GHS Classification Guidance for Enterprises 2013 Revised Edition

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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 held in July 2003 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 [1] 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 SDS under PRTR Law[2], Industrial Safety and Health Law, Poisonous and Deleterious Substances Control Law, etc. (about 1500 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 enterprises concerned decided the Japanese principles for these parts, while taking international harmonization into account (based on the 2007 revised edition of UN GHS), and the principles were established as the Japanese Industrial Standard (JIS) Z 7252-2009: Classification method of chemicals based on “Globally Harmonized System of Classification and Labeling of Chemicals (GHS)” in FY2008. Later, it was revised reflecting the update of the UN GHS. In this Guidance, JIS Z 7252: Classification method of chemicals based on the “Globally Harmonized System of Classification and Labeling of Chemicals (GHS)” under revision is referred to as “Classification JIS.”

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[1] Ministry of Health, Labour and Welfare, Ministry of Economy, Trade and Industry, Ministry of the Environment, Consumer Affairs Agency, Government of Japan, Fire and Disaster Management Agency, Ministry of Agriculture, Forestry and Fisheries, Ministry of Land, Infrastructure and Transport and Tourism, Ministry of Foreign Affairs of Japan, the committee of UNSCEGHS (United Nations Sub-Committee of Experts on GHS), Japan Chemical Industry Association, and OECD Task Force attended.

[2] “Act on Confirmation, etc. of Release Amounts of Specific Chemical Substances in the Environment and Promotion of Improvements to the Management Thereof”

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 was produced. The “GHS Classification Guidance for the Japanese Government”, however, is a guidance to perform GHS classification of chemicals efficiently by utilizing hazard and toxicity information, and guidance for enterprises in their GHS classification of chemicals including mixtures has been desired. Therefore, “GHS Classification Guidance for Enterprises", which is consistent with Classification JIS was created separately from “GHS Classification Guidance for the Government.”

This “GHS Classification Guidance for Enterprises” includes GHS classification procedures for mixtures, which enterprises mainly produce and sell. This guidance provides classification procedures and information sources so that enterprises can carry out GHS classification on their own. It should be noted that enterprises shall be responsible for the results of GHS classification they carry out in accordance with this guidance.

This guidance is a manual based on JIS which shows the Japanese principles for GHS classification, while providing for global harmonization, to allow GHS classification to be carried out correctly and effectively by enterprises. It includes opinions of the Technical experts group of the GHS Inter-ministerial Committee for parts requiring expert's judgment as possible as references for classification.

It should be noted, however, that UN GHS includes classifications that are not adopted by JIS, and this guidance includes original Japanese judgments and considerations unique to this guidance.(Regarding classifications that have not been adopted by JIS, explanations are given where possible at the related part. Refer to them.) In the present guidance, parts inside the double-lined frames are copies extracted from the Second revised edition of UN GHS.

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.

Because fourth revised edition of UN GHS was published, parts inside the double-lined frames were revised to the copies of the fourth revised edition of UN GHS.

Any results obtained through execution of the classification with consulting this guidance, including the responsibility for the results, shall belong to the enterprises.

1st edition on March 2009
2nd edition on March 2010
3rd edition on August 2013

1-2 Chemicals to be subject to the GHS

(1) Applicable scope of the GHS

1) Substance: It means chemical elements and their compounds in the natural state or obtained by any production process, including any additives necessary to preserve the stability of the product and any impurities deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition. (Note 1)

2) Mixture (including alloy): It means a mixture or a solution composed of two or more substances in which they do not react. Alternatively, alloy means metallic material, homogeneous on a macroscopic scale, consisting of two or more elements so combined that they cannot be readily separated by mechanical means. Substances produced in the form of mixture in the production process, which are composed of two or more chemical compounds are also regarded as mixtures.

(Note 1) Substances, for example metallic elements, in which their chemical structures are same but properties change depending on particle size and the like must be classified according to the property. Especially for solids, it is often inappropriate to determine hazard of "products" based solely on their generally known hazard as chemical substances. Therefore, mainly for solids, enterprises should treat "chemical substances" as "products" and carry out predetermined tests as appropriate, and classify on the product bases.

In line with UN GHS and Classification JIS, substances or mixtures shall be correctively referred to as “chemicals,” which is synonymous with “products.” However, it should be noted that the term “product” is used with the same meaning as “article” in Poisonous and Deleterious Substances Control Law.

(2) Not applicable scope of the GHS (due to types of products and the like)

Materials to which GHS is not applied fundamentally are the following (1) and (2).

1) Molded article: Products other than liquids, powders, or particles, which formed into specified shapes or designs in manufacturing, and the whole or parts maintain the functions in the final applications depending on the shapes or designs. Under usual using conditions, the material releases very small amount, for example a trace amount, of chemicals included, and does not show any physico-chemical risks to handlers or hazards to health. Molded articled which release harmful materials are subjects to the GHS.

2) Materials being intentionally ingested or exposed such as pharmaceuticals, food additives, and cosmetics, and pesticide residues in foods and the like.

1-3 Fundamental Principles in conducting GHS classification

Enterprises shall conduct GHS classification regarding his producing or selling chemicals, using available data.

If they do not have data for classification, they should conduct classification by carrying out predetermined tests, etc. as appropriate.

However, as shown in the following GHS document, if accepted test data already exist, retesting is not required.

【The 4th revised edition of UN GHS】 (1.1.2.5 (b))

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

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

The accepted test data may include in reasonable range of handling experience, considerations based on chemical knowledge, classification results by the existing classification systems, and the like, on the chemicals. In many cases, based on such handling experience, considerations based on chemical knowledge, classification results by the existing classification systems, and the like, chemicals can be judged whether or being applicable to the Category and items needless to be tested can be shown.

For GHS classification, it should be classified based on the information of the form or physical state that are used (or may be used) after being placed on the market.

1-4 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	English terms in the original UN documents
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.	Classification not possible
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 liquid or gas is designated as “Not applicable.” When considering chemical structure, a substance not having chemical groups related to the evaluation items (Table 2-3-6-1, 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, but "Classification not possible" should be chosen instead of “"Not classified.”	Not classified

.http://www.safe.nite.go.jp/ghs/h18_bunrui.html#kaisetsuyougo; website of National Institute of Technology and Evaluation, Interpretation and glossary are partially modified.)

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 a result, some hazard classes in UNRTDG classification involves only higher hazard levels without taking into account lower hazard levels (see 2-3-9).

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

Generally, substances judged as “Not classified” in GHS classification do not mean “Not hazardous” but mean that “No evidence of hazard was found to classify the substance into any hazard class.”

Furthermore, as stated in "3-3-1 Acute Toxicity", it should be noted that classification standard for GHS 4th revised edition and JIS Classification are not identical. For example, Acute Toxicity, Category 5 in the GHS 4th revised edition is classified as "Not classified" in the JIS Classification.

It should be noted that judgment criteria for the classification are not exactly the same between UN GHS and this guidance. Therefore, English terms in the original UN documents and Japanese terms in this guidance do not exactly correspond to each other.

For the description of GHS classification results, the “GHS data input form” (GHS Inter-ministerial Committee, FY 2006) 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 the following web site of the National Institute of Technology and Evaluation (NITE).

http://www.safe.nite.go.jp/english/ghs_index.html“Supporting tools for GHS Classification” can be downloaded from the website of the National Institute of Technology and Evaluation

1-5 Classification criteria and procedure for mixtures

(1) Classification criteria and procedure for physical hazards

Criteria for classification of hazards relating to chemicals shall be stipulated in Part 2.

Recommended procedure for classification of mixtures shall be as follows:

a) Classification of a mixture shall be carried out based on the test data of the mixture itself, if available.

b) If a mixture contains known physical hazard components, classification procedure for the hazard shall be carried out. It should be noted that classification by calculation may be acceptable for flammable gases and oxidizing gases.

(2) Classification criteria and procedure for health hazards and environmental hazards

Classification criteria for hazards of chemicals with regard to health hazards and environmental hazards shall be stipulated in Part 3 and in Part 4, respectively.

Recommended criteria for classification of mixtures shall be as follows:

a) Classification of a mixture shall be carried out based on the test data of the mixture itself, if available.

b) Unless the test data of a mixture is available, it is preferable to judge whether classification of the mixture is possible or not, taking the bridging principle (see 5.5) into account.

c) If neither a) nor b) is applicable, hazards shall be estimated according to known information about the hazards of the component substances. In this case, classification shall be carried out using the method of classification of mixtures stipulated in Annexes B and C.

In many cases, reliable data on the mixtures as a whole are hardly expected with regard to the hazard classes of germ cell mutagenicity, carcinogenicity, and reproductive toxicity. Therefore, mixtures shall be classified with regard to these hazards based on the available information about each individual component using the concentration limits provided by Annex of each. If data on the whole mixture are so decisive as to be stated in the Annex, classification of the mixture may be modified based on the data on a case-by-case basis.

Part2 Physical Hazards Guidance

2-1 Summary of GHS classification

Figure 2-1-1 shows the workflow of GHS classification (Physical Hazards).

Figure 2-1-1 Narrowing down the applicable hazard classes (1)
Narrowing down based on states of chemicals

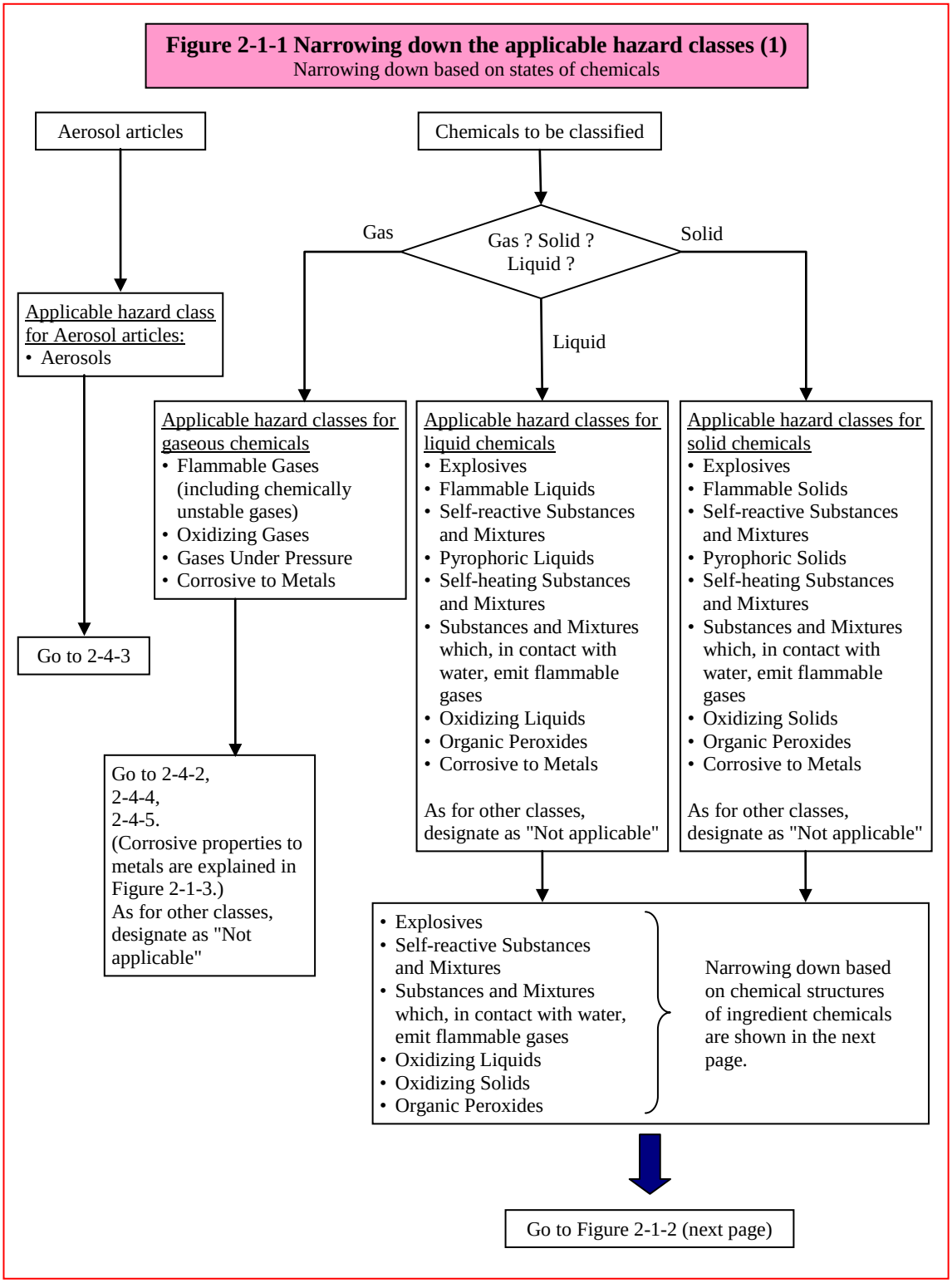


Figure 2-1-2 Narrowing down the applicable hazard classes (2)

Narrowing down based on molecular structures of ingredient chemicals

If chemicals (mixture ingredients) do not contain in their molecules chemical groups shown in Table 2-3-7-1.

As for Explosives, designate as "Not applicable".

If chemicals (mixture ingredients) do not contain in their molecules chemical groups shown in Tables 2-3-7-1 or 2-3-8-1.

As for Self-reactive Substances and Mixtures, designate as "Not applicable".

If chemicals (mixture ingredients) do not contain in their molecules metals or metalloids.

As for Substances and Mixtures which, in contact with water, emit flammable gases, designate as "Not applicable".

1. Organic substances which do not contain oxygen, chlorine, or fluorine, or which contain any of these elements that are bound to carbon or hydrogen only.
2. Inorganic substances not containing oxygen or any halogen element.

As for Oxidizing Liquids and Oxidizing Solids, designate as "Not applicable".

1. Inorganic substances
2. Organic compounds which in their molecules do not contain any of -O-O- linkage.

As for Organic Peroxides, designate as "Not applicable".

Narrowing down based on contents of ingredient chemicals and the like

Chemicals containing explosive chemical groups and mixtures containing them, and provided that
1. Containing chemical groups in Table 2-3-7-1 including oxygen but the calculated result of oxygen balance is less than -200.
   (Calculation) As for carbon, hydrogen, and oxygen in molecular formula (CxHyOz),
   Oxygen balance = -1600 x (2x + y/2 -z)/molecular weight
2. In mixtures of inorganic oxidizing substances and organic substances, total concentrations of inorganic oxidizing substances is less than 15% by mass when the Category of oxidizing substances is 1 or 2, or less than 30% by mass when the Category of oxidizing substances is 3.

As for Explosives, designate as "Not classified".

In mixtures including organic peroxides,
1. When the content of hydrogen peroxide is not more than 1.0%, and activated oxygen amount based on organic peroxides is not more than 1.0%.
2. When the content of hydrogen peroxide is more than 1.0% and not more than 7.0%, and activated oxygen amount based on organic peroxides is not more than 0.5%.

As for Organic Peroxides, designate as "Not classified".

Go to Figure 2-1-3 (next page)

Figure 2-1-3 Narrowing down the applicable hazard classes (3)
Narrowing down based on existing information, in-house information, etc.

(1) Judgment based on handling experiences:
(It should be noted that the responsibility for judgment shall belong to the enterprises)
1. It is recognized not to react with water.
2. It is known that the substance (mixture) dissolves into water and makes a stable mixture.
(In cases of 1, 2, Substances and Mixtures which, in contact with water, emit flammable gases - "Not classified")
3. It is recognized not to auto-ignite under handling in air.
(Pyrophoric Liquids and Solids - "Not classified")

(2) Judgment based on fundamental chemical knowledge on oxidation/reduction reactions (including combustion and metal corrosion):
(Note that the responsibility for judgment shall belong to the enterprises)
1. Reductive substances (Oxidizing Liquids and Solids, Corrosive to Metals - "Not classified")
2. Oxidative substances
(Substances and Mixtures which, in contact with water, emit flammable gases - "Not classified")
3. Neutral oxidative/reductive substances
(Oxidizing Liquids and Solids, Substances and Mixtures which, in contact with water, emit flammable gases - "Not classified")
4. Substances being not oxidative and with pH near neutral (Corrosive to Metals - "Not classified")
5. Noncombustible or flame-resistant substances
(Flammable Liquids, Flammable Solids, Self-heating Substances and Mixtures - "Not classified")

(3) Judgment based on existing classification results, etc.:
(Note that the responsibility for judgment shall belong to the enterprises)
1. As for very similar articles, GHS classification is available. (examine and utilize for categorization.)
2. Published classification result by NITE is available. (examine and utilize for categorization.)
3. UNRTDG classification result is available. (examine and utilize for categorization.)
4. Classification result according to the Fire Defense Law is available.
(examine and utilize for categorization.)
5. In-house data can be utilized for GHS classification are available.
(examine and utilize for categorization.)

(4) Judgment based on preliminary measurement results:
1. Organic substances including chemical groups associated with explosive properties but the exothermic decomposition energy is less than 500 J/g and the onset of exothermic decomposition is below 500°C.
(Explosives - "Not classified")
2. Substances including chemical groups associated with explosive properties or self-reactivity but their heat of decomposition is less than 300 J/g, or their SADT is greater than 75°C for a 50 kg package.
(Self-reactive Substances and Mixtures - "Not classified")

(5) Tests are impossible or needless:
1. Due to hazards of such as Explosives (including desensitized explosives), Self-reactive Substances and Mixtures, and Organic Peroxides, predetermined tests are impossible.
(Flammable Liquids, Flammable Solids, Self-heating Substances and Mixtures)
2. It can be expected to be "No hazard" based on the amount of consumption of the product, packaging units, and handling methods of articles[2].

→ (Omit the predetermined tests.)
"Classification not possible"
Ground (No data available)

(6) Handling and testing methods are not established in GHS.
1. Desensitized explosives - (Explosives)
2. Liquids - (Self-heating Substances and Mixtures)
3. Gases, solids - (Corrosive to Metals)

→ "Classification not possible"
Ground (Testing methods are not established.)

When hazards cannot be ignored, it is preferable to perform predetermined tests and categorize.

1) "enterprises" include consignors.

2) For example, "benzene substituted by deuterium(s)" is distributed with only small units as a reagent. Flammable liquids may be classified as "Classification not possible" without performing measurement of flash points. It is consistent with GHS rules to designate as "Category 2" by estimating from normal benzene.

2-2 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.

2-2-1 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 that of the United Nations Recommendations on the Transport of Dangerous Goods (UNRTDG) (hereinafter abbreviated as UNRTDG classification) that has been utilized under an international consensus, the classification in GHS accords, in principle, with that of UNRTDG classification. However, as GHS classification includes dangerous goods whose transportation is prohibited (e.g., unstable explosives) and substances not applicable to dangerous goods in UNRTDG classification, some hazard classes categories could not be found in UNRTDG classification (Table 2-3-9-1).

Although GHS hazard classification shall be performed based on predetermined test results (or information with the equivalent values), in whose many items, testing methods of UNRTDG are adopted. Accordingly, in GHS classification to a given substance on the basis of its physicochemical properties and designating its UNRTDG classification, the result can be utilized as reference for GHS classification. For this purpose, the recommendations (1), UNRTDG can be utilized as database, and related literatures (2) and (3) may be used as complement. As for classifications by the GHS Inter-ministerial Committee in Japan, refer to (4).

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

The recommendations are presented, like the GHS recommendations, by the UN Committee of Experts on the Transport of Dangerous Goods (CETDG /GHS), and have 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://jonai.medwel.cst.nihon-u.ac.jp/uploadfiles/file/pdf/orange1.pdf (Japanese version, Fifteenth revised edition, 2007)

A website (of the National Institute of Technology and Evaluation) posting UN numbers and TGD classification results for individual substances is given below. Preferably, the UN numbers and TGD classification results on the website 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 edition is the latest version is for 2008, and the classification is identical to that of (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 website 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 3rd revised version was released in 2008). (edition of “Emergency Response Guidebook: Application to the Container Yellow Card Labeling System”, Japan Chemical Industry Association). According to the Guidebook, Japan's yellow cards are required to indicate one of the guide numbers 111-172.

(4) Classifications by the GHS Inter-ministerial Committee in FY 2006

At the following URL, the list of substances (1424 substances) classified by the GHS Inter-ministerial Committee in FY 2006 is posted. These substances are mainly chemicals, and their GHS classification was performed based on literature information.

http://www.safe.nite.go.jp/ghs/list.html

2-2-2 Data collection systems of physical properties

Available databases for physical properties that can be used other than UNRTDG classification are as follows.

Table 2-2-2-1 Reference documents for data of physical properties, physicochemical testing methods, and the like

No.	Name of the document	Brief introduction
1.	The Chemical Risk Information Platform (CHRIP) http://www.safe.nite.go.jp/english/db.html	It is a search system for chemicals of the National Institute of Technology and Evaluation, which include abundant information such as physicochemical properties, CAS numbers, METI numbers, domestic laws and regulations, and UN numbers.
2.	Gmelins Handbuch der Anorganischen Chemie and Gmelin Handbook of Inorganic and Organometallic Chemistry 8th Ed (Gmelin)	It contains property information of inorganic compounds (including organometallic compounds), etc. and is said to have information of 1.1million substances. It was originated by Leopold Gmelin in 1817. The series has been published in English since 1980, and the latest digitized version is available in CD format.
3.	Beilsteins Handbuch der Organischen Chemie and Beilstein Handbook of Organic Chemistry 5th ed. (Beilstein)	It contains synthesis methods and physicochemical propertied of organic compounds (7million substances), etc. It was originated by K.Beilstein. The publication of the 4th edition was started in 1914, and supplementary volumes were published subsequently. The book started to be published in English from its 5th enlarged edition, published in 1980. It is also digitized and provided in CD format now.
4.	The Merck Index 14th Ed (Merck)	This is a handbook for reagents and pharmaceutical materials and includes 10 thousands substances.
5.	Chemical Abstracts (CA)	It is widely used as an information source for general chemicals (including patents).
6.	International Critical Tables of Numerical Data, Physics, Chemistry and Technology (ICT)	It contains physical data of chemical materials, and in which thermodynamic data are abundantly described.
7.	European Chemicals Agency (ECHA): IUCLID data can be downloaded from http://esis.jrc.ec.europa.eu/index.php?PGM=dat	Hazard data are not peer-reviewed and care should be taken in using, while physical properties may be used.

8.	(1) Hazardous Substances Data Bank (HSDB) http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB (2) International Chemical Safety Cards (ICSC) http://www.ilo.org/dyn/icsc/showcard.home Japanese version: http://www.nihs.go.jp/ICSC/	They are Risk Assessment Documents, and include physical properties also. ICSC is provided by the International Program on Chemical Safety (IPCS). ICSC, for which ILO in charge of physical hazards such as flashpoints, auto-ignition points, and explosive limits, and WHO in charge of human health hazards, are translated into 16 languages other than English including Japanese. At present, cards for about 1,700 chemicals are prepared, and chemicals are searchable by CAS number.
9.	Manual of Tests and Criteria, fifth revised edition http://jonai.medwel.cst.nihon-u.ac.jp/uploadfiles/file/pdf/TDG%20Manual%20of%20T&C%205th%20jp.pdf (Japanese edition)	It includes testing methods defined by UNRTDG. A bilingual English and Japanese UNRTDG Manual of Tests and Criteria Rev.5 is published by The Chemical Daily Co., Ltd.
10.	OECD, eChemPortal http://www.echemportal.org/echemportal/index?pageID=0&request_locale=en	This is the site of eChemPortal of OECD. Physicochemical data can be searched from the CAS number or the name of the substance.
11.	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.

Other information sources are as follows.

○ Ullmanns Encyklopaedie der Technischen Chemie and Ullmann’s Encyclopedia: Industrial Organic Chemicals (Ullmann)

○ Handbook of Physical Properties of Organic Chemicals (about 13000 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.

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

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

○ CRC Handbook of Chemistry and Physics (CRC)

○ HODOC File (Handbook of Data on Organic Compounds) (HODOC) (25580 substances as of 2008)

This is a database version of the CRC handbook.

○ Sax’s Dangerous Properties of Industrial Materials (Sax)

Wiley-VCH Publishing has published this database of dangerous physical properties of industrialized products, and its 12th edition was published in 2012. Data on reactivity, combustibility and explosibility of approximately 28000 substances are listed. Information of the database can be searched by CAS number.

○Lange’s Handbook of Chemistry 16th Ed. (2005)

○SRC PhysProp Database

(http://www.srcinc.com/what-we-do/databaseforms.aspx?id=386)

2-2-3 Data collections of physicochemical hazard data

General data collections on physical hazard data are as follows. 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. As some hazard databases include health hazard data, the ones that predominantly contain the descriptions of physical hazards are shown in this section.

Table 2-2-3-1 Data collections of physical hazard data

No	Name of the document	Brief introduction
1	Hommel Handbook of Dangerous Goods (Hommel)	The 1987 version was translated into Japanese by Rokuro Arai and published by Springer-Verlag Tokyo in 1991.
2	Incompatible Hazard Handbook of Chemicals, the 2nd edition (Tokyo Fire Department)	The first edition was supervised by Tadao Yoshida and Masamitsu Tamura and published by Nikkan Kogyo Shinbun in 1997
3	Dangerous Goods Data Book, the 2nd edition	It was compiled by the Tokyo Consolidated Fire Prevention Association and published by Maruzen in 1993.
4	Bretherick’s Handbook of Reactive Chemical Hazards and Bretherick's Handbook of Dangerous Goods (5th edition) (Bretherick)	Its Japanese version was translated and supervised by Masamitsu Tamura and published by Maruzen in 1998
5	Chemical Substances Safety Data Book, revised and enlarged edition	This data book, edited by the Chemical Substances Safety Information Workshop and supervised by Yoichi Uehara, was first published by Ohmusha in 1997.

Other information sources are as follows:

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

○ Dangerous Goods Data Book (Tokyo Fire Department)

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

○ International Chemical Safety Cards (ICSC)

http://www.ilo.org/dyn/icsc/showcard.home

Japanese version of International Chemical Safety Cards (ICSC): http://www.nihs.go.jp/ICSC/

○ Fire Protection Guide to Hazardous Materials (NFPA)

This Fire Prevention Guide was compiled by NFPA (the U.S. National Fire Protection Association). The 14th edition is now available, listing data on physical hazards such as flashing points, ignition points, and explosion limits, and individual substances can be searched by CAS number.

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

The evaluation of physical hazards of Gases in GHS is based on the following ISO Standards. 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 10156:2010 Gases and gas mixtures – Determination of fire potential and oxidizing ability for the selection of cylinder valve outlets (2010-04-01)

B) ISO 5145 Cylinder valve outlets for gases and gas mixtures – Selection and dimensioning. (2004-04-15)

Assessment methods for Oxidative gases and Flammable gases are described in A). In B), classification of gas substances is described, which is informative.

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

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

○ SIDS Initial Assessment Report

This report (SIAP) is published by OECD and its Japanese version is published by the Japan Chemical Industry Ecology-Toxicology & Information Center (JETOC) (an incorporated association). The SIDS report can be downloaded from below:

http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html.

The Japanese version can also be downloaded from below:

http://www.jetoc.or.jp/safe/siap_top.html

○ International Uniform Chemical Information Database (IUCLID)

This database is developed by the European Chemicals Agency (ECHA) and can be downloaded from

http://esis.jrc.ec.europa.eu/index.php?PGM=dat

2-2-4 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, which were relocated to Table 3-2, Annex VI of the CLP regulations after the establishment of CLP Regulations, cannot be used for reference as they are in GHS classification and categorization. The Japanese version of this document was published by JETOC in 2009 as “EU: List of Dangerous Substances (8th 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) Utilization of Fire Defense Law test data

In Japan, physical hazards are regulated by Fire Defense Law, and testing methods and evaluation criteria based on the Fire Defense Law are defined. Test data of individual articles have been accumulated. Until now, in examination of GHS category judgment, Fire Defense Law test and GHS test have not been compared, however it is preferable to utilize Fire Defense Law test data in the range where possible.

Table 2-2-4-1 Correspondence Table of Fire Defense Law hazardous materials to GHS hazard classes

Fire Defense Law	GHS
Dangerous material Class 1 "Oxidizing Solids"	2. 14 "Oxidizing Solids"
Dangerous material Class 2 "Flammable Solids"	2.7 "Flammable Solids"
Dangerous material Class 3 "Pyrophoric materials and Water-prohibiting materials"	2.9 "Pyrophoric Liquids" 2.10 "Pyrophoric Solids" 2.12 "Substances and mixtures which, in contact with water, emit flammable gases"
Dangerous material Class 4 "Inflammable Liquids"	2.6 "Flammable Liquids"
Dangerous material Class 5 "Self-reactive materials"	2.15 "Organic Peroxides" 2.8 "Self-reactive Substances and Mixtures"
Dangerous material Class 6 "Oxidizing Liquids"	2.13 "Oxidizing Liquids"

Since most testing methods of Fire Defense Law are different from that defined in GHS, most classification judgments of Fire Defense Law are not available in GHS classification. Accordingly, it is preferable to perform GHS test for articles which already designated as hazardous materials by Fire Defense Law. While, as for materials designated as "non-dangerous materials" by Fire Defense Law, their test results may be utilized for estimation of "Not applicable" in GHS. As for evaluation of test results of individual dangerous materials, explanation will be given in items of corresponding GHS hazardous substances or mixtures.

(3) 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.

2-3 Classification of Physical Hazards based on physical, chemical states and chemical structure

2-3-1 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.

2-3-2 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.

2-3-3 Gases

Gases are defined as (i) substance whose vapour pressure exceeds 300 kPa (absolute pressure) 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 in the 4th revised edition of UN GHS.

2-3-4 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 4th 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 A of the European Agreement Concerning the International Carriage of Dangerous Goods by Road (ADR).

2-3-5 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 4th 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.

2-3-6 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 2-3-7), they shall be tested as “explosives” (2-4-1) and “self-reactive substances and mixtures” (2-4-8). When they contain chemical groups related to self-reactivity (see 2-3-8), they shall be tested as “self-reactive substances and mixtures” (2-4-8).

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” (2-4-12).

Organic compounds containing oxygen, fluorine, or chlorine, any of which is bound to elements other than carbon and hydrogen, and inorganic compounds containing oxygen or halogen should be tested as "oxidizing liquids" (2-4-13) or "oxidizing solids" (2-4-14).Organic compounds containing the -O-O- structure in their molecules, or mixtures containing such compounds, should be tested as “Organic Peroxides”(2-4-15).

The following table summarizes the above.

Table 2-3-6-1 Classification of Physical Hazards based on physical, chemical states and chemical structure

Section	Hazard Class	Gas	Liquids	Solid	Classifiable chemical structure
2-4-1	Explosives	X	○	○	Substances containing chemical groups related to explosibility in their molecules (see 2-3-7)
2-4-2	Flammable Gases (including chemically unstable gases)	○	X	X	
2-4-3	Aerosols	○	○	○	
2-4-4	Oxidizing Gases	○	X	X	
2-4-5	Gases Under Pressure	○	X	X	
2-4-6	Flammable Liquids	X	○	X	
2-4-7	Flammable Solid	X	X	○	(Powdered, granular, or pasty substances are to be assessed.)
2-4-8	Self-reactive Substances and Mixtures	X	○	○	Substances containing chemical groups related to explosibility as well as chemical groups related to self-reactivity in their molecules (see 2-3-7, 2-3-8)
2-4-9	Pyrophoric Liquids	X	○	X	
2-4-10	Pyrophoric Solids	X	X	○	
2-4-11	Self-heating Substances and Mixtures	X	∆	○	
2-4-12	Substances and mixtures which, in contact with water, emit flammable gases	X	○	○	Substances containing metals or metalloids (Si, Ge, As, Sb, Bi, etc.)
2-4-13	Oxidizing Liquids	X	○	X	Organic compounds containing oxygen, fluorine, or chlorine, any of which is bound to elements other than carbon and hydrogen, and inorganic compounds containing oxygen or halogen
2-4-14	Oxidizing Solids	X	X	○	
2-4-15	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) in the 4th revised edition of UN GHS
2-4-16	Corrosive to Metals	Δ	○	Δ	

○:Classifiable, X:Not applicable, △: Classifiable, but no test method has been designated

When a substance does not contain chemical groups mentioned in the column for “classifiable chemical structure” in Table 2-3-6-1, the “classification result” should be “not applicable”.
Example: ”Not applicable” in the classification 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”. As for substances with higher hazards, lower hazards may not be evaluated or are needless to be evaluated. For example, for Explosives, self-reactivity is needless to be evaluated. And for Pyrophoric Solids, self-heating may not be evaluated. If such are clearly shown in GHS document, they are classified as "Not applicable" with regard to hazard classes with low precedence.

