall be excluded from description. Judgement by experts shall be sought for where necessary about whether the effects are secondary or not. When such a judgment is difficult, all organs affected shall be cited.
- b) Effects on respiratory system by site of contact are included here, and are placed in Category 1 (pneumoconiosis, etc.). However, such effects by site of contact other than respiratory tract, for example, irritation/inflammation reaction in digestive system in a

case of oral administration of a corrosive/irritant, are considered to be subsumed under other toxicity items such as skin corrosion, and are not classified in specific target organ toxicity.

- c) When only minimal symptoms (slight fever, languor, etc.) are reported, the substance is placed in “Not classified”.
- d) All organs described as affected in List 1 shall be indicated. However, when organs listed in multiple assessment documents based on the same type of tests are not the same, indicate the commonly listed organs. When a toxic symptom alone is described and the affected organ cannot be identified, put “systemic toxicity” instead. When the target organ is identified, fundamentally, a description of toxic symptom is not required.
- e) When the affected organ can be identified, indicate the applicable category along with the affected organ in parentheses in “GHS classification”. When the affected organ cannot be identified, put “systemic toxicity” in parentheses.

[Decision criteria 1b]: Animal tests meeting all of conditions below

- a) Any animal species is applicable.
- b) Exposure amount is identified and toxic symptom is induced within the guidance value range of Category 1
- c) The test is described in List 1 or an OECD TG test in List 2, is according to GLP, and has received some degree of approval (by multiple reviewers)

(Notes)

- a) As for toxic effects, read the UN GHS third revised edition and the following documents carefully.
- b) Effects on organs that are obviously known to be secondary effects shall be excluded from description. Judgement by experts shall be sought for where necessary as to whether the effects are secondary or not.
- c) Effects on respiratory system by site of contact are included here and are placed in Category 1 (pneumoconiosis, etc.). However, such effects by site of contact other than respiratory tract, for example, irritation/inflammation reaction in digestive system in a case of oral administration of a corrosive/irritant, are considered to be subsumed under other toxicity items such as skin corrosion and are not classified in specific target organ toxicity.
- d) When only minimal symptoms (slight fever, etc.) are reported, the substance is placed in “Not classified”.
- e) All organs described as affected in List 1 shall be indicated. However, when organs listed in multiple assessment documents based on the same type of tests are not the

same, indicate the commonly listed organs. When a toxic symptom alone is described and the affected organ cannot be identified, put “systemic toxicity” instead. When the target organ is identified, fundamentally, a description of toxic symptom is not required.

- f) As for conversion of exposure amount, “(3) Items on information sources and data” and “(4) Guidance for classification and judgment” of 3-2-1 Acute Toxicity in this guideline shall be used (except for the criteria for dealing with animal species difference).
- g) When the affected organ can be identified, indicate the applicable category along with the affected organ in parentheses in “GHS classification”. When the affected organ cannot be identified, put “systemic toxicity” in parentheses.

2) Substances meeting [Decision criteria 2a] or [Decision criteria 2b] below are placed in Category 2.

[Decision criteria 2a]: Substances for which evidence of inducing toxic effects in humans are available in List 2.

(Notes)

According to 1) [Decision criteria 1a](Notes)a) through e)

[Decision criteria 2b]: Animal tests meeting all of conditions below

- a) Any animal species is applicable
- b) Exposure amount is identified and toxic symptom is induced within the guidance value range of Category 2. (When multiple documents are available, judgment shall be based on one with the smallest exposure amount.)
- c) The test is described in List 1 or List 2

(Exception)

When a test for any animal species in which the exposure amount is identified and is within the guidance value range of Category 1, but when the test is described in List 2 alone and does not meet the condition of [Decision criteria 1b] c) (does not meet the condition that is according to GLP and has received some degree of approval (by multiple reviewers)), substances with such test results are exceptionally classified in Category 2. Indicate as follows as special remarks, “This substance can be placed in Category 1 judging from the guidance value, but its data in List 2 alone are available, and its test does not meet the [Decision criteria 1b] c). Consequently, the substance is classified in Category 2 in accordance with the guidance.”

(Notes)

According to 1) [Decision criteria 1b](Notes)a) through b)

3) Substances applicable to [Decision criteria 3] below shall be placed in Category 3.

[Decision criteria 3]: Human evidence or animal test that meets all conditions below

- a) When toxicity meeting criteria of respiratory tract irritation or classification criteria of narcotocsis is recognized for only a short period after exposure.
- b) The effect is reversible.
- c) The human evidence or animal test is listed in List 1 or List 2.

(Notes)

- a) Category 3 (transient target organ effects) is defined as “effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function”. Presently in GHS, classification criteria for Category 3 are shown regarding respiratory tract irritation and narcotic effects. When descriptions suggesting narcotic effects based on inhibition of nerve system function and action are found in the original literatures, the substance in question is to be classified in Category 3. If there is any reversible effect other than these effects, such effect shall be indicated in the special remarks in the present classification work but shall not be the basis of classification.
- b) As for respiratory tract irritation, when a more serious organ effect, including one on respiratory system, is observed, the substance is classified in Category 1 or Category 2. As for narcotic effects, only if the effect is not essentially transient, the substance producing the effect is classified as Category 1 or Category 2.
- c) When a substance is either a respiratory tract irritant or a narcotic, indicate it clearly. (Example entry : Category 3 (respiratory tract irritation))

C) On treatment of vapour inhalation guidance value in classification of specific target organ toxicity (single exposure)

As for the classification of specific target organ toxicity (single exposure), “guidance values” for categorization based on animal data are shown in the p.170 Table 3-14 (UN GHS third revised edition Table 3.8.1). All of them are indicated in the unit of mg/L for vapour inhalation. However, there are no notes regarding vapour inhalation like those for acute toxicity in Table 3.1.1. Therefore, regarding specific target organ toxicity (single exposure), the toxicity manifestation concentration in mg/l at vapour inhalation should be examined and evaluated by comparing it with the value shown in the Table 3.8.1. If the original data is given in ppmV, the data should be converted into mg/L and compared.

If the concentration is exceeding saturated vapour pressure, the value is treated as that of mist (or dust) by referring to the case of acute toxicity.

### 3-2-9 Specific Target Organ Toxicity-Repeated Exposure

#### (1) Definitions

Definitions of Specific Target Organ Toxicity-Repeated Exposure in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (3.9.1)**

- 3.9.1.1 The purpose of this document is to provide a means of classifying substances that produce specific target organ 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 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 recognized that human data will be the primary source of evidence for this hazard class.
- 3.9.1.4 A assessment should take into consideration not only significant changes in a single organ or biological system but also generalized changes of a less severe nature involving several organs.
- 3.9.1.5 Specific target organ 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 toxicity – Single exposure* (Chapter 3.8) and are therefore excluded from the present chapter. Other specific toxic effects, such as acute /toxicity, serious eye damage/eye irritation, skin corrosion/irritation, respiratory or skin sensitization, carcinogenicity, germ cell mutagenicity, reproductive toxicity and aspiration toxicity are assessed separately in the GHS and consequently are not included here.

(2)Classification criteria

A) Classification criteria based on JIS Classification

**Table 3-15: Hazard categories for specific target organ toxicity following 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 :

- a) reliable and good quality evidence from human cases or epidemiological studies; or
- b) 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 to be used as part of weight-of-evidence evaluation (see Table 3.16).

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 in order to help in classification (see Table 3.16). In exceptional cases, human evidence can also be used to place a substance in Category 2 (see Table 3.16).

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 toxicant. Attempts should be made to determine the primary target organ, organ/system of toxicity, and classify for that purpose, e.g. hepatotoxicants, 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.

**Table 3-16: Guidance value ranges for toxicity-repeated exposure**

		Guidance values (dose/concentration)	
Route of exposure	Units	Category 1	Category 2
Oral (rat)	mg/kg bw/d	10	10-100
Dermal (rat or rabbit)	mg/kg bw/d	20	20-200
Inhalation (rat) gas	ppmV/6h/d	50	50-250
Inhalation (rat) vapour	mg/litre/6h/d	0.2	0.2-1.0
Inhalation (rat) dust/mist/fume	mg/litre/6h/d	0.02	0.02-0.2

B) Classification criteria in GHS (Reference information)

The same categories are adopted for classification criteria in JIS Classification and GHS. Their guidance value ranges are also the same. For detailed descriptions, refer to the UN GHS third revised edition 3.9.2 about categories, and the UN GHS third revised edition Tables 3.9.1 and 3.9.2 about guidance values.

(3) Items on information sources and data

A) Data availability

- Sufficient information for classification cannot be obtained from simple descriptions in existing MSDSs. A literature search should be carried out for reliable reviews and primary information relevant to toxic actions.
- Substances with R-Phrases<sup>15</sup> (R33, R48, or combination of these) in EU DSD classification are feared to possess specific target organ toxicity (repeated exposure).
- T, R48 correspond to Category 1, and Xn, R48 correspond to Category 2.
- OECD test guidelines include test methods relating to Specific Target Organ Toxicity (Repeated Exposure) below.
  - OECD TG 407 Repeated dose 28-day oral toxicity study in rodents
  - OECD TG 408 Repeated dose 90-day oral toxicity study in rodents
  - OECD TG 409 Repeated dose 28-day oral toxicity study in non-rodents
  - OECD TG 410 Repeated dose dermal toxicity : 21 / 28-day study
  - OECD TG 411 Repeated dermal toxicity : 90-day study
  - OECD TG 412 Repeated dose Inhalation toxicity study : 28-day or 14-day study
  - OECD TG 413 Subchronic Inhalation toxicity 90-day study

<sup>15&13</sup> For R-Phrase, see Appendix.

#### B) Order of Precedence when Conflicting Data Exist

- 1) Data from evaluation by reliable organizations (for example, data obtained from reference documents shown in List 1, R-48).
- 2) If appropriate sources of information based on data cannot be obtained easily, try to obtain the original EU assessment documents from the EU DSD classification R-Phrase<sup>13</sup> (R48) corresponding to specific target organ toxicity-repeated exposure. When the assessment documents become available, classify on the basis of the documents.
- 3) Report data which can be considered to be reliable (Measurements are according to GLP, or which are the basis of judgment are clearly shown and evaluated, etc.).
- 4) Data collected from other sources of information (for example, data from references shown in List 2 or List 3).

#### C) Comparison with conventional classification systems

Systems in accord with GHS includes R-Phrase R48 in EU DSD classification.

EU CLP classification H372 accords with Category 1, and H373 accords with Category 2.

#### D) Guidance concerning data

- If information on specific, non lethal, target organ toxicity arising from a single exposure are available, experts should judge whether the toxicity has significant health effects in humans or not.
- The exposure route by which the classified substance has produced damage should be specified.
- Examples are provided below of toxic effects in humans or experimental animals that must be taken into consideration in classification of specific target organ toxicity.

**【GHS 3<sup>rd</sup> revised edition】 (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:

- (a) 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;

- (b) 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);
- (c) Any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters;
- (d) Significant organ damage that may be noted at necropsy and/or subsequently seen or confirmed at microscopic examination;
- (e) Multifocal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;
- (f) Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g. severe fatty change in the liver);
- (g) Evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

Hazards listed below are treated separately in the UN GHS third revised edition and hence are not included in specific target organ toxicity.

- Acute Toxicity (3-2-1)
- Skin Corrosion/Irritation (3-2-2)
- Serious Eye Damage/Eye Irritation (3-2-3)
- Respiratory or Skin Sensitization (3-2-4)
- Germ Cell Mutagenicity (3-2-5)
- Carcinogenicity (3-2-6)
- Reproductive Toxicity (3-2-7)
- Aspiration Hazard (3-2-10)

#### (4) Guidance for classification and judgment

##### A) Background of this item and points to be noted

As for background of this item, refer to Part 1, Introduction.

In classification, take the following points into account.

- \* Unless a description that definitely denies hazards or recognizes extremely low hazards is available in List 1, the determination of “Not classified” should be performed carefully. When determining as “Not classified”, clearly show the evidence for “Not classified” such as the route and the testing method being the basis of the judgement. If there is any question, a given substance should rather be classified in “Classification not possible” due to insufficient information for judgment.
- \* When an affected organ can be identified, indicate the applicable category along with the affected organ in parentheses. When the organ cannot be identified, put “systemic

toxicity” in parentheses. (Example entry: Category 1 (liver, kidney, blood), or Category 1 (systemic toxicity))

\* When the same substance is classified into different categories depending on the affected organs, indicate the category for each of the affected organs. (Example entry: Category 1 (liver, kidney), Category 2 (blood)).

\*As for substances of which only mixture data are available (provided mixed or diluted with solvents without toxicity), their GHS classification as chemical substances are performed by estimating from concentrations appropriately, and the estimation processes are to be described as a ground for classification.

#### B) Regarding classification procedure

1) Substances meeting [Decision criteria 1a] or [Decision criteria 1b] below are placed in “Category 1”.

[Decision criteria 1a]: Substances for which evidence of inducing toxic effects in humans are available in List 1.

(Notes)

- a) Effects on organs that are obviously known to be secondary effects shall be excluded from the description. Judgement by expert’s shall be sought for where necessary about whether the effects are secondary effects or not. When such a judgment is difficult, all organs affected shall be cited.
- b) Effects on respiratory system by site of contact are included here, and are placed in Category 1 (pneumoconiosis, etc.). However, such effects by site of contact other than respiratory tract, for example, irritation/inflammation reaction in digestive system in a case of oral administration of a corrosive/irritant, are considered to be subsumed under other toxicity items such as skin corrosion and are not classified into specific target organ.
- c) When only minimal symptoms (slight fever, languor, etc.) are described, the substance is placed in “Not classified”.
- d) All organs described as affected in List 1 shall be indicated. However, when organs listed in multiple assessment documents based on the same type of tests are not the same, indicate the commonly listed organs. When a toxic symptom alone is described and the affected organ cannot be identified, put “systemic toxicity” instead. When the target organ is identified, fundamentally, description of toxic symptom is not required.
- e) When the affected organ can be identified, indicate the applicable category along with the affected organs given in parentheses are indicated in “GHS classification”. When the affected organ cannot be identified, put “systemic toxicity” in parentheses.

[Decision criteria 1b]: Animal tests meeting all of conditions below

- a) Any animal species is applicable
- b) Exposure amount is identified and is induced within the guidance value range of Category 1
- c) The test is described in List 1 or an OECD TG test in List 2, is according to GLP, and has received some degree of approval (review by plural persons)

(Animal tests)

- A standard animal test is a 28-day, 90-day or life test (up to 2 years) in rats or mice, and includes hematological examination, clinical chemical examination, and close macroscopic and histopathological examinations to demonstrate toxic effects on target tissues/organs.
- Refer also to data of repeated dose studies conducted using animal species other than rat and mouse.
- Take into account that other long-term exposure tests, such as a carcinogenicity test, neurotoxicity test or reproductive toxicity test, can provide evidence of specific target organ toxicity used for classification evaluation.

(Notes)

- a) As for toxic effects, read the UN GHS third revised edition and the following documents carefully.
- b) Effects on organs that are obviously known to be secondary effects shall be excluded from the description. Judgement by experts shall be sought for where necessary as to whether the effects are secondary effects or not.
- c) Effects on respiratory system by site of contact are included here and are placed in Category 1 (pneumoconiosis, etc.). However, such effects by site of contact in other than respiratory tract, for example, irritation/inflammation reaction in digestive system in a case of oral administration of a corrosive/irritant, are considered to be subsumed under other toxicity items such as skin corrosion and are not classified in specific target organ toxicity.
- d) When only minimal symptoms (slight fever, etc.) are reported, the substance is placed in “Not classified”.
- e) All organs described as affected in List 1 shall be indicated. However, when descriptions of organs listed in multiple assessment documents based on the same type of tests are the same, indicate the commonly listed organs. When a toxic symptom alone is described and the affected organ cannot be identified, put “systemic toxicity” instead. When the target organ is identified, fundamentally, description of toxic symptom is not required.

- f) Data required for repeated exposure include those for repeated exposure for 14 days or more (and in case of inhalation exposure, exposure period is one hour or more for each exposure). When comparing the exposure amount with the guidance value, the guidance value shall be corrected (inverse proportional calculation by the number of exposed day and exposed time per day) by comparing the number of days and exposed time per day with the conditions of the guidance value (90 days, 6 hours/day). When repeated exposure period is longer than 90 days, however, the exposure time per day alone shall be corrected, and correction by the number of days shall not be performed.
- g) When the affected organ can be identified, indicate the applicable category along with the affected organ given in parentheses in “GHS classification”. When the affected organ cannot be identified, put “systemic toxicity” in parentheses. (Example entry: Category 1 (liver, kidney, blood), or Category 1 (systemic toxicity))

2) Substances meeting [Decision criteria 2a] or [Decision criteria 2b] below are placed in Category 2.

[Decision criteria 2a]: Substances for which evidence of inducing toxic effects in humans are available in List 2.

(Notes)

According to 1) [Decision criteria 1a](Notes)a) through e)

[Decision criteria 2b]: Animal tests meeting all of conditions below

- a) Any animal species is applicable
- b) Exposure amount is identified and toxic symptom is induced within the guidance value range of Category 2. (When multiple documents are available, judgment shall be based on one with the smallest exposure amount.)
- c) The test that is described in List 1 or List 2

(Exception)

When a test for any animal species in which the exposure amount is identified and is within the guidance value range of Category 1, but when the test is described in List 2 alone and does not meet the condition of [Decision criteria 1b] c)(does not meet the condition that is according to GLP and has received some degree of approval (by multiple reviewers)), substances with such test results are exceptionally classified in Category 2. Indicate as follows as special remarks, "This substance can be placed in Category 1 judging from the guidance value, but its data in List 2 alone are available, and its test does not meet the [Decision criteria 1b] c). Consequently, the substance is classified in Category 2 in accordance with the guidance.