When it is not regarded as “Not applicable” in UN GHS and if predetermined tests cannot be carried out, classify as "Classification not possible". For example, for solid Explosives, tests for Flammable Liquids are not possible (see Figure 2-1-3 (5) 1).

2-3-7 Chemical groups related to explosibility

【GHS 4th 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:

Table 2-3-7-1 Chemical groups concerned with explosive properties

Generic term of chemical groups	Names of chemical groups	Chemical structure of chemical groups	Comment
Unsaturated C-C bond	Acetylenes acetylides 1,2-dienes	-C≡C- -C≡C-M -C=C=C-	R: alkyl, cycloalkyl functional groups R': alkyl, cycloalkyl functional groups M: Metals such as copper, silver Y: Cl, Br, I M': Na, K, Li, NH_4
C-metals	Grignard reagents organo-lithium compounds	R^1-MgX R^2-Li	
Contiguous nitrogen atoms (NN compounds)	Azides hydrazines aliphatic azo compounds diazonium salts sulfonyl hydrazides	R^0-N=N=N R^1-NH=NH R^2-N≡N R^3-N^+≡N-Y^- -SO_2-$NHNH_2$	
Contiguous oxygen atoms	Peroxides Ozonides	-O-O- -C-O-O-O-C-	
Contiguous N-O compounds	Hydroxylamines nitrate salts nitrate esters nitro compounds nitroso compounds N-oxides 1,2-oxazoles	-C-NHOH M-NO_3 R^1-ONO_2 R^2-NO_2 R^3-NO ≡N→O 	
N-halogen	Chloroamines	H_2NCl	

	Fluoroamines	NH_2F	
O-halogen	Chlorates	M'-ClO_3	
	perchlorates	M'-ClO_4	
	iodosyl compounds	-IO	

(quoted from "Manual of Test and Criteria" of UNRTDG. Chemical groups were added.)

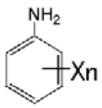
2-3-8 Chemical groups related to self-reactivity

【GHS 4th revised edition】(2.8.4.2 (a))

(a) There are no chemical groups present in the molecule associated with explosive or self-reactive properties; examples of such groups are given in Tables A6.1 and A 6.2 in the Appendix 6 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria;*

Examples of the chemical groups are shown in Table 2-3-8-1.:

Table 2-3-8-1 Chemical groups concerned with self-reactive properties

Generic term of chemical groups	Names of chemical groups	Chemical structure of chemical groups	Comment
Inter- reacting groups	Aminonitriles haloanilines organic salts of oxidizing acids	-$CHNH_2C{\equiv}N$ 	X: Cl, Br, I, n: 1-5 Oxidative acids: nitric acid, chloric acid, chromic acid
S=O	Halogenated sulfonyl compounds, sulfonyl cyanides, sulfonyl hydrazides	-SO_2X -SO_2CN -$SO2NHNH_2$	for example, -SO_2Cl
P-O	Phosphites	$P(O)_3$	
Strained rings	Epoxides Aziridines	 Epoxides  aziridines	
Unsaturated hydrocarbons	Olefins Cyanates	-C=C- -OCN	

(quoted from "Manual of Test and Criteria" of UNRTDG. Chemical groups were added.)

2-3-9 Relationship between UNRTDG classification and GHS Categorization

UN Regulation on the Transport of Dangerous Goods has been in effect for nearly half a century with improvements, and test data has also been accumulated. Chemical substances and mixtures given UN numbers with appropriate procedures can be classified using its classification information regarding the items. Especially for GHS physicochemical hazard evaluation, UNRTDG classification serves as a prime ground.

Although GHS physicochemical classification nearly corresponds with classifications on the Transport of Dangerous Goods, there are some differences. Comparisons are shown in Table 2-3-9-1.

Within health hazards, for skin corrosion, test method and evaluation category of GHS Category 1 corresponds with that of UNRTDG Class 8. GHS sub-category 1A, 1B, 1C are identical to UNRTDG Class 8 Packing group I, II, III. The term "some authorities" used in Table 3.2.1 in the UN GHS document 3.2.2.4 refers to Maritime Bureau of Ministry of Land, Infrastructure, Transport and Tourism of Japan or U.S.DOT (Department of Transportation of the U.S.) or transportation authorities of each country.

For acute toxicity, GHS acute toxicity and UNRTDG Division 6.1 are in correspondence, and their testing methods are in common, but the boundaries of Categories are not in accord. It is possible to determine packing group and so on by applying acute toxicity data which were used for GHS classification, to UNRTDG Division 6.1 definitions.

As for hazards to the aquatic environment, GHS classification has been adopted by IMO and also has been included in Japanese Dangerous Goods Regulations, and was notified through official gazettes on 22 December 2008. Packages which fall into GHS Category Acute 1, Category Chronic 1 and Category Chronic 2 are regarded as "environmentally hazardous materials".

GHS classification procedures adopted by the government are as follows.

When referring to UNRTDG classification, points to consider for search methods and the utilization of UNRTDG classifications are as follows.

(1) Use documents already shown in 2-2-1 for searching UNRTDG classification. In this item, search procedures and relationships with Japanese Dangerous Goods Regulations will be described.

1) Determine the UN number of the substance.

- Search for the UN number by the name of the substance and CAS number on the Chemical Risk Information Platform (CHRIP).

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

CHRIP includes UNRTDG classes.

- The UN number can be searched from the "Emergency Response Guidance".

2) Search for the UNRTDG classification

- Search for from Home page of UN (in English)
  http://www.unece.org/trans/danger/publi/unrec/rev15/English/03E_Part3.pdf
  Use the research function and search for the UNRTDG classification by the UN number or the substance name.
- The UNRTDG classification may be searched from the Annex 1 of the "Public Notice to provide Standards, etc., for Carriage of Dangerous Goods by Ship" (hereinafter abbreviated as "Dangerous Goods Notice")
  (http://wwwkt.mlit.go.jp/notice/pdf/201307/00006015.pdf), or " Public Notice to provide Regulations for the Carriage and Storage of Dangerous Goods by Ship". The published classification, however, lags behind the published classification by UN.
  When searching out from Dangerous Goods Notice, Pick up the "UN number", "substance name", "classification", "class", "packing group", and "subsidiary class".

(2) In both of Guidance for the Japanese Government and for Enterprises, utilization of UNRTDG classification is limited to Physical Hazards (Class 1 to 5), and classes 6 and 8 are not used in GHS classification.

(3) Corrosion in UNRTDG, including both of metal corrosion and skin corrosion, is not consistent with "Corrosive to Metals" in GHS classification.

(4) UNRTDG includes hazards other than the primary hazard (the primary hazard class), that is subsidiary hazard classes. Care should be taken of subsidiary classes.

(5) The method to use both the primary hazard class and subsidiary hazard classes as the situation demands will be explained later.

(6) Table 2-3-9-1 shows the correspondence between UNRTDG and GHS classifications.

Table 2-3-9-1 Comparison between GHS classification and UNRTDG classification

GHS Class	GHS Category	UNRTDG (Note ( ) is a subsidiary 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

Table 2-3-9-1 Comparison between GHS classification and UNRTDG classification

GHS Class	GHS Category	UNRTDG (Note ( ) is a subsidiary hazard)
2) Flammable Gases (including chemically unstable gases)	Category 1	2.1 and 2.3 (2.1)
	Category 2*	As for GHS Category 2 Flammable Gases, information is not available from UNRTDG.
3) Aerosols	Category 1*	Although the same testing methods and judging criteria as that of GHS are used for aerosols (UN1950), difference in category 1-3 is not designated in the list of dangerous substances in UNRTDG 3.2.[#]
	Category 2*	
	Category 3*	
4) Oxidizing Gases	Category 1	2.2(5.1) or 2.3(5.1)
5) Gases Under Pressure	Group Compressed	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 200 kPa (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	
	Group Refrigerated	
	Group Dissolved gas*	
6) Flammable Liquids	Category 1	3 I
	Category 2	3 II
	Category 3	3 III
	Category 4*	Since they are not dangerous goods, they have no UN number.
7) Flammable Solid	Category 1	4.1 II
	Category 2	4.1 III
8) Self-reactive Substances and Mixtures	Type A*	Since their transport is prohibited, they have no UN number of dangerous goods transport.
	Type B	UNRTDG4.1, UN3221, 3222, 3231, 3232
	Type C	UNRTDG4.1, UN3223, 3224, 3233, 3234
	Type D	UNRTDG4.1, UN3225, 3226, 3235, 3236
	Type E	UNRTDG4.1, UN3227, 3228, 3237, 3238
	Type F	UNRTDG4.1, UN3229, 3230, 3239, 3240
	Type G*	Since they are not dangerous goods, they have no UN number.
9) Pyrophoric Liquids	Category 1	4.2 I (Liquids)
10) Pyrophoric Solids	Category 1	4.2 I (Solid)
11) Self-heating	Category 1	4.2 II

Table 2-3-9-1 Comparison between GHS classification and UNRTDG classification

GHS Class	GHS Category	UNRTDG (Note ( ) is a subsidiary hazard)
Substances and Mixtures	Category 2	4.2 III
12) Substances and mixtures which, in contact with water, emit flammable gases	Category 1	4.3 I, 4.2(4.3)
	Category 2	4.3 II
	Category 3	4.3 III
13) Oxidizing Liquids	Category 1	5.1 I
	Category 2	5.1 II
	Category 3	5.1 III
14) Oxidizing Solids	Category 1	5.1 I
	Category 2	5.1 II
	Category 3	5.1 III
15) Organic Peroxides	Type A*	Since their transport is prohibited, they have no UN number of dangerous goods transport.
	Type B	UNRTDG5.2, UN3101, 3102, 3111, 3112
	Type C	UNRTDG5.2, UN3103, 3104, 3113, 3114
	Type D	UNRTDG5.2, UN3105, 3106, 3115, 3116
	Type E	UNRTDG5.2, UN3107, 3108, 3117, 3118
	Type F	UNRTDG5.2, UN3109, 3110, 3119, 3120
	Type G*	Since they are not dangerous goods, they have no UN number.
16) Corrosive to Metals	Category 1*	The UN dangerous goods transport Class 8 includes Skin Corrosion.

* A Category which is inconsistent with that of UN transport classification. Information is not sufficient enough to assign GHS classification based on the UN number and the UNRTDG class.
# Under special order 63 in UNRTDG, GHS Category 1 and 2 are designated UNRTDG 2.1, GHS Category 3 is designated UNRTDG 2.2.

UNRTDG classification in which each chemical has individual UN numbers has been examined by experts in the organization concerned, and is reliable. However, the classification of N.O.S (not otherwise specified: a generic term for not specifiable substances, for example, "all other Explosives") classification is left to the judgment by the enterprise (including consignors). 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 in the Government project.

○ Precedence in UNRTDG Classification

In UNRTDG 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 UNRTDG 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 UNRTDG classification. In this guidance, the tables below are used for the judgment.

- UNRTDG 17th revised edition (2011) 2.0.3.3 Precedence of hazard characteristics (P.53-54),
- IMDGC 2010Ed. 2.0.3 Classification of substances, mixtures and solutions with multiple hazards (precedence of hazard characteristics) (P.41-42), or
- The “Dangerous Goods Regulations, Appendix 1, Recital 3” (see below).

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

As shown in the “Dangerous Goods Regulations, Appendix 1, Recital 3”, Explosives, Self-reactive Substances and Mixtures, Pyrophoric Substances, and Organic Peroxides have the highest precedence. Substances belonging to theses 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, Appendix 1, Recital 3.

The “Dangerous Goods Regulations, Appendix 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, 17th revised edition, 2011". Note that the latest Table of the Dangerous Goods Regulations, Annex 1, Recital 3 has empty columns.

For example, azodicarbonamide (UN 3242 Division 4.1, Packing Groups II) shall be flammable solids Category 2 in GHS classification. Since it is not classified in the higher precedence Division 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 Groups I takes precedence, it is not relevant. Since, however, Packing Groups II and III have lower precedence, test results in UNRTDG classification can not be estimated. Accordingly, based on UNRTDG 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.

Table of the Dangerous Goods Regulations, Appendix1, Recital 3

	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
.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, 17th revised edition, 2011". Note that the underlined figures in this table are empty in the latest table of the Dangerous Goods Regulations, Appendix 1, Recital 3.

Subsidiary risks

If a UNRTDG classification includes a subsidiary class, classification may be performed by utilizing the table of the Dangerous Goods Regulations, Appendix 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 Division 6.1, Subsidiary risk 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 risk 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 risk 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 UNRTDG classification alone.
(Depending on its flashing point of 37°C, it shall be Category 3.)

2-4 Classification and details of physical hazards

2-4-1 Explosives

(1) Definitions

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

【GHS 4th revised edition】(2.1.1)

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

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

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

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

2.1.1.2 The class of explosives comprises:

(a) Explosive substances and mixtures;

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

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

(2) Classification criteria in GHS

【GHS 4th revised edition】(2.1.2)

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:

(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);

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

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

(i) combustion of which gives rise to considerable radiant heat; or

(ii) which burn one after another, producing minor blast or projection effects or both;

(d) Division 1.4 Substances, mixtures and articles which present no significant hazard: substances, mixtures and articles which present only a small hazard in the event of ignition or initiation. The effects are largely confined to the package and no projection of fragments of appreciable size or range is to be expected. A n 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 (Narrowing down the applicable classes by the state and molecular structure of the substance)

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 relating to explosibility (Table 2-3-7-1), it shall be “Not applicable”, and indicate “It does not contain chemical groups relating to explosibility” for “Classification Grounds and Problems”.

B) Judgment of Not classified (Narrowing down the applicable classes by the contents of ingredients or preliminary measurement results)

For substances having explosive chemical groups including oxygen and falling under the provisions in the UN GHS 4th revised edition 2.1.4.2.2(b)-(d) (based on calculation result of oxygen balance, exothermic decomposition energy, and content of inorganic oxides), “Classification result” shall be “Not classified”, and “based on calculation result (calculated value: XX)” shall be indicated for “Classification Grounds”. In case oxygen balance is -144, a negative number, it shall be described as “Although oxygen balance is -144, higher than the criteria: -200,” instead of “oxygen balance is above -200,” because positive and negative number expression is sometimes confusing.

【UN GHS 4th 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 A6.1 in Appendix 6 of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria; or

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

The oxygen balance is calculated for the chemical reaction:

$C_xH_yO_z + [x + (y/4) - (z/2)] O_2 \rightarrow xCO_2 + (y/2)H_2O$

using the formula:

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

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

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

less than 15%, by mass, if the oxidizing substance is assigned to Category 1 or 2;

less than 30%, by mass, if the oxidizing substance is assigned to Category 3.

C) Classification based on existing classifications ant the like (such as UNRTDG)

If the Category is not determined after following the procedure described below, perform the predetermined tests (or tests providing the equivalent judgment), and determine the Category.

1) Substances cited in (7) shall be classified according to the UNRTDG Classification.
2) Based on results of test series for UNRTDG 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.

3) Alternatively, when the existing classification results shown in Figure 2-1-3 (3) are available, after examination of the classification result and the evidence data, the Category may be determined.

4) In UNRTDG classification, explosives take precedence over other hazards along with pyrophoric substances, self-reactive substances and mixtures, and organic peroxide. Therefore, if a substance has been classified as another lower hazard class (except N.O.S.), "Classification Result" can be "Not classified" with an indication for "Classification Grounds and Problems" that "It is classified in ○○, so considered to be not applicable to hazards of the highest precedence, "explosives"."

(4) Testing methods

Classify unstable explosives and explosives of Category 1.1 through Category 1.6 with the following tests as the center.

Explosive properties: (UNRTDG Manual of Tests and Criteria Item 12, Test series 2)

Intentional explosives (including chemicals and articles produced intended for substantial explosion or effect of explosive article) shall start with UN Test series 3 skipping UN Test series 2.

Sensitivity: (UNRTDG Manual of Tests and Criteria Item 13, Test series 3)

Thermal stability: (UNRTDG Manual of Tests and Criteria Item 13.6.1, Test series 3 (C))

- Articles designated as packaged articles may be categorized into Division 1.1 to 1.6, and UNRTDG furthermore sub-categorizes to clearly show the technical requirements.
- If explosives are desensitized by wetting with water or alcohols or diluting with other substances, they may be classified other than explosives as desensitized explosives.
- Unstable explosives are explosives being thermally unstable and too sensitive for usual handling.

(5) Data availability

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

(6) Comparison with conventional classification systems

Divisions 1.1-1.6 in GHS follow the definition of Divisions of UNRTDG 2.1.1.4.

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

The UNRTDG list of dangerous goods (for example, the Annex 1: Dangerous Goods Regulations) includes the following substance.:

Division	Explanation	Examples of UN number and substance
Division 1.1	equivalent to UNRTDG 1.1	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 (the followings are omitted.)
Division 1.2	equivalent to UNRTDG 1.2	At present, only articles have UN numbers, but substances may be included in accordance with the definition.
Division 1.3	equivalent to UNRTDG 1.3	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

		(the followings are omitted.)
Division 1.4	equivalent to UNRTDG 1.4	0407 TETRAZOL-1-ACETIC ACID 0448 5-MERCAPTOTETRAZOL-1-ACETIC ACID
Division 1.5	equivalent to UNRTDG 1.5	0331 EXPLOSIVE, BLASTING, TYPE B(AGENT, BLASTING, TYPE B)
Division 1.6	equivalent to UNRTDG 1.6	There is no article with a specific name that fall under this division.
Unstable explosives	Explosive substances and articles whose transport is prohibited, and explosives listed in 1979 Notice 549 from the Ministry of Transport " Public Notice to provide Standards, etc., for Carriage of Dangerous Goods by Ship" Article 5 (1).	(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) (the followings are omitted.)
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 Division 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.	UNRTDG 3 EmS:F-E 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

		(the followings are omitted.)

A substance which is a self-reactive substance or organic peroxide, Type B, has subsidiary risk 1 (Explosives) in UNRTDG. However, it shall be classified as “Classification not possible” if there are no test data on explosives provided by UNRTDG. It shall be noted that though, it is assigned 1.3 by IMDG, they might have determined for convenience for isolation from other hazards in shipping. Therefore, it cannot be guaranteed that self-reactive substance, Type B, or organic peroxide, Type B, is classified as Explosives 1.3 as a result of the test.

2-4-2 Flammable Gases (including chemically unstable gases)

(1) Definitions

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

【GHS 4th 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.

A *chemically unstable gas* is a flammable gas that is able to react explosively even in the absence of air or oxygen.

(2) Classification criteria in GHS

【GHS 4th 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 (difference between the upper and lower limits of the concentration temperatures) 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 (the upper and lower limits of the concentration temperatures) while mixed in air.

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

NOTE 2: *Aerosols should not be classified as flammable gases. See Chapter 2.3.*

2.2.2.2 A flammable gas that is also chemically unstable is additionally classified in one of the two categories for chemically unstable gases using the methods that described in Part III of the Manual of Tests and Criteria according to the following table:

Table 2.2.2 Criteria for chemically unstable gases

Category	Criteria
A	Flammable gases which are chemically unstable at 20°C and a standard pressure of 101.3 kPa
B	Flammable gases which are chemically unstable at a temperature greater than 20°C and/or a pressure greater than 101.3 kP.

(3) Guidance for Classification

A) Judgment of Not applicable (Narrowing down the applicable classes by the state and molecular structure of the substance)

Chemicals which do 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 UNRTDG Classification

Substances designated as Class 2.1 (or Subsidiary Class 2.1) in the UNRTDG classification Table shall be categorized in GHS Category 1.

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 4th revised edition 2.2.2.

Alternatively, when the existing classification results shown in Figure 2-1-3 (3) are available, after examination of the classification result and the evidence data, the Category may be determined.

(4) Data availability

Physical properties of gaseous substances with single ingredient are relatively easy to obtain from such as literatures. 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) Sources of information for classification results under conventional systems

A) UN Dangerous Goods Transportation

The definition of Division 2.1 described in UNRTDG 2.2.2.1 accords with that of GHS Category 1.

Category 1 =UNRTDG 2.1and 2.3 (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

B) Other classification

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[3]12(hereinafter, abbreviated as R12) meet these criteria (Categories 1 and 2), but no categorization is shown.

(6) Classification of mixtures

1) UN GHS 4th revised edition recommends use of ISO-10156:2010 as the testing method. If the test data are available, they may be used, however, only few measured data on mixtures are available. Accordingly, categorization with the method in the following 2) should be considered.

2) UN GHS 4th revised edition shows methods, when ingredients are known, to calculate and determine the Category according to the same ISO. They give, however, the judgment that "the GHS Category of the substance is Category 1 or 2", and they can not distinguish Category 1 and Category 2.

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[3] For R-Phrase, see Appendix.

● Calculation method (1) When consisting of inert gases and flammable gases:

Formula:

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

Wherein,

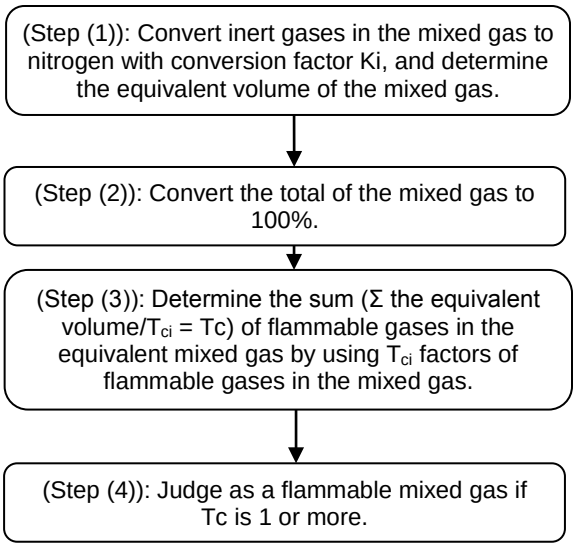
V_i%, each content of flammable gas;

T_{ci}, the maximum concentration of the flammable gas in nitrogen that makes the mixture not flammable in air;

i;, the i-th gas in the mixture;

n, the number of gases in the mixture, and

Ki, the equivalence factor to inert gas/nitrogen.



Value of Ki is described in ISO10156:2010.

Gas	N_2	CO_2	He	Ar	Ne	Kr	Xe	SO_2	SF_6	CF_4	C_3F_8
Ki	1	1.5	0.9	0.55	0.7	0.5	0.5	1.5	4	2	1.5

Value of Tci is described in ISO10156:2010.

Gas	CAS No.	UN No.	T_{ci} in %	L_i in %
Acetylene	74-86-2	3374	3,0	2,3
Ammonia	7664-41-7	1005	40,1	15,4
Arsine	7784-42-1	2188	3,9	3,9
Bromomethane	74-83-9	1062	13,9	8,6
1,2-Butadiene	590-19-2	1010	2,0	1,4
1,3-Butadiene	106-99-0	1010	2,0	1,4
n-Butane	106-97-8	1011	3,6	1,4
1-Butene	106-98-9	1012	3,3	1,5
cis-Butene	590-18-1	1012	3,3	1,5

- Calculation method (2) When including 0.5% or more of oxidizing gases (for example, oxygen) as ingredients:

- Determine the sum Tc according to the calculation method (1). Ignore oxidizing gases.

- Determine Tct2 according to the following formula.

Formula:

$$\sum \frac{A_i}{0.9 \times L_i \times 100} = \text{Tct2}$$

wherein

A_i, concentrations of ingredient flammable gases; L_i, lower flammable limits of the gases. Refer to ISO 10156:2010 (the above table).

Judgment: Both Tc and Tct2 < 1 → "Not classified",

Tc < 1, Tct2 ≥ 1 → Applicable to flammability, and it is preferable to confirm by testing.

Calculation examples:

Example-1; In case of a mixed gas consisting of 7% of hydrogen and 93% of CO_2

Step	Calculation	Note
(1)	$7H_2 + 1.5 \times 93CO_2 = 7H_2 + 139.5CO_2$	K_i of CO_2 is 1.5.
(2)	100 x 7/146.5 (H_2) + 100 x 139.5/146.5 (CO_2) = 4.8% (H_2) + 95.2% (CO_2)	
(3)	4.8/5.5% = 0.87 → Tc	Tc of hydrogen is 5.5%.
(4)	Since Tc is less than 1, this mixed gas is not a flammable gas.	

Example-2; When including inert gases:

In case of a mixed gas consisting of 2% of hydrogen and 8% of CH_4 and 25% of Argon and 65% of Helium

Step	Calculation	Note
(1)	2 (H_2) + 8 (CH_4) + 0.55 x 25 (N_2) + 0.9×65 (N_2) = 2 (H_2) + 8 (CH_4) + 72.25 (N_2) (conversion from total 82.25% to 100%)	Nitrogen conversion K_i of Ar is 0.55, and K_i of He is 0.9.
(2)	2.43% (H_2) + 9.73% (CH_4) + 87.84% (N_2)	Converted to 100%.
(3)	2.43%/5.5% + 9.73%/8.7% = 1.56 → Tc	Tc of hydrogen is 5.5%, and Tc of CH_4 is 8.7%.
(4)	Since Tc is more than 1, this mixed gas is a flammable gas.	

Example-3; When including 0.5% or more of oxidizing gases (for example, oxygen) as ingredients: In case of a mixed gas consisting of 1% of hydrogen and 4% of CH_4 and 11% of oxygen and 84% of Helium

Step	Calculation	Note
(1)	1% (H_2) + 4% (CH_4) + 0.9 x 84% (He) (conversion from total 80.6% to 100%)	Ignore oxygen. K_i of He is 0.9.
(2)	1.24% (H_2) + 4.96% (CH_4)	Converted to 100%.
(3)	1.24%/5.5% +4.96%/8.7% = 0.80 → Tc	Tc of hydrogen is 5.5%, and Tc of CH_4 is 8.7%.
(4)	1/(0.9 x 4) + 4/(0.9 x 4.4) = 1.29 → Tct2	Application of the formula
(5)	Tc is 0.80 and Tct2 is 1.29, and the mixed gas is applicable to Flammable gases, it is preferable to confirm by testing.	

(7) Classification of chemically unstable gases

"Chemically unstable gases" is a hazard class newly added to GHS 4th revised edition (2011). It is added to the hazard class of Flammable Gases as chemically unstable gases and additionally classified as Category A or B.

GHS 4th revised edition only indicates that the test methods are described in Part III of the Manual of Tests and Criteria of UNRTDG. However no description about it was found in its 5th revised edition (2009). In 2011, supplementary volumes to the 5th revised edition were published, and the test methods of chemically unstable gases were added as Part III Section 35. These are such newly determined test methods that information currently available is limited to the descriptions of the Manual of Tests and Criteria, Part III, section 35 of UNRTDG. The point is as follows:

1) A chemically unstable gas is a flammable gas that is able to react explosively even in the absence of air or oxygen. (Therefore, a mixture of oxygen and flammable gas stipulated in Chapter 5 of ISO 10156:2010 shall not be deemed chemically unstable from the perspective of this test method.)
2) Functional groups that represent chemical instability in gases include triple bond, adjacent or conjugated double bond, halogenated double bond, and strained ring. (Flammable gases which do not include any of these are not considered chemically unstable, but expert judgment is needed for final decision.)
3) The test for Category A shall be performed at ambient temperature and pressure. If the test gas shows a given pressure rise in the test, it is classified in Category A.
4) Further tests at 65°C and the corresponding initial pressure shall be performed for the gas that has not been classified in Category A in the test. If the test gas shows a given pressure rise, it shall be classified in Category B. The UN GHS 4th revised edition indicates only "a pressure above 101.3kPa and/or above 20°C". By the Ammendment I (2011) of Manual of Tests and Criteria, UNRTDG, it has been decided that the test is performed at 65°C. The corresponding initial pressure means the internal pressure of high pressure gas cylinder at 65°C. For liquefied test gases, the corresponding initial pressure is the vapour pressure at 65°C.
5) Table 2-4-2-1 shows information about chemically unstable gases that is described in Table 35.1 of the Manual of Tests and Criteria.

Table 2-4-2-1 Test result of chemically unstable gases (UNRTDG Test Manual Sec.35 (2011))

Chemical name	Molecular formula	CAS No.	UN No.	Classification	Specific concentration limit
Acetylene	C2H2	74-86-2	1001	Cat. A	See Table 2-4-2-2

			3374		
Bromotrifluoroethylene	C2BrF3	598-73-2	2419	Cat. B	8.4mol%(LEL)
1,2-Butadiene	C4H6	590-19-2	1010	Not classified	
1,3-Butadiene	C4H6	106-99-0	1010	Not classified	
1- Butyne	C4H6	107-00-6	2452	Cat. B	See Table 2-4-2-2
Chlorotrifluoroethylene	C2ClF3	79-38-9	1082	Cat. B	4.6mol%(LEL)
Ethylene oxide	C2H4O	75-21-8	1040	Cat. A	See Note)
Vinyl methyl ether	C3H6O	107-25-5	1087	Cat. B	3mol%(LEL)
Propadiene	C3H4	463-49-0	2200	Cat. B	See Table 2.4.2
Propyne	C3H4	74-99-7	3161	Cat. B	See Table 2-4-2-2
Tetrafluoroethylene	C2F4	116-14-3	1081	Cat. B	10.5mol%(LEL)
Trifluoroethylene	C2HF3	359-11-5	1954	Cat. B	10.5mol%(LEL)
Vinyl bromide	C2H3Br	593-60-2	1085	Cat. B	5.6mol%(LEL)
Vinyl chloride	C2H3Cl	75-01-4	1086	Cat. B	3.8mol%(LEL)
Vinyl fluoride	C2H3F	75-02-5	1860	Cat. B	3mol%(LEL)

(Note) Ethylene oxide 15 mol% to gas mixtures containing noble gas and 30 mol% to other gas mixtures

(7-1) GHS classification of pure gases

1) Substances other than flammable gases do not require any description about chemical instability.
2) Flammable gases which do not contain any functional group representing chemical instability shall be classified in “Category 1” or “Category 2” only with the indication for “Classification Grounds and Problems” that “No functional group that represents chemical instability is contained.”
3) As for substances shown in Table 2-4-2-1, category shall be assigned in addition to the hazard class: Flammable gases with the indication that “Test result is available in UNRTDG Test Manual (2011)” for “Classification Grounds and Problems”
4) Flammable gases which contain a functional group that represents chemical instability but are not listed in Table 2-4-2-1 shall be classified in “Category 1” or “Category 2” only with the indication for “Classification Grounds and Problems” that “Functional group that represents chemical instability is contained, but no information about the test results were available”
5) In case the results of the test performed in accordance with the UNRTDG Test Manual

Sec.35 are obtained from another source than the UNRTDG Test Manual, it can be adopted.

(7-2) GHS classification for gas mixtures

1) Gas mixtures containing chemically unstable gases must be assessed in line with criteria for mixture, but the test methods have been decided so recently that data accumulation is extremely scant. Current available criteria are only based on the specified concentration limits shown in the right-end columns of Table 2-4-2-1 and Table 2-4-2-2.
2) Gas mixtures containing only one chemically unstable gas in concentrations below the specific concentration limit are not considered as chemically unstable and therefore are not tested for classification purposes.
3) Information about maximum filling pressure of binary mixtures of several gas substances with acetylene is obtained as well. It is shown in Table 2-4-2-2. For other gas mixtures, specified concentration limit shall be the partial pressure 1 bar absolute of acetylene.
4) According to it, these concentration limits may also be applied to butyne-1, allene, and propylene.
5) Specific concentration limit of ethylene oxide is experimentally determined (see Table 2-4-1-1 Note).
6) Specific concentration limit of 3 mol% is given to vinyl methyl ether and vinyl fluoride.
7) Specific concentration limits of other chemically unstable gases than the above are specified as LEL.
8) Maximum pressure for gas mixtures containing chemically unstable gases in concentrations over the specific concentration limits should be limited in order to avoid condensation.

Table 2-4-2-2 Specific concentration limits for binary mixtures with acetylene

(UNRTDG Test Manual Sec.35 (2011))

Concentration limit for acetylene in mol%	Maximum (filling) pressure in bar for a mixture with						
	N_2	CO_2	NH_3	H_2	CH_4	C_3H_8	C_2H_4
3.0	200.0				200.0		
4.0	100.0						
5.0				40.0			40.0
6.0	80.0						
8.0	60.0						
10.0	50.0	38.0	5.6	20.0	100.0	6.0	20.0
15.0	30.0	30.0		10.0			10.0
20.0	25.0	20.0	6.2	5.0	50.0	6.6	7.5
25.0	20.0	15.0					5.0
30.0	10.0	10.0	6.9		25.0	7.3	
35.0			7.3				
40.0					15.0	8.2	
45.0							
50.0					5.0	9.3	
60.0						10.8	

2-4-3 Aerosols

(1)Definitions

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

【GHS 4th 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 4th 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).