(Notes)

According to 1) [Decision criteria 1b](Notes)a) through g)

C) On treatment of vapour inhalation guidance value in classification of specific target organ toxicity (repeated exposure)

As for the classification of specific target organ toxicity (repeated exposure), “guidance values” for categorization based on animal data are shown in Table 3-16 (UN GHS third revised edition tables 3.9.1 and 3.9.2). all of them are indicated in the unit of mg/L for vapour inhalation. However, there are no notes regarding vapour inhalation like those for Acute Toxicity in Table 3.1.1. Therefore, regarding Specific Target Organ Toxicity (Repeated Exposure), the toxicity manifestation concentration in unit of mg/L at vapour inhalation should be examined, and evaluated by comparing it with the value shown in the Table. If the original data is given in ppmV, the data should be converted into mg/L, and compared.

If the concentration is exceeding saturated vapour pressure, the value is treated as that of mist (or dust) by referring to the case of acute toxicity.

## 3-2-10 Aspiration Hazard

### (1) Definitions

Definitions of Aspiration Hazard in UN GHS are as follows, and they are adopted in this guidance.

**【GHS 3<sup>rd</sup> revised edition】 (3.10.1)**

3.10.1.1 The purpose of this chapter is to provide a means of classifying substances or mixtures that may pose an aspiration toxicity hazard to humans.

3.10.1.2 *Aspiration* means the entry of a liquid or solid chemical product directly through the oral or nasal cavity, or indirectly from vomiting, into the trachea and lower respiratory system.

3.10.1.3 Aspiration toxicity includes severe acute effects such as chemical pneumonia, varying degrees of pulmonary injury or death following aspiration.

3.10.1.4 Aspiration is initiated at the moment of inspiration, in the time required to take one breath, as the causative material lodges at the crossroad of the upper respiratory and digestive tracts in the laryngopharyngeal region.

3.10.1.5 Aspiration of a substance or mixture can occur as it is vomited following ingestion. This may have consequences for labelling, particularly where, due to acute toxicity, a recommendation may be considered to induce vomiting after ingestion. However, if the substance/mixture also presents an aspiration toxicity hazard, the recommendation to induce vomiting may need to be modified.

**3.10.1.6 *Specific considerations***

3.10.1.6.1 A review of the medical literature on chemical aspiration revealed that some hydrocarbons (petroleum distillates) and certain chlorinated hydrocarbons have been shown to pose an aspiration hazard in humans. Primary alcohols, and ketones have been shown to pose an aspiration hazard only in animal studies.

3.10.1.6.2 While a methodology for determination of aspiration hazard in animals has been utilized, it has not been standardized. Positive experimental evidence with animals can only serve as a guide to possible aspiration toxicity in humans. Particular care must be taken in evaluating animal data for aspiration hazards.

3.10.1.6.3 The classification criteria refer to kinematic viscosity. The following provides the conversion between dynamic and kinematic viscosity:

$$\text{Dynamic viscosity (mPa}\cdot\text{s)} / \text{Density (g/cm}^3\text{)} = \text{Kinematic viscosity (mm}^2\text{/s)}$$

**3.10.1.6.4 *Classification of aerosol/mist products***

Aerosol and mist products are usually dispensed in containers such as self-pressurized containers, trigger and pump sprayers. The key to classifying these products is whether a pool of product is

formed in the mouth, which then may be aspirated. If the mist or aerosol from a pressurized container is fine, a pool may not be formed. On the other hand, if a pressurized container dispenses product in a stream, a pool may be formed that may then be aspirated. Usually, the mist produced by trigger and pump sprayers is coarse and therefore, a pool may be formed that then may be aspirated. When the pump mechanism may be removed and contents are available to be swallowed then the classification of the products should be considered.

(2) Classification criteria

A) Classification criteria based on JIS Classification

**Table 3-17: Hazard categories for aspiration toxicity**

Categories	Criteria
Category 1 : Chemicals known to cause human aspiration toxicity hazards or to be regarded as if they cause human aspiration toxicity hazard	A substance is classified in Category 1: a) Based on reliable and good quality human evidence (See note);OR b) If it is a hydrocarbon and has a kinematic viscosity $\leq 20.5 \text{ mm}^2/\text{s}$ , measured at 40°C.

Note : Examples of substances included in Category 1 are certain hydrocarbons, turpentine, and pine oil.

B) Classification criteria in GHS (Reference information)

In GHS classification, in addition to JIS classification, category 2 is set. Explanation of classification criteria by GHS is as follow.

【GHS 3<sup>rd</sup> revised edition】

**Table 3.10.1: Hazard categories for aspiration toxicity**

Categories	Criteria
<b>Category 1:</b> Chemicals known to cause human aspiration toxicity hazards or to be regarded as if they cause human aspiration toxicity hazard	A substance is classified in Category 1: (a) Based on reliable and good quality human evidence (See note 1); or (b) If it is a hydrocarbon and has a kinematic viscosity $\leq 20.5 \text{ mm}^2/\text{s}$ , measured at 40°C.
<b>Category 2:</b> Chemicals which cause concern owing to the presumption that they cause human	On the basis of existing animal studies and expert judgment that takes into account surface tension, water solubility, boiling point, and volatility, substances, other than those classified in Category 1, which

aspiration toxicity hazard	have a kinematic viscosity $\leq 14 \text{ mm}^2/\text{s}$ , measured at 40°C (See note 2).
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**NOTE 1:** *Examples of substances included in Category 1 are certain hydrocarbons, turpentine and pine oil.*

**NOTE 2:** *Taking this into account, some authorities would consider the following to be included in this Category: n-primary alcohols with a composition of at least 3 carbon atoms but not more than 13; isobutyl alcohol, and ketones with a composition of no more than 13 carbon atoms.*

\* It should be noted that in the GHS third revised edition, it is described as “Although the definition of aspiration includes the entry of solids into the respiratory system, classification according to (b) in UN GHS table 3.10.1 for Category 1 or Category 2 is intended to apply to liquid substances and mixtures only” (3.10.1.6.4).

### (3) Items on information sources and data

\*Regarding procedure of classification, refer to “3-1-1 Sources of information available for classification”

#### A) Data availability

Although some methodologies for determining aspiration hazards in animals have been utilized, none of them has been standardized. Positive test evidence with animal merely serves as a guide to possible aspiration toxicity hazard to humans.

#### B) Order of Precedence when Conflicting Data Exist

Refer to “3-1-2 Order of Precedence when Conflicting Data Exist”.

#### C) Comparison with conventional classification systems

This class represents a new concept for classification, but R65 in EU DSD classification is in accord with it.

In EU CLP classification, H304 accords with Category 1.

#### D) Guidance concerning data

- A review of the medical literature on chemical aspiration (for example, p45.2-2 : ICSC) revealed that some hydrocarbons (petroleum distillates) and certain chlorinated hydrocarbons have been shown to pose an aspiration hazard to humans. Primary alcohols, and ketones have been shown to pose an aspiration hazard only in animal studies.
- Examples of substances falling under Category 1 and Category 2 are shown in (2) Classification criteria B), the UN GHS third revised edition, and Notes 1 and 2 of

Table 3.10.1, respectively.

- The classification criteria refer to kinematic viscosity. The conversion formula between dynamic viscosity and kinematic viscosity is indicated below.

$$\text{Dynamic viscosity (mPa}\cdot\text{s)} / \text{Density (g/cm}^3\text{)} = \text{Kinematic viscosity (mm}^2\text{/s)}$$

(4) Guidance for classification and judgment

A) Background of this item and points to be noted

As for background of this item, refer to Part 1, Introduction.

In classification, take the following points into account.

- \* Unless a description that definitely denies hazards or recognizes extremely low hazards is available in List 1, the determination of “Not classified” should be performed carefully. If there is any question, a given substance should rather be classified in “Classification not possible” due to insufficient information for judgment.
- \* If data are available only for a mixture, the mixture itself is classified, and this shall be stated in "Grounds".
- \* As for Aspiration hazard, a substance cannot be classified as "Not classified" in JIS classification with the judgement that the substance does not fall into UN GHS category 1 on the grounds that it falls into Category 2. As for Category 2 substances, if accident case on human is reported, it will be re-classified into Category 1, and thus cannot be judged as Category 1 if it falls into Category 2.

B) Regarding classification procedure

1) A substance meeting [Decision Criteria 1a] or [Decision Criteria 1b] shall be placed in Category 1.

[Decision Criteria 1a]: A document in List 1 or List 2 contains a description to the effect that human chemical pneumonia was caused by accidental aspiration.

(Note)

- a) Any kinematic viscosity shall not be considered.
- b) Liquids and solids, not gases, are subject to classification. Since aspiration hazard concerns, not aspiration of substances suspended in gas phase, accidental aspiration of liquids and solids, aerosol/dust/mist substances are judged by referring to the UN GHS third revised edition 3.10.1.6.5 and considering nature of substances, performance of the containers in which the substances are provided (spray can, etc.), etc. (Substances aspirated into respiratory tract/respiratory system while suspended in gas phase are placed in “Not applicable”).

[Decision Criteria 1b]: A substance which is a hydrocarbon and has kinematic viscosity of 20.5 mm<sup>2</sup>/s or less at 40°C.