NOTE1: *Flammable components do not cover pyrophoric, self-heating or water-reactive substances and mixtures because such components are never used as aerosol contents.*

NOTE2: *Aerosols do not fall additionally within the scope of chapters 2.2 (flammable gases), 2.5 (gases under pressure), 2.6 (flammable liquids), and 2.7 (flammable solids). Depending on their contents, aerosols may however fall within the scope of other hazard classes, including their labeling elements.*

2.3.2.2 A flammable aerosol is classified in one of the three 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. Aerosols which do not meet the criteria for inclusion in Category 1 or Category 2 (extremely flammable or flammable aerosols) should be classified in Category 3 (nonflammable aerosols).

(2.3.4.1 Decision logic)

To classify an aerosol as 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^3 or less, or the deflagration density is 300 g/ m^3 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,

Category 3: ・aerosols whose content of flammable components is 1% or less and the heat of combustion is smaller than 20 kJ/g, or
・spray aerosols which are not classified in Category 1 or 2 in the enclosed space ignition test
・foam aerosols which are not classified in Category 1 or 2 in the foam test

(3) Guidance for Classification

A) Judgment of “Not applicable” (Narrowing down the applicable classes by the state and molecular structure of the substance)

For substances to undergo the government classification procedure, “Classification result” of aerosols shall be “Not applicable”, and “Not an aerosol product” shall be indicated for “Classification Grounds and Problems”.

B) Judgment of “Category 3” (Narrowing down the applicable classes by the contents of ingredients or preliminary measurement results)

A product which contains no flammable components or a product contains 1% or less flammable components and whose heat of combustion is smaller than 20 kJ/g shall be classified as “Category 3.”

Alternatively, when the existing classification results shown in Figure 2-1-3 (3) are available, after examination of the classification result and the evidence data, the Category may be determined.

When an aerosol contains more than 1% flammable components or it has a heat of combustion of at least 20 kJ/g, and it has not been submitted to the given test procedures, it should be classified as aerosols, Category 1.

If the Category can not be determined after procedure described above, perform the predetermined tests (or tests providing the equivalent judgment), and determine the Category.

(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.

2-4-4 Oxidizing Gases

(1)Definitions

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

【GHS 4th 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.

Note: *"Gases which cause the combustion of other material more than air does" means pure gases or gas mixtures with an oxidizing power greater than 23.5% as determined by a method specified in ISO 10156:2010.*

(2)Classification criteria in GHS

【GHS 4th 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.

(3) Guidance for Classification

If the Category is not determined after following the procedure described below, perform the predetermined tests (or tests providing the equivalent judgment), and determine the Category.

A) Judgment of "Not applicable" (Narrowing down the applicable classes by the state and molecular structure of the substance)

A chemical which does not meet the GHS definition of gases shall be judged as "Not applicable".

B) Classification based on existing classifications (such as UNRTDG)

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

The following gases described in ISO10156-2: 2010 Table 3 shall be also classified in "Category 1" with regard to pure gases.

Name of gas	Oxygen equivalency coefficient (C i)
Bis-trifluoromethylperoxide	C i = 40
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 = 0.3
Nitrogen dioxide	C i = 1
Nitrogen trifluoride	C i = 1.6
Nitrogen trioxide	C i = 40
Nitrous oxide	C i = 0.6
Oxygen difluoride	C i = 40
Ozone	C i = 40
Tetrafluorohydrazine	C i = 40

For reference: in 2005, global test methods on “oxidizing gases” were established as ISO10156-2, whose revision ISO 10156:2010 is currently effective. 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. Oxidizing gases with no measurement performed shall be Ci = 40 for safety reason.

C) Judgment of "Not Classified"

Other (non-oxidizing) gases than described above shall be judged as “Not classified”. “Oxidizing gases” cannot be classified in “Not classified” for the reason that “it does not contain oxygen.” Halogenated gas is also applicable to oxidizing gases.

D) Classification based on data in existing literatures

Alternatively, when the existing classification results shown in Figure 2-1-3 (3) are available, after examination of the classification result and the evidence data, the Category may be determined.

(4)Data availability

The coefficients of oxygen equivalency of nitrous oxide (0.6) and oxygen (1) are described in the GHS 4th revised edition. Toxic/corrosive oxidizing gases, which are described in the

ISO-10156-2010, are all listed on the above (3) B).

(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, there are no classification criteria for classification or categorization of oxidizing gases. Gases having Division 5.1 subsidiary risk apply; they are considered not exhaustive. Oxidizing gases fall under Schedule 122 in ERG and S-W in EmS, on the basis of which oxidizing gases can be selected.

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

Gases classified as Division 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 Division 2.2 and 2.3 can fall under “oxidizing gases” even if their subsidiary risks 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

(7) Classification of mixtures

1) GHS document recommends testing methods according to ISO 10156: 2010. Japanese Fire Defense Law and High Pressure Gas Control Law do not include the equivalent classification methods. The testing methods are to determine flammable range of the three component system of "oxidizing gas, ethylene, and nitrogen", and are too complicated to have hardly been used for testing of mixed gases.

2) Examples of single gases classified in this Class are shown in (6).

3) A method to judge by calculation whether or not mixed gases are applicable is shown in GHS 4th revised edition 2.4.4.2. The method is based on ISO 10156: 2010.

4) Guidance

The criterion that a gas mixture should be considered as more oxidizing than air if the oxidizing power of the gas mixture is higher than 0.235 (23.5%) is adopted. The oxidizing power (OP) is calculated as follows:

$$OP = \frac{\sum_{i=1}^{n} X_i C_i}{\sum_{i=1}^{n} X_i + \sum_{k=1}^{p} K_k B_k}$$

Where:
- X_i: molar fraction of the i:th oxidizing gas in the mixture;
- C_i: coefficient of oxygen equivalency of the i:th oxidizing gas in the mixture;
- K_k: coefficient of equivalency of the inert gas k compared to nitrogen;
- B_k: molar fraction of the k:th inert gas in the mixture
- n: total number of oxidizing gases in the mixture
- p: total number of inert gases in the mixture

Example mixture: 9% (O_2) + 16% (N_2O) + 75% (He)

Calculation step 1:

Ascertain the coefficient of oxygen equivalency (C_i) for the oxidizing gases in the mixture and the nitrogen equivalency factors (K_k) for the non-flammable, non-oxidizing gases.

C_i (N_2O) = 0.6 (nitrous oxide)

C_i (O_2) = 1 (oxygen)

K_k = 0.9 (helium)

Calculation step 2:

Calculate the oxidizing power of the gas mixture.

$$OP = \frac{\sum_{i=1}^{n} X_i C_i}{\sum_{i=1}^{n} X_i + \sum_{k=1}^{p} K_k B_k} = \frac{0.09 \times 1 + 0.16 \times 0.6}{0.09 + 0.16 + 0.75 \times 0.9} = 0.201$$

$$20.1 < 23.5$$

Therefore, the mixture is not considered an oxidizing gas.

2-4-5 Gases Under Pressure

(1)Definitions

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

【GHS 4th 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 4th revised edition】(2.5.2)

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

Table 2.5.1: Criteria for gases under pressure

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

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

NOTE: *Aerosols should not be classified as gases under pressure. See Chapter 2.3.*

(3) Guidance for Classification

If the Category is not determined after following the procedure described below, perform the

predetermined tests (or tests providing the equivalent judgment), and determine the Category.

A) Judgment of "Not applicable" (Narrowing down the applicable classes by the state and molecular structure of the substance)

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 hazard 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 various information sources and in-house data and conditions assumed during transport.

Alternatively, when the existing classification results shown in Figure 2-1-3 (3) are available, after examination of the classification result and the evidence data, the Category may be determined.

(4) Data availability

The data required are vapour 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. The government’s classification procedure shall not take into account the state of gases when compressed in cylinder and the pressure, etc., which depends 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 vapour 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 vapour 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. In addition to temperature range and intrinsic pressure of the gas substance set by manufacturers, literature data such as temperature, vapour pressure curve, critical temperature, etc. should be used for classification.

(7) Classification of mixtures

Manufacturers shall categorize by judging the state of gas in the pressure vessel through

changes of temperature and pressure during filling.

2-4-6 Flammable Liquids

(1)Definitions

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

【GHS 4th 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 4th 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.*

NOTE 4: *Aerosols should not be classified as flammable liquids. See Chapter 2.3.*

(3) Guidance for Classification

If the Category is not determined after following the procedure described below, perform the predetermined tests (or tests providing the equivalent judgment), and determine the Category.

A) Judgment of "Not applicable" (Narrowing down the applicable classes by the state and molecular structure of the substance)

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

B) Judgment of "Not classified"

Incombustible Liquids shall be judged as “Not classified”. (Hazardous Materials among category IV of the Fire Service Act, class IV petroleums, oil extracted from animals plants 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, if judgment is impossible, measure the flash point, and determine the classification.

C) Classification based on data from existing literatures

Regarding GHS classification of flammable liquids, categories based on flash points obtained from various information sources and in-house data shall take precedence, and classification based on UNRTDG 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 UNRTDG classification, as for Category 4, UNRTDG classification results can not be used for GHS classification.

Alternatively, when the existing classification results shown in Figure 2-1-3 (3) are available, after examination of the classification result and the evidence data, the Category may be determined.

(4) Data availability

Since such measurements are obligatory under the Fire Service Act, 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 Hazardous Materials in the Fire Service Act]

For Class 4 Hazardous Materials of the Fire Service Act, 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 Service Act are obtained with open-cup method.

(Note) In general, the measured flash points with open-cup method become larger than that with closed-cup method. The differences are considered to be several degrees centigrade around 60°C, ten and several degrees centigrade around 90°C. If the flash points exceed 200°C, the difference may be scores of degrees centigrade. When the substance is designated as Type 3 petroleum with flash point of 80-90°C, the substance may be categorized as "GHS Category 4". If the flash points exceed 90°C by little, it is preferable to re-measure with closed-cup method. If the flash points are

not more than 80°C, categorize based on the data (or flash points with closed-cup method) according to GHS definitions.

(5) Comparison with conventional classification systems

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

Category1 = 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

(7) Classification of mixtures

In the case of mixtures containing known flammable liquids in defined concentrations, although they may contain non-volatile ingredients, for example, polymers or additives, if the calculated flash point of the mixture, using the following method, is at least 5°C greater than the relevant classification criterion (23°C and 60°C, respectively) the calculated flash point shall be judged as a flash point of the mixture provided that

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

b) The lower explosion limit of each ingredient is known (an appropriate correction has to be applied when these data are extrapolated to other temperatures than test conditions) as well as a method for calculating the lower explosion limit of the mixture;

c) The temperature dependence of the saturated vapour pressure and that of the activity coefficient is known for each ingredient as present in the mixture;

d) The liquid phase is homogeneous;

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

2-4-7 Flammable Solids

(1)Definitions

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

【GHS 4th 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 4th 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

NOTE1: *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.*

NOTE 2: *Aerosols should not be classified as flammable solids. See Chapter 2.3.*

(3) Guidance for Classification

If the Category is not determined after following the procedure described below, perform the predetermined tests (or tests providing the equivalent judgment), and determine the Category.

A) Judgment of "Not applicable" (Narrowing down the applicable classes by the state and molecular structure of the substance)

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 and in-house data, or knowledge regarding oxidation/reduction reactions, shall be “Not classified”.

C) Classification based on existing classifications and the like (such as UNRTDG)

If the name of a substance is included in UNRTDG classification, the substance may be classified according to it, however it shall be categorized after good examination since hazards of solid articles depend on their shapes and particle sizes.

If there is any doubt, perform the predetermined test on the article, and categorize.

Alternatively, when the existing classification results shown in Figure 2-1-3 (3) are

available, after examination of the classification result and the evidence data, the Category may be determined.

(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 Division 4.1 of UNRTDG.

Division 4.1 also includes 2-4-8 “Self-reactive Substances and Mixtures” and 2-4-1 “Desensitized explosives”. Therefore, ERG should be also considered.

Related ERG Schedules are as follows:

133 Flammable Solid

134 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

A) UN Dangerous Goods Transportation

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

Category 1 = UNRTDG 4.1II ERG133, 134, 170

Category 2 = UNRTDG 4.1III ERG133, 134, 170

(Example of category 1)

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

(Example of category 2)

4.1II 133	1312	BORNEOL
	1328	HEXAMETHYLENETETRAMINE

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

B) Evaluation results according to the Fire Defense Law

Articles fall into Class 2 Dangerous Goods in Japanese Fire Defense Law may be applicable to GHS hazard class. Since testing methods of the Fire Defense Law are different from that of GHS classification, the articles must be tested with testing methods of GHS and categorized.

2-4-8 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 4th 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 4th 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

If the Category is not determined after following the procedure described below, perform the predetermined tests (or tests providing the equivalent judgment), and determine the Category.

A) Judgment of "Not applicable" (Narrowing down the applicable classes by the state and molecular structure of the substance)

1) Gases, explosives, and liquids and solids classified as organic peroxides and oxidizing substances shall be “Not applicable”.

2) Substances not containing chemical groups related to explosibility or self-reactivity (Table 2-3-8-1) 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 4th 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 existing classifications (such as UNRTDG)

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

Some substances in transport-prohibited substances listed in “Notice to settle Transportation Standards and the like of Dangerous Goods by Ship”, Article 5 (2) to (4), based on the Dangerous Goods Regulations, Article 7 (1), belong to the self-reactive substance TYPE A. And some of the substances contain a required stabilization agent. If the substances are designated to UN numbers for lower hazard classes as "stabilized articles" in UNRTDG, the stabilized articles shall be classified as "self-reactive articles Type G".

Alternatively, when the existing classification results shown in Figure 2-1-3 (3) are

available, after examination of the classification result and the evidence data, the Category may be determined.

In UNRTDG classification, self-reactive substances or mixtures take precedence over other hazards along with explosives, pyrophoric substances, and organic peroxide. Therefore, if a substance has been classified as another lower hazard class (except N.O.S.), the “Classification result” can be “Type G” with identification for the “Classification Grounds and Problems” that “It is classified in ○○, so is considered to be not applicable to hazards of the highest precedence, “self-reactive substances”.”.

(4) Data availability

Few measurement data related to the flow chart of UN GHS 4th 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 4th revised edition GHS2.8.4 is exactly the same as that of UNRTDG (Figure 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

A) UN Dangerous Goods Transportation

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 categorized as Type G are not applied to UNRTDG.

B) Evaluation results according to the Fire Defense Law

Articles fall into Class 5 Dangerous Goods in Japanese Fire Defense Law may be applicable to GHS hazard class. Since testing methods of the Fire Defense Law are different from that of GHS classification, the articles must be tested with testing methods of GHS and categorized.

2-4-9 Pyrophoric Liquids

(1)Definitions

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

【GHS 4th 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 4th 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

If the Category is not determined after following the procedure described below, perform the predetermined tests (or tests providing the equivalent judgment), and determine the Category.

A) Judgment of "Not applicable" (Narrowing down the applicable classes by the state and molecular structure of the substance)

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”.

The GHS classification guidance for Japanese government states "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"". This note is for classification personnel in the government who has no experience of handling the actual substances. Enterprises should make judgment of "Not classified"

according to the method described in the first paragraph of B).

C) Classification based on existing classifications (such as UNRTDG)

When the name of a substance is included in UNRTDG classification, even if the article is empirically considered not to self-ignite, the predetermined tests shall be performed for the article and confirmed. When UNRTDG classification is not conducted, judge based on handling experience. If it is confirmed that the substance does not self-ignite on contact with air of ambient temperature, the substance may be classified as “Not classified”.

Alternatively, when the existing classification results shown in Figure 2-1-3 (3) are available, after examination of the classification result and the evidence data, the Category may be determined.

In UNRTDG classification, pyrophoric substances take precedence over other hazards along with explosives, self-reactive substances, and organic peroxide. Therefore, if a substance has been classified as another lower hazard class (except N.O.S.), the “Classification result” can be “Not classified” with the indication for the “Classification Grounds and Problems” that “It is classified in ○○, so considered to be not applicable to hazards of the highest precedence,”pyrophoric liquids”.”

(4) Data availability

Data are described in reliable literatures and SDSs.

(5) Comparison with conventional classification systems

The definition of Pyrophoric Liquids in UN GHS 4th 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 “I”.

In EmS, Pyrophoric Liquids, along with Solid described in 2-4-10, 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 2-4-11.

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

A) UN Dangerous Goods Transportation

It is judged that Category 1 is identical with UNRTDG4.2 I (Liquids).

(Example)UNRTDG4.2 I

1366	DIETHYLZINC
1370	DIMETHYLZINC
1380	PENTABORANE

2445	LITHIUM ALKYLS 4.2 4.3
2870	ALUMINIUM BOROHYDRIDE
	ALUMINIUM BOROHYDRIDE IN DEVICES
3053	MAGNESIUM ALKYLS
3076	ALUMINIUM ALKYL HYDRIDES
3254	TRIBUTYLPHOSPHANE
3255	tert-BUTYL HYPOCHLORITE

(Note) These are quoted from UNRTDG, 14th edition. After UNRTDG's 15th edition, each individual name of organometallic compounds is deleted and generic names such as 3392 Organometallic substances, Liquids, Pyrophoric and N.O.S are used. It is possible to refer to the classification of individual compounds listed in an old edition of UNRTDG for GHS classification.

B) Evaluation results according to the Fire Defense Law

Articles fall into Class 3 Dangerous Goods in Japanese Fire Defense Law may be applicable to this GHS hazard class. If the Category can not be determined based on handling experience, it is preferable to perform the predetermined tests and categorize.

2-4-10 Pyrophoric Solids

(1)Definitions

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

【GHS 4th 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 4th 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

If the Category is not determined after following the procedure described below, perform the predetermined tests (or tests providing the equivalent judgment), and determine the Category.

A) Judgment of "Not applicable" (Narrowing down the applicable classes by the state and molecular structure of the substance)

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”.

The GHS classification guidance for Japanese government states "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"". This note is for classification personnel in the government who has no experience of handling the actual substances. Enterprises should make judgment of "Not classified" according to the method described above.

Alternatively, when the existing classification results shown in Figure 2-1-3 (3) are available, after examination of the classification result and the evidence data, the Category may be determined.

C) Classification based on existing classifications and the like (such as UNRTDG)

When the name of a substance is included in UNRTDG classification, even if the article is empirically considered not to self-ignite, the predetermined tests shall be performed for the article and confirmed. When UNRTDG classification is not conducted, judge based on handling experience. If it is confirmed that the substance does not self-ignite on contact with air of ambient temperature, the substance may be classified as “Not classified”.

In UNRTDG classification, pyrophoric substances take precedence over other hazards along with explosives, self-reactive substances, and organic peroxide. Therefore, if a substance has been classified as another lower hazard class (except N.O.S.), the “Classification result” can be “Not classified” with the indication for the “Classification Grounds and Problems” that “It is classified in ○○, so considered to be not applicable to hazards of the highest precedence, “pyrophoric solids”.”

(4) Data availability

Data are described in reliable literatures and SDSs.

(5) Comparison with conventional classification systems

The definition of Pyrophoric Solids in GHS2.10.1 is identical with that of UNRTDG2.4.3.2.1. 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 2-4-11.

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

A) UN Dangerous Goods Transportation

It is judged that Category 1 is identical with UNRTDG4.2 I (Solid).

(Example)UNRTDG4.2 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

(Note) “2005 MAGNESIUM DIPHENYL” is quoted from UNRTDG, 14th edition. After UNRTDG’s 15th edition, each individual name of organometallic compounds is deleted and generic names such as 3391 Organometallic substances, Solids, Spontaneous combustion, and N.O.S. come to be used. It is possible to refer to UN classification of individual compounds listed in an old edition for GHS classification.

B) Evaluation results according to the Fire Defense Law

Articles fall into Class 3 Dangerous Goods in Japanese Fire Defense Law may be applicable to this GHS hazard class. If the Category can not be determined based on handling experience, it is preferable to perform the predetermined tests and categorize.

2-4-11 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 4th 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 is a process where the gradual reaction of the substance or mixture with oxygen (in air) generates heat. If the rate of heat production exceeds the rate of heat loss, then the temperature of the substance or mixture will rise which, after an induction time, may lead to self-ignition and combustion..*

(2)Classification criteria in GHS

【GHS 4th 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^3;

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

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

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

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

(3) Guidance for Classification

If the Category is not determined after following the procedure described below, perform the predetermined tests (or tests providing the equivalent judgment), and determine the Category.

A) Judgment of "Not applicable" (Narrowing down the applicable classes by the state and molecular structure of the substance)

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 existing classifications (such as UNRTDG)

When the name of a substance is included in UNRTDG classification, it is preferable to test the article. When UNRTDG classification is not conducted, judge whether or not to perform the tests with referencing the judging results of combustibility and the like.

D) Classification based on data from prescribed literatures

If the data of screening test described in the UN GHS 4th 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 “Category 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 UNRTDG 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). Therefore, “No established test method suitable for liquid substances” instead of “No data available.” shall be indicated for “Classification Grounds and Problems” “No data available” shall be indicated for solids with a melting point over 140 °C. On the other hand, solids with a melting point of 140 °C or lower, “No established test method suitable for solid substances with a melting point of 140 °C or lower” shall be indicated.

Alternatively, when the existing classification results shown in Figure 2-1-3 (3) are available, after examination of the classification result and the evidence data, the Category may be determined.

(4) Data availability

Few data for each substance has been published.

(5)Comparison with conventional classification systems

In Division 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 Category 1, and Packing Group III corresponds to Category 2. Division 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 Division 4.1, as described in 2-3-1.

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

A) UN Dangerous Goods Transportation

Substances classified into UNRTDG 4.2 EmS: S-J fall under this class.

(Example of category 1) UNRTDG4.2 Π 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-PHOSPHABICYCLONONANES (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

B) Fire Defense Law

In Japanese Fire Defense Law, no Classes for such a kind of hazards is set.

2-4-12 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 4th 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 4th revised edition】(2.12.2)

A substance or mixture which, in contact with water, emit flammable gases is classified in one of the three categories for this class, using test N.5 in 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 liters 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 liters 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 liters 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 preliminary 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

If the Category is not determined after following the procedure described below, perform the predetermined tests (or tests providing the equivalent judgment), and determine the Category.

A) Judgment of "Not applicable" (Narrowing down the applicable classes by the state and molecular structure of the substance)

1) Substances for gases shall be judged as “Not applicable”.

2) Substances not containing metals and metalloids in their chemical structure shall be judged as “Not applicable”.

B) Judgment of "Not classified"

A substance containing metals or metalloids in its chemical structure, if it is confirmed that experience in production or handling, and various information sources show that the substance reacts slowly with water at ambient temperatures, but does not release gases or release non-flammable gases in contact with water, shall be classified as “Not classified.” (for example, if its water solubility (instead of “no reaction to water”) is known, it shall be “Not classified” because it does not emit flammable gases. Example: It contains metalloid (Si), but is considered not to react to water violently from the data on water solubility ○○mg/L (source, year of publication).

Reference: UN GHS 4th revised edition 2.12.4.2(b)(c)

C) Classification based on existing classifications and the like (such as UNRTDG)

If the name of a substance is included in UNRTDG classification, the substance shall be classified according to it. As for substances whose applicability was discussed in the following "(7) Discussion on GHS Water-Reactive Flammable Substances and Metalloids", perform "test N. 5", and categorize depending on the result.

Alternatively, when the existing classification results shown in Figure 2-1-3 (3) are available, after examination of the classification result and the evidence data, the Category may be determined.

As for mixtures, when the flammable gas generation rate of the water-reactive substance is known, and another neutral substance is generated and it is considered not to inhibit contact between the water-reactive substance and water, the product of the content of the water-reactive substance and the gas generation rate may be considered as the gas

generation rate of the mixture.

(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 GHS2.12.2 completely accord with the definition of UNRTDG Division 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

A) UN Dangerous Goods Transportation

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

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

1) 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

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

2) 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.

B) Evaluation results according to the Fire Defense Law

Articles fall into Class 3 Dangerous Goods Water-prohibited Goods in Japanese Fire

Defense Law may be applicable to this GHS hazard class. If the Category can not be determined based on chemical compositions and handling experience, it is preferable to perform the predetermined tests and categorize.

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

A) Description of UN GHS 4th revised edition 2.12

Section 2.12.4.2 of UN GHS 4th 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 and 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 4th revised edition 2.12.4.2(a), requires the application of quite an advanced electron theory.

Most of the substances listed in Division 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 Division 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 4th revised edition 2.12.4.2(a), ”The chemical structure of the substance or mixture does not contain metals and 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 4th 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 4th 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 and 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 4th 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 4th 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.

2-4-13 Oxidizing Liquids

(1)Definitions

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

【GHS 4th 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 4th 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

If the Category is not determined after following the procedure described below, perform the predetermined tests (or tests providing the equivalent judgment), and determine the Category. In a case of a mixture, a chemical substance being oxidative but designated as "Not classified" may

be enforced its oxidizing properties by another mixed substance. Test and categorize the mixture.

A) Judgment of "Not applicable"

1) Gases and solid chemicals 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"

If it is confirmed based on the 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”.

If an organic compound contains chlorine as chloride ions, it shall be classified as “Not classified” because a chloride ion does not contribute to oxidization.

C) Classification based on existing classifications and the like (such as UNRTDG)

If the name of a substance is included in UNRTDG classification, the substance shall be classified according to it. As for substances being doubted to be oxidizing, if evident information for judging are not available, perform the predetermined tests, and categorize.

Alternatively, when the existing classification results shown in Figure 2-1-3 (3) are available, after examination of the classification result and the evidence data, the Category may be determined.

Mixtures that meet classification criteria for oxidizing liquids and contain organic flammable substances above 5% should be taken into account for the classification with regard to self-reactive substances and mixtures.

(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 Division 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

A) UN Dangerous Goods Transportation

The following categorization is possible. :

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 more than 20% but not more than 40% hydrogen peroxide

2427 POTASSIUM CHLORATE, AQUEOUS SOLUTION with more than 8% but not more than 20% potassium chlorate

(Example of category 3)

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

B) Evaluation results according to the Fire Defense Law

Articles fall into Class 6 Dangerous Goods in Japanese Fire Defense Law may be applicable to this GHS hazard class. It is preferable to perform the predetermined tests and categorize.

2-4-14 Oxidizing Solids

(1)Definitions

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

【GHS 4th 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 4th 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 III, 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[1], 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.

1 Code of Safe Practice for Solid Bulk Cargoes, IMO, 2005.

(3) Guidance for Classification

If the Category is not determined after following the procedure described below, perform the predetermined tests (or tests providing the equivalent judgment), and determine the Category. In a case of a mixture, a chemical substance being oxidative but designated as "Not classified" may be enforced its oxidizing properties by another mixed substance. Test and categorize the mixture.

A) Judgment of "Not applicable" (Narrowing down the applicable classes by the state and molecular structure of the substance)

1) Gases and liquid chemicals 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) Judgment of “Not Classified”

If it is confirmed based on the review documents that a substance to be assessed is “reductive material”, fill in “Classification result” with “Not classified”, and fill in “Classification Grounds and Problems” with “Reductive material”.

If an organic compound contains chlorine as chloride ions. it shall be classified as “Not classified” because a chloride ion does not contribute to oxidization.

C) Classification based on existing classifications and the like (such as UNRTDG)

If the name of a substance is included in UNRTDG classification, the substance shall be classified according to it. As for substances being doubted to be oxidizing, if evident information for judging is not available, perform the predetermined tests, and categorize.

Alternatively, when the existing classification results shown in Figure 2-1-3 (3) are available, after examination of the classification result and the evidence data, the Category may be determined.

Mixtures that meet classification criteria for oxidizing solids and contain organic flammable substances above 5% should be taken into account for the classification with regard to self-reactive substances and mixtures.

(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 Division 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

A) UN Dangerous Goods Transportation

The following categorization is possible. :

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

B) Evaluation results according to the Fire Defense Law

Articles fall into Class 6 Dangerous Goods in Japanese Fire Defense Law may be applicable to this GHS hazard class. It is preferable to perform the predetermined tests and categorize.

2-4-15 Organic Peroxides

(1)Definitions

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

【GHS 4th 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 4th 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 peroxy 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 ≤ 50°C;
(b) Organic peroxide type D showing a medium effect when heated under confinement[1] with an SADT ≤ 50°C or showing a low or no effect when heated under confinement with an SADT ≤ 45°C;and
(c) Organic peroxide types E and F with an SADT ≤ 45°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

If the Category is not determined after following the procedure described below, perform the predetermined tests (or tests providing the equivalent judgment), and determine the Category.

A) Judgment of "Not applicable" (Narrowing down the applicable classes by the state and molecular structure of the substance)

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 an Organic Peroxide fall below the values stipulated in UN GHS 4th 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 existing classifications and the like (such as UNRTDG)

If the name of a substance is included in UNRTDG classification (for example, it is listed in the table of IMDGC 2.5.3.2.4), the substance shall be classified according to the UN number. Substances which cannot be judged by above procedure will be categorized after predetermined tests.

Alternatively, when the existing classification results shown in Figure 2-1-3 (3) are available, after examination of the classification result and the evidence data, the Category may be determined.

In UNRTDG classification, organic peroxide takes precedence over other hazards along with explosives, self-reactive substances, and pyrophoric substances. Therefore, if a substance has been classified as another lower hazard class (except N.O.S.), the “Classification result” can be “Type G” with the indication for “Classification Grounds

and Problems" that "It is classified in ○○, so considered to be not applicable to hazards of the highest precedence, "organic peroxides"."

(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 decision logic 2.15 of GHS 2.15.4 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 decision logic 2.15 of GHS 2.15.4 is exactly the same as that of UNRTDG (Figure 2.5.1).

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

A) UN Dangerous Goods Transportation

Chemicals which belong to UNRTDG5.2 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 UNRTDG2.5.3.2.4 (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％)

3102 tert-BUTYL MONOPEROXYMALEATE

3111 DIISOBUTYRYL PEROXIDE(>32～52％, diluent B>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(≤52％, paste)

3117 DIPROPIONYL PEROXIDE(≤27％, diluentB≥73％)

3118 tert-BUTYL PEROXYNEODECANOATE(≤42％, stable frozen-water dispersion element)

(Example of Type F)

3109 PEROXYACETIC ACID, TYPE F, stabilized(≤43％)

3110 DICUMYL PEROXIDE(>52％～100％)

3119 DICETYL PEROXYDICARBONATE(≤42％, (stable water dispersion element))

3120 DI-(2- ETHYLHEXYL) PEROXYDICARBONATE (≤52％, stable frozen-water dispersion element)

B) Evaluation results according to the Fire Defense Law

Articles fall into Class 5 Dangerous Goods in Japanese Fire Defense Law may be applicable to GHS hazard class. Since testing methods of the Fire Defense Law are different from that of GHS classification, the articles must be tested with testing methods of GHS and categorized.

2-4-16 Corrosive to Metals

(1)Definitions

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

【GHS 4th 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 4th 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 aluminum 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 aluminum indicates the substance or mixture being tested is corrosive the follow-up test on the other metal is not required.*

(3) Guidance for Classification

If the Category is not determined after following the procedure described below, perform the predetermined tests (or tests providing the equivalent judgment), and determine the Category.

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”. If only either of them has information about its resistance to corrosion, the substance shall be classified as “Not classified” and information of usable metals shall be indicated in such description as “It should be noted …” for “Classification Grounds and Problems”.

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 UNRTDG 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. The point is as follows:

・ In the case of gases, “Classification result” shall be classified as “Classification not possible” with regard to “Corrosive to Metals,” and “No established test method suitable for gas substances” shall be indicated for “Classification Grounds and Problems.”

・In the case of liquids with a boiling point of 55°C or lower, “Classification result” shall be classified as “Classification not possible“ with regard to “Corrosive to Metals,” and “No established test method suitable for low-temperature-boiling liquids” shall be indicated for “Classification Grounds and Problems.”

・ In the case of solids with a melting point of higher than 55°C, “Classification result” shall be classified as “Classification not possible” with regard to “Corrosive to Metals,” and “No established test method suitable for solid substances” shall be indicated for “Classification Grounds and Problems.”

・ As for the above three cases, it is also permissible to simply indicate “No data” instead

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”.

Alternatively, when the existing classification results shown in Figure 2-1-3 (3) are available, after examination of the classification result and the evidence data, the Category may be determined. In this case, "being not oxidizing and its pH is near neutral" is shown as the evidence to classify "Not classified", the goal pH is in the range of about 3 to 11.

(4) Data availability

Few numerical data on metal corrosion rate have been published.

(5) Comparison with conventional classification systems

Definitions of Corrosive to Metals, Category 1 in UN GHS, completely accords with that of the Class 8 III “Metal corrosivity” described in UNRTDG2.8.2.5(c) (ii).