(Note)

- a) The existence or absence of human evidence shall not be considered.
- b) Viscosity depends on temperature, and that of liquids generally become smaller as temperature rises. Therefore, as for liquids, the substance with kinematic viscosity of 20.5 mm<sup>2</sup>/s or less at ambient temperature is placed in Category 1. Since, however, the dependence of liquid viscosity on temperature is not linear in most cases, it is preferable to confirm the viscosity of the substance at 40°C by referring to chemical technology books such as the *Chemical Technology Handbook*, or to estimate it by using the empirical formula recognized for the substance. The basic data such as the value of viscosity and measuring temperature and their references shall be given in “Grounds”.
- c) liquids and solids, not gases, are subject to classification. Since aspiration hazard concerns, not aspiration of substances suspended in gas phase, but to accidental aspiration of liquids and solids, aerosol/dust/mist substances are judged by referring to the UN GHS third revised edition 3.10.1.6.5, and considering nature of substances, performance of the containers in which the substances are provided (spray can, etc.), etc. (Substances aspirated into respiratory tract/respiratory system while suspended in gas phase are placed in “Not applicable”).
- d) Here, “hydrocarbon” means substances consisting of carbon and hydrogen including nonlinear one, but halogenized hydrocarbon is not included.

(General notes regarding kinematic viscosity)

(Note 1) In many cases, viscosity is indicated in cgs units (dyn · s/cm<sup>2</sup> = poise (or P)).

Use the following conversion formula when appropriate.

$$1 \text{ poise} = 0.1 \text{ Pa} \cdot \text{s}$$

(Note 2) The classification criteria refer to kinematic viscosity. The conversion formula between dynamic viscosity and kinematic viscosity is indicated below. It should be noted that both of SI unit and CGS unit are used in the formula.

$$\text{Dynamic viscosity (mPa} \cdot \text{s)} / \text{Density (g/cm}^3\text{)} = \text{Kinematic viscosity (mm}^2\text{/s)}$$



## Part4. Environmental Hazards Guidance

### 4-1 Information available for classification

#### 4-1-1 Sources of Information available for classification

In UN GHS, available data are reviewed for classification.

In this guidance, procedures are shown below to reduce variations in classification results as much as possible, while facilitating classification.

Upon conducting surveys for classification, review all of the acquired or accessible assessment documents shown in List 1 and look for information on the relevant substances. If the selected source provides no or insufficient information needed, search other information sources.

When the required information cannot be obtained from sources in List 1, repeat the process with sources in List 2.

Examples of major information sources containing a general introduction or useful databases are shown below. Information sources listed under each List are similar in reliability, but they may vary in toxicity indexes and substances listed. This should not limit the use of reliable and useful information sources other than those listed here.

Some on-line sites shown below revise posted information when appropriate, and acquiring the latest information from them is preferable.

(1) Sources for test data for Hazardous to the aquatic environment

List1 :

Information sources provided by international organizations, governments of major countries, etc. , and whose reliability has been recognized. Basically, these are assessment documents and books whose primary reference can be traced and whose accuracy can be confirmed whenever needed.

When, however, the confirmation of reliability for individual pieces of information is needed, the source literature should be checked. If the literature lacks reliability, it should not be used as evidence for classification.

The following information can also be searched at, for example, the National Institute for Environmental Studies, “Webkis-plus”.

(Chemical Safety Database) (<http://db-out3.nies.go.jp/kis-plus/>). (Japanese text only)

1-1)	Organisation	Ministry of the Environment Government
	Source	Test for the Ecological Effects of Chemical Substances
	URL	<a href="http://www.env.go.jp/chemi/sesaku/02e.pdf">http://www.env.go.jp/chemi/sesaku/02e.pdf</a>
1-2)	Organisation	Environmental Risk Assessment Office, Ministry of the Environment Government
	Source	Environmental Risk Assessments for Chemical Substances
	URL	<a href="http://www.env.go.jp/en/chemi/chemicals/profile_erac/index.html">http://www.env.go.jp/en/chemi/chemicals/profile_erac/index.html</a>
1-3)	Organisation	National Institute of Technology and Evaluation(NITE)
	Source	Initial Risk Assessment
	URL	<a href="http://www.safe.nite.go.jp/english/risk/initial_risk.html">http://www.safe.nite.go.jp/english/risk/initial_risk.html</a>
	Note	Chemicals Evaluation and Research Institute, Japan(CERI) • National Institute of Technology and Evaluation (NITE) “Hazard Assessment Report” <a href="http://www.cerij.or.jp/ceri_en/hazard_assessment_report/yugai_index_en.htm">http://www.cerij.or.jp/ceri_en/hazard_assessment_report/yugai_index_en.htm</a> <a href="http://www.safe.nite.go.jp/english/sougou/view/SelectingListsList_en_faces">http://www.safe.nite.go.jp/english/sougou/view/SelectingListsList_en_faces</a>
1-4)	Organisation	OECD
	Source	SIDS Report(SIDS)
	URL	<a href="http://www.chem.unep.ch/irptc/sids/OECD/SIDS/sidspub.html">http://www.chem.unep.ch/irptc/sids/OECD/SIDS/sidspub.html</a>
	Note	SIAP(SIDS Initial Assessment Report) (Japanese version) Japan Chemical Industry Ecology-Toxicology & Information Center

		<a href="http://www.jetoc.or.jp/HP_HP_SIDS/SIAPbase.htm">http://www.jetoc.or.jp/HP_HP_SIDS/SIAPbase.htm</a>
1-5)	Organisation	WHO/IPCS
	Source	Environmental Health Criteria(EHC)(No.1~No.237,as of Sep.2008)
	URL	<a href="http://www.who.int/ipcs/publications/ehc/en/index.html">http://www.who.int/ipcs/publications/ehc/en/index.html</a> <a href="http://www.inchem.org/pages/ehc.html">http://www.inchem.org/pages/ehc.html</a>
	Note	EHC Japanese version : <a href="http://www.nihs.go.jp/hse/ehc/index.html">http://www.nihs.go.jp/hse/ehc/index.html</a>
1-6)	Organisation	WHO/IPCS
	Source	Concise International Chemical Assessment Documents (CICAD)
	URL	<a href="http://www.who.int/ipcs/publications/cicad/pdf/en/">http://www.who.int/ipcs/publications/cicad/pdf/en/</a>
	Note	CICAD Japanese version <a href="http://www.nihs.go.jp/hse/cicad/cicad.html">http://www.nihs.go.jp/hse/cicad/cicad.html</a>
1-7)	Organisation	EU European Chemicals Bureau (ECB)
	Source	EU Risk Assessment Report : EU RAR (vol.1~vol.91,as of Sep.2008)
	URL	<a href="http://ecb.jrc.ec.europa.eu/documentation/">http://ecb.jrc.ec.europa.eu/documentation/</a> <a href="http://ecb.jrc.ec.europa.eu/home.php?CONTENU=/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/">http://ecb.jrc.ec.europa.eu/home.php?CONTENU=/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/</a>
1-8)	Organisation	Environment Canada/ Helth Canada
	Source	Assessment Report Environment Canada : Priority Substance Assessment Reports
	URL	<a href="http://www.ec.gc.ca/substances/ese/eng/psap/final/main.cfm">http://www.ec.gc.ca/substances/ese/eng/psap/final/main.cfm</a> (Abstract only on the web site)
1-9)	Organisation	Australia NICNAS
	Source	Priority Existing Chemical Assessment Reports
	URL	<a href="http://www.nicnas.gov.au/publications/car/pec/default.asp">http://www.nicnas.gov.au/publications/car/pec/default.asp</a>
1-10)	Organisation	European Center of Ecotoxicology and Toxicology of Chemicals(ECETOC)
	Source	Technical Report ・ TR91(Aquatic Hazard AssessmentII)(TR91)
	URL	<a href="http://www.ecetoc.org/publications">http://www.ecetoc.org/publications</a> (list and abstract only)
1-11)	Organisation	WHO/FAO
	Source	Pesticide Data Sheets(PDSs)
	URL	<a href="http://www.inchem.org/pages/pds.html">http://www.inchem.org/pages/pds.html</a>
1-12)	Organization	United States Environmental Protection Agency (EPA)
	Source	Pesticides “Regeneration Eligibility Decision”
	URL	<a href="http://www.epa.gov/pesticides/reregistration/status.htm">http://www.epa.gov/pesticides/reregistration/status.htm</a>

List 2 :

Useful information sources of other assessment documents than listed in List1.

2-1)	Organisation	AQUIRE
	Source	Aquatic Toxicity Information Retrieval(AQUIRE)
	URL	<a href="http://cfpub.epa.gov/ecotox/">http://cfpub.epa.gov/ecotox/</a>
	Note	Database on chemical substance and aquatic toxicity established in 1981 by EPA. It is now combined with terrestrial hazardous database, making it as Ecotox database. Japanese Version : <a href="http://www.jaici.or.jp/stn/dbsummary/db.html">http://www.jaici.or.jp/stn/dbsummary/db.html</a>
2-2)	Organisation	EU European Chemicals Bureau (ECB)
	Source	International Uniform Chemical Information Database (IUCLID) IUCLID CD-ROM (Update Version Edition 2 - 2000)
	URL	<a href="http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=dat">http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=dat</a>
2-3)	Organisation	National Library of Medicine(NLM)
	Source	Hazardous Substance Data Bank(HSDB)
	URL	<a href="http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB">http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB</a>
2-4)	Organisation	EU European Chemicals Bureau (ECB)
	Source	The N-CLASS Database on Environmental Hazard Classification (N-Class)
	URL	<a href="http://www.kemi.se/nclass/">http://www.kemi.se/nclass/</a>
	Note	Database established in corporation of ECB and The Nordic Council of Ministers. The information on N(R50-53) of EU lists of dangerous goods can be obtained.
2-5)	Organisation	German Chemical Society-Advisory Committee on Existing Chemicals of Environmental Relevance
	Source	BUA Report(BUA)
	URL	<a href="http://www.hirzel.de/bua-report/download.html">http://www.hirzel.de/bua-report/download.html</a>
	Note	Full report can not be available from web site.