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

A) UN Dangerous Goods Transportation

Since metal corrosive properties is classified into UNRTDG Class 8 along with skin corrosive properties, whether a substance has metal corrosive properties or not cannot be judged from the fact that the substance is classified in Class 8. Metal corrosive properties thus cannot be attributed to a substance based on “Dangerous Goods Regulations Annex

1” alone. Therefore, a substance of which metal corrosion rate is clearly known shall be classified into this class, if it meets the criteria. If the metal corrosion rate of a substance is not clear, “presumed” shall be indicated on the label for the substance.

Packing instructions such as P001 in UNRTDG show strength, etc., of the container and do not always guarantee that the metal used is chemically resistant to the relevant substance. Some containers have inner lining against corrosion. Packing instruction shall not be used as the classification grounds of “Not classified.”

GHS classification is based on UNRTDG, which was developed in relation to the leakage treatment of substances. The corrosive properties 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 corrosive properties in GHS, such a kind of criterion has not been adopted. 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 corrosive properties, 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.

B) Fire Defense Law

In Japanese Fire Defense Law, no Classes for such a kind of hazards is set.

Part3 Health Hazards Guidance

3-1 Summary of GHS classification

A. Identification of a chemical

In classification, firstly identify classifying chemical. Items required for identification are shown in 1-2 in this Guidance.

- Judge whether or not classification of the chemical is necessary. (refer to 1-2)
- Determine if the chemical is a substance or a mixture.
- If it is a mixture, examine the ingredients composing it is composed of.

B. In cases, as hazard and toxicity information, in-house data or existing data are available

(1) When in-house data or existing literature information (data) on the health hazards of the chemical are available, classify based on the data.

(2) When a plurality of data are available, the enterprises should probe into and determine the used testing method of the data, the used testing method is one of the testing methods which can be used for classification, which is the most reliable among data.

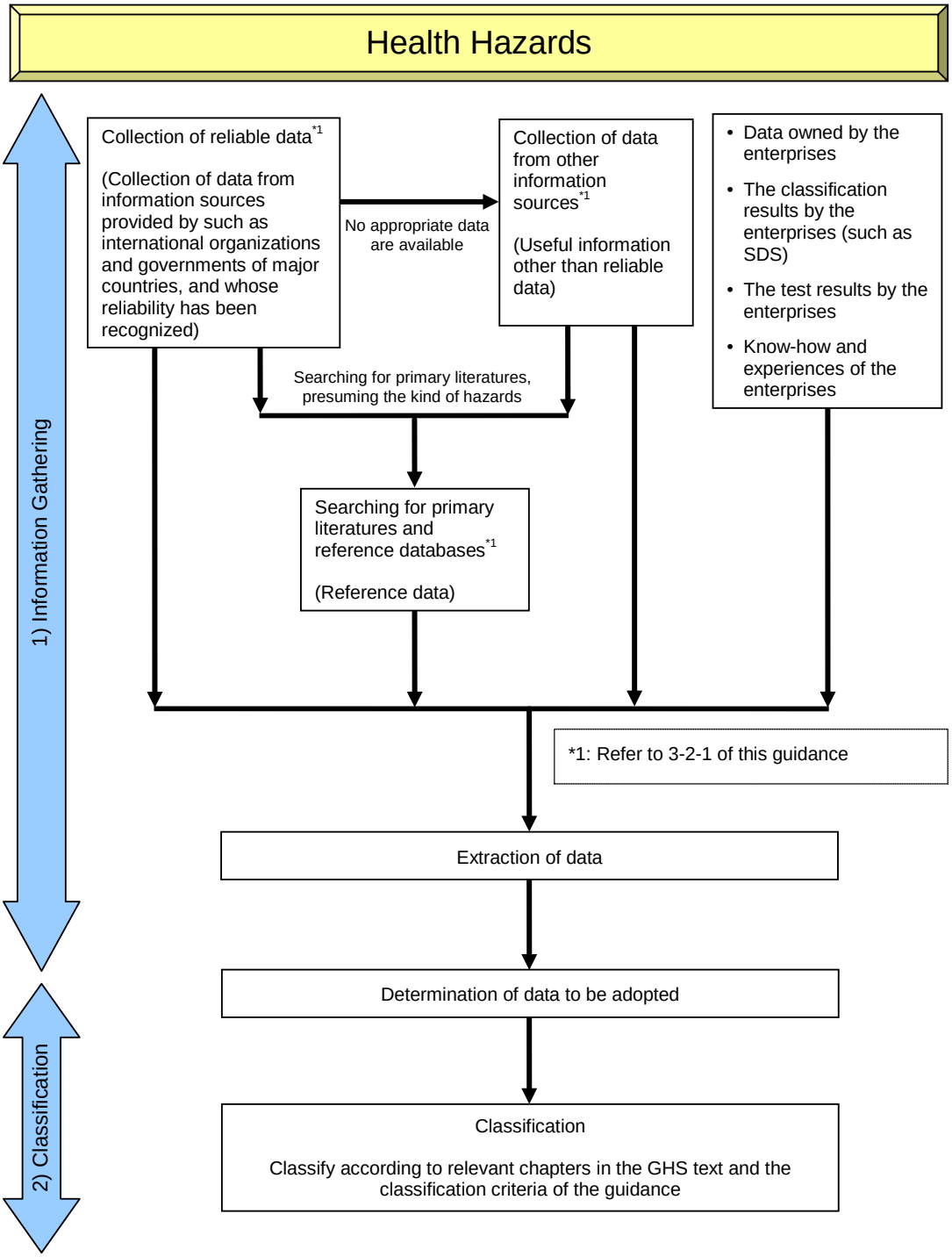
C. Classifying by utilizing existing classifications

(1) In some cases, although no data are available, classification may be completed by utilizing existing classifications (such as SDSs classified by enterprises) as reference.

(2) It is preferable to check the evidence data for such as EU classification (EU CLP classification, etc).

The figure below shows the workflow of GHS classification (Health hazards).

Figure 3-1-1 GHS Classification Workflow (Health Hazards)



3-2 Information and data available for classification

3-2-1 Sources of information available for classification

In UN GHS, available data are reviewed for classification. Available data are as follows. The enterprises should cyclopaedically review all of accessible data among below sources of information and classify on its own judgment. When the following information is not available, it may consult suitable experts in the field regarding matters such as classification methods on its own judgment.

In any cases, any results obtained through execution of the classification with consulting this guidance, including the responsibility for the results, shall belong the enterprises.

- ✓ Information sources provided by international organizations, governments of major countries, etc. , whose reliability has been recognized.
- ✓ Useful information sources other than described above.
- ✓ Data bases of primary literatures for searching and referencing
- ✓ Data owned by the enterprises
- ✓ The classification results by the enterprises (such as SDS)
- ✓ The test results by the enterprises
- ✓ Know-how and experiences of the enterprises

In classification of chemicals for health hazards and environmental hazards, obtained information is prioritized from List 1 to 3 depending on how much its accuracy is confirmed, to show the order of precedence of the information to be applied to classification.

List 1 includes 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 any information requires confirmation of accuracy, the source literatures should be checked, and if it lacks reliability, it shall not be used as evidence of classification. Results of biological tests which were performed using internationally recognized test guidelines (e.g. OECD) according to GLP and judged to be valid by reviews of experts in national committees, etc. shall be treated equally.

List 2 includes databases, etc. of summaries of primary documents, which cannot be traced to confirm accuracy of information.

List 3 includes databases for searching primary literatures and reference databases.

Although Lists 1-3 appear in explanation of each classification item, enterprises are entrusted to judge to which list the information they have collected belongs to.

In the "GHS Classification Guidance for the Japanese Government", information sources applicable to Lists1-3 are shown to reduce variations in classification results as much as possible and to perform classification work efficiently. In classification, enterprises are required to review available data exhaustively.

For your reference, information sources applicable to Lists 1 to 3 that the Japanese government uses for classification are shown below. It should be noted that the order of precedence from List 1 to List 3 is an index to show to what degree the accuracy of the obtained information is confirmed and does not limit the range of data to use.

[Reference] The principles for the precedence of information sources in the "GHS Classification Guidance for the Japanese Government"

Upon conducting investigations for classification, review all of the acquired or accessible assessment documents shown in List 1 regarding each of hazard shown in 3-3-1 to 3-3-10 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.

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 “3-2-3(2) Epidemiologic data”.

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	Chemicals Evaluation and Research Institute, Japan (CERI) and National Institute of Technology and Evaluation (NITE)
	Source	Initial Risk Assessment
	URL	http://www.safe.nite.go.jp/english/risk/initial_risk.html
	Note	Chemicals Evaluation and Research Institute, Japan (CERI) and National Institute of Technology and Evaluation (NITE) “Hazard Assessment Report” http://www.safe.nite.go.jp/english/sougou/view/IntrmSrchIntlRskList_en.faces
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	http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
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, Paragraph 3
	URL	http://www.jaish.gr.jp/anzen/hor/hombun/hor1-8/hor1-8-32-1-0.htm
1-4)	Organization	Japan Bioassay Research Center
	source	Ministry of Health, Labour and Welfare (Result from Carcinogenicity Studies)
	URL Note	http://anzeninfo.mhlw.go.jp/user/anzen/kag/ankg02.htm Japanese text
1-5)	Organization	Environmental Risk Assessment Office, Ministry of the Environment (Japan)
	Source	Environmental Risk Assessment for Chemical Substances
	URL	http://www.env.go.jp/chemi/risk/index.html
1-6)	Organization	Japan Society For Occupational Health (JSOH)
	Source	Recommendations for allowable concentrations (published every year)
1-7)	Organization	OECD SIDS
	Source	Initial Assessment Report (SIAR)
		Initial Targeted Assessment Report (ITAR)
	URL	http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=44C0151D-03E8-46

		4F-9BE4-50085BD01218 http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html
	Note	Documents created by OECD SIAM (current CoCAM) are firstly published at OECD's website and then partially at UNEP's website except for 1-13). OECD: HPV-SIAP Japanese version Japan Chemical Industry Ecology-Toxicology & Information Center http://www.jetoc.or.jp/safe/siap_top.html
1-8)	Organization	WHO/IPCS
	Source	Environmental Health Criteria (EHC)
	URL	http://www.who.int/ipcs/publications/ehc/en/index.html http://www.inchem.org/pages/ehc.html
	Note	EHC Japanese version: http://www.nihs.go.jp/hse/ehc/index.html It should be noted that a Japanese version is available only of limited volumes.
1-9)	Organization	WHO/IPCS
	Source	Concise International Chemical Assessment Documents (CICAD)
	URL	http://www.who.int/ipcs/publications/cicad/pdf/en/ http://www.inchem.org/pages/cicads.html
	Note	CICAD Japanese version http://www.nihs.go.jp/hse/cicad/cicad.html It should be noted that a Japanese version is available only of limited volumes.
1-10)	Organization	WHO International Agency for Research on Cancer (IARC)
	Source	IARC Monographs Program on the Evaluation of Carcinogenic Risk to Humans (IARC Monographs)
	URL	http://monographs.iarc.fr/ or searchable by CAS number: http://monographs.iarc.fr/ENG/Classification/ClassificationsCASOrder.pdf
	Note	SIDS or WHO Assessment Documents (such as EHC, CICAD, IARC, JMPR) can be searched or viewed via the website (1) below. Some hazardous assessment documents of international organization and some major countries (Japan, U.S. etc) are linked to the (2) below. (1) http://www.inchem.org/ (2) http://www.safe.nite.go.jp/english/sougou/view/SelectingListsList_en.faces

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	http://www.who.int/ipcs/publications/jecfa/monographs/en/index.html http://www.inchem.org/pages/jecfa.html
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	http://www.who.int/ipcs/publications/jmpr/en/ http://www.inchem.org/pages/jmpr.html
1-13)	Organization	EU European Chemicals Bureau (ECB)
	Source	EU Risk Assessment Report: EU RAR
	URL	http://esis.jrc.ec.europa.eu/
1-14)	Organization	European Center of Ecotoxicology and Toxicology of Chemicals (ECETOC)
	Source	Technical Report and JACC Report
	URL	http://www.ecetoc.org/publications (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) (2012 supplement, 2012) and “TLVs and BEIs” (ACGIH, published every year)
	URL	Not available on web sites. Can be purchased from “TLVs and BEIs” WEB. http://www.acgih.org/home.htm
1-16)	Organization	U.S. EPA (Environmental Protection Agency)
	Source	Integrated Risk Information System (IRIS)
	URL	http://www.epa.gov/iris/
1-17)	Organization	U.S. National Toxicology Program (NTP)
	URL	http://ntp-server.niehs.nih.gov/
1-17-1)	Source	NTP Database Search Home Page(http://tools.niehs.nih.gov/ntp_tox/index.cfm) [For Standard Toxicology & Carcinogenesis Studies, Reproductive Studies, Developmental Studies, Immunology Studies, Genetic Toxicity Studies] or http://ntp-server.niehs.nih.gov/ → Study Results & Research Projects → Study Data Searches

	URL	http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm
1-17-2)	Source	Report on Carcinogens (12th, 2011)
	URL	http://ntp-server.niehs.nih.gov/ → Public Health →Report on Carcinogens →⇒12th Report on Carcinogens
1-17-3)	Source	Carcinogenicity Technical Report
	URL	http://ntp-server.niehs.nih.gov/ → Study Results & Research Projects ⇒ Reports & Publications → Long-Term → All Long-Term Reports → TR-000-500 and greater (Carcinogenicity Report)
1-18)	Organization	Agency for Toxic Substances and Disease Registry (ATSDR)
	Source	Toxicological Profile
	URL	http://www.atsdr.cdc.gov/toxprofiles/index.asp
1-19)	Organization	Environment Canada/Health Canada
	Source	Assessment Report Environment Canada: Priority Substance Assessment Reports
	URL	http://www.ec.gc.ca/substances/ese/eng/psap/final/main.cfm (Abstract only on the web site)
1-20)	Organization	Australia NICNAS
	Source	Priority Existing Chemical Assessment Reports
	URL	http://www.nicnas.gov.au/publications/car/pec/default.asp
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	http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics
	Note	“List of MAK and BAT values” is not an assessment document.
1-22)	Source	Patty’s Toxicology (6th edition, 2012)(Patty)
	Note	E. Bingham, B. Cohrssen (Eds): 6 volumes
1-23)	Organization	U. S. Environmental Ptotection Agency (EPA)
	Source	Pesticides “Reregistration Eligibility Decision”
	URL	http://www.epa.gov/pesticides/reregistration/status.htm
1-24)	Organization	U.S. HPV Challenge Program (HPV-IS) (EPA evaluated)
	Source	High Production Volume Information System (HPVIS)
	URL	http://www.epa.gov/hpvis/

List 2:

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

2-1)	Organization	EU European Chemicals Bureau (ECB)
	Source	International Uniform Chemical Information Database (IUCLID) IUCLID CD-ROM (Updated, Edition 2 - 2000)
	URL	http://esis.jrc.ec.europa.eu/
2-2)	Organization	U.S. National Library of Medicine (NLM)
	Source	Hazardous Substance Data Bank (HSDB)
	URL	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB
2-3)	Organization	German Chemical Society-Advisory Committee on Existing Chemicals of Environmental Relevance
	Source	BUA Report (BUA)
	URL Note	http://www.hirzel.de/bua-report/download.html Full report can not be available from web site.
2-4)	Organization	Food and Agricultural Materials Inspection Center, Ministry of Agriculture, Forestry, and Fisheries (Japan)
	Source	A pesticide abstract and evaluation report
	URL	http://www.acis.famic.go.jp/syouroku/index.htm
2-5)	Organization	Japan Crop Protection Association
	Source	Pesticide safety information (List open for the public)
	URL	http://www.jcpa.or.jp/labo/anzen/a.html
2-6)	Organization	Food Safety Commission, Cabinet Office, Government of Japan
	Source	Evaluation of effect for the food safety
	URL	http://www.ffcr.or.jp/zaidan/FFCRHOME.nsf/pages/info,cao
2-7)	Organization	Ministry of Health, Labour and Welfare (Japan)
	Source	Research on the revision of the safety of the existing additive
	URL	http://www.ffcr.or.jp/zaidan/MHWinfo.nsf/0f9d5ee834a5bcff492565a10020b585/01ec065c06a3601f49257328000c3afa?OpenDocument
	Note	Information regarding safety for the food additive

List 3:

These are databases for searching primary literature and reference databases. In the case where data are available in List 1 or 2, these databases should be referred to for confirmation of data reliability, if appropriate.

Although hazard information of an individual product is available from existing SDSs, 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 of Japan Science and Technology Agency (JDreamII online database)
  http://pr.jst.go.jp/db/db.html

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) "Detailed risk evaluation documents": 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/evaluation_document/Chemical_hazard_data.html
- 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, 2012)” :
  http://www.sciencedirect.com/science/book/9781437778694

- U.S. National Institute for Occupational Safety and Health (NIOSH) (Registry of Toxic Effects of Chemical Substances (RTECS)):
  http://www.cdc.gov/niosh/npg/npgdrtec.html
  It should be noted that substances listed in the above URL are only small part of RTECS.
  http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CHEM
  Information about acute toxicity included in RTECS can be searched in the above ChemIDplus of TOXNET.
  RTECS database offered in the paid search site STN: the Scientific and Technical Information Network run by Japan Association for International Chemical Information provides information almost all substances revealed.
- WHO/IPCS "International Chemical Safety Cards" (ICSC):
  http://www.cdc.gov/niosh/ipcs/icstart.html
  (ICSC Japanese version: http://www.nihs.go.jp/ICSC/)

3-3) EU classification

http://esis.jrc.ec.europa.eu/index.php?PGM=cla (searchable from "SEARCH ANNEX VI")

Classification based on Table 3-1, Annex VI of EU CLP regulations (hereinafter referred to as "EU CLP classification". R-phrases shall be referred to as EU DSD classification) can be referred to in performing GHS classification in accordance with this guidance.

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

In this guidance, classification based on the Annex VI Table3-1 of EU CLP regulations is abbreviated as EU CLP classification, and R-Phrase is referred to as EU DSD classification. EU classification refers to both EU CLP classification and EU DSD classification, unless otherwise specified.

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

"NIOSH Pocket Guide to Chemical Hazards"

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

In addition, United Nations Recommendations on the Transport of Dangerous Goods (UNRTDG) can be referred to for classification.

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

(1) In case multiple data exist in reliable information source such as in List 1

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 preferable that the enterprises seek for suitable expert's judgment in the field based on its decision.

(2) In case multiple data exist in other information sources

A) Among data collected from other useful information sources (e.g. information sources in List 2), data considered reliable (data in accordance with GLP, data for which supporting data are clearly indicated and evaluated, or data considered to have the highest scientific validity after examination of dosage selection in the test, selection of test animal species, validity of the administration route, etc.) shall be adopted. This decision procedure shall be 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. Expert judgment shall be sought for if classification based on the reliability of data shown in the above A) or B) is impossible.

3-2-3 Management of information in special cases

Points to note 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 Name of the substance, CAS No. ZZZZ-ZZ-Z" to indicate the existence of another substance to be referred. 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 noted as 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 state/forms, they should be listed.

Example: Carcinogenicity of lead

Type of lead compound	GHS classification	IARC’s assessment as an evidence	Year of IARC assessment
Lead	Category 2	2B	1987
Inorganic lead compound	Category 1B	2A	2006
Organic lead compound	Not classified	3	2006

B) If hazard assessment results are not clear depending on the states/forms, a comment shall be added as classification evidence.

Example: Carcinogenicity of cadmium: GHS classification Category1A, 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 corresponding to 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 corresponding to List 2, 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 3-2-3-1: 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
Rat (Young)	0.1	10		0.1
Rat (Matured)	0.4	20		0.05
Guinea pig	0.75	30		0.04
Rabbit	2	60		0.03
Dog	10	250		0.025
Cat	2	100	Moist, semi-solid diet	0.05
Ape	5	250		0.05
Dog	10	750		0.075

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 3-2-3-2: 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 per concentration in water of 1ppm (mg/kg body weight /day)
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, Appendix table 4 (partially revised)

3-2-4 Bridging Principles

Bridging principles are described based on the Classification JIS as follows.

Although this Chapter is supposed to deal with only health hazards, both health hazards and environmental hazards are dealt with in this chapter from the perspective of bridging principle which is important in classification of mixtures.

The hazards of a mixture can be characterized without the necessity for additional testing. In order to identify health hazards and/or environmental hazards of a mixture, when there are sufficient data on its individual ingredients and tested similar mixtures, it shall be classified by using these data in accordance with bridging principles of (1)-(6) and Table 3-2-4-1. It should be noted that this principle is applicable to only hazards shown in Table 3-2-4-1.

This ensures that the classification process utilize the available data to the greatest extent possible in characterizing the hazards of the mixture without necessity for additional testing in animals.

(1) Dilution

If the tested mixture is a chemical that has a potential to cause acute toxicity, skin corrosion/irritation, serious eye damage/irritation, specific target organ toxicity (single-exposure, repeated-exposure), or aquatic environmental hazards, when it is diluted with a diluent that belongs to hazardous category of equivalent or lower than the least hazardous ingredient of the applicable hazard, and is not expected to affect the applicable hazards of its other ingredients, the new diluted mixture may be classified as equivalent to the original tested mixture. If the tested mixture is a chemical that has a potential to cause respiratory/skin sensitization, germ cell mutagenicity, carcinogenicity, reproductive toxicity, or aspiratory hazard, when it is diluted with diluent that contain no applicable hazard and is expected to affect the applicable hazard of other ingredients, the new diluted mixture may be classified as equivalent to the original tested mixture.

(2) Batching

The toxicity of a tested production batch of a mixture can be assumed to be substantially equivalent to that of another untested production batch of the same commercial product when produced by or under the control of the same manufacturer, unless there is no reason to believe there is significant variation such that the toxicity of the untested batches has changed. If the latter occurs, a new classification is necessary.

(3) Concentration of highly toxic mixtures

If a tested mixture is classified in Category 1 or Sub-category 1A of health hazards or aquatic environmental hazards (refer to 3.3.1 to 3.3.10, and 4-2), and the concentration of a toxic ingredient classified in Category 1 or Sub-category 1A is increased, the resulting untested mixture may be classified in Category 1 or Sub-category 1A without additional testing.

(4) Interpolation within one toxicity category

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

(5) Substantially similar mixtures

Given the following:

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

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

c) The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii).

d) Data on toxicity for A and C are available and substantially equivalent; they are in the same hazard category and are not expected to affect the toxicity of B.

If mixture (i) or (ii) are already classified by testing, then the other mixture can be assigned the same hazard category.

(6) Aerosols

An aerosol form of a mixture may be classified in the same hazard category as the tested, non-aerosolized form of the mixture which has been tested on hazards provided the added propellant does not affect the toxicity of the mixture on spraying. It should be noted that mixtures containing ingredients to cause acute toxicity or specific targeted organ toxicity (single exposure and repeated exposure) may be classified in the same hazard category as non-aerosol form of a mixture tested for oral and dermal toxicity, but classification of aerosolized mixtures for inhalation toxicity should be considered separately.

Table 3-2-4-1 Bridging principles in toxicity

Toxicity	Dilution (see (1))	Batching (see (2))	Concentration of highly toxic mixtures (see (3))	Interpolation within one toxicity category (see (4))	Substantially similar mixtures (see (5))	Aerosols (see (6))
Acute toxicity (see 3-3-1)	●	●	●	●	●	●
Skin corrosion/irritation (see 3-3-2)	●	●	● a)	●	●	●
Serious eye damage/eye irritation (see 3-3-3)	●	●	● b)	●	●	● d)
Respiratory or skin sensitization (see 3-3-4)	●	●	●	●	●	●
Germ cell mutagenicity (see 3-3-5)	●	●			●	
Carcinogenicity (see 3-2-6)	●	●			●	
Reproductive toxicity (see 3-3-7)	●	●			●	
Specific target organ toxicity (single exposure) (see 3-3-8)	●	●	●	●	●	●
Specific target organ toxicity (repeated exposure) (see 3-3-9)	●	●	●	●	●	●
Aspiration hazard (see 3-3-10)	●	●	●	●	●	
Hazardous to the aquatic environment (see 4-2)	●	●	● c)	●	●	

Note: Toxicities to which individual bridging principle is applied are shown in above table with ● mark. Notes for application are shown with a)-d).

a) Regarding concentration of mixtures with high skin corrosion/irritation potential: if a tested mixture classified with the most severe classification sub-category for corrosion is concentrated, the more concentrated untested mixture may be classified in the highest corrosion sub-category without additional testing. If a tested mixture classified with the most severe classification for skin irritation is concentrated and does not contain corrosive ingredients, the more concentrated mixture may be classified in the highest irritation category without additional testing.

b) Regarding concentration of mixtures with high toxicity to cause serious eye damage/irritation, if a tested mixture classified with the most severe classification sub-category for eye damage is concentrated, the more concentrated mixture may be classified in the highest serious eye damage category without additional testing. Regarding concentration of mixtures with skin/eye irritation, if a tested mixture

classified with the most severe classification category for skin/eye irritation is concentrated and does not contain ingredients which have potential to cause serious eye damage, the more concentrated mixture may be classified in the highest irritation category without additional testing.

c) In classification of a mixture which is generated by concentrating a mixture classified as the most severe categories of aquatic environmental hazards (Chronic: Category 1 and Acute: Category 1), if ingredients classified as Chronic: Category 1 or Acute: Category 1 are further concentrated, the resulting mixture may be classified as equivalent to the original mixture without additional testing.

d) An aerosol form of a mixture with potential to cause serious damage/irritation to eyes may be classified as the same hazard category as the tested non-aerosolized form of the mixture provided the added propellant does not affect the toxicity of the mixture. It is preferable that “mechanical” eye damage due to physical force of spraying should be evaluated.

3-2-5 Concentration limits

According to Classification JIS, “concentration limit” shall be defined as below in this guidance.

Concentration limit:

limit value of concentration of ingredients used for classification of untested mixtures based on the hazard of its ingredients

3-3 Classification of health hazards

3-3-1 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 4th 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 Classification JIS

Classification JIS assigns acute toxicity of chemical substances from oral, endermatic or inhalation route to one of four toxicity classes.

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

Exposure route	Category 1	Category 2	Category 3	Category 4
Oral (mg/kg bodyweight)	ATE≤5	5<ATE≤50	50<ATE≤300	300<ATE ≤2 000
Dermal (mg/kg bodyweight)	ATE≤50	50<ATE≤200	200<ATE≤1 000	1 000<ATE ≤2 000
Gases (ppmV)	ATE≤100	100<ATE≤500	500<ATE≤2 500	2 500<ATE ≤20 000
Vapours[a)] (mg/L)	ATE≤0.5	0.5<ATE≤2.0	2.0<ATE≤10	10<ATE ≤20
Dusts[b)] **and mists**[c)] (mg/L)	ATE≤0.05	0.05<ATE≤0.5	0.5<ATE≤1.0	1.0<ATE ≤5

The acute toxicity estimate (ATE) for the classification of a substance is derived using any of the following:

(a) existing LD_{50} (oral or dermal) or LC_{50} (inhalation) judged usable for classification;

(b) the conversion value of acute toxicity range values obtained from table 3-3-1-2 that

relates to the results of a range test; or

(c) the conversion value from table 3-3-1-2 that relates to a classification category;

Inhalation ATE values in the table are based on 4 hour testing exposures. Conversion of existing 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.

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 substances the test atmosphere may consist of a vapour which is near the gaseous phase. In these latter cases, classification should be based on ppmV (volume fraction) as follows: Category 1 (100 ppmV), Category 2 (500 ppmV), Category 3 (2 500 ppmV), and Category 4 (20 000 ppmV).

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

Note 2: 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 less than 1 to about 100 μm.

Note a) Vapour: the gaseous form of a chemical released from its liquid or solid state.

b) Dust: Solid particles of a chemical suspended in a gas (usually air).

c) Mist: Liquid droplets of a chemical suspended in a gas (usually air).

Note 3: ATE, an abbreviation of Acute Toxicity Estimate refers to both acute toxicity value and acute toxicity estimate.

Table 3-3-1-2 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

Exposure routes	**Classification category or experimentally obtained acute toxicity range estimate**	**Converted Acute Toxicity point estimate** (see Note 2)
Oral	0 <Category1 ≤5	0.5
(mg/kg bodyweight)	5 <Category2 ≤50	5
	50 < Category3 ≤300	100
	300 <Category4 ≤2000	500
Dermal	0 <Category1 ≤50	5
(mg/kg bodyweight)	50 <Category2 ≤200	50
	200 <Category3 ≤1 000	300
	1 000 <Category4 ≤2 000	1 100
Gases	0 < Category1 ≤100	10

(ppmV) (see Note 1)	100 <Category2 ≤500 500 <Category3 ≤2 500 2 500 <Category4 ≤20 000	100 700 4 500
Vapours (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
Dust/mist (mg/L)	0 < Category1 ≤ 0.05 0.05 <Category2 ≤ 0.5 0.5 < Category3 ≤ 1.0 1.0 < Category4 ≤ 5.0	0.005 0.05 0.5 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 end of the range of Categories 1 and 2, and at a point approximately 1/10th from the lower end of the range for Categories 3 and 4.

If all the ingredients of a mixture are in the same category, the category of the mixture shall be identical with that of its ingredients. For example, if all the ingredients of a mixture fall into Category 2, although the converted value is the upper limit of Category 1, Category of the mixture shall be Category 2 instead of Category 1.

B) Classification criteria in GHS (reference information)

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

【GHS 4th 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)	5	50	300	2 000	5 000
Dermal (mg/kg body weight)	50	200	1 000	2 000	*See detailed criteria in Note (g)*
Gases (ppmV)	100	500	2 500	20 000	*See detailed*

See Notes (a), (b) and (c)					*criteria in Note (g)*
Vapours (mg/l) *See Notes (a), (b), (c), (d) and (e)*	0.5	2.0	10	20	
Dusts and Mists; (mg/l) *See Notes (a), (b) (c) and (f)*	0.05	0.5	1.0		

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 supersatured vapours or by physical shearing of liquids. Dusts and mists generally have sizes ranging from less than 1 to about 100μm;

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

(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 LD50 in the range of 2 000-5 000 mg/kg bodyweight and equivalent doses for inhalation. The specific criteria for Category 5 are:

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

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

- *reliable information is available indicating significant toxic effects in humans; or*
- *any mortality is observed when tested up to Category 4 values by the oral, inhalation, or dermal routes; or*
- *where expert judgement confirms significant clinical signs of toxicity, when tested up to Category 4 values, except for diarrhoea, piloerection or an ungroomed appearance; or*
- *where expert judgment 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 procedures including information gathering can be referred to "3-1 Summary of GHS classification".

A) Data availability

- Classification should be performed based on the toxicity values reported in information available for classification.
- 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.

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 (UDP)
OECD TG 402 Acute dermal toxicity
OECD TG 403 Acute inhalation toxicity
OECD TG 436 Acute Inhalation Toxicity - Acute Toxic Class Method
These guidelines are accessible from the below URL.
http://oberon.sourceoecd.org/vl=5727011/cl=16/nw=1/rpsv/cw/vhosts/oecdjournals/1607310x/v1n4/contp1-1.htm

- EU CLP classification criteria completely accord with that of GHS in JIS classification.
  On the European Commission website, EU harmonized CLP and DSD (Dangerous Substances Directive) classification results are shown in Table 3-1 and Table 3-2 in Annex VI, respectively, which are referable.
  http://ec.europa.eu/enterprise/sectors/chemicals/documents/classification/index_en.htm
- Hazard statements[4] regarding acute toxicity (H300, H301, H302, H310, H311, H312, H330, H331, and H332) of EU CLP classification and 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[5] and the like) regarding acute toxicity of EU DSD classification are referable.

B) Order of Precedence where multiple data exist

Refer to “3-2-2 Order of Precedence where multiple 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 Division 6.1 is not sub-categorized by exposure route.

[4] See Annex for EU hazard statements.
[5] For R-Phrase, see Appendix.

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	
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_{50} values, and “Inhalation; vapours” and “Inhalation; dusts and mists” are LC_{50} values. “Inhalation; gases” is not defined in the present EU DSD classification.

D) Guidance concerning data

It should be noted that unit of inhalation toxicity data varies depending on the properties of the 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)

(ppmV) = {(mg/L)× 24.45 × 10^3 } / molecular weight

(mg/L) = {(ppmV)× molecular weight × 10^{-3}} / 24.45

(4)Guidance for classification and judgment

A) Points to be noted in this item

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

In any route, a substance which is applicable to “Category 5” of UN GHS classification corresponds to “Not classified” in the Classification JIS. However, care should be exercised when calculating acute toxicity estimate (ATE mix) of a mixture; it is necessary to take into account the value applicable to Category 5.