### List 3 :

These are databases for searching and accessing primary literatures. In the case where data are available in List 1 or 2, these databases could be referred to if appropriate.

Although hazard information of an individual product is available from existing MSDSs, etc., its direct use for GHS classification should be avoided.

#### 3-1) Database for primary literatures

- Pub-Med/NLM(For original literature)  
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>
- NLM TOXNET(Online database including original literature)  
<http://toxnet.nlm.nih.gov/index.html>
- JICST (JDream II)  
<http://pr.jst.go.jp/db/db.html> (Japanese text only)

#### 3-2) General information database on chemical substances

- National Institute of Technology and Evaluation  
Chemical Risk Information Platform(CHRIP) : <http://www.safe.nite.go.jp/english/db.html>
- Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA)  
“GESTIS-database on hazardous substances” (GESTIS) :  
<http://www.dguv.de/ifa/en/gestis/stoffdb/index.jsp>
- Ministry of the Environment Government : Chemical Substances Fact Sheets  
<http://www.env.go.jp/chemi/communication/factsheet.html> (Japanese text only)
- National Institute for Environmental Studies “WebKis-Plus Chemical Substances Database”  
(WebKis-Plus) : <http://w-chemdb.nies.go.jp/> (Japanese text only)
- National Institute of Advanced Industrial Science and Technology (AIST)  
“Risk Assessment Documents” : [http://unit.aist.go.jp/riss/crm/mainmenu/e\\_1.html](http://unit.aist.go.jp/riss/crm/mainmenu/e_1.html)
- Chemicals Evaluation and Research Institute, Japan(CERI) “Chemical Substance Hazard Data” :  
[http://www.cerij.or.jp/ceri\\_en/hazard\\_assessment\\_report/yugai\\_idx\\_en.htm](http://www.cerij.or.jp/ceri_en/hazard_assessment_report/yugai_idx_en.htm)
- Hazardous Substance Fact Sheet (New Jersey Department of Health and Senior Services) :  
<http://web.doh.state.nj.us/rtkhsfs/indexfs.aspx>
- “Sittig’s Handbook of Toxic and Hazardous Chemicals and Carcinogens (4th edition,2002)”(Sittig)
- The National Institute for Occupational Safety and Health (NIOSH) [Registry of Toxic Effects of Chemical Substances] (RTECS) : <http://www.cdc.gov/niosh/npg/npgdrtec.html>
- WHO/IPCS “International Chemical Safety Cards” (ICSC) :  
<http://www.cdc.gov/niosh/ipcs/nicstart.html>  
(ICSC Japanese Version : <http://www.nihs.go.jp/ICSC/>)

### 3-3)EU classification

- When classification based on Table3-1 AnnexVI of EU CLP regulations (hereinafter abbreviated as "EU CLP classification". R-phrase will be referred to as EU DSD classification) together with its evidence information is not available, the substance shall fall under "Classification not possible".
- If EU CLP classification and EU DSD classification together with their evidence information are available and if their classification criteria are different from those of GHS classification, EU CLP classification and EU DSD classification may be used for GHS classification only when the evidence information is scientifically valid.
- If EU CLP classification and EU DSD classification together with their evidence information are available and if their classification criteria accord with that of GHS classification, GHS classification may be performed according to these EU classifications.

In this guidance, classification based on the AnnexVI of EU CLP regulations is abbreviated as EU CLP classification, and R-Phrase is referred to as EU DSD classification. When it is stated as EU classifications unless otherwise specified, it refers to both EU CLP classification and EU DSD classification.

Fundamentally, classification shall be performed based on quality, reliability, and consistency of evidence obtained from the information source, with the evidence weighted and expert's judgment added where appropriate.

Information in multiple databases (CHRIP, EnviChem, ESIS, HPVIS, HSNO CCID, INCHEM, NICNAS PEC, OECD HPV, SIDS IUCLID, SIDS UNEP) can be searched at the OECD portal site for chemical materials information (<http://webnet3.oecd.org/echempportal/>).

(2) Sources of information for data on bioaccumulativity and degradability

List 1 :

Information sources provided by international organizations, government of major countries, etc, which reliability has been recognized. If data cannot be obtained from these sources of information, try the information sources in List 1 described above.

1-1)	Source	Existing Chemical Substances Safety Evaluation Data
	URL	<a href="http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html">http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html</a>
1-2)	Source	PHYSPROP Database(SRC,2005)
	URL	<a href="http://www.syrres.com/esc/physprop.htm">http://www.syrres.com/esc/physprop.htm</a>

List 2 :

Useful information sources of other assessment documents than listed in List1.

2-1)	Source	AQUIRE(Aquatic Toxicity Information Retrieval) (AQUIRE)
	URL	<a href="http://cfpub.epa.gov/ecotox/">http://cfpub.epa.gov/ecotox/</a>
	Note	Database on chemical substances and aquatic toxicity established by EPA in 1981. It is now combined with terrestrial hazardous substances, mainly as Ecotox database.
2-2)	Organisation	EU European Chemicals Bureau (ECB)
	Source	International Uniform Chemical Information Database (IUCLID) IUCLID CD-ROM (Update Version Edition 2 - 2000)
	URL	<a href="http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html">http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html</a>
2-3)	Organisation	National Library of Medicine(NLM)
	Source	Hazardous Substance Data Bank(HSDB)
	URL	<a href="http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB">http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB</a>
2-4)	Source	logKow estimation software(KOWWIN, CLOGP)
	URL	<a href="http://www.syrres.com/what-we-do/product.aspx?id=138">http://www.syrres.com/what-we-do/product.aspx?id=138</a>
2-5)	Source	BIOWIN (Biodegradation estimation software)
	URL	<a href="http://www.syrres.com/what-we-do/product.aspx?id=138">http://www.syrres.com/what-we-do/product.aspx?id=138</a>

## 4-2 Classification of Hazardous to the Aquatic Environment

In the JIS classification, the GHS classification criteria for environmental hazards are established only for “aquatic environmental hazards”. In UN GHS third revised edition, criteria for “aquatic environmental hazards” and “hazardous to the ozone layer” are established, which are addressed in Section 4.1 and 4.2 respectively. As described in Part 1, since this guidance is meant to be consistent with the Classification JIS, it only focuses on “aquatic environmental hazards” which is described in UN GHS third revised edition. In addition, regarding “aquatic environmental hazards”, there are Annex 9 “Guideline on Hazards to the Aquatic Environment” and Annex 10 “Guidance on Transformation/Dissolution of Metals and Metal Compounds”. GHS classification should be performed by referring to them.

### (1) Definitions

Definitions of Acute Aquatic Toxicity and Chronic Aquatic Toxicity in UN GHS are as follows, and they are adopted in this guidance.

#### **【GHS 3<sup>rd</sup> revised edition】 (4.1.1.1)**

*Acute aquatic toxicity* means the intrinsic property of a substance to be injurious to an organism in a short-term aquatic exposure to that substance.

*Acute (short-term) hazard*, for classification purposes, means the hazard of a chemical caused by its acute toxicity to an organism during short-term aquatic exposure to that chemical.

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 ( $M^{\circ}$ ) 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 bioavailability.

*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 the intrinsic property of a substance to cause adverse effects to aquatic organisms during aquatic 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 characterized 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.

$EC_x$  means the concentration associated with x% response.

*Long-term hazard*, for classification purposes, means the hazard of a chemical caused by its chronic toxicity following long-term exposure in the aquatic environment.

*NOEC (No Observed Effect Concentration)* means the test concentration immediately below the lowest tested concentration with statistically significant adverse effect. The NOEC has no statistically significant adverse effect compared to the control.

## (2) Classification criteria

### A) Classification criteria based on JIS Classification

#### Acute Toxicity

##### Category: Acute 1

96 hr LC <sub>50</sub> (for fish)	≤1 mg/l and/or
48 hr EC <sub>50</sub> (for crustacea)	≤1 mg/l and/or
72 or 96hr ErC <sub>50</sub> (for algae or other aquatic plants)	≤1 mg/l

##### Category: Acute 2

96 hr LC <sub>50</sub> (for fish)	>1-≤10 mg/l and/or
48 hr EC <sub>50</sub> (for crustacea)	>1-≤10 mg/l and/or
72 or 96hr ErC <sub>50</sub> (for algae or other aquatic plants)	>1-≤10 mg/l

##### Category: Acute 3

96 hr LC <sub>50</sub> (for fish)	>10-≤100 mg/l and/or
48 hr EC <sub>50</sub> (for crustacea)	>10-≤100 mg/l and/or
72 or 96hr ErC <sub>50</sub> (for algae or other aquatic plants)	>10-≤100 mg/l

#### Chronic toxicity

##### Category: Chronic 1

96 hr LC <sub>50</sub> (for fish)	≤1 mg/l and/or
48 hr EC <sub>50</sub> (for crustacea)	≤1 mg/l and/or
72 or 96hr ErC <sub>50</sub> (for algae or other aquatic plants)	≤1 mg/l

and the substance is not rapidly degradable and/or the log  $K_{ow} \geq 4$  (unless the experimentally determined BCF is <500)

<b><u>Category: Chronic 2</u></b>	
96 hr LC <sub>50</sub> (for fish)	>1 to ≤10 mg/l and/or
48 hr EC <sub>50</sub> (for crustacea)	>1 to ≤10 mg/l and/or
72 or 96hr ErC <sub>50</sub> (for algae or other aquatic plants)	>1 to ≤10 mg/l
and the substance is not rapidly degradable and/or the log K <sub>ow</sub> ≥4 (unless the experimentally determined BCF is <500), unless the chronic toxicity NOECs are >1 mg/l	
<b><u>Category: Chronic 3</u></b>	
96 hr LC <sub>50</sub> (for fish)	>10to≤100mg/l and/or
48 hr EC <sub>50</sub> (for crustacea)	>10to≤100mg/l and/or
72 or 96hr ErC <sub>50</sub> (for algae or other aquatic plants)	>10to≤100 mg/l
and the substance is not rapidly degradable and/or the log K <sub>ow</sub> ≥4 (unless the experimentally determined BCF is <500) unless the chronic toxicity NOECs are >1 mg/	
<b><u>Category: Chronic 4</u></b>	
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 <sub>ow</sub> ≥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	

B) Classification criteria in GHS(Reference information)

The classification criteria described in the UN GHS third revised edition 4.1.2 can be summarized as follows.

(a) Acute (short-term) aquatic hazard

**Category: Acute 1**

96 hr LC <sub>50</sub> (for fish)	≤1 mg/l and/or
48 hr EC <sub>50</sub> (for crustacea)	≤1 mg/l and/or
72 or 96hr ErC <sub>50</sub> (for algae or other aquatic plants)	≤1 mg/l

**Category: Acute 2**

96 hr LC <sub>50</sub> (for fish)	>1 - ≤10 mg/l and/or
48 hr EC <sub>50</sub> (for crustacea)	>1 - ≤10 mg/l and/or
72 or 96hr ErC <sub>50</sub> (for algae or other aquatic plants)	>1 - ≤10 mg/l

**Category: Acute 3**

96 hr LC <sub>50</sub> (for fish)	>10 -≤100 mg/L and/or
48 hr EC <sub>50</sub> (for crustacea)	>10 -≤100 mg/L and/or
72 or 96hr ErC <sub>50</sub> (for algae or other aquatic plants)	>10 -≤100 mg/L

(b) Long-term aquatic hazard

- (i) Non-rapidly degradable substances for which there are adequate chronic toxicity data available

**Category Chronic 1:**

Chronic NOEC or EC <sub>x</sub> (for fish)	≤ 0.1 mg/l and/or
Chronic NOEC or EC <sub>x</sub> (for crustacea)	≤ 0.1 mg/l and/or
Chronic NOEC or EC <sub>x</sub> (for algae or other aquatic plants)	≤ 0.1 mg/l

**Category Chronic 2:**

Chronic NOEC or EC <sub>x</sub> (for fish)	≤ 1 mg/l and/or
Chronic NOEC or EC <sub>x</sub> (for crustacea)	≤ 1 mg/l and/or
Chronic NOEC or EC <sub>x</sub> (for algae or other aquatic plants)	≤ 1 mg/l

- (ii) Rapidly degradable substances for which there are adequate chronic toxicity data available

**Category Chronic 1:**

Chronic NOEC or EC <sub>x</sub> (for fish)	≤ 0.01 mg/l and/or
Chronic NOEC or EC <sub>x</sub> (for crustacea)	≤ 0.01 mg/l and/or
Chronic NOEC or EC <sub>x</sub> (for algae or other aquatic plants)	≤ 0.01 mg/l

**Category Chronic 2:**

Chronic NOEC or EC <sub>x</sub> (for fish)	≤ 0.1 mg/l and/or
Chronic NOEC or EC <sub>x</sub> (for crustacea)	≤ 0.1 mg/l and/or
Chronic NOEC or EC <sub>x</sub> (for algae or other aquatic plants)	≤ 0.1 mg/l

**Category Chronic 3:**

Chronic NOEC or EC <sub>x</sub> (for fish)	≤ 1 mg/l and/or
Chronic NOEC or EC <sub>x</sub> (for crustacea)	≤ 1 mg/l and/or
Chronic NOEC or EC <sub>x</sub> (for algae or other aquatic plants)	≤ 1 mg/l

- (iii) Substances for which adequate chronic toxicity data are not available

**Category Chronic 1:**

96 hr LC <sub>50</sub> (for fish)	≤ 1 mg/l and/or
48 hr EC <sub>50</sub> (for crustacea)	≤ 1 mg/l and/or
72 or 96hr ErC <sub>50</sub> (for algae or other aquatic plants)	≤ 1 mg/l

and the substance is not rapidly degradable and/or the experimentally determined BCF is ≥ 500 (or, if absent, the log K<sub>ow</sub> ≥ 4).

**Category Chronic 2:**

96 hr LC <sub>50</sub> (for fish)	> 1 but ≤ 10 mg/l and/or
48 hr EC <sub>50</sub> (for crustacea)	> 1 but ≤ 10 mg/l and/or
72 or 96hr ErC <sub>50</sub> (for algae or other aquatic plants)	> 1 but ≤ 10 mg/l

and the substance is not rapidly degradable and/or the experimentally determined

BCF is  $\geq 500$  (or, if absent, the  $\log K_{ow} \geq 4$ ).

**Category Chronic 3:**

96 hr LC<sub>50</sub> (for fish) > 10 but  $\leq 100$  mg/l and/or

48 hr EC<sub>50</sub> (for crustacea) > 10 but  $\leq 100$  mg/l and/or

72 or 96hr ErC<sub>50</sub> (for algae or other aquatic plants) > 10 but  $\leq 100$  mg/l

and the substance is not rapidly degradable and/or the experimentally determined BCF is  $\geq 500$ ) (or, if absent, the  $\log K_{ow} \geq 4$ ).

(c) "Safety net" classification

**Category Chronic 4:**

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  $\log K_{ow} \geq 4$ , 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.

(3) Items on information sources and data

A) Data availability

Most information sources (shown in 4-1) of data for classification on acute aquatic toxicity, bioconcentration (Bioconcentration factor, octanol/water partition coefficient), rapid degradability (biotic or abiotic), and chronic aquatic toxicity can be easily accessed from web sites. Broad collection of related information is important since data on stability of substances in water, water-solubilities, etc. are also used in classification.

EU classification results, which are similar to GHS classification, are available as reference information. They cannot, however, be directly used in GHS classification since classification criteria for chronic aquatic toxicity in EU classification is different from that in GHS classification and since its evidence information is hard to obtain.

B) Requirements for data to be collected and utilized

1) Information on hazardous to the aquatic environment ; Values of acute toxicity by aquatic exposure

a) Requirements for data to be collected

Tests shall be conducted by using fish, crustacea, and algae (or other aquatic plants) -especially, organisms recommended by standard test methods such as OECD test guidelines and ASTM or their congeners.

The test period and endpoints (effect indicators) are as follows:

- Fish : 96 hour LC<sub>50</sub> (lethal)

- Crustacea : 24 or 48 hour EC<sub>50</sub>(immobile), LC<sub>50</sub>(lethal)
- Daphnia : 24 or 48 hour EC<sub>50</sub> (immobile), LC<sub>50</sub> (lethal)
- Decapoda, Amphipoda, Mysidacea : 24, 48, or 96 hour EC<sub>50</sub> (immobile), LC<sub>50</sub> (lethal)
- Algae(or other aquatic plants) : 72 or 96 hour (for cyanobacteria) with Algae, seven day or 14 day with ErC50 (growth rate method : the concentration at which mean growth rate during test period is inhibited by 50%) and other higher aquatic plants (for example, Lemna spp). Although data for less than seven days are available, they should not be used because these toxicity values from short test period often cause underestimation of toxicity.

As toxicity indexes, TLM (median Tolerance Limit) is treated as the same with LC<sub>50</sub>, and IC<sub>50</sub> (50% inhibition concentration), with EC<sub>50</sub>.

When GLP compliant tests are not known or applicable, classification may be carried out by making estimation using methods such as QSAR. As for QSAR, the following information is helpful.

Research Center of Environmental Risk, National Institute for Environmental Studies, “KAshinho Tool for Ecotoxicity (KATE)”

#### b) Requirements for usable data

In principle, data according to GLP shall be used. Yet, even if it is not clear or is not the case that a test is according to GLP, if an expert judged that the test is reliable based on its detailed information (preferably from primary literature), the data from the test are used for categorization judgment. Nonetheless, even if the test is conducted according to GLP, if an expert judged that there is a doubt about the test procedure applied from the scientific point of view, the data from the test shall not be used as the basis of classification. Especially, when acute aquatic toxicity levels are above the water solubility, data shall not be used for classification in principle.