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 “3-2-2 Order of precedence when multiple 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 3-3-1-2 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 for assessing the Acute Toxicity LC_{50} in inhalation route

1) Values for inhalation toxicity are based on 4 hour tests in laboratory animals. In the case multiple values exist, one should be selected according to the method described in "3-2-2 Order of precedence when multiple multiple data exist". If their reliability is equivalent, the most appropriate values shall be adopted based on the following criteria; values other than 4 hour tests shall be converted to a 4-hour equivalent.

a) Data based on the 30 minutes to 24 hours test shall be used. Data close to 4 hours test shall be prioritized.

b) If data satisfying the condition a) 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_{50}) is classified as Category 1 (inhalation).

Method for converting LC_{50} value B for A hours into LC_{50} estimate value D for C hours: ・Gas/vapour: $D = B\sqrt{A} / \sqrt{C}$ ・Dusts/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-hours 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_{50} 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_{50} may be described in ppmV, or for gas, its LC_{50} may be described in mg/L. In many assessment documents, LC_{50} 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.

ppmV ≒ mg/L × 1000 × 24.45 / molecular weight (for conversion at 25°C and atmospheric pressure)

(Example) Saturated vapour pressure for certain substance is 0.9 kPa (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 = 0.9 kPa / 101.3 kPa

= 0.008 884 5

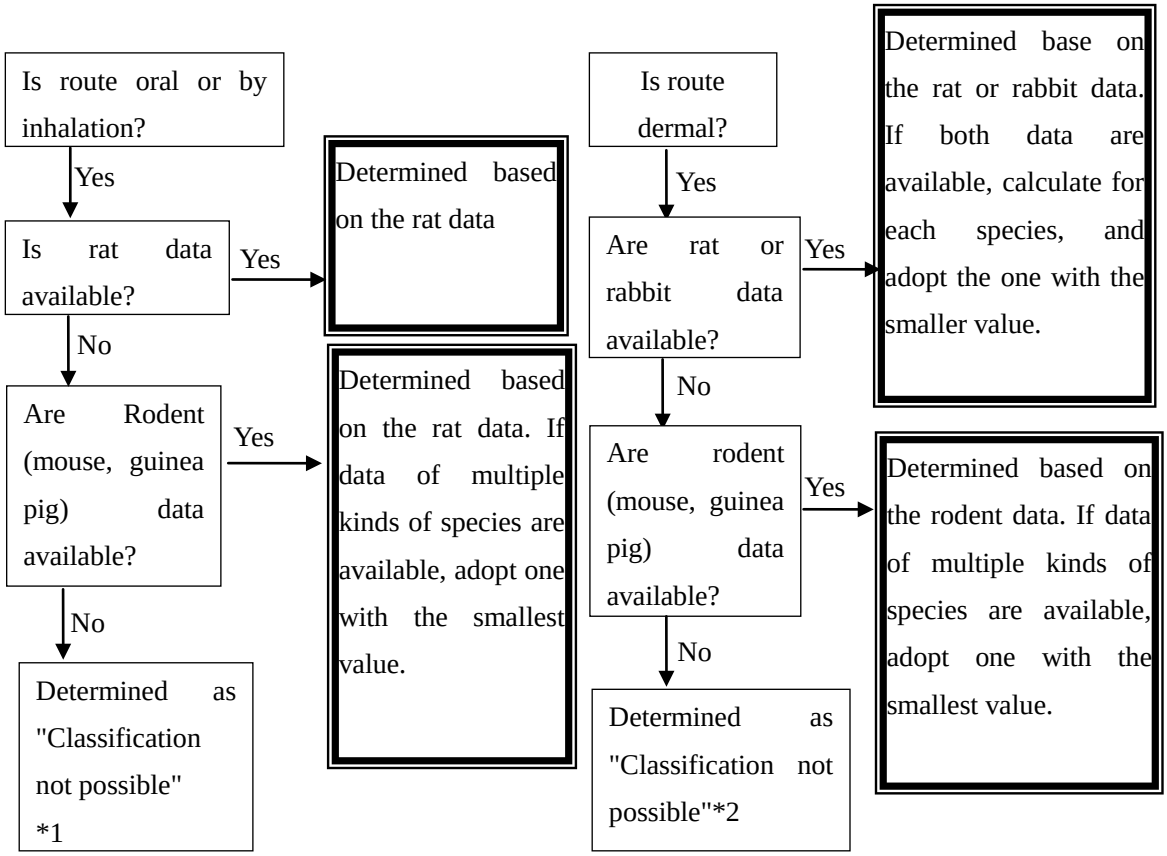
= 8 885 ppm

Therefore, the saturated vapour pressure concentration of a substance that has a saturated vapour pressure of 0.9 kPa (25°C) is 8 885 ppm. When calculating in mmHg, atmospheric pressure should be converted to 760 mmHg.

D) Precautions for dealing with species difference in experimental animals

Figure 3-3-1-1 shows precautions for dealing with species difference in experimental animals.

Figure 3-3-1-1 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.

E) 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 4th revised edition, it is required for classification to take notice of Note (e) 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 4th 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 (2 500 ppmV), and Category 4 (20 000 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 gases. In text 3.1.2.6.2, the same point is repeatedly described.

In line with Note (e) of Table 3.1.1 and the gist of the paragraph 3.1.2.6.2 of the UN GHS 4th revised edition, classification of acute toxicity in the case of “inhalation” shall be 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 101.3 kPa”), 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 4th revised edition Table 3.1.1.
    c) When the ATE (LC_{50}) 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℃ 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.

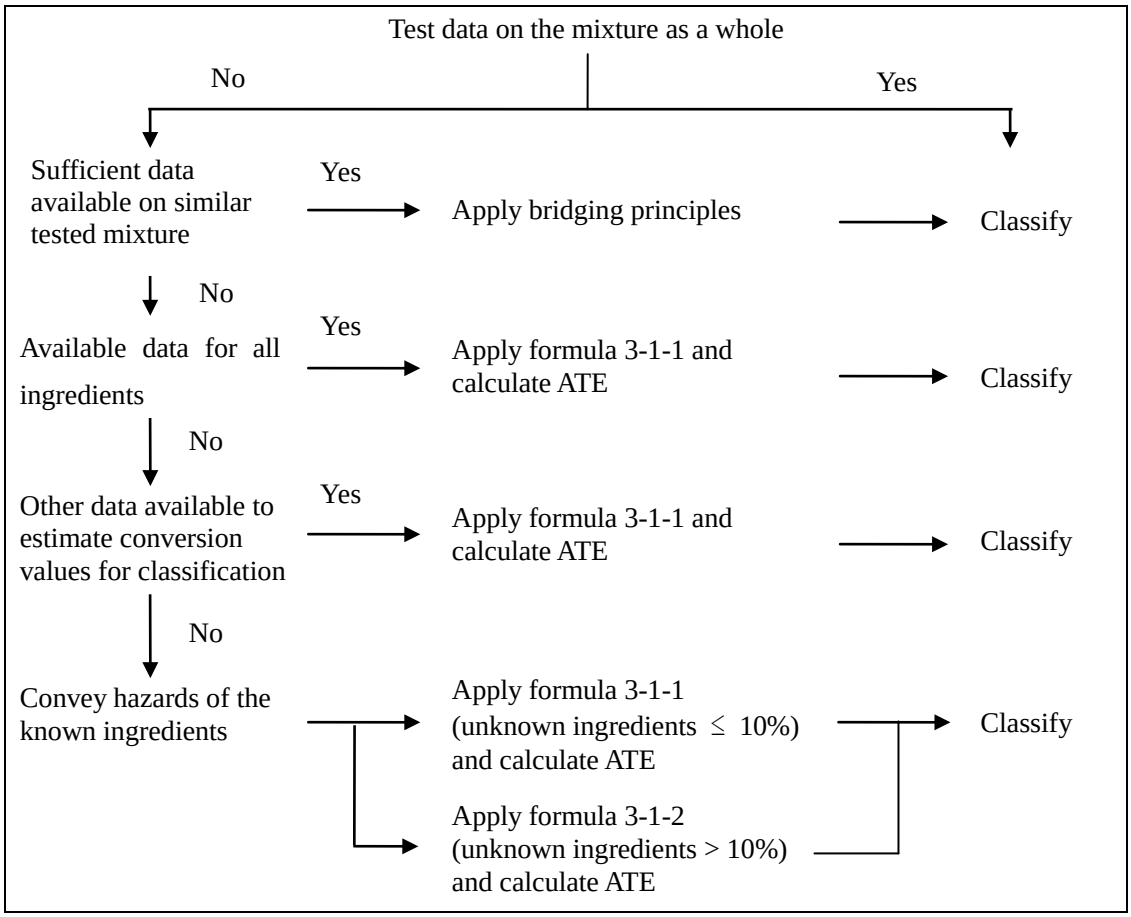
5) Since it is also presumed that vapour generated from solid is inhaled, the vapour which is generated from solid (other than gases/ liquids) is treated as “vapour” when it is clearly indicated as “vapour” or the inhalation concentration is indicated in unit of ppmV. However, when a concentration is 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”.

(5) Classification methods for mixtures

A) Tiered approach used for classification of mixtures for acute toxicity

The criteria for substances classify acute toxicity by use of acute toxicity and acute toxicity estimate values (tested or estimated). For mixtures, the approach to classify for acute toxicity is tiered, and is dependent upon the amount and quality of information available for the mixture and for its ingredients. It is called "tiered approach" in the UN GHS 4th revised edition. The flow chart of Figure 3-3-1-2 below outlines the process to be followed.

Figure 3-3-1-2: Tiered approach to classification of mixtures for acute toxicity



B) Items to be noted in classification of mixtures for acute toxicity

Classification of mixtures for acute toxicity can be carried out for each case of exposure. In case a mixture is studied (estimated or tested) in terms of only one exposure route for all ingredients, the mixture shall be classified for the route only.

In order to make use of all available data for classifying the hazards of mixtures, the following assumptions are made and are applied where appropriate to the applicable tiered approach:

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

2) Where a classified mixture is used as an ingredient of another mixture, the actual or derived acute toxicity estimate (ATE) value for that mixture may be used when calculating the classification of the new mixture using the formulas of 3-1-1 and 3-1-2.

3) If the converted acute toxicity point estimates for all ingredients of a mixture are within the same category, then the mixture should be classified in that category.

4) Table 3-3-1-2 shows conversion of range data (or acute toxicity hazard category information) to point estimates for classification of the new mixture using the formulas.

C) Classification of mixtures where acute toxicity test data on the mixture as a whole are not available: Classification by bridging principles (See 3-2-4.)

1) Dilution

The UN GHS 4th revised edition describes "dilution" as follows. :

"If a tested mixture is diluted with a diluent that has an equivalent or lower toxicity classification than the least toxic original ingredient, and which is not expected to affect the toxicity of other ingredients, then the new diluted mixture may be classified as equivalent to the original mixture."

The above description means the following. :

a) By "dilution", the ingredients (including nontoxic ingredients such as water) that has an equivalent or lower toxicity classification than the least toxic original ingredient increase. Accordingly, the new mixture has never higher toxicity than that of the original mixture. And the category of the new mixture which is shown by toxicity range shall be the same as that of the original mixture.

b) This principle may be applied when a mixture is diluted with a mixture, however, in some cases, this principle is not applicable, unless all ingredients of the diluting mixture have an equivalent or lower toxicity classification than the least toxic original ingredient of the mixture to be diluted.

Example-1: When mixture A contains ingredients that are classified as acute toxicity Category 2 and 3, and mixture itself is classified as acute toxicity Category 3, and when mixture A is diluted with acute toxicity Category 4 solvent, then the new mixture B can be classified as Category 3. In this case, acute toxicity data from the same route of administration such as oral, dermal, and so on must be used.

Example-2: Mixture C was classified in Category 3, as the test result of acute toxicity (oral) value: LD_{50} = 250 mg/kg. When mixture C is diluted with the same amount of water, acute toxicity value of the resulting mixture D is 500 mg/kg as a result of application of the later described additivity formula, and mixture D is classified as Category 4.

When diluting with ingredients other than water, toxicity category may increase as a result, and thus sufficient care is required.

2) Batching

The toxicity of a tested production batch of a mixture can be assumed to be substantially equivalent to that of another untested production batch of the same commercial product when produced by or under the control of the same manufacturer, unless there is no reason to believe there is significant variation such that the toxicity of the untested batches has changed. If the latter occurs, a new classification is necessary.

3) Concentration of highly toxic mixtures

If a tested mixture is classified in Category 1, and the concentration of the ingredients of the tested mixture that are in Category 1 is increased, the resulting untested mixture should be classified in Category 1 without additional testing. This applies to the cases that a solvent of a mixture classified as Category 1 is concentrated through distillation, etc. or that concentration of a mixture is increased by adding same ingredient.

4) Interpolation within one toxicity category

For three mixtures A, B, and C with identical ingredients, where mixtures A and B have been tested and are in the same toxicity category, and where untested mixture C has the same toxicologically active ingredient as mixtures A and B but has concentrations of toxicologically active ingredients intermediate to the concentrations in mixtures A and B, then mixture C shall be classified in the same toxicity category as A and B.

Example-3:

There are three mixtures A, B, and C, and each is consisting of ingredients M, N, and O, and the concentrations (%) of M, N, and O in mixtures A, B, and C are Mi, Ni, and Oi (i = A, B, and C), respectively (for each i, Mi + Ni + Oi = 100). The categories for acute toxicity of mixtures A and B are shown in the following table, but that of mixture C is not known and will be determined by the bridging principle. If ingredient O has acute toxicity and its concentrations O_A, O_B, and O_C are large in the order of $O_A > O_C > O_B$, the mixture C may be classified in Category 2.

Mixture	Ingredients (concentration, %)			Category of the mixture
	M	N	O	
A	M_A	N_A	O_A	2
B	M_B	N_B	O_B	2
C	M_C	N_C	O_C	?

This principle is applicable only when the existing analogous mixtures have been tested. And take care to classify, even if the existing analogous mixtures have been tested, when higher toxicity category is reasonably expected by applying this principle mechanically based on toxicity information of ingredients and the like.

5) Substantially similar mixtures

Given the following:

a) Two mixtures (i) A + B;

(ii) C + B

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

c) The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii).

d) Data on toxicity for A and C are available and substantially equivalent; they are in the same hazard category and are not expected to affect the toxicity of B.

If mixture (i) or (ii) are already classified by testing, then the other mixture can be assigned the same hazard category.

- This principle applies to the case that a ingredient of a mixture is exchanged by another ingredient with the same hazard category at the same amount.

6) Aerosols

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

(6) Classification based on additivity formulas

(Explanation of additivity formulas)

The additivity formula methods are methods by using formula 3-1-1 and formula 3-1-2, when toxicity and concentrations of ingredients of a mixture are known, to determine the ATE of the mixture, then the hazard classification category of the mixture is determined based on Table 3-3-1-1.

(Notes on determination of ATE with additivity formulas)

A) Data available for all ingredients

When data are available for all ingredients of a mixture, ATE of ingredients should be calculated as follows:

1) Include ingredients with a known acute toxicity, which fall into any of the GHS acute toxicity categories;
2) Assume ATE of the ingredients that are presumed not acutely toxic (e.g. water, sugar) as infinite in calculation;
3) Assume ingredients that do not demonstrate acute toxicity in the oral limit dose test at a dose of 2000 mg/kg bodyweight as infinite. Ingredients that fall within the scope are considered ingredients with a known ATE.

The ATE of the mixture is determined by calculation from the ATE values for all relevant ingredients according to the following formula below for oral, dermal, or inhalation toxicity:

$$\frac{100}{ATE_{\text{mix}}} = \sum_{i=1}^{n} \frac{C_i}{ATE_i} \quad \cdots\cdots\cdots\cdots\cdots\cdots \text{formula 3-1-1}$$

wherein: ATE_{mix} = ATE of the mixture

C_i = concentration of ingredient i

ATE_i = Acute toxicity estimate of ingredient i

n shows the number of ingredients and i is running from 1 to n.

For example, if the number of ingredients is three and each ATE and concentrations are known, $ATE_{mix} = 100/ (C_1/ATE_1 + C_2/ATE_2 + C_3/ATE_3)$.

B) When information of an ingredient or multiple ingredients of a mixture are not available, the following methods may be applied.

a) Where an ATE is not available for an individual ingredient of the mixture, but available information such as listed below can provide a derived conversion value, the formula 3-1-1 may be applied. If estimated from data for other exposure route, required information is often not available and seek for experts' judgment. When such procedures are not possible, used data obtained from the same exposure route.

1) Extrapolation between oral, dermal, and inhalation acute toxicity estimates. Such an evaluation could require appropriate pharmacodynamic (P/D) and pharmacokinetic (P/K) data and experts' judgment;

2) Evidence from human exposure that indicates toxic effects but does not provide lethal dose data;

3) Evidence from any other toxicity tests/assays available on the substance that indicates toxic acute effects but does not necessarily provide lethal dose data; or

4) Data from closely analogous substances using structure-activity relationships.

In case data requirements for specific ingredients include acute toxicity evaluation for the dermal and inhalation routes, the values to be used in the formula need to be from the required exposure route.

b) In the event that an ingredient without any useable information at all is used in a mixture at a concentration ≥ 1%, it shall be concluded that clear acute toxicity estimate value is not applicable to the mixture. In such cases, the mixture should be classified based on the known ingredients only, and additional statement “x% of the

mixture consists of ingredient (s) of unknown toxicity" should be stated in the classification result.

c) If the total concentration of the ingredient (s) with unknown acute toxicity is ≤ 10%, then the formula 3-1-1 should be used. If the total concentration of the ingredient (s) with unknown acute toxicity is > 10%, the additivity formula presented in formula 3-1-1 should be corrected to adjust for the total percentage of the unknown ingredient (s) as follows:

$$\frac{100-\left(\sum C \text{ unknown if } >10\%\right)}{ATE_{\text{mix}}}=\sum_{i=1}^{n}\frac{C_{\text{i}}}{ATE_{\text{i}}} \quad \cdots\cdots\cdots\cdots \text{formula 3-1-2}$$

wherein: $C_{unknown}$ if > 10%: the total percentage of the unknown ingredient(s) if the concentration of the unknown ingredient (s) > 10%

ATE_{mix}: ATE of the mixture

C_i: concentration of ingredient i

ATE_i: Acute toxicity estimate of ingredient i

n: shows the number of ingredients and i is running from 1 to n.

Example-4: Classification for acute toxicity (dermal) of ingredients consisting of the following ingredients※

Ingredient	Ingredient 1	Ingredient 2	Ingredient 3	Ingredient 4
Concentration (%)	5	44	48	3
Acute toxicity (dermal)	LD_{50}: 40 mg/kg	ATE: 200 < LD_{50} < 1000 mg/kg	LD_{50}: 90 mg/kg	Category 4

※ This is provided that

a) Acute toxicity data as a mixture are not available.

b) Acute toxicity data of similar mixtures are not available and therefore, bridging principle cannot be applied.

1) As for ingredient 2, the value range 200 < LD_{50} < 1 000 mg/kg is converted to ATE=300 according to Table 3-1-2.

2) As for ingredient 4, which is classified in Category 4, is ATE = 1 100 mg/kg according to Table 3-1-2.

3) When ATE_{mix} is calculated applying formula 3-1-1 to the concentration set for each ingredient,

$$ATE_{mix} = 100 / (5/40 + 44/300 + 48/90 + 3/1100) = 123$$

As a result, the ATE_{mix} of the mixture is 123 mg/kg, and the mixture is classified in Category 2 according to Table 3-3-1-1.

However, it should be noted that, if the exposure route is inhalation of the vapour, the units of ATE must be unified, and the prerequisite condition whether all ingredients vaporize or the mixture reaches an equilibrium between liquid and vapour phases must be determined.

3-3-2 Skin Corrosion/Irritation

(1)Definitions

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

【GHS 4th 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. Corrosive reactions are typified by ulcers, bleeding, bloody scabs, and, by the end of observation at 14 days, by discoloration due to blanching of the skin, complete areas of alopecia, and scars. Histopathology should be considered to 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.

(2)Classification criteria

A) Classification criteria based on Classification JIS

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

Table 3-3-2-1 Skin corrosion category and sub-categories [a)]

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” in paragraph 1.3.2.4.7.1 of the UN GHS 4th revised edition.

Table 3-3-2-2 Categories of skin irritation[a)]

Category	Criteria
Skin irritation (Category2)	Any one of the below shall serve as the criterion. 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 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 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.

Note a) The use of human data is discussed in "Evidence from humans" in paragraph 1.3.2.4.7 of the UN GHS 4th revised edition.

B) Classification criteria in GHS (Reference Information)

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

【GHS 4th revised edition】 (3.2.2)

Table 3.2.1: Skin corrosion category and sub-categories [a]

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

[a] *The use of human data is discussed in 3.2.2.1 and in Chapter 1.3 (paragraph 1.3.2.4.7)*

Table 3.2.2 Skin irritation categories [a]

Categories	**Criteria**
Irritant (Category 2) (applies to all authorities)	(1) Mean value of ≥ 2.3 ≤4.0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or (2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or (3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.
Mild irritant (Category 3) (applies to only some authorities)	Mean value of ≥ 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 Chapter 1.3 (paragraph 1.3.2.4.7)*

(3) Items on information sources and data

∗ Classification procedures including information gathering can be referred to "3-1 Summary of GHS 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 Test Guideline 435 (*in vitro* membrane barrier test method) provides *in vitro* test method for classification into skin corrosion sub-categories (1A, 1B, and 1C).
- If it is not easy to obtain appropriate irritation data based on observation results (e.g., average Draize Score values (for each animal) of erythema/eschar or edema), PII (skin primary irritation index), findings such as "Severe", "Moderate", "Mild (Slightly)"[6] and others regarding skin corrosion/irritation in test reports can be referred to.
- Hazard statements[7] (H314 and H315) relating to skin corrosion/irritation in EU CLP classification and R-Phrases[8] (R34, R35, R38, R36/38, R37/38, R36/37/38) relating to skin corrosion/irritation in EU DSD classification can be referred to.
- 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 (TER)
  OECD TG 431 *In vitro* skin corrosion: Human skin model test
  OECD TG 435 *In vitro* membrane barrier test method for skin corrosion
  OECD TG 439 *In Vitro* Skin Irritation: Reconstructed Human Epidermis Test Method

B) Order of precedence when multiple data exist

Refer to "3-2-2 Order of precedence when multiple data exist".

C) Comparison with conventional classification systems

- Substances classified as H314 in EU CLP classification and as R34, R35 corrosive (C) in EU DSD classification fall under Category 1.
- Substances classified as H315 in EU CLP fall under Category 2. Substances classified as Irritant (Xi) with R38 and combination of R-Phrases[9] (R36/38, R37/38, R36/37/38) in EU classification fall under Category 2 (in GHS classification). In classification, confirmation with detailed data is required.
- Comparison between EU classification and GHS classification is as follows.

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[6] Some observations distinguish "mild" and "slightly", but in IUCLD, "slightly" is used instead of" mild".
[7] See Annex for EU hazard statement
[8] For R-Phrase, see Appendix.
[9] For R-Phrase, see Appendix.

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

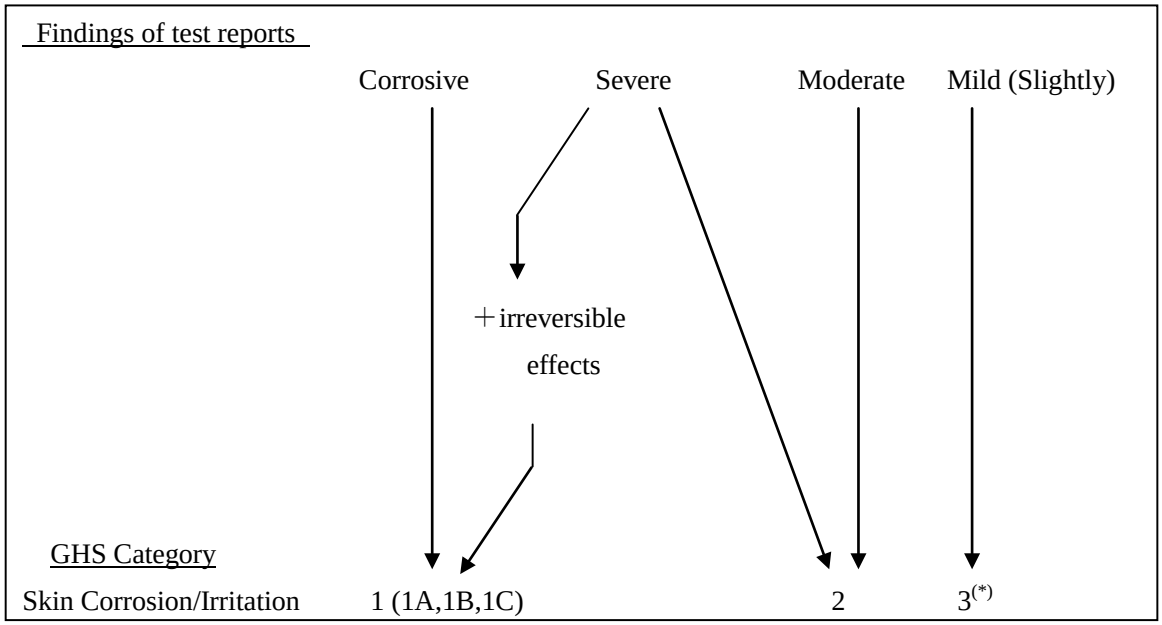
EU DSD classification	Xi R38	
EU CLP classification	H315	
GHS classification	Category2	Category3

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.

D) Guidance concerning data

In many cases, findings of test reports are given using the evaluative scale of “severe”, “moderate”, and “mild (slightly)” [10], 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 PII 3-5) or severe (corresponding to PII 5-8). 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.

[10] Some observations distinguish “mild” and “slightly”, but in IUCLD, “slightly” is used instead of” mild”.



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

E) Decision by physicochemical properties

Substances considered as strong acids (pH ≤ 2) or strong alkalis (pH ≥ 11.5) based on their physicochemical properties shall be classified as Category 1. However, in this case, as described in the UN GHS 4th revised edition, it must be shown that its buffer power maintains pH on exposure. In classification, buffering capacity of acids and bases should be taken into account.

(4)Guidance for classification and judgment

A) Points to be noted in this item

Classification with regard to skin corrosion and irritation shall be conducted according to the workflow of decision logic 3.2.1 (3.2.5.1) that is the clear criteria of UN GHS 4th 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 4th revised edition (Table 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”.

A substance which is applicable to “Category 3” of UN GHS classification corresponds to “Not classified” in the Classification JIS. Therefore, “Not classified” shall be indicated if classification result based on the Classification JIS is described.

B)Judgment 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) Judgment 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 ≥ 2.3 to ≤ 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) 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.

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 should be noted that since IUCLID has no classification category of “Mild” and uses “Slightly”, slight irritation shall be classified as “Not classified” (Category 3 of UN GHS classification criteria).
- 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

Analysis based on structure-activity relationship can be used for classification. On the other hand, this is not taken into account in classification based on the GHS Classification Guidance for the Japanese Government, in principle. However, if there is a description to the effect that “the substance is judged to be applicable to Category XX as a result of analysis by structure-activity relationship” in reliable information sources, the substance is classified based on the result.

E) Decision by physicochemical properties

In the case of pH $\leq$ 2 and 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), OECD TG435 (Corrositex®), or OECD TG439 (*in vitro* Skin Irritation: Reconstructed Human Epidermis Test Method) is available, the substance shall be

classified in accordance with the decision criteria with which each of the test is internationally accepted. Other *in vitro* tests are not considered.

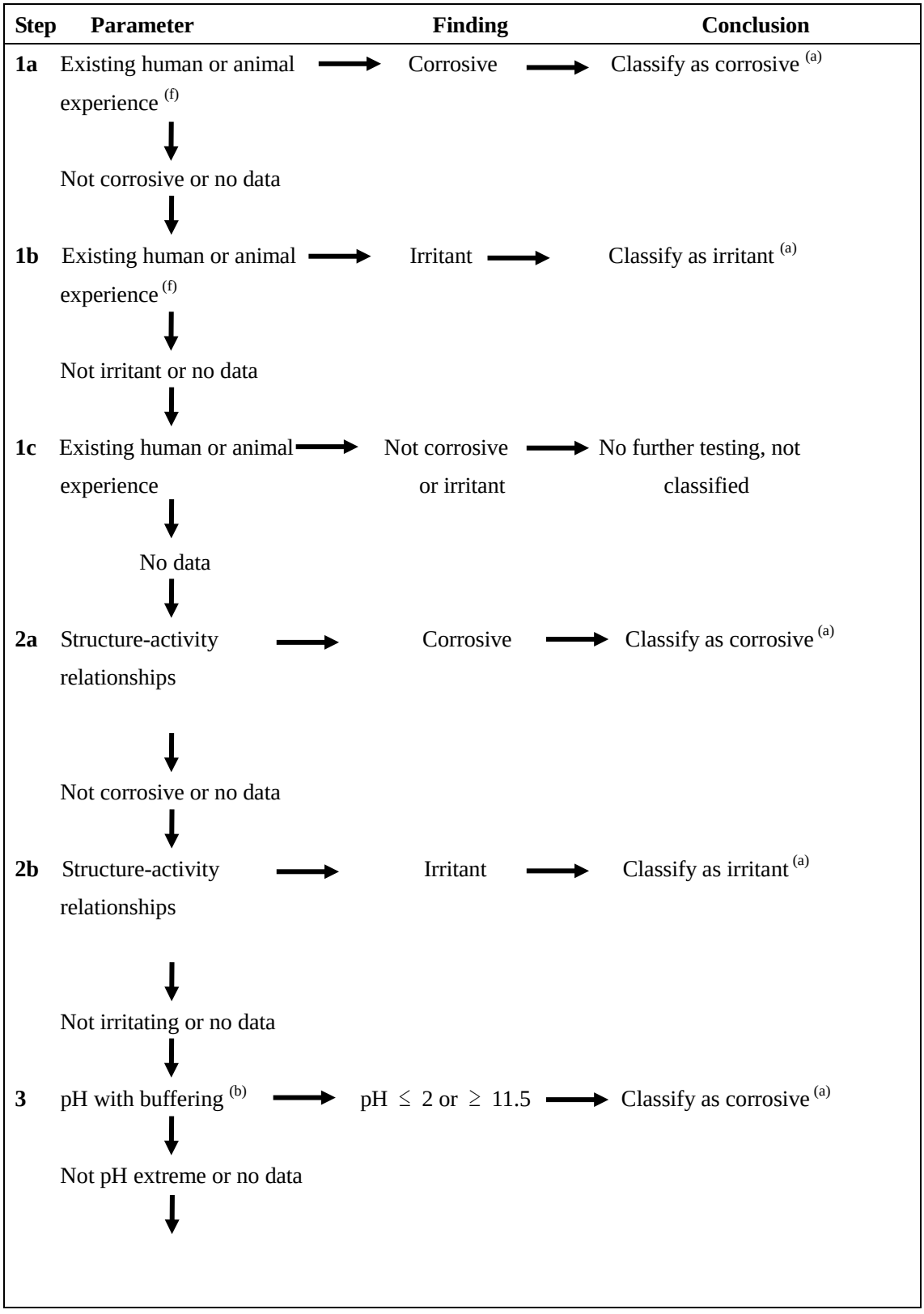
G) Strategy of tiered testing and evaluation for skin corrosion and skin irritation

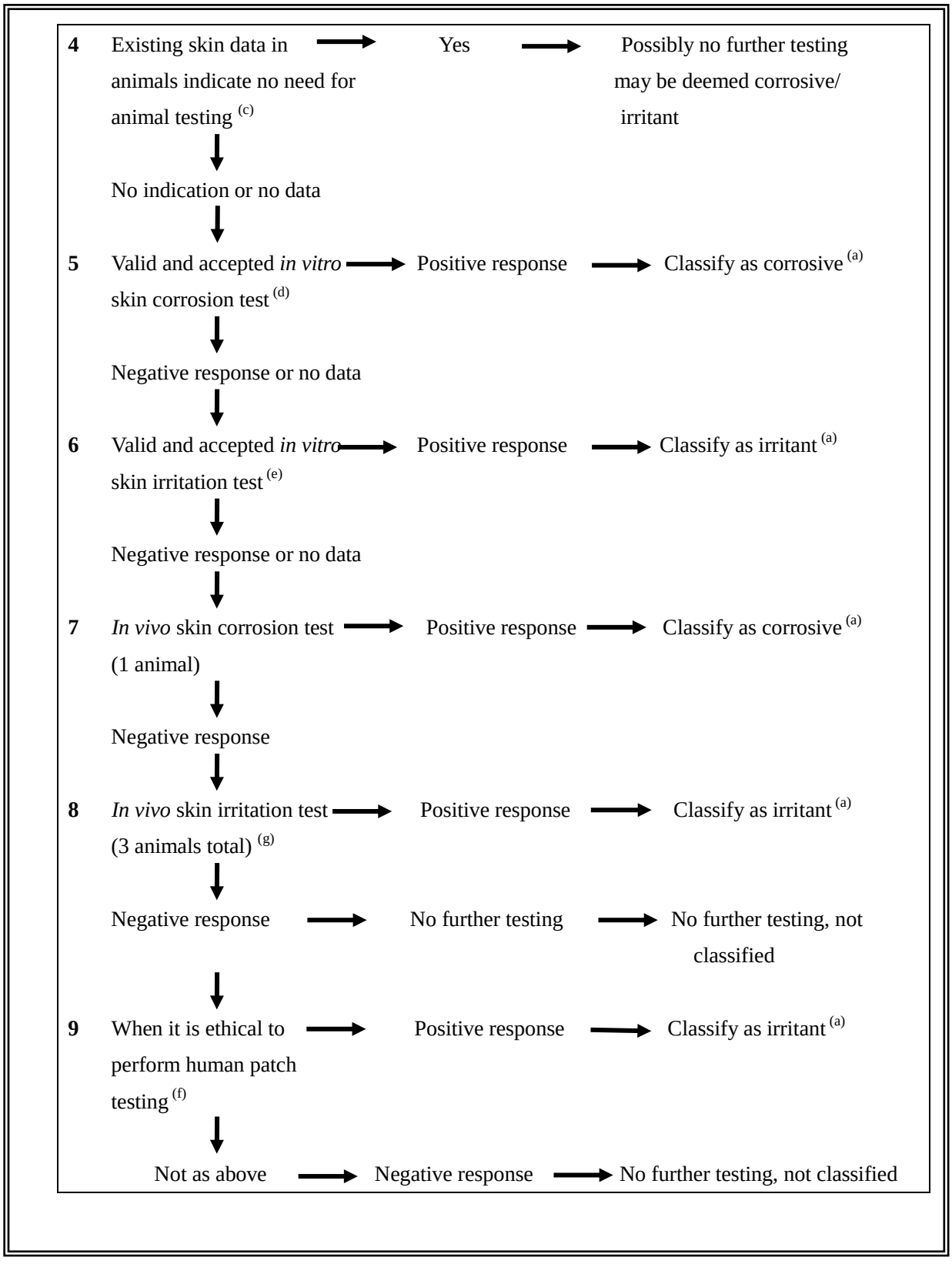
The strategy of tiered testing and evaluation for skin corrosion/irritation described in the UN GHS 4th revised edition (3.2.1) is as follows.

Necessity of revision of this flow diagram has been discussed in the “United Nations Sub-Committee of Experts on the Globally Harmonized System of Classification and Labeling of Chemicals (UNSCEGHS)”.

【GHS 4th revised edition】(quoted and partially revised)

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




4 Existing skin data in animals indicate no need for animal testing (c)
Yes
Possibly no further testing may be deemed corrosive/ irritant
No indication or no data
5 Valid and accepted *in vitro* skin corrosion test (d)
Positive response
Classify as corrosive (a)
Negative response or no data
6 Valid and accepted *in vitro* skin irritation test (e)
Positive response
Classify as irritant (a)
Negative response or no data
7 *In vivo* skin corrosion test (1 animal)
Positive response
Classify as corrosive (a)
Negative response
8 *In vivo* skin irritation test (3 animals total) (g)
Positive response
Classify as irritant (a)
Negative response
No further testing
No further testing, not classified
9 When it is ethical to perform human patch testing (f)
Positive response
Classify as irritant (a)
Not as above
Negative response
No further testing, not classified

[Note for the above figure]

(a) Classify in categories shown in (2) B).

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

(c) 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

(d) Examples of internationally agreed *in vitro* test methods for skin corrosion are OECD TG 430, TG 431 and TG 435; see “F) Decision by *in vitro* test methods”.

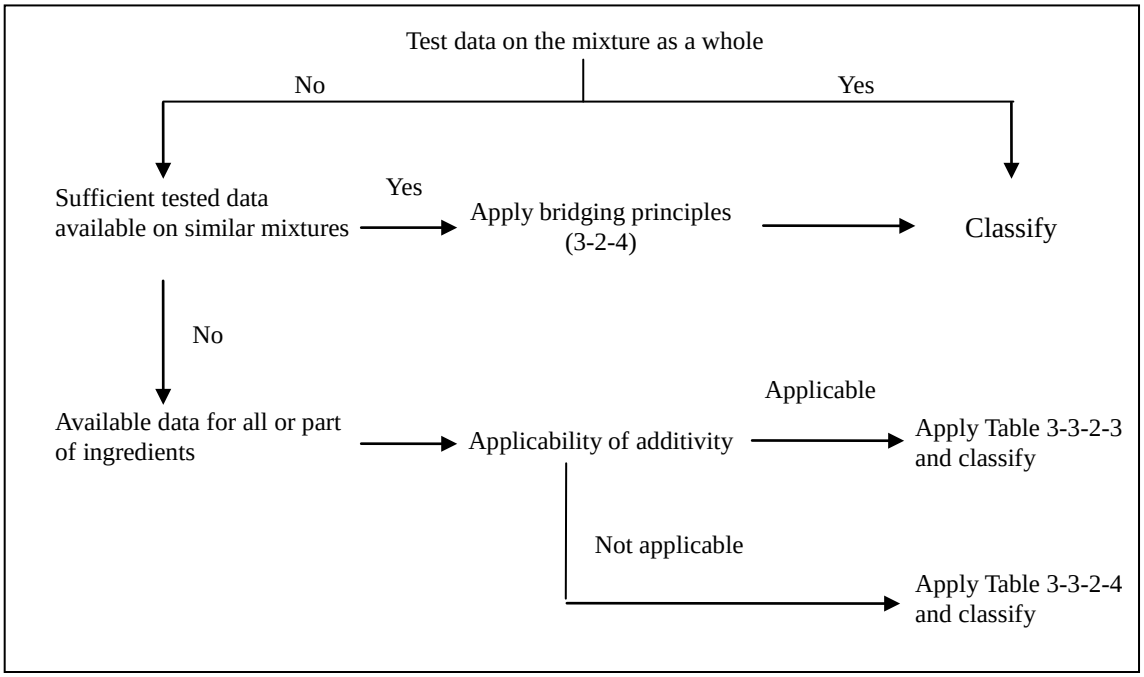
(e) An example of internationally agreed *in vitro* test methods for skin irritation is OECD TG 439; see “F) Decision by *in vitro* test methods”.

(f) This evidence can 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.

(5) Classification methods for mixtures

A tiered approach to classify skin corrosion/irritation in the same way as acute toxicity is described.

Figure 3-3-2-1 Tiered approach to classification of mixtures for skin corrosion/irritation



A) Classification of mixtures when data on the mixture as a whole are available

1) The mixture will be classified using the criteria for chemical substances, and taking into account the testing and evaluation strategies to develop data for these hazard classes.
2) There are alternative tests available for skin corrosivity of certain types of chemicals that can give an accurate result for classification purposes, as well as being simple and relatively inexpensive to perform. When considering testing of the mixture, classifiers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for skin corrosion and irritation to help ensure an accurate classification, as well as avoid unnecessary animal testing.
3) A mixture is considered corrosive (Skin Category 1) if it has a pH $\leq$ 2 or a pH $\geq$11.5. If consideration of alkali/acid reserve suggests the substance or mixture may not be corrosive despite the low or high pH value, then further testing needs to be carried out to confirm this, preferably by use of an appropriate validated in vitro test.

B) Classification of mixtures when data on the mixture as a whole are not available

1) Where the mixture itself has not been tested to determine its skin irritation/corrosion, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be

used in accordance with the bridging principles (3-2-4). This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without the necessity for additional testing in animals. For skin corrosion/irritation, "dilution", "batching", "concentration of mixtures of the highest toxicity", "interpolation within one toxicity category", "substantially similar mixtures", and "aerosols" among bridging principles are applicable.

C) Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

1) In order to make use of all available data for the purpose of classifying the skin irritation/corrosion hazards of mixtures, the following assumption is applied.
   - The relevant ingredients of a mixture are those which are present in concentrations ≥ 1% (w/w for solids, liquids, dusts, mists, and vapours, and v/v for gases), unless there is a presumption (e.g. in the case of corrosive ingredients in particular) that a ingredient present at a concentration < 1% can still be relevant for classifying the mixture for skin irritation/corrosion.
2) In general, the approach to classification of mixtures as irritant or corrosive to skin when data are available on the ingredients, but not on the mixture as a whole, is based on the theory of additivity, such that each irritant or corrosive ingredient contributes to the overall irritant or corrosive properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive ingredients when they are present at a concentration below the concentration limit for classification with Category 1, but are at a concentration that will contribute to the classification of the mixture as an irritant. The mixture is classified as corrosive or irritant when the sum of the concentrations of such ingredients exceeds the concentration limit. Table 3-3-2-3 below provides the concentration limits to be used to determine if the mixture is considered to be an irritant or a corrosive to the skin.
3) Classification of mixtures with ingredients for which additivity approach does not apply
   - In classifying certain types of chemicals such as acids, bases, inorganic salts, aldehydes, phenols, and surfactants, for which additivity approach does not apply and which are sometimes corrosive or irritant at concentrations even < 1%, above classification methods 1) and 2) do not work. Therefore, classification shall be performed based on Table 3-3-2-4.
   - A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach shown in Table 3-3-2-3 should be classified as

Skin Category 1 if it contains ≥ 1% of a corrosive ingredient and as Skin Category 2 when it contains ≥ 3% of an irritant ingredient. These are summarized in Table 3-3-2-4 below.

- Skin hazards by acids, bases, inorganic salts, aldehydes, phenols, and surfactants are disclosed in website of EU on cosmetics, but specific material names are not shown.
  http://ec.europa.eu/consumers/sectors/cosmetics/files/doc/antest/(5)_chapter_3/3_eye_irritation_en.pdf
- For hazard information of surfactants, refer to SDS of manufacturers.

4) Classification of mixtures when the theory of additivity applies for ingredients

- Ingredients other than 3) are assumed to be applicable to the theory of additivity, and classified based on Table 3-3-2-3.
- On occasion, reliable data may show that the skin corrosion/irritation of an ingredient will not be evident when present at a level above the generic concentration cut-off values mentioned in tables 3-3-2-3 and 3-3-2-4. In these cases the mixture could be classified according to those data. On occasion, when it is expected that the skin corrosion/irritation of an ingredient will not be evident when present at a level above the generic concentration cut-off values mentioned in tables 3-3-2-3 and 3-3-2-4, testing of the mixture may be considered.

Table 3-3-2-3 Concentration of ingredients of a mixture to be classified (skin corrosion/irritation)

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:	
	Skin corrosive	Skin irritant
	Category 1	Category 2
Skin Category 1	≥ 5%	< 5%, ≥ 1%
Skin Category 2	-	≥ 10%
(10 x skin Category 1) + skin Category 2	-	≥ 10%

Table 3-3-2-4 Concentration of ingredients of a mixture for which the additivity approach does not apply (skin corrosion/irritation)

Ingredient	Concentration	Mixture classified as: Skin
Acid with pH ≤ 2	≥ 1%	Category 1
Base with pH ≥ 11.5	≥ 1%	Category 1
Other corrosive (Category 1)	≥ 1%	Category 1

ingredients for which additivity does not apply		
Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

3-3-3 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 4th 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.

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.

(2)Classification criteria

A) Classification criteria based on Classification JIS

Table 3-3-3-1 Irreversible eye effects categories

An eye irritant Category 1 (irreversible effects on the eye) is a test material that produces:

a) 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

b) at least in 2 of 3 tested animals, a positive response of :

corneal opacity ≥3; and/or

iritis >1.5 ;

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

Table 3-3-3-2 Reversible eye effects categories

An eye irritant Category 2A (irritating to eyes)is a test material that produces:

at least in 2 of 3 tested animals, a positive response of :

corneal opacity ≥ 1; and/or

iritis ≥1; and/or

conjunctival redness ≥ 2; and/or

conjunctival oedema (chemosis) ≥ 2

calculated as the mean scores following grading at 24, 48, and 72 hours after installation of the test material, and which fully reverses within an observation period of normally 21 days.

Within this category, an eye irritant is considered mildly irritating to eyes (Category 2B) when the effects on eyes are fully reversible within 7 days of observation.

B) Classification criteria in GHS

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

(3) Items on information sources and data

* Classification procedures including information gathering can be referred to "3-1 Summary of GHS 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 it is difficult to obtain appropriate irritation data based on observation results (e.g. Draize Score mean values of each animal and AOI: acute ocular irritation index), findings such as “Severe”, “Moderate”, “Mild (Slightly)[11]” and others regarding eye damage/eye irritation in test reports can be referred to. 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. However, it is preferable to review the cited original literature, to examine its scientific validity, and then to classify in accordance with the results.
    - Hazard statements H318 and H319 relating to eye damage/eye irritation in EU CLP classification and R-Phrases[12] (R36, R41, R36/37, R36/38, R36/37/38) relating to serious eye damage/eye irritation in EU DSD classification can be referred to.
    - The OECD test guideline provides the following test method relating to serious eye damage/eye Irritation.

[11] As described in the footnote in 3-3-2 Skin Corrosion/Irritation , some observations distinguish "mild" and "slightly", but in IUCLD, "slightly" is used instead of "mild".

[12] For R-Phrase, see Appendix.

OECD TG 405 Acute eye irritation / corrosion

OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants

OECD TG 438 Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants

B) Order of precedence when multiple data exist

Refer to "3-2-2 Order of precedence when multiple data exist".

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[13] (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.
- Comparison between EU classification and GHS classification is as follows.

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)[14]", and these can be considered to correspond to Categories 1, 2A, and 2B, 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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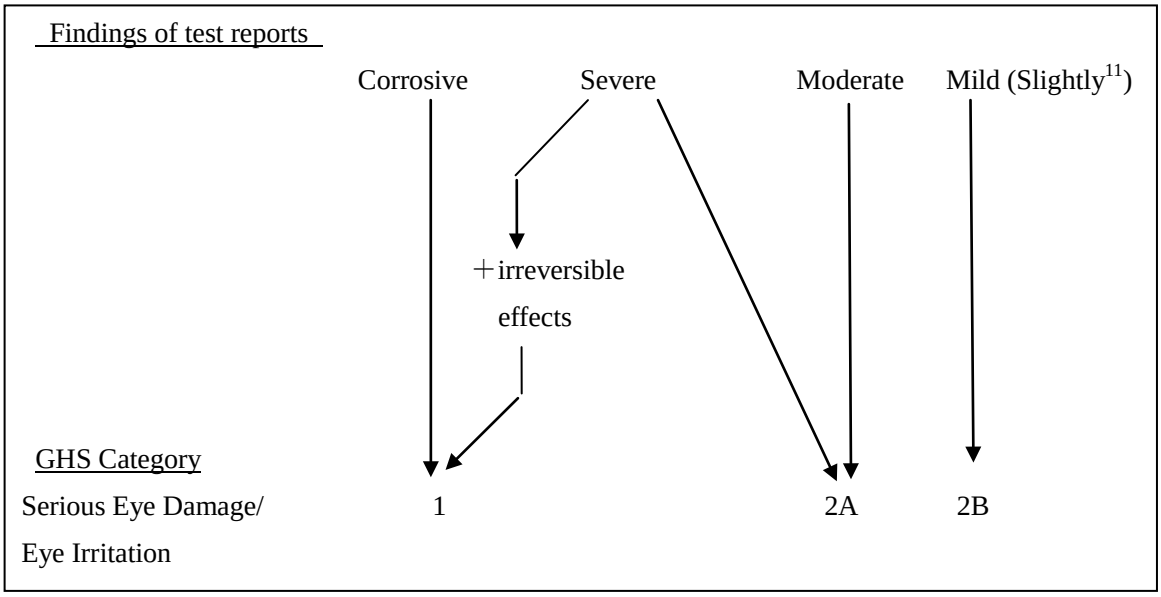
[13] For R-Phrase, see Appendix.

[14] As described in the footnote 9 in 3-3-2 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"



(4)Guidance for classification and judgment

A) Points to be noted in this item

As for serious eye damage/eye irritation, classification should be conducted according to the workflow of “decision logic 3.3.1” (3.3.5.1), which is the definite decision criteria of UN GHS 4th revised edition. In classification, refer to the technical advices such as judging method based on pre-existing test data described below.

Sub-categorization of eye irritation can be performed only when data is available which shows that the grade of eye irritation reaction which allows the application of the GHS eye irritation judgment (the UN GHS 4th revised edition, table 3.2.2) (for example, Draize method for rabbit or human findings) is mild and showing full reversibility within 7 days . 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 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.

B) Judgement by reliable existing revelation course

If there is a case that ascribes to a substance irreversible effects on eye (Category 1) or reversible effects on eye (Category 2) in human or animal results, the substance shall be classified as such. Similarly, if data are available for skin corrosion in human or animal results,

the substance shall be classified as a substance having irreversible effects on eyes (Category 1). Refer to the UN GHS 4th revised edition, table 3.3.1 (Example: accidental cases)

C) Judgement by existing reliable 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 ≥ 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 ≥ 1 and/or iritis ≥ 1 and/or conjunctival redness ≥ 2 and/or conjunctival oedema ≥ 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 (Slightly) (15 ≤ AOI < 30) is classified in Category 2B. It should be noted that since IUCLID has no classification category of “Mild” and uses “Slightly”, slight irritation shall be classified as 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

Analysis based on structure-activity relationship can be used for classification.

On the other hand, this is not taken into account in classification based on the GHS

Classification Guidance for the Japanese Government in principle. However, if there is a description to the effect that “the substance is judged to be applicable to Category XX as a result of analysis by structure-activity relationship” in reliable information sources, the substance is classified based on the result.

E) Decision by physicochemical properties

In the case of pH ≤ 2 or pH ≥ 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”, YOUNG. J, 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

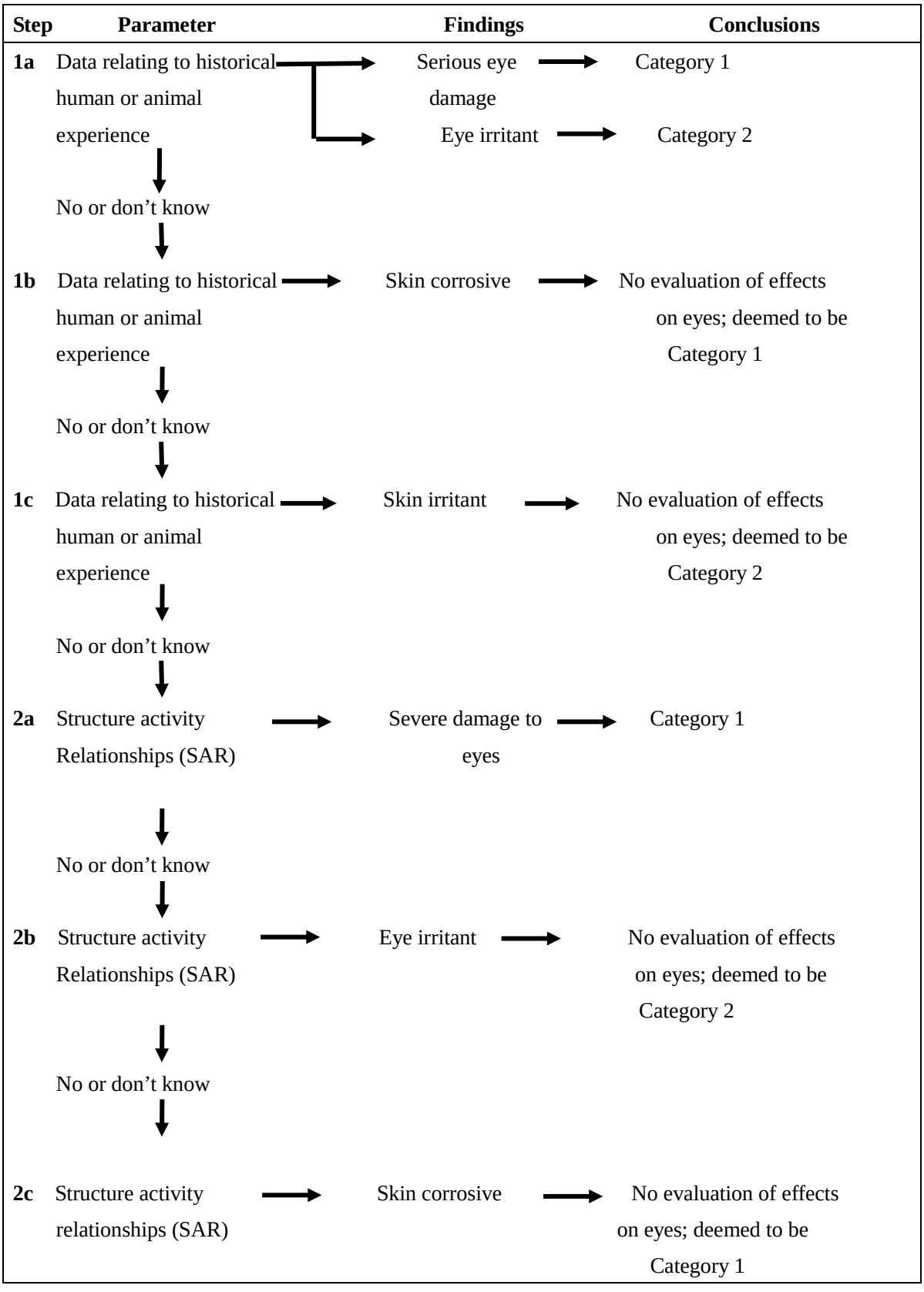
The strategy of tiered testing and evaluation for Serious Eye Damage/Eye Irritation described in the UN GHS 4th revised edition, Figure 3.3.1 is as follows.

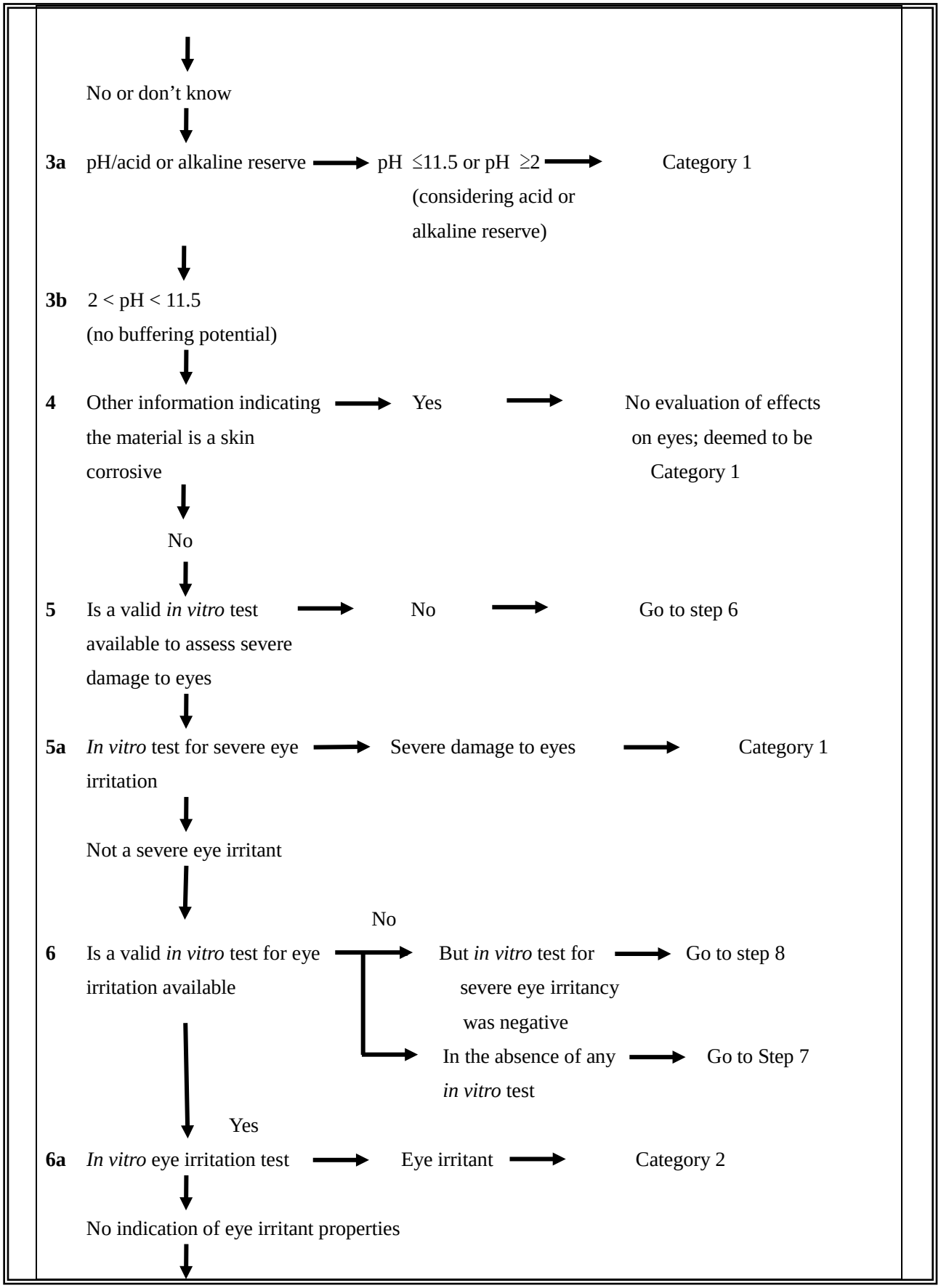
Discussion on the necessity for revising this flow diagram has arisen in the “United Nations Sub-Committee of Experts on the Globally Harmonized System of Classification and Labeling of Chemicals (UNSCEGHS)”.

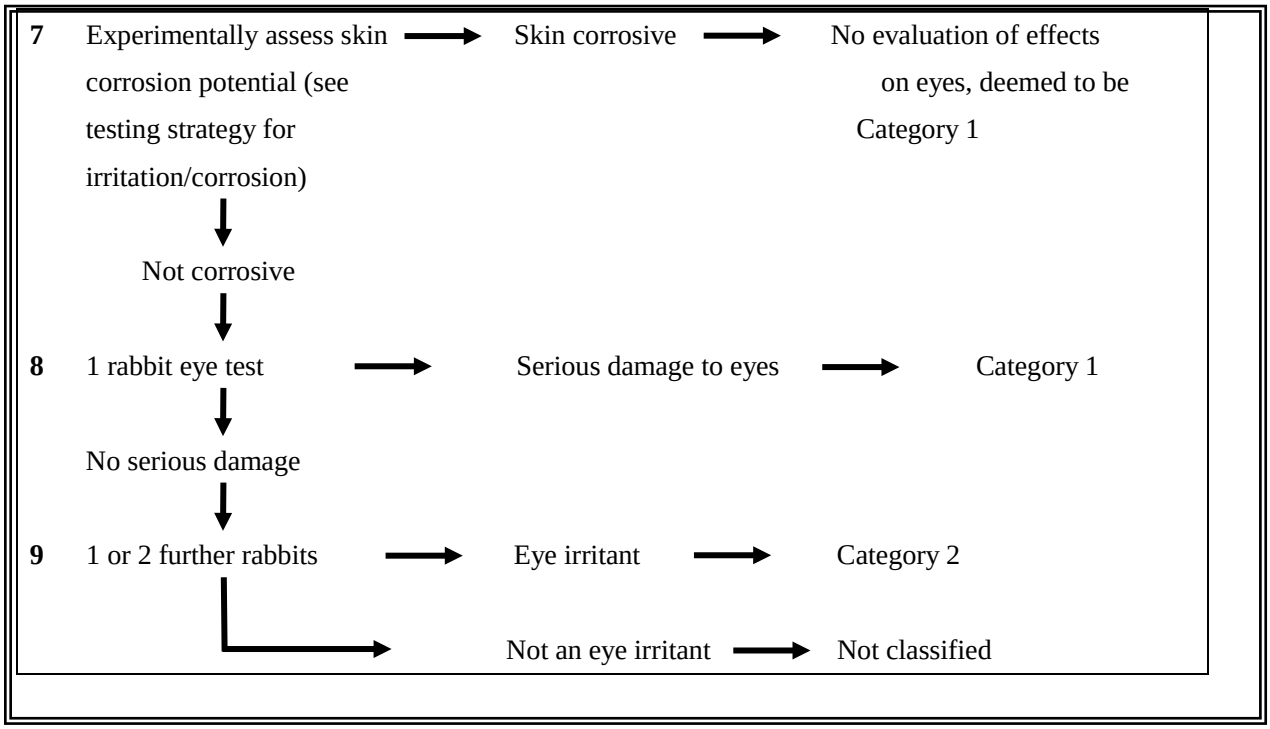
(Also, refer to Skin irritation/corrosion test and summary of the results.)

【GHS 4th revised edition】(quoted and partially revised)

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




No or don't know
3a pH/acid or alkaline reserve
pH ≤11.5 or pH ≥2
(considering acid or alkaline reserve)
Category 1
3b 2 < pH < 11.5
(no buffering potential)
4 Other information indicating the material is a skin corrosive
Yes
No evaluation of effects on eyes; deemed to be Category 1
No
5 Is a valid *in vitro* test available to assess severe damage to eyes
No
Go to step 6
5a *In vitro* test for severe eye irritation
Severe damage to eyes
Category 1
Not a severe eye irritant
No
6 Is a valid *in vitro* test for eye irritation available
But *in vitro* test for severe eye irritancy was negative
Go to step 8
In the absence of any *in vitro* test
Go to Step 7
Yes
6a *In vitro* eye irritation test
Eye irritant
Category 2
No indication of eye irritant properties



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 judgment: 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: SAR (structure-activity 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 approaches. The SAR analysis may identify serious eye damage, corrosion and irritation potential for both skin and eye effects:

(i) Step 2a - reliable determination of eye irritancy only by theoretical evaluations – in most cases it will only be appropriate for substances that are homologous to agents with very well known properties;

(ii) Step 2c - theoretical evaluation of skin corrosivity - skin corrosive substances should not be instilled into the eyes of animals; such substances should be considered as leading to serious damage to the eyes as well (Category 1).

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

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

Step 5: *These must be alternative methods for the assessment of eye irritation/ or serious damage to eyes (e.g. irreversible corneal opacity) which have been validated in accordance with internationally agreed principles and criteria (see section 1.3.2 in Chapter 1.3 of UN GHS 4th revised edition).*

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, Chapter 3.2.2 of UN GHS 4th revised edition).*

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.*

(5) Classification methods of mixtures

A tiered approach to classify serious eye damage/eye irritation in the same way as acute toxicity and skin corrosion/irritation is described as follows.

Figure 3-3-3-1: Tiered approach to classification of mixtures for serious eye damage/eye irritation

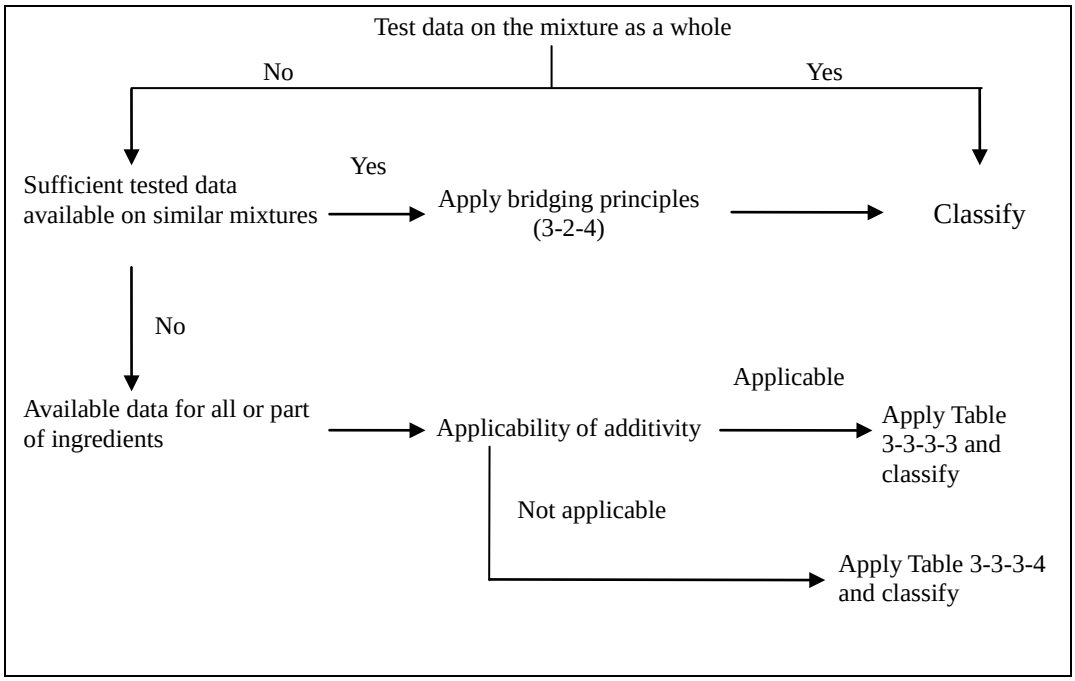


Figure 3-3-3-1 is briefly explained as follows.