As for the concept of hazard evaluation for poorly water-soluble substances (handling of toxicity levels over water-solubility), refer to descriptions regarding difficult to test substances in the UN GHS third revised edition Annex 9. When almost all of the parent substance is degraded for the duration of the test and the remaining degradation products are recognized to be toxic, the toxicity of the degradation products are considered to be that of the parent substance (as for handling of degradation products, refer to the UN GHS third revised edition Annex 9 A9.2.6.3). In such cases, it is preferable to note that the classification is based on the hazard especially from the degradation products.

Standard test methods and test conditions to be applied to individual organism groups

are shown below.

As for data in List 1 without indication of accordance with the test guidelines below and other relevant criteria, such data shall be adopted in which organism species, exposure time, and endpoint each accord with those stipulated in the test guidelines and other relevant criteria.

- Fish : In tests using fish, 96 hour LC<sub>50</sub> is used which is according to OECD test guideline 203 or corresponding test methods.
- Crustacea : In tests using crustacea, 48 hour EC<sub>50</sub> according to OECD test guideline 202 (Daphnia Acute Immobilization test) or corresponding test methods should be the standard test. If 48 hour EC<sub>50</sub> is not available, 24 hour EC<sub>50</sub> (according to the previous OECD test guideline 202) may be referred.

Except for tests using Daphnia younger than 24 hours, the values of 96 hour LC<sub>50</sub> from, for example, tests using Mysidacea or other species, US EPA850.1035(Mysidacea Acute Toxicity), or corresponding tests may be used. When data according to OECD-TG(1984 or 2004) are not available, 24 or 48 hour LC<sub>50</sub>(not immobile but lethal) may be adopted. As for data in List 2, an expert's decision is required.

- Algae, Cyanobacteria(Cyanophyceae), and higher aquatic plants : OECD test guideline 201 (revised in 2006) includes growth inhibition tests for Algae and Cyanobacteria(Cyanophyceae). As a response variable for calculation of toxicity in an Algae growth inhibition test, growth rate (rate, rate method), area under the growth curve (area, area method), final cell number (FCC method), yield (yield method), etc. have been used. In GHS classification, 72 hour growth rate method, which is judged to be scientifically valid in OECD test guidelines, is used preferentially. If it is not clear whether obtained data are based on the rate method or others, the data may be used only tentatively (to be reviewed when rate method data become available). Data with exposure time longer than 96 hours shall not be used.
- Other higher aquatic plants : OECD test guideline 221 (approved in 2004) showing a growth inhibition test method using a higher plant, Lemna, and acute EC<sub>50</sub> according to US EPA850.4400 may be utilized. As in the case of Algae, ErC<sub>50</sub> (rate method) takes precedence over other toxicity values. If it is not clear whether obtained data based on the rate method or others such as area method, the data may be tentatively used. Data with exposure time of seven days take precedence over that of 14 days, and data with exposure time of less than seven days should not be used because such data often cause underestimation of toxicity.

## 2) Test data on chronic aquatic toxicity

In the UN GHS third revised edition, chronic aquatic toxicity categories are agreed to be categorized based on chronic aquatic toxicity values. However, a method based on acute toxicity categories is shown here. Test data on chronic aquatic toxicity becomes evidence to classify cases with NOEC of over 1 mg/L in "Not classified" in classification of chronic aquatic toxicity. For example, when acute toxicity values for both Oryziatidae and Daphnia are classified in Acute 2, and, at the same time, in Chronic 2 because of their rapid degradability and bioaccumulativity, the substance shall not be excluded from Chronic 2 unless its NOECs exceed 1mg/L for both Oryziatidae and Daphnia.

a) Requirements for data to be collected

Tests shall be conducted by using fish, crustacea, and algae (or other aquatic plants) -especially, their species recommended by standard test methods such as OECD test guidelines and ASTM or their congeners.

The exposure time and endpoints (effect indicators) are as follows:

- Fish : in early life stage test, 28 days or more, NOEC (hatching success rate, growth (change of length and weight), spawning success rate, and survival rate)
- Crustacea : 7 days or more, NOEC (the period up to the first spawning, number of eggs per female, growth, and survival rate)
- Algae(or other aquatic plants) :
  - Algae: 72 or 96 hours, NOEC (growth inhibition)
  - Other aquatic plants : No available long-term chronic toxicity test (those officially approved for use in classification)

b) Requirements for usable data

In principle, when aquatic environmental hazard levels are above the water solubility, the data shall not be used for classification.

As for the concept of hazard evaluation for unstable substances with hydrolysis (handling of hazard of degradation products), or poorly water-soluble substances (handling of toxicity levels over water-solubility), refer to descriptions regarding difficult to test substances in the UN GHS third revised edition Annex 9. When almost all of the parent substance is degraded for the duration of the test and the remaining degradation products are recognized to be toxic, the toxicity of the degradation products are considered to be that of the parent substance (as for handling of degradation products, refer to the UN GHS third revised edition Annex 9 A9.2.6.3). In such cases, it is preferable to note that the classification is based on the hazard especially from the degradation products.

In principle, data according to GLP shall be used. Nonetheless, even if it is not clear whether a test is conducted in according to GLP, if an expert judged that data are reliable

based on test conditions, etc., the data shall be adopted. When there is hesitation about decision, judgement by expert's shall be sought for a final decision.

For individual species, see below. As for data in List 1 without indication of accordance with the test guidelines below and other relevant criteria, such data shall be adopted in which organism species, exposure time, and endpoint each accord with those stipulated in the test guidelines and other relevant criteria.

■ Fish :

Chronic or long-term toxicity tests using fish shall be conducted according to OECD Test Guideline 210 (Fish early life stage test), Fish Life Cycle Test(US EPA 850.1500), or corresponding test methods(one- or two-generation test). Although OECD Test Guideline 210 is designed for sub-chronic toxicity, its test results may be utilized as indexes of chronic aquatic toxicity since they provide good indexes for chronic toxicity, .

The appendix to OECD Test guideline 210 defines exposure time for each species (for example, the case of Oryziatidae, up to 30 days (at minimum 28 days) after hatching), while a Fish Life Cycle Test(US EPA850.1500) provides no definition on the duration. Accordingly, for data requiring confirmed reliability, the exposure time adopted is considered to be appropriate if the compliance to OECD Test Guideline 210, the Fish Life Cycle Test, or corresponding test methods is clearly noted.

Endpoints are based on hatching success rate, growth (change in length and weight), spawning success rate, and survival rate.

■ Crustacea :

Chronic toxicity tests using crustacea shall be conducted in accordance with OECD Test Guideline 211 (Daphnia reproduction), US EPA OPPTS 850.1035 (Mysidacea chronic toxicity), or corresponding test methods (NOECs of 21 days for Daphnia, NOECs of 7 days or more for Ceriodaphnia).

Endpoints are based on the period up to the first spawning, number of eggs per female, growth, and survival rate.

■ Algae (or other aquatic plants) :

- Algae : Since OECD Test Guideline 201 (Algae growth inhibition test, 72 or 96 hours) is not a long-term test, its NOECs are not generally used as evidence for exclusion from chronic aquatic toxicity. Yet, when the classification as acute aquatic toxicity is based on test result on a single species of algae or another aquatic plant, and when NOECs exceed 1 mg/L for other species of algae, NOECs may be used as evidence for exclusion.

In principle, growth inhibition (NOEC) by growth rate method is used for an endpoint.

When it is not clear whether the method for concluding NOECs is based on growth rate method, the NOECs may be tentatively used.

• Other aquatic plants : Since there is no officially approved test method for long-term chronic aquatic toxicity, evidence in List 2 for exclusion from chronic aquatic toxicity requires an expert's judgment.

### 3) Data on bioaccumulation and rapid degradability

#### a) Requirements for usable data

Data on bioaccumulation (BCF , log Kow), rapid degradability (bio degradability, hydrolysis, etc.) shall be based on test methods specified by the Chemical Substances Control Law, OECD Test Guidelines, ASTM Standard Test Methods, etc., and they are deemed as reliable. In principle, data according to GLP shall be used. If, however, it is not clear whether a test is according to GLP, if an expert judged that data are reliable based on test conditions, etc., the data shall be adopted.

#### i) a) Data on bioaccumulation

As for data on bioaccumulation, when measured BCF values in fish are available, such as data for degradability of existing chemical substances by microorganisms, concentration in fish, etc., they should take precedence, but results based on the properties such as low concentration cannot be directly used. If measured BCF values are not available, measured log Kows values are used as benchmarks. When measured log Kows values are not available, or they are considered to be not reliable, estimation of log Kows by established methods such as QSAR may be carried out.

Results from the following types of tests or corresponding tests may be accepted.

OECD Test Guideline 305 and the former 305A-D (BCF)

OECD Test Guideline 107 and 117 (Kow)

When test results described above are not available, test results (Kow) from OECD Test Guideline 123 (Draft) and the corresponding tests may be adopted under an expert's judgment.