A) Classification of mixtures when data on the mixtures as a whole are available

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

2) A mixture is considered corrosive (Skin Category 1) if it has a pH $\leq$ 2 or a pH $\geq$ 11.5. If consideration of alkali/acid reserve suggests the substance or mixture may not be corrosive despite the low or high pH value, then further testing needs to be carried out to confirm this, preferably by use of an appropriate validated in vitro test.

B) Classification of mixtures when data on the mixtures as a whole are not available

1) Where the mixture itself has not been tested to determine its eye damage/irritation potential, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following agreed bridging principles (3-2-4). This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without necessity for additional testing in animals.

For serious eye damage/eye irritation, "dilution", "batching", "concentration of mixtures with the highest toxicity", "interpolation within one toxicity category",

"substantially similar mixtures", and "aerosols" among bridging principles are applicable.

C) Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

1) In order to make use of all available data for purposes of classifying the eye irritation/serious eye damaging properties of the mixtures, the following assumption is applied.

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

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

3) Table 3-3-3-3 provides the concentration limits to determine if a mixture should be classified in eye irritation or serious eye damage category.

Table 3-3-3-3 Concentration of ingredients of a mixture to be classified

(serious eye damage/eye irritation)

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:	
	Irreversible eye effects	Reversible eye effects
	Category 1	Category 2
Eye or skin Category 1	≥ 3%	≥ 1% but < 3%
Eye Category 2/2A	-	≥ 10%
(10 x eye Category 1) + eye Category 2/2A	-	≥ 10%
Eye Category 1 + skin Category 1	≥ 3%	≥ 1% but < 3%
10 x (skin Category 1 + eye Category 1) + eye Category 2A/2B	-	≥ 10%

[Explanation of Table 3-3-3-3]

In the table, the criteria used to determine if the mixture should be classified an irritant or a seriously damaging to the eye is defined with categories and concentration limits.

If the ingredient is classified in corrosive Category 1, consider eye corrosion and skin corrosion.

For example, if the ingredient(s) are classified in eye Category 1 and skin Category 1, and the concentration or the sum of concentrations are 3% or more, classify the mixture in Category 1. If they are less than 3%, then the sum is multiplied by the weighting factor of 10 and added to the concentration of ingredients of eye irritant Category 2, and when the resultant sum is more than 10%, classify the mixture in Category 2.

Thus, if the sum of each category exceeds the concentration limits, the mixture is classified an irritant or a seriously damaging to the eye.

D) Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture (in cases ingredients of a mixture for which the additivity approach does not apply)

1) Particular care must be taken when classifying certain types of chemicals and their mixtures.

If certain types of compounds are ingredients of mixtures, the mixtures may show skin corrosion/irritation even at ingredient concentrations < 1%, therefore examine data carefully , and classify base on the data.

2) The certain types of chemicals are defined as acids, bases, inorganic salts, aldehydes, phenols, and surfactants in the 4th revised edition of UN GHS. However, compounds causing corrosion or irritation are not specified.

3) Classification of mixtures with ingredients for which the additivity approach does not apply is summarized in Table 3-3-3-4.

- Mixtures containing 1% or more of such corrosive ingredients are classified in eye Category 1.
- Mixtures containing 3% or more of such irritant ingredients are classified in eye Category 2. In principle, a mixture categorized as Eye Category 2 should be labeled as Category 2A, since it is required to label either as Category 2A or 2B.

E) Classification when reliable data may show that the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic concentration limits mentioned in Tables 3-3-3-3 and 3-3-3-4: On occasion, reliable data may show that the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic concentration limits mentioned in Tables 3-3-3-3 and 3-3-3-4. In these cases the mixture could be classified according to those data.

On occasion, when it is expected that the skin corrosion/irritation or the reversible/irreversible eye effects of an ingredient will not be evident, testing of the mixture may be considered. In those cases, the strategy should be applied as referred to Tables 3-3-3-3 or 3-3-3-4. Also, if there are data showing that (an) ingredient(s) may be corrosive or irritant at a concentration of < 1% (corrosive) or < 3% (irritant), the mixture should be classified accordingly.

Table 3-3-3-4 Concentration of ingredients of a mixture for which the additivity approach does not apply

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

3-3-4 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 4th 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.

A *skin sensitizer* is a substance that will lead to an allergic response following skin contact.

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.

(2)Classification criteria

A) Classification criteria based on Classification JIS (Reference information)

<Respiratory sensitization>

Classification JIS states that chemical substances shall be classified in respiratory sensitizer Category 1 in accordance with any one of the following criteria where data are not sufficient for sub-categorization,

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.

It also states “Where data are sufficient, chemical substances shall be allocated to sub-category 1A (strong respiratory sensitizers) or sub-category 1B for other respiratory

sensitizers".

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[a)]. 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[a)]. Severity of reaction may also be considered.

Note: At present, recognized and validated animal models for the testing of respiratory hypersensitivity are not available. Under a certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.

<Skin sensitization>

Classification JIS states that substances shall be classified in skin sensitizer Category 1 in accordance with any one of the following criteria where data are not sufficient for sub-categorization,

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.

It also states "Where data is sufficient, substances shall be allocated to sub-category 1A (strong skin sensitizers) or sub-category 1B for other skin sensitizers".

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.

B) Classification criteria in GHS (Reference information)

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

(3) Items on information sources and data

∗ Classification procedures including information gathering can be referred to "3-1 Summary of GHS 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.
- It is sometimes difficult to decide whether a substance is a respiratory/skin sensitizer or not in case it causes sensitization but shows an extremely low frequency of occurrence to the size of population exposed. It is necessary for a decision on classification to take into account the frequency of sensitization and intensity of the effects, and preferably to seek expert judgment.
- As for skin sensitization, if there is positive data from appropriate animal studies, sub-categorization of a skin sensitizer is possible based on the positive rate and exposure concentration in accordance with the relevant criteria.
- Judgment 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 4th Ed. Springer (413 substances)

  -“Japanese Standard Allergens, 2008” Japanese Society for Contact Dermatitis (25 substances) http://www.jsdacd.org/html/allergen.html
- EU CLP (H334 and H317), EU DSD (R42, R43, and 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, and Germany’s MAK list: Labeling of Sensitization substance (Sa, Sh, and Sah) can be referred to.
- OECD test guidelines include the following test methods relating to skin sensitization.

  OECD TG 406 Skin sensitization

  OECD TG 429 Skin sensitization: Local Lymph Node Assay (LLNA)

  OECD TG 442A Skin sensitization: Local Lymph Node Assay (DA)

  OECD TG 442B Skin sensitization: Local Lymph Node Assay (BrdU-ELISA)

B) Order of precedence when multiple data exist

Refer to “3-2-2 Order of precedence when multiple 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. Particularly, occupational sensitizers to the airway Groups 1 and 2 classified by Japan Society for Occupational Health shall be dealt with as equivalent to Category 1A.
- 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. Particularly, skin sensitizer Groups 1 and 2 classified by Japan Society for Occupational Health shall be dealt with as equivalent to Category 1A.
- 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) Points to be noted in this item

In classification, take the points below into account.

∗ Determination of “Not classified” should be made carefully except the case that any reliable information source (e.g. List 1) denies hazard potential of the substance or provides description that its hazard potential is extremely low. If any question arises, the substance should rather be classified in “Classification not possible” due to insufficient information for judgment.

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]: Reliable information source (e.g. List 1) concludes that the substance is positive; the expression “conclude” does not mean suggest or “has potential”, but clearly state it is 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]: Any of assessment documents of reliable information sources (e.g. List 1) concludes that there is evidence that the substance causes specific respiratory hypersensitivity in humans.

Regarding evidence in humans, refer to the UN GHS 4th revised edition 3.4.2.1.2.

Evidence refers to the following points.

【GHS 4th 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 low level 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 4th revised edition 3.4.2.1.3 footnote 2), Animal test results of respiratory hypersensitivity shall be referred to, but not become an evidence for classification. 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 4th revised edition 3.4.2.2.4. “Specific considerations”.

【GHS 4th revised edition】 (3.4.2.2.4)

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]: Reliable information source (e.g. List 1) concludes that the substance is positive.

[Decision Criteria 2]: If there is evidence in humans that can lead to specific symptom by skin contact,

[Decision Criteria 3]: In reliable information sources (e.g. List 1 or List 2), there is an epidemiological study report showing allergic contact dermatitis caused by the substance, or there are two or more case reports of allergic contact dermatitis from separate medical institutions.

[Decision Criteria 4]: If a positive result is obtained in the following animal tests.

○ Decision Criteria for positive results (Classification into Category 1)

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 any reliable information source (e.g. in List 1) although the ratio is not clear. Where it is reported in any reliable information source (e.g. List 1) that the substance is tested and clearly concluded to have potential to cause skin sensitization, the substance is classified in Category 1. In other cases, the substance shall be classified as “Classification not possible”.

* As for reliable information sources (e.g. List 2), if an animal test was performed by the test method approved by OECD shown below, the ratio of sensitized animal is clear, and positive results in skin sensitization is concluded, then the substance shall be classified in Category 1. In other cases, the substance shall be classified as “Classification not possible” even if a test was carried out.

○ Criteria for sub-categorization

Allocate sub-category in accordance with the Tables 3-3-4-1 and 3-3-4-2 which include data with values based on animal test results.

Table 3-3-4-1 Animal test results for sub-category 1A

Assay	Criteria
Local lymph node assay	EC3 value ≤ 2%
Guinea pig maximization test	≥ 30% responding at ≤ 0.1% intradermal induction dose or ≥ 60% responding at > 0.1 % to ≤ 1% intradermal induction dose
Buehler assay	≥ 15% responding at ≤ 0.2% topical induction dose or ≥ 60% responding at > 0.2 % to ≤ 20% topical induction dose

Table 3-3-4-2 Animal test results for sub-category 1B

Assay	Criteria
Local lymph node assay	EC3 value > 2%
Guinea pig maximization test	≥ 30% to < 60% responding at > 0.1 % to ≤ 1% intradermal induction dose or ≥ 30% responding at > 1 % intradermal induction dose
Buehler assay	≥15% to < 60% responding at > 0.2% to ≤ 20％ topical induction dose or ≥15％ responding at > 20% topical induction dose

○ 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.)

Table 3-3-4-3 Animal tests on skin sensitization approved by OECD

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 made 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 above 3 animal testing methods are used for sub-categorization in 1A or 1B. However, LLNA: DA method (OECD TG442A) and BrdU-ELISA method (OECD TG442B), of which criteria for subcategorization has yet to be clearly defined, need to be used after careful decision.

The following skin sensitization test methods, which are not approved by OECD, should be adopted based on each enterprise's judgment.

Table 3-3-4-4 Animal tests on skin sensitization not 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

(5) Classification methods for mixtures

Classification of mixtures for respiratory/skin sensitization shall be basically performed based on the test data of the mixture itself by weight of evidence evaluation of the data as described later in A). If test data of the mixture itself are not available, classification may be performed in accordance with bridging principle as described later in B). In case test data or classification category information of all or part of ingredients of the mixture are available, classification can be performed using concentration limit of each ingredient as described later in C).

A) Classification of mixtures when data are available for the mixture itself

When reliable and good quality evidence from human experience or appropriate studies in experimental animals is available for the mixture, then the mixture can be classified according to the procedure described in the criteria for chemical substances.

B) Classification of mixtures when data are not available for the complete mixture

- Where the mixture itself has not been tested to determine its sensitizing properties, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, classification in accordance with bridging principles (3-2-4) shall be considered.
- To respiratory/skin sensitization, "dilution", "batching", "concentration of highly toxic mixture", "interpolation within one toxicity category", "substantially similar mixture" and "aerosols" of bridging principles are applicable.
- If bridging principle cannot be applied, availability of category information or data on all or part of ingredients of the mixture shall be considered. If it is available, classification shall be performed applying later described C).

C) Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

1) At least one ingredient of a mixture has been classified as a respiratory or skin sensitizer and sensitization category information or test data are available.
2) If the ingredient is present at or above the concentration limit shown in Table 3-3-4-5, the mixture should be classified as a respiratory or skin sensitizer. Even if one or more substances classified as a respiratory or skin sensitizer are present, a concentration of each ingredient shall be compared with concentration limit each by each instead of summing the concentrations of these ingredients.
3) When only test data of the sensitizer ingredient are available, classify the data into GHS classification from the chemical substance data according to the classification

method for a chemical substance, and then classify the mixture by using Table 3-3-4-5.

Table 3-3-4-5: Concentration limits of ingredients of a mixture classified as skin sensitizers or respiratory sensitizers

Ingredient classified as:	Concentration limits triggering classification of a mixture as:		
	Respiratory sensitizer		Skin sensitizer
	Solid/Liquid	Gas	All physical states
Respiratory sensitizer Category 1	≥ 1.0%	≥ 0.2%	–
Respiratory sensitizer Sub-category 1A	≥ 0.1%	≥ 0.1%	–
Respiratory sensitizer Sub-category 1B	≥ 1.0%	≥ 0.2%	–
Skin sensitizer Category 1	–	–	≥ 1.0%
Skin sensitizer Sub-category 1A	–	–	≥ 0.1%
Skin sensitizer Sub-category 1B	–	–	≥ 1.0%

Note for using Table 3-3-4-5:

If a skin sensitizer or a respiratory sensitizer is present in the mixture at a concentration above 0.1%, even if it is less than the concentration limit, ingredient information including classification category information and the concentration or the concentration range must be stated in SDS. This principle is also applied to impurities and stabilizing additives that are elements composing chemical substances and the like, other than mixtures. Furthermore, if concentration limits are defined by legal controls, accord to them.

3-3-5 Germ Cell Mutagenicity

(1)Definitions

Definitions of Germ Cell Mutagenicity in UN GHS are as follows.

【GHS 4th 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 Classification JIS

Table 3-3-5-1 Hazard categories for Germ Cell mutagens

Category 1: Chemical substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells present in humans.
Category 1A: Chemical substances known to induce heritable mutations in germ cells present

in humans

Allocation of a chemical to Category 1A is based on positive evidence from human epidemiological studies

Category 1B: Chemical substances which should be regarded as if they induce heritable mutations in the germ cells of humans.

Allocation of a chemical substances to Category 1B 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 humans.

Category 2: Chemical substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells present in humans.

Allocation of a chemical to Category 2 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: Chemical substances 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 Classification JIS and those of GHS, the same categories are adopted.

(3)Items on information sources and data

*Regarding procedure of classification, refer to “3-2-1 Sources of information available for classification”

A) Data availability

1) In the UN GHS 4th 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 3-3-5-2, 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 4th 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 4th 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” here basically refers to data obtained from *in vivo* mutagenicity/genotoxicity test that are generally used and further refers to 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 (e.g. sex-linked or recessive lethal test, wing spot test, etc.) are not generally used in this classification since biological dynamics and reproduction development process are not the same between insects and mammals. However, where other appropriate mammalian *in vivo* mutagenicity/genotoxicity test data are not available, and there are positive results from drosophila sex-linked or recessive lethal test, expert judgment shall be sought for to see usability of 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 i*n 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) OECD test guidelines include the following test methods relating to mutagenicity/ genotoxicity. Now, TGs 473, 474, 475, and 487 are being revised, whereas TGs 477, 479, 480, 481, 482, and 484 are to be deleted.

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

TG 488 Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays

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

Table 3-3-5-2 Test data as the basis of GHS classification (*: added to the examples in the GHS)

(1) An example of test data showing mutagenic effects in the germ cells present in humans, without demonstration of transmission to progeny

Analysis of aneuploidy in sperm cells of exposed people

(2) Examples of *in vivo* heritable germ cell mutagenicity tests in mammals are:

- Rodent dominant lethal test (OECD Test Guideline 478)
- Mouse heritable translocation assay (OECD Test Guideline 485)
- Mouse specific locus test

(3) Examples of *in vivo* somatic cell mutagenicity tests in mammals are:

- Mammalian bone marrow chromosome aberration test (OECD Test Guideline 475)
- Mouse spot test (OECD Test Guideline 484)
- Mammalian erythrocyte micronucleus test (OECD Test Guideline 474)
- *Metaphase or micronucleus formation analysis of peripheral lymphocytes of exposed people (Human monitoring)
- Mammalian peripheral lymphocytes chromosome aberration test
- *Gene mutation tests with transgenic animal models in somatic cells (OECD 488)

(4) Examples of *in vivo* mutagenicity tests in germ cells present in mammals are:

- Mammalian spermatogonial chromosomal aberration test (OECD Test Guideline 483)
- Spermatid micronucleus assay
- Gene mutation tests with transgenic animal models in germ cells* (OECD Test Guideline 488)

(5) Examples of *in vivo* genotoxicity tests in germ cell in mammals are:

- Sister chromatid exchange (SCE) analysis in spermatogonia
- Unscheduled DNA synthesis (UDS) test in testicular cells
- Assays of (covalent) binding or adduct formation to germ cell DNA*
- Assays of DNA damage in germ cells (comet assay, alkaline elution assay, etc.)*

(6) Examples of *in vivo* genotoxicity tests in somatic cells in mammals are:

- Liver UDS test (OECD Test Guideline 486)
- Bone marrow or peripheral lymphocytes SCE analysis
- Assays of (covalent) binding or adduct formation to somatic cell DNA*
- Assays of DNA damage in somatic cells (comet assay, alkaline elution assay, etc.)*

(7) Examples of *in vitro* mutagenicity tests are:

- *In vitro* mammalian cell chromosome aberration test (OECD Test Guideline 473)
- *In vitro* mammalian cell micronucleus test* (OECD Test Guideline 487)
- *In vitro* mammalian cell gene mutation test (OECD Test Guideline 476)
- Bacterial reverse mutation tests (OECD Test Guideline 471)

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 judgment.

- 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 multiple data exist

By referring to "3-2-2 Order of precedence when multiple 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 weight of evidence that are more likely to lead to a judgment that a tested substance has the potential 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 cultured cells rather than mammalian cultured cells).
3) As can be seen from the classification criteria described in the UN GHS 4th 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 Category2.
- 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

Refer to Part 1, Introduction for the background of this item.

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".

* Refer to the UN GHS 4th revised edition for germ cell mutagenicity and this item, and classify substances according to Figure 3-5-1 Hazard categories for germ cell mutagens in the UN GHS 4th revised edition.
* The workflow, “Classification Workflow of Germ Cell Mutagenicity (Figure 3-3-5-1) in this guidance, which is based on the information in UN GHS 4th revised edition, Figure 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 4th revised edition are

included as “examples of *in vivo* mutagenicity tests in germ cell in mammals” which is shown in Table 3-3-5-2.

B) Classification Criteria

Shown below are examples of test results corresponding to each GHS Category and the classification workflow in Figure 3-3-5-1 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 positive evidence from epidemiological studies in human germ cells is available

Substances known to induce heritable mutations in germ cells present in humans through information of human epidemiological studies shall be classified in Category 1A. It should be noted that 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:

Substances which should be regarded as if they induce heritable mutation in humans shall be classified in Category 1B when positive result(s) are obtained from many tests including *in vivo* mutagenicity tests in germ cells present in mammals. Specifically, the following cases are applicable:

a) Positive results from tests showing mutagenic effects in the germ cells present in humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed humans.
b) Positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals (e.g. Rodent dominant lethal test, Mouse heritable translocation assay, Mouse specific locus test, etc.)
c) Positive result(s) from *in vivo* somatic cell mutagenicity tests in mammals (e.g. mammalian bone marrow chromosome aberration test, mouse spot test, mammalian erythrocyte micronucleus test) in combination with some evidence that the substance has potential to cause mutations to germ cells present in mammals: for example, positive result(s) from *in vivo* mutagenicity tests in germ cells present in mammals (e.g.

mammalian spermatogonial chromosomal aberration test, spermatid micronucleus assay), or in vivo genotoxicity tests in germ cells (e.g. 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 substance or its metabolite(s).

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 which cause concern for humans owing to the possibility that they may induce heritable mutagenicity in humans shall be classified in Category 2. For example, the following cases apply:

a) Positive result(s) obtained from *in vivo* somatic cell mutagenicity tests in mammals (e.g. mammalian bone marrow chromosome aberration test, mouse spot test, mammalian erythrocyte micronucleus test), but no data is available to show that the substance should be regarded as if they induce mutagenicity in germ cells present in mammals

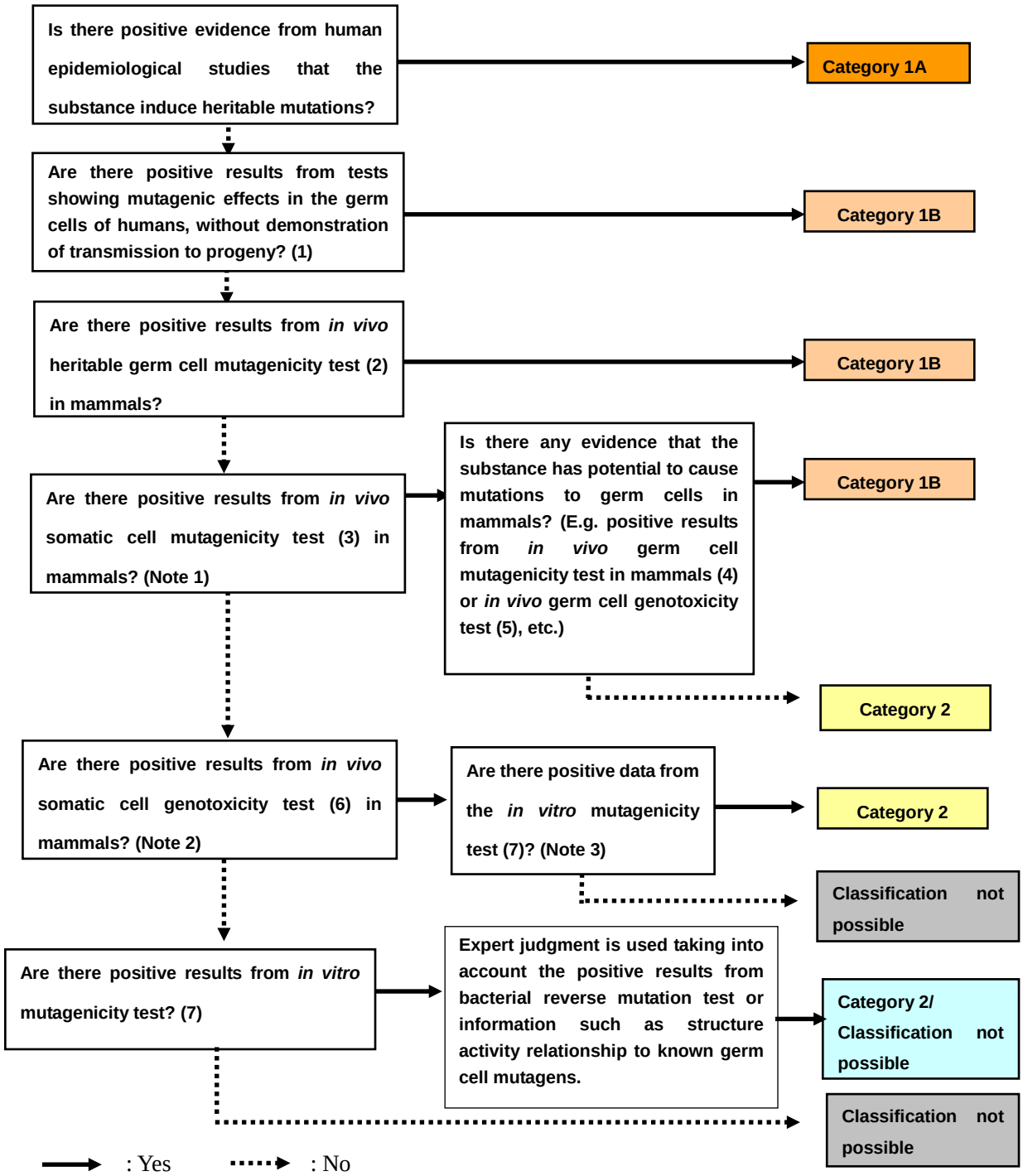
b) Positive results from *in vivo* genotoxicity tests in mammalian somatic cells (unscheduled DNA synthesis (UDS) test in mammalian liver, sister chromosome exchange (SCE) test analysis in mammalian bone marrow, etc.) and positive results from *in vitro* mutagenicity tests (chromosomal abnormality test in mammalian cultured cells, gene mutation test in mammalian cultured cells, bacterial reverse mutation test, etc.). It should be noted that expert judgment should be used for classification on an as needed basis.

c) Positive results from *in vitro* mutagenicity tests in mammalian cultured cells and from bacterial reverse mutation test, or structure activity relationship to known germ cell mutagens (Category 1, that is heritable mutagens) even in the absence of *in vivo* test data. It should be noted that expert judgment should be used for classification. By the way, the sentence in UN GHS, “Substances which are positive in *in vitro* mammalian mutagenicity assays, and which also show structure activity relationship to known germ cell mutagens” is interpreted as “positive results in Ames test (presumption from structure activity relationship is acceptable) as well as positive results in mammalian *in vitro* mutagenicity tests (in most cases, chromosome aberration test or mouse lymphoma assay)”. In case a substance is positive in 2 kinds of mutagenicity tests including mammalian *in vitro* test, which includes presumption from structure-activity relationship, expert judgment shall be used.

4) Not classified: (Classification not possible)

In case any of the above 1) through 3) does not apply: this includes the cases that no data on mutagenicity tests are obtained or that no test data with positive results are obtained.
Substances which were classified as “not classified” in accordance with GHS Classification Guidance for the Japanese Government revised in 2010 can be classified as “Classification not possible”.

Figure 3-3-5-1 Classification Workflow of Germ Cell Mutagenicity



Note 1: Positive results from appropriately performed/evaluated in vivo germ cell mutagenicity tests (4) shall be treated similarly.

Note 2: Positive results from appropriately performed/evaluated in vivo genotoxicity tests (5) shall be treated similarly.

Note 3: Expert judgment shall be used for decision of classification as needed basis.

(5) Classification methods for mixtures

Classification of mixtures for germ cell mutagenicity will be basically performed based on the available data of the individual ingredients of the mixture by using the concentration limit as described later in A). If test data of the mixture itself are available, classification may be performed in accordance with it as described later in B). In case test data are not available for the mixture itself, it can be considered that classification is performed in accordance with bridging principle as described later in C).

A) Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

The mixture will be classified as a mutagen when at least one ingredient has been classified as a Category 1or Category 2 mutagen and is present at or above the concentration limit as shown in Table 3-3-5-3 for Category 1 and 2, respectively.

B) Classification of mixtures when data are available for the complete mixture

Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients classified as germ cell mutagens, but if test data for the mixture itself is available, classification may be performed based on the data. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of germ cell mutagenicity test systems. Adequate documentation supporting the classification should be retained and made available for review upon request.

C) Classification of mixtures when data are not available for the mixture itself

Where the mixture itself has not been tested to determine its germ cell mutagenicity hazard, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data may be used in accordance with bridging principles (3-2-4).

This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without necessity for additional testing in animals. To germ cell mutagenicity, "dilution", "batching", and "substantially similar mixtures" in bridging principles can be applied, but "concentration of highly toxic mixtures", "interpolation within one toxicity category", and "aerosols" shall not be applied.

Table 3-3-5-3: Concentration limits of ingredients of a mixture classified as germ cell mutagens

Ingredient classified as:	Concentration limits triggering classification of a mixture as:		
	Category 1 mutagen		Category 2 mutagen
	Category 1A	Category 1B	
Category 1A mutagen	≥ 0.1%		–
Category 1B mutagen		≥ 0.1%	–
Category 2 mutagen	–	–	≥ 1.0%

Note: The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).

3-3-6 Carcinogenicity

(1)Definitions

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

【GHS 4th revised edition】 (3.6.1)

The term *carcinogen* denotes a substance or a mixture of chemical substances which induce cancer or increase its incidence. Substances and mixtures which have induced benign and malignant tumors 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 tumor formation is not relevant for humans.

Classification of substance or mixture 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 substance or mixture may represent.

(2)Classification criteria

A) Classification criteria based on Classification JIS

Hazard categories for carcinogens in Classification JIS are shown below.

Table 3-3-6-1 Hazard categories for carcinogens

Category 1: Known or presumed human carcinogens

The placing of a substance in Category 1 is done on the basis of epidemiological and/or animal data. An individual chemical may be further distinguished:

Category 1A: Known to have carcinogenic potential for humans; the placing of a chemical is largely based on human evidence.

Category 1B: Presumed to have carcinogenic potential for humans; the placing of a chemical is largely based on animal evidence.

Based on strength of evidence and additional considerations (weight of evidence), 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: Carcinogen Category 1A and Carcinogen Category 1B

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: Carcinogen Category 2 Carcinogen

B) Classification criteria in GHS (Reference information)

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

(3) Items on information sources and data

＊ Classification procedures including information gathering can be referred to "3-1 Summary of GHS classification".

A) Data availability

- Many descriptions on carcinogenicity can be found in hazard-related reports, reviews, assessment documents, 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]).
- Information provided by IARC and EU represents study results led by many experts, and prioritized in principle. Besides, information by the Japan Society for Occupational Health, US-EPA, US-NTP, ACGIH, and the Germany DFG shall be referred to, if any. In classification, it should be noted that it is necessary to take into account the year of evaluation by each organization.
- 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 multiple data exist

Refer to “3-2-2 Order of precedence when multiple data exist”.

C) Comparison with conventional classification systems

- The principles of GHS classification for Carcinogenicity generally accords with those of the IARC Carcinogenicity group classification and the Carcinogenicity category classification of EU classification.
- If a conventional classification system is to be used, it should correspond to GHS categories as Table 3-3-6-2.

Table 3-3-6-2 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		

(Note 1) When classification for carcinogenicity is performed according to the above table, classification result may be adopted without searching for information about toxicity information, or epidemiological/occupational exposure, etc. It should be noted that if only EU classification result is available, the basis of classification should be confirmed by searching.

(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 IARC classification are as follows:

Group1: Carcinogenic to humans

Group2A: Probably carcinogenic to humans

Group2B: Possibly carcinogenic to humans

Group3: Not classifiable as to carcinogenicity to humans

Group4: Probably not 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 related to 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) Points to be noted in this item

In classification, take the following points into account.

* Regarding 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) GHS classification of substances which have been already evaluated by the following organizations shall be performed in accordance with Table 3-3-6-2 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 judgment shall be used on an as needed basis).

(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.

・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. Refer to Note 2 of Table 3-3-6-2 for the abbreviations in each classification.)

・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 3-3-6-2 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” if there is no problem 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) 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) Nitrosofuran-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 α2u-globulin

b) Rodent liver Carcinogenicity proved to be similar with the carcinogenic mechanism of phenobarbital

c) Rat thyroid bland 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

For your reference, the concept and the supporting evidence for classification of UN GHS 4th revised edition and Classification JIS are shown bellow.

Concept of classification and their supporting evidence
(1) Classification as a carcinogen is made on the basis of evidence from reliable and acceptable methods. It is preferable that the evaluation should be based on all existing data,

peer-reviewed published studies, and appropriate additional data.

(2) Carcinogen classification is a one-step, criterion-based process that involves two interrelated determinations: evaluation of strength of evidence and consideration of all other relevant information to place chemicals with human cancer potential into hazard categories.

(3) Strength of evidence involves the enumeration of tumors in human and animal studies and determination of their level of statistical significance.

1) Sufficient human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the agent and an increased incidence of tumors.

2) Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated.

3) Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient.

4) The terms "sufficient" and "limited" are used here as they have been defined by the International Agency for Research on Cancer (IARC).

(4) Additional considerations (weight of evidence)

Beyond the determination of the strength of evidence for carcinogenicity, a number of other factors should be considered that influence the overall likelihood that an agent may pose a carcinogenic hazard in humans.

1) Some of the important factors are shown in 2). The factors can be viewed as either increasing or decreasing the level of the concern for human carcinogenicity. The relative emphasis according to each factor depends upon the amount and coherence of evidence bearing on each.

Generally there is a requirement for more complete information to decrease than to increase the level of concern. Additional considerations should be used in evaluating the tumor findings and the other factors in a case-by-case manner.