#### ii) b) Data on rapid degradability

Both biotic and abiotic degradability (for example, hydrolysis) must be taken into account. When a substance degrades biotically or abiotically in the practical aquatic environment by > 70% in 28 days, or a test result based on oxygen consuming amount or carbon dioxide production amount exceeds 60%, or a test result based on dissolved

organic carbon exceeds 70%, the substance is considered as rapidly degradable. A substance of which the test result based on oxygen consuming amount or carbon dioxide production amount exceeds 60%, or of which the test result based on dissolved organic carbon exceeds 70%, and which has been determined as readily degradable in the Existing Chemical Substance Evaluation according to the Chemical Substance Control Law, may be determined as rapidly degradable in GHS classification. When the decision result of “hardly degradable” is applied to GHS classification, other degradability data must be taken into account. If these test results are not available, the prediction result by a biodegradability prediction software may be utilized. The prediction results can be utilized only for a decision that the substance is not rapidly degradable. Being readily degradable may be evidence for excluding a substance from the category of aquatic environment hazards.

When data on rapid degradability are not available, the substance is assumed to be without rapid degradability.

Results from OECD Test Guidelines 301A-F (readily degradability test) and the corresponding tests may be accepted.

When test results described above are not available, results from the following types of tests and the corresponding tests may be adopted under an expert's decision.

OECD Test Guidelines 302A, 302B, 302C, 303A, 303B, 304A, 306, 307, 308, and 309

OECD Test Guidelines 310 and 311 (both of them are Draft)

### C) Order of precedence when conflicting Data exist

#### 1) When data in List 1 are available:

- a) Data from tests conducted according to internationally recognized test guidelines (such as OECD) and GLP take precedence.
- b) When data falling under 1) are not available, data from tests conducted according to internationally recognized test guidelines (such as OECD) whose compliance to GLP is not clear take precedence.
- c) When classification of data based on reliability as shown in 1) and 2) is not possible, the latest data take precedence.
- d) If there are multiple data with the same reliability, in principle the safer data (i.e., the smallest concentration for aquatic environment hazards, the highest value for bioaccumulation, the lowest value for rapid degradability) shall be adopted. When four or more data sets, however, are available for the same life stage, condition, and test period of the same species, their geometric mean shall be adopted as the representative data of the species.
- e) When one set of data substantially deviates from others, it is recommended to review

the original literature and to confirm reliability of the data set. In addition, confirm that the relevant information sources are the latest available.

2) When there is no data in List 1:

- a) Among data collected from other information sources (for example, information sources shown in List 2), data considered to be reliable (GLP-conforming data or data whose evidence are specified and assessed) are adopted. When there is hesitation about decision, judgement by expert's shall be sought for where necessary.
- b) In that case, it should be confirmed that assessment documents and database used are the latest available or that references cited are reliable.
- c) Among data which experts judged to be reliable to a certain extent, the safer data (i.e., the smallest concentration for aquatic environment hazards, the highest value for bioaccumulation, the smallest value for rapid degradability) shall be finally adopted. However, when four or more data sets are available for the same life stage, condition, and test period of the same species, their geometric mean shall be adopted as the representative data of the species.

#### D) Comparison with conventional classification systems

The definitions of EU DSD classification are almost in accord with GHS categories.

R50 : Very toxic to aquatic organisms.

R51 : Toxic to aquatic organisms.

R52 : Harmful to aquatic organisms.

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

Based on the four relevant R-Phrase<sup>16</sup> above, the following categories may be estimated.  
categories

Category: Acute 2 = EU·R51(and R51/53)

Category: Acute 3 = EU·R52(and R52/53)

Category: Chronic 1 ≐ EU·R50/53

Category: Chronic 2 ≐ EU·R51/53

Category: Chronic 3 ≐ EU·R52/53

(Note) As indicated in “4-2 Classification of Hazardous to the Aquatic Environment, (2) Classification criteria B) Classification criteria in GHS(Reference information)”, especially for chronic toxicity, it should be noted that the classification criteria described in UN GHS second revised edition 4.1.2 differs from that of UN GHS third revised edition.

Accordance of EU CLP classification categories and GHS categories are as follows.

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<sup>16</sup> For R-Phrase, see Appendix.

Category: Acute 1 = EU CLP•H400

Category: Chronic 1 = EU CLP•H400

Category: Chronic 2 = EU CLP•H410

Category: Chronic 3 = EU CLP•H411

Category: Chronic 4 = EU CLP•H413

The definitions of R50, 51, and 52 correspond with that of Acute 1, Acute 2, and Acute 3 of GHS classification, respectively. However, the former is different from the latter in that Crustacea is limited to Daphnia, and that the testing time for algae is fixed at 72 hours. The requirement for R53 is  $\log K_{ow} \geq 3.0$  or  $BCF > 100$ , and is slightly wider than that in GHS classification. Moreover, test data serving as evidence are not sufficiently published, and some of them appear to be determined based on structure-action relationship or data of analogous substances. Accordingly, its data on biodegradability and bioaccumulation should be confirmed. In addition, it should be noted that R-Phrases<sup>17</sup> are often added and revised. Consequently, R-Phrases are only used as reference for GHS classification.

In EU DSD classification, many of substances categorized in aquatic toxicity are ELINCS substances (only registered companies can produce and import) for which base set tests have been conducted, and information on EINECS substances for general use is relatively limited except for that of agrochemicals.

In Japan, chemical substances are classified as Classes 1-2 Specified Chemicals, Classes 1-2 Controlled Chemicals (under the Chemical Substances Control Law), and fish acute toxicity A-D for agrochemical registry data (under the Agricultural Chemicals Control Law). Since the relationship between these definitions and that of GHS classification is not clear, those classifications cannot be used for GHS classification.

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For R-Phrase, see Appendix.



## Appendix EU R-Phrase referred in this guidance

R10	Flammable
R11	Highly flammable
R12	Extremely flammable
R15	Contact with water liberates extremely flammable gases
R20	Harmful by inhalation.
R21	Harmful in contact with skin.
R22	Harmful if swallowed.
R23	Toxic by inhalation.
R24	Toxic in contact with skin.
R25	Toxic if swallowed.
R26	Very toxic by inhalation.
R27	Very toxic in contact with skin.
R28	Very toxic if swallowed.
R34	Causes burns.
R35	Causes severe burns.
R36	Irritating to eye
R36/37	Irritating to eyes and respiratory system.
R36/38	Irritating to eyes and skin.
R36/37/38	Irritating to eyes, respiratory system and skin.
R37	Irritating to respiratory system.
R37/38	Irritating to respiratory system and skin.
R38	Irritating to skin.

R39	Danger of very serious irreversible effects.
R39/23	Toxic: danger of very serious irreversible effects through inhalation.
R39/24	Toxic: danger of very serious irreversible effects in contact with skin.
R39/25	Toxic: danger of very serious irreversible effects if swallowed.
R39/23/24	Toxic: danger of very serious irreversible effects through inhalation and in contact with skin.
R39/23/25	Toxic: danger of very serious irreversible effects through inhalation and if swallowed.
R39/24/25	Toxic: danger of very serious irreversible effects in contact with skin and if swallowed.
R39/23/24/25	Toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed.
R39/26	Very toxic: danger of very serious irreversible effects through inhalation.
R39/27	Very toxic: danger of very serious irreversible effects in contact with skin.
R39/28	Very toxic: danger of very serious irreversible effects if swallowed.
R40	Limited evidence of a carcinogenic effect
R41	Risk of serious damage to eyes.
R42	May cause sensitization by inhalation.
R42/43	May cause sensitization by inhalation and skin contact.
R43	May cause sensitization by skin contact.
R45	May cause cancer.
R46	May cause heritable genetic damage.
R48	Danger of serious damage to health by prolonged exposure.

R48/20	Harmful: danger of serious damage to health by prolonged exposure through inhalation.
R48/21	Harmful: danger of serious damage to health by prolonged exposure in contact with skin.
R48/22	Harmful: danger of serious damage to health by prolonged exposure if swallowed.
R48/20/21	Harmful: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin.
R48/20/22	Harmful: danger of serious damage to health by prolonged exposure through inhalation and if swallowed.
R48/21/22	Harmful: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed.
R48/20/21/22	Harmful: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed.
R48/23	Toxic: danger of serious damage to health by prolonged exposure through inhalation.
R48/24	Toxic: danger of serious damage to health by prolonged exposure in contact with skin.
R48/25	Toxic: danger of serious damage to health by prolonged exposure if swallowed.
R48/23/24	Toxic: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin.
R48/23/25	Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed.
R48/24/25	Toxic: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed.
R49	May cause cancer by inhalation.
R50	Very toxic to aquatic organisms.
R50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
R51	Toxic to aquatic organisms.
R51/53	Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

R52	Harmful to aquatic organisms.
R52/53	Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
R53	May cause long-term adverse effects in the aquatic environment.
R60	May impair fertility.
R61	May cause harm to the unborn child.
R62	Possible risk of impaired fertility.
R63	Possible risk of harm to the unborn child.
R64	May cause harm to breastfed babies.
R65	Harmful: may cause lung damage if swallowed.
R67	Vapours may cause drowsiness and dizziness.
R68	Possible risk of irreversible effects.