2) Factors that either increase or decrease the level of the concern for human carcinogenicity

a) Some important factors which may be taken into consideration, when assessing the overall level of concern are:

Example 1: Tumor type and batch ground incidence;

Example 2: Multisite responses;

Example 3: Progression of lesions to malignancy;

Example 4: Reduced tumor latency;

b) Additional factors which may increase or decrease the level of concern include:

Example 5: Whether responses are in single or both sexes;

Example 6: Whether responses are in a single species or several species;

Example 7: Structural similarity or not to a chemical(s) for which there is good evidence of carcinogenicity;

Example 8: Routes of exposure;

Example 9: Comparison of absorption, distribution, metabolism, and excretion between test animals and humans;

Example 10: The possibility of a confounding effect of excessive toxicity at test doses;

Example 11: Mode of action and its relevance for humans, such as mutagenicity, cytotoxicity with growth stimulation, mitogenesis, immunosuppression.

3) Mutagenicity

It is recognized that genetic events are central in the overall process of cancer development. Therefore, evidence of mutagenic activity in vivo may indicate that a chemical has a potential for carcinogenic effects.

4) The following additional considerations apply to classification of chemicals into either Category 1 or Category 2. A chemical that has not been tested for carcinogenicity may in certain instances be in Category 1 or Category 2 based on tumor data from a structural analogue together with substantial support from consideration of other important factors such as formation of common significant metabolites, e.g. for benzidine congener dyes.

a) The classification should also take into consideration whether or not the chemical is absorbed by a given route(s) ; or whether there are only local tumours at the site of administration for the tested route(s), and adequate testing by other major route(s) show lack of carcinogenicity.

b) It is important that whatever is known of the physico-chemical, toxicokinetic, and toxicodynamic properties of the substances, as well as any available relevant information on chemical analogues, i.e. structure activity relationship, is taken into consideration when undertaking classification.

(5) Classification methods for mixtures

Classification of mixtures for carcinogen shall be basically performed based on the available data of the individual ingredients of the mixture by using the concentration limits as described later in A). If test data of the mixture itself are available, classification may be performed in accordance with the test data as described later in B). In case test data are not available for the mixture itself, classification can be performed in accordance with bridging principles described later in C).

A) Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture.

The mixture will be classified as a carcinogen when at least one ingredient has been classified as a Category 1 or 2 carcinogen and is present at or above the concentration limit as shown in Table 3-3-6-3 for Category 1 and 2, respectively.

B) Classification of mixtures when data are available for the mixture itself

Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients classified as carcinogen, but if test data for the mixture itself is available, it can be considered to perform classification based on the data. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of carcinogen test systems. Adequate documentation supporting the classification should be retained and made available for review upon request.

C) Classification of mixtures when data are not available for the mixture itself

Where the mixture itself has not been tested to determine its carcinogenic effects, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data may be used in accordance with the bridging principles (3-2-4). This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without necessity for additional testing in animals. To germ cell mutagenicity, "dilution", "batching", and "substantially similar mixtures" in bridging principles can be applied, but "concentration of highly toxic mixtures", "interpolation within one toxicity category", and "aerosols" shall not be applied.

Table 3-3-6-3: Concentration limits of ingredients of a mixture classified as carcinogens (*)

Ingredient classified as:	Concentration limits triggering classification of a mixture as:		
	Category 1 carcinogen		Category 2 carcinogen
	Category 1A	Category 1B	
Category 1A carcinogen	≥ 0.1%	–	–
Category 1B carcinogen	–	≥ 1.0%	–
Category 2 carcinogen	–	–	≥ 1.0%
Note: The concentration limits above apply to solids and liquids (w/w units) as well as gases (v/v units).			

Note for using Table 3-3-6-3:

If a Category 2 carcinogen ingredient is present in the mixture at a concentration of more than 0.1% (concentration limit), even less than the concentration limit, ingredient

information including classification category information and the concentration or the concentration range must be stated in SDS. This principle is also applied to impurities and stabilizing additives that are elements composing chemical substances and the like, other than mixtures. Furthermore, if concentration limits are defined by legal controls, accord to them.

3-3-7 Reproductive Toxicity

(1)Definitions

Definitions of Reproductive Toxicity in UN GHS are as follows.

【GHS 4th 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 behavior, 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 Classification JIS

Hazard categories of Reproductive toxicants and effects on lactation in Classification JIS are presented below.

Table 3-3-7-1 Hazard categories for Reproductive toxicants

Category 1: Known or presumed human reproductive toxicant

This category includes chemicals 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 chemical has the capacity to interfere with reproduction in humans. For regulatory purposes, a chemical 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 chemical in this category is largely based on evidence from humans.

Category 1B: presumed human reproductive toxicant

The placing of the chemical 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 (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 3-3-7-2 Hazard categories for effects on or via lactation

Effects on or via lactation

Effects on or via lactation are allocated to this separate single category. Not many substances have information on the potential to cause adverse effects to 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 any of the following:

a) absorption, metabolism, distribution, and excretion studies that would indicate the likelihood the chemical would be present in potentially toxic levels in breast milk,

b) results of one or two generation studies in animals which provide clear evidence of adverse effect in offspring due to transfer in breast milk or adverse effect on the quality of the breast milk,

c) human evidence indicating a hazard to babies during the lactation period.

B) Classification criteria in GHS (Reference information)

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

(3)Items on information sources and data

* Classification procedure can be referred to "3-2-1 Sources of Information available for classification".

A) Data availability

- Assessment concerning reproductive toxicity has been reported in SIDS, EHC, or ECETOC.
- A large amount of data is 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 multiple data exist

Refer to “3-2-2 Order of precedence when multiple 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, or R64) corresponding to reproductive toxicity. When the assessment documents are obtained, classify on the basis of the documents.

C) Comparison with conventional classification systems

- The concept of the EU category classification on reproductive toxicity corresponds to that of the GHS category classification.
- Substances classified as CLP: Repr. 1A, H360 and EU DSD Category 1, R60 and R61 correspond to GHS Category 1A.
- Substances classified as CLP: Repr. 1B, H360 and EU DSD Category 2, R60 and R61 correspond to GHS Category 1B.
- Substances classified as CLP: Repr. 2, H361 and EU DSD Category 3, R62 and R63 correspond to GHS Category 2.
- Since substances assigned EU CLP LACT.-H362 and EU DSD R64 are applicable to “the additional category for effects on or via lactation”, the hazard statement “May cause harm to breast-fed children” shall be applied.

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.

* Be sure to search descriptions relating to the substance in all assessment documents listed in reliable information sources (e.g. List 1).
* Determination of “Not classified” should be made carefully except the case that reliable information source (e.g. List 1) denies hazard potential of the substance or provides description that its hazard potential is extremely low. If any question arises, the 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 behavior, 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 interfere 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 4th 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 4th 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: Chemicals 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 reliable information (e.g. List 1).

* If any other substance is considered to fall under Category 1A, it is preferable to use expert judgment.

* In case a substance falls under “3) d) Substance requiring caution in classification” given later and information enough to prove that the substance falls under Category 1A is not obtained as a result of literature survey based on this classification guidance, expert judgment shall be used.

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.

A substance for which reliable information source (e.g. List 1) describes that clear reproductive toxicity* (except for small changes in sperm measurement items, incidence of spontaneous defects in fetus, variant/ossification retardation, fetal/pup body weight, and postnatal development indexes) is manifested in animal tests 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: Chemicals suspected to have toxicity for human reproduction/development

(Decision criteria)

Substances which meet any of the following conditions with information in reliable information (e.g. List 1 or List 2) except for those applicable to “Category 1” and “Not classified”.

a) Substances of which manifestation of clear reproductive toxicity (except for small changes in sperm measurement items, incidence of spontaneous defects in fetus, variant/ossification retardation, fetal/pup body weight, and postnatal development indexes) in animal tests at a dose at which general toxicity in parental animals is manifested is described.

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) Chemicals of which general toxicity for parental animals in animal tests is not described but clear manifestation of reproductive toxicity (except for small changes in sperm measurement items, incidence of spontaneous defects in fetus, variant/ossification retardation, fetal/pup body weight, and postnatal development indexes) is described.

(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 reliable information source (e.g. List 2) describes that clear reproductive toxicity (except for small changes in sperm measurement items, incidence of spontaneous defects in fetus, variant/ossification 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 cannot

be considered to be sufficient. (Substance not classified in Category 1A) *

* This includes a case that there is a description in reliable information (e.g. List 2) that reproductive toxicity of the substance is recognized with humans.

Not classified: Substances presumed 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 b) 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. Expert judgment shall be used on an as needed basis.

c) Effects on or via lactation

In case descriptions regarding effects on or via lactation are found, expert judgment shall be used. 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
- Coumarin 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 4th 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.

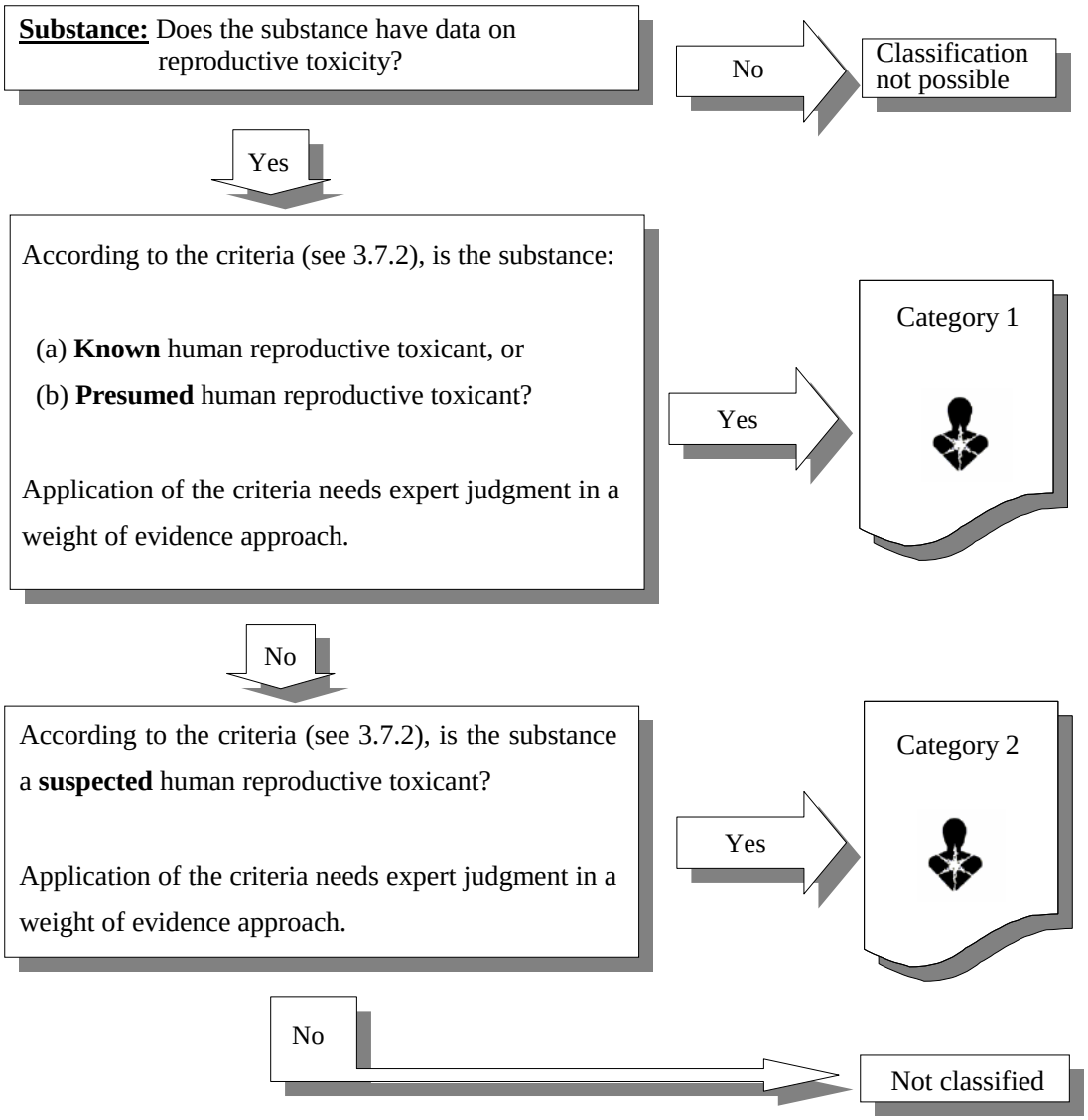
No.	Test guideline	Limit dose
414	Prenatal Development Toxicity Study	1000 mg/kg body weight / day
415	One-Generation Reproduction Toxicity Study	1000 mg/kg body weight
416	Two-Generation Reproduction Toxicity Study	1000 mg/kg body weight / day

Reference1. Schardein JL, Chemically Induced Birth Defects-3rd edition, Marcel Dekker, New York, 2000
Reference2. Shepard TH, Lemire RJ, Catalog of Teratogenic Agents, 11th edition, Johns Hopkins Univ. Press, Baltimore, 2004

【UN GHS 4th revised edition】 (3.7.5.1)

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

3.7.5.1.1 Decision logic 3.7.1 for substances



(5) Classification methods for mixtures

The reproductive toxicity classification of mixtures will be based on the available test data of the individual constituents of the mixture using concentration limits for the ingredients of the mixture as described later in A). If test data of the mixture itself are available, it can be considered that classification should be performed in accordance with the data as described later in B). In case test data are not available for the mixture itself, classification can be performed in accordance with the bridging principle as described later in C).

A) Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

A mixture shall be classified in accordance with the following procedures if at least one ingredient of it has reproductive toxicity, of which category information is available:

1) The mixture will be classified as a reproductive toxicant when at least one ingredient has been classified as a Category 1or 2 reproductive toxicant and is present at or above the concentration limit as shown in Table 3-3-7-3 for Category 1 and 2, respectively.

2) The mixture will be classified for effects on or via lactation when at least one ingredient has been classified for effects on or via lactation and is present at or above the concentration limit as shown in Table 3-3-7-3 for the additional category for effects on or via lactation.

B) Classification of mixtures when data are available for the mixture itself

Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients classified as a reproductive toxicant, but if test data for the mixture itself is available, it can be considered that classification is performed based on the data. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of reproductive toxicity test systems. Adequate documentation supporting the classification should be retained and made available for review upon request.

C) Classification of mixtures when data are not available for the mixture itself

Where the mixture itself has not been tested to determine its reproductive toxicity, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data may be used in accordance with the bridging principles (3-2-4). This ensures that the classification

process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without necessity for additional testing in animals. To germ cell mutagenicity, "dilution", "batching", and "substantially similar mixtures" in bridging principles can be applied, but "concentration of highly toxic mixtures", "interpolation within one toxicity category", and "aerosols" shall not be applied.

Table 3-3-7-3: Concentration limits of ingredients of a mixture classified as reproductive toxicants

Ingredient classified as:	Concentration limits triggering classification of a mixture as:			
	Category 1 reproductive toxicant		Category 2 reproductive toxicant	Additional category for effects on or via lactation
	Category 1A	Category 1B		
Category 1A reproductive toxicant	≥ 0.3%	-	-	-
Category 1B reproductive toxicant	-	≥ 0.3%	-	
Category 2 reproductive toxicant	-	-	≥ 3.0%	-
Additional category for effects on or via lactation	-	-	-	≥ 0.3%
Note: The concentration limits above apply to solids and liquids (w/w units) as well as gases (v/v units).				

Note for using Table 3-3-7-3:

If a Category 1 and 2 reproductive toxicant or substance classified in the additional category for effects on or via lactation is present in the mixture as an ingredient at a concentration above 0.1%, even if it is less than the concentration limit (0.3% or 3.0%) in GHS, ingredient information including classification category information and the concentration or the concentration range must be stated in SDS. This principle is also applied to impurities and stabilizing additives that are elements composing chemical substances and the like, other than mixtures. Furthermore, if concentration limits are defined by legal controls, accord to them.

3-3-8 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 4th 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 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);
(d) 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).

(2) Classification criteria

A) Classification criteria based on Classification JIS

Table 3-3-8-1 Hazard categories for Specific Target Organ Toxicity (Single Exposure)

Category 1: Chemicals 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 any of the following:

a) reliable and good quality evidence from human cases or epidemiological studies,

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: Chemicals 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 chemical 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 in Table 3.14 in order to help in classification. In exceptional cases, human evidence can also be used to place a chemical 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 includes narcotic effects and respiratory tract irritation. Chemicals may be classified specifically for these effects in accordance with B) Classification criteria in GHS: UN GHS 4th revised edition, 3.8.2.2.1 and 3.8.2.2.2.

For these Categories 1 through 3, the specific target organ/system that has been primarily affected by the classified chemical may be identified, or the substance may be identified as a general toxicant. Attempts should be made to determine the primary target organ 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 3-3-8-2: Guidance value ranges for single-dose exposures

		Guidance value (C) ranges for:		
Route of exposure	Units	Category 1	Category 2	Category 3
Oral (rat)	mg/kg body weight	C≤300	300<C≤2000	Guidance values do not apply
Dermal (rat or rabbit)	mg/kg body weight	C≤1000	1000<C≤2000	
Inhalation (rat) gas	ppmV/4h	C≤2500	2500<C≤20000	
Inhalation (rat) vapour	mg/L/4h	C≤10	10<C≤20	
Inhalation (rat) dusts/mist/fume	mg/L/4h	C≤1.0	1.0<C≤5.0	

In case oral administration of irritating chemical is tested in particular, it should be noted that gavage administration or administration via feedstuff/water results in different target organ toxicity and toxicity manifestation mechanisms, which can lead to completely different extrapolation to humans; for example, findings of lesion such as erosion or ulcer that only appears by gavage administration cannot be extrapolated to humans.

B) Classification criteria in GHS (reference information)

The same categories are adopted for classification criteria in Classification JIS and GHS. Their guidance value ranges are also the same. For detailed descriptions, refer to the UN GHS 4th revised edition 3.8.2 about categories, and the UN GHS 4th 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 4th 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, pruritus 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, and 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 4th 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. The criteria for narcotic effects as Category 3 are:

(3) Items on information sources and data

* Classification procedures including information gathering can be referred to "3-1 Summary of GHS classification".

A) Data availability

- In case existing SDS descriptions are used, it is necessary to review quoted primary report. It is recommended that the primary report be reviewed for confirmation of the classification result in case SDS with which GHS classification is performed is used.
- Sufficient information for classification cannot be obtained from simple descriptions in existing SDSs. A literature search should be carried out for reliable reviews and primary information relevant to toxic actions.
- Substances assigned EU CLP hazard statements[15] H370, H371, H335, or H336 related to specific target organ toxicity and EU DSD R-Phrases[16] (R39, R68, R37, or R67) cause concern owing to the possibility that they may produce specific target organ toxicity (single exposure).
- In order to utilize R-Phrase, it is preferable to review EU assessment report for classification and to study the contents.

B) Order of precedence when multiple data exist

Refer to “3-2-2 Order of precedence when multiple data exist”.

C) Comparison with conventional classification systems

EU CLP H370 and EU DSD T^{+}, R39, T, R39 correspond to Category 1. EU CLP H371 and EU DSD R68 correspond to Category 2. EU CLP H335, H336 and EU DSD R37, R67 correspond to Category 3 for single-dose exposure: respiratory tract irritation and narcotic action, respectively.

D) Guidance concerning data

[15] See Annex for EU hazard statements.
[16] For R-Phrase, see Appendix.

- 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 4th 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 4th revised edition and hence are not included in specific target organ toxicity.
  - Acute Toxicity (3-3-1)
  - Skin Corrosion/Irritation (3-3-2)
  - Serious Eye Damage/Eye Irritation (3-3-3)
  - Respiratory or Skin Sensitization (3-3-4)

- Germ Cell Mutagenicity (3-3-5)
- Carcinogenicity (3-3-6)
- Reproductive Toxicity (3-3-7)
- Aspiration Hazard (3-3-10)

(4)Guidance for classification and judgment

A) Points to be noted in this item

In classification, take the following points into account.

* Determination of “Not classified” should be made carefully except the case that reliable information source (e.g. List 1) denies hazard potential of the substance or provides description that its hazard potential is extremely low. 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 judgment. If any question arises, the 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. When such an organ cannot be identified, consider to be “systemic toxicity”. (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]: Reliable information sources (e.g. List 1) show evidence that the substance induces toxic effects in humans.

(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) In case only minimal symptoms (slight fever, languor, etc.) are reported, the substance shall not be classified based on the data only.

d) Consider all affected organs that are described in reliable information sources (e.g. List 1). However, when organs listed in multiple assessment documents based on the same type of tests are not the same, consider the commonly listed organs. When a toxic symptom alone is described and the affected organ cannot be identified, classify as “systemic toxicity”. When the target organ is identified, fundamentally, indication of toxic symptom is not required.

e) If an affected organ can be identified, the applicable category and the affected organ shall be clearly stated. If not, “systemic toxicity” shall be considered.

[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) OECD TG test described in reliable information sources (e.g. List 1 or List 2) as well as in accordance with GLP, and has received certain approval (by one or more reviewers).

(Notes)

a) As for toxic effects, read the UN GHS 4th revised edition and the following documents carefully.

b) Effects on organs that are obviously known to be secondary effects shall be excluded from description. Judgment 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) In case only minimal symptoms (slight fever, etc.) are reported, the substance shall not be classified based on the data only.

e) Consider all affected organs that are described in reliable information sources (e.g. List 1). However, when organs listed in multiple assessment documents based on the same type of tests are not the same, consider the commonly listed organs. When a toxic symptom alone is described and the affected organ cannot be identified, classify as "systemic toxicity". When the target organ is identified, fundamentally, indication 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 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 other sources.

(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 reliable source (e.g. List 1).

(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 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.

(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 narcotics is recognized for only a short period after exposure.

b) The effect is reversible.

c) The test is described in reliable source (e.g. List 1).

(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 as special remarks, but shall not become the basis of classification

b) As for respiratory tract irritation, if more serious effect on organs including respiratory system is observed, the substance shall be classified in Category 1 or Category 2. As for narcotic effects, only if the effect is not transient in nature, the substance shall be classified in Category 1 or Category 2.

c) Indicate whether a substance is either a respiratory tract irritant or a narcotic clearly. (Example: Category 3 (respiratory tract irritant))

C) On treatment of vapour inhalation guidance value in classification of specific target organ toxicity (single exposure)

For the classification of specific target organ toxicity (single exposure), “guidance values” for categorization based on animal data are shown in Table 3-3-8-2 (UN GHS 4th revised edition Table 3.8.1). Vapour inhalation is indicated in the unit of mg/L. 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.

(5) Indication of the classification results

As for description of classification results, a substance classified in any category is not required to clearly state the route of exposure, but one assigned "Not classified" is required to clearly state on which administration route the data are based. For example, description "Not classified (oral)" is preferable.

(6) Classification methods for mixtures

Classification of mixtures for specific target organ toxicity shall be basically performed based on the test data of the mixture itself by weight of evidence evaluation of the data as described later in A). If test data of the mixture itself are not available, classification may be performed in accordance with bridging principle as described later in B). In case test data or classification category information of all or part of ingredients of the mixture are available, classification can be performed using concentration limit of each ingredient as described later in C).

A) Classification of mixtures when data on the mixture itself are available

In cases when reliable and good quality evidence from human cases or animal studies regarding the mixture is available, the mixture can be classified based on the weight of evidence evaluation of this data. When evaluating data regarding the mixture, care should be taken that dose, duration, observations or analysis would not make the conclusion indefinite.

B) Classification of mixtures when data on the mixture itself are not available

Test data of a mixture itself is not available, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data may be used in accordance with the bridging principles (3-2-4).

This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without necessity for additional testing in animals. For specific target organ toxicity (single exposure), "dilution", "batching", "concentration of mixtures of the highest toxicity", "interpolation within one toxicity category", "substantially similar mixtures", and "aerosols" among bridging principles are applicable, but if the affected organs are limited, the application may be difficult.

C) Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

In cases when at least one ingredient of the mixture has specific target organ toxicity (single exposure) and all information on ingredients of the mixture having specific target organ toxicity (Category and the affected organ) is available:

1) A mixture will be classified as a specific target organ toxicant (single exposure) when at least one ingredient has been classified as a Category 1 or Category 2 specific target organ toxicant (single exposure) and is present at or above the concentration limit as mentioned in Table 3-3-8-3 for Category 1 and 2 respectively.
2) In classifying a mixture whose ingredients are classified in different categories based on the concentration limits, it is preferable to consider the target organ by each category taking into account whether concentration of each ingredient is applicable to the concentration limit.

D) Mixture should be classified for either or both single and repeated dose toxicity independently.

E) Toxicants affecting more than one organ system

The potentiation or synergistic interactions should be considered when toxicants affecting more than one organ system are used in combination. If other ingredients in the mixture are known to potentiate its toxic effect, consultation with experts is preferable.

F) When extrapolating toxicity of a mixture that contains Category 3 ingredient(s)

Care should be exercised when extrapolating the toxicity of a mixture that contains Category 3 ingredient(s). If a mixture contains ingredients applicable to Category 3 for its respiratory tract irritation or narcotic effects, the concentrations of the ingredients shall be summed up for each effect and if the sum becomes 20% or more, the mixture shall be classified in Category 3 based on the effect. However, expert judgment, if available, takes precedence. Even if the sum is below 20%, if the effect is expected, the mixture shall be classified in Category 3. When the criterion of summed concentration of below 20% is applied without expert judgment, the procedure should be informed.

G) Concentration limits of ingredients that would trigger classification of the mixture

If a mixture is classified based on the categories of its ingredients, classification is performed as follows:

1) (requested condition) At least one ingredient has been classified as a Category 1 or Category 2 specific target organ toxicant (single exposure).
2) (classification method) When the ingredient of (1) is present in a mixture at or above the concentration limit shown in Table 3-3-8-3, the category shall be determined as the specific target organ toxicant according to the table. All information contributing to the classification of the target organ based on that of the ingredients shall be indicated.

Table 3-3-8-3: Concentration limits of ingredients of a mixture as a specific target organ toxicant that would trigger classification of the mixture as Categories 1 and 2

Ingredient classified as:	Concentration limits triggering classification of a mixture as:	
	Category 1	Category 2
Category 1 target organ toxicant	≥ 10%	1.0% ≤ ingredient < 10%
Category 2 target organ toxicant	–	≥ 10%

Note: If a Category 2 specific target organ toxicant is present in the mixture as an ingredient at a concentration of more than 1.0%, even below concentration limit, ingredient information including classification category information and the concentration or the concentration range must be stated. This principle is also applied to impurities and stabilizing additives that are elements composing chemical substances and the like, other than mixtures. Furthermore, if concentration limits are defined by legal controls, accord to them.

3) Examples of use of the table

Example-1: When a liquid mixture A contains 12% (w/w) of "ingredient A-1 “specific target organ toxicant (single-exposure) Category 1 (liver)", the liquid mixture A is classified as "specific target organ toxicant (single- exposure) Category 1 (liver)".

Example-2: If a liquid mixture B contains 2 ingredients, which are ingredient B-1: specific target organ toxicant (single-exposure) Category 1 (liver)" with 5% (w/w) concentration, and ingredient B-2: "specific target organ toxicant (single- exposure) Category 2 (respiratory system)" with 15% (w/w) concentration, the liquid mixture B is classified as "specific target organ toxicant (single-exposure) Category 2 (liver and respiratory system)".

Example-3: A liquid mixture C contains 3 ingredients, which are ingredient C-1: “specific target organ toxicant (single-exposure) Category 1 (liver)" with 3.5% (w/w) concentration, ingredient C-2: specific target organ toxicant (single-exposure) Category 2 (kidney)" with 5% (w/w)

concentration, and ingredient C-3: “specific target organ toxicant (single-exposure) Category 1 (lung)" with 7% (w/w) concentration, the liquid mixture C is classified as “specific organ toxicant (single-exposure) Category 2 (liver and lung).

3-3-9 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 4th 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 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 Classification JIS

Table 3-3-9-1: Hazard categories for specific target organ toxicity following repeated exposure

Category 1: Chemicals 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 chemical in Category 1 is done on the basis of any of the following :

a) reliable and good quality evidence from human cases or epidemiological studies,

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 to be used as part of weight-of evidence evaluation are provided in Table I.2.9.

Category 2: Chemicals 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 chemical 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 in Table I.2.9 in order to help in classification. In exceptional cases, human evidence can also be used to place a substance in Category 2 (see I.2.6).

In classifying in either category, the specific target organ/system that has been temporarily affected by the classified chemical may be identified, or the chemical 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 3-3-9-2: Guidance value ranges for toxicity-repeated exposure

		Guidance value (C) ranges (dose/concentration)	
Route of exposure	Units	Category 1	Category 2
Oral (rat)	mg/kg bw/d	C≤10	10＜C≤100
Dermal (rat or rabbit)	mg/kg bw/d	C≤20	20＜C≤200
Inhalation (rat) gas	ppm/6h/d	C≤50	50＜C≤250

Inhalation (rat) vapour	mg/litre/6h/d	C≤0.2	0.2＜C≤1.0
Inhalation (rat) dust/mist/fume	mg/litre/6h/d	C≤0.02	0.02＜C≤0.2

B) Classification criteria in GHS (Reference information)

The same categories are adopted for classification criteria in Classification JIS and GHS. Their guidance value ranges are also the same. For detailed descriptions, refer to the UN GHS 4th revised edition 3.9.2 about categories, and the UN GHS 4th revised edition Tables 3.9.1 and 3.9.2 about guidance values.

(3)Items on information sources and data

* Classification procedures including information gathering can be referred to "3-1 Summary of GHS classification".

A) Data availability

1) Sufficient information for classification cannot be obtained from simple descriptions in existing SDSs. A literature search of the primary information of a review article or on toxic effects is necessary because information about target organs is not described in most cases. It should be noted that information of SDS of a substance or a mixture which has been classified in accordance with GHS[17] and has descriptions about target organs can be used. In this case, it is sometimes preferable to study the evidence of classification.

2) Substances assigned EU CLP H372, H373 relating to specific target organ toxicity[18] and R-Phrases[19] (R33, R48, or combination of these) in EU DSD classification cause concern owing to the possibility that they may produce specific target organ toxicity (repeated exposure).

3) Substances classified as EU USD T, R48 corresponds to Category 1 and those classified as R33 and Xn, R48 correspond to Category 2. In these cases, it is preferable to carefully study the evidence of classification in the assessment document or other document. Target organ cannot be specified by R-phases.

4) Weight of evidence of all data, including human incidents, epidemiology, and studies conducted in experimental animals, is used to substantiate specific target organ toxic effects. This taps the considerable body of industrial toxicology data. Evaluation should be based on all existing data, including peer-reviewed published studies and additional data acceptable to regulatory agencies.

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[17] Examples: JISZ7250:2005, GHS Guideline for MSDS and labeling (Oct. 2008) by Japan Chemical Industry Association (JCIA), etc

[18] See Annex for EU hazard statements.

[19] For R-Phrase, see Appendix.

5) The information required to evaluate specific target organ toxicity comes either from repeated exposure in humans, e.g. exposure at home, in the workplace or environmentally, or from studies conducted in experimental animals. The standard animal studies in rats or mice that provide this information are 28 day, 9 day or lifetime studies (up to 2 years). From this point of view, it should be noted that the evaluation is different from that of single exposure.

B) Order of precedence when multiple data exist

Refer to "3-2-2 Order of precedence when multiple data exist".

C) Comparison with conventional classification systems

Substances classified as EU CLP H372 and EU DSD T, R48 corresponds to Category 1 and those classified as EU CLP H373 and EU DSD Xn, R48 correspond to Category 2.

D) Guidance concerning data

- SDS information about a mixture can be used under the condition of (3) A) 1).
- 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 4th 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 detoxification 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 4th revised edition and hence are not included in specific target organ toxicity.

- Acute Toxicity (3-3-1)
- Skin Corrosion/Irritation (3-3-2)
- Serious Eye Damage/Eye Irritation (3-3-3)
- Respiratory or Skin Sensitization (3-3-4)
- Germ Cell Mutagenicity (3-3-5)
- Carcinogenicity (3-3-6)
- Reproductive Toxicity (3-37)
- Aspiration Hazard (3-3-10)

(4)Guidance for classification and judgment

A) Background of this item and points to be noted

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 judgment. 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]: Reliable information sources (e.g. List 1) show evidence that the substance induces toxic effects in humans.

(Notes)

a) Effects on organs that are obviously known to be secondary effects shall be excluded from the description. Judgment by expert 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) In case only minimal symptoms (slight fever, languor, etc.) are reported, the substance shall not be classified based on the data only.

d) All organs described as affected in reliable information source (e.g. List 1) shall be considered. However, when organs listed in multiple assessment documents based on the same type of tests are not the same, consider 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 is 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 OECD TG test described in reliable information sources (e.g. List 1) as well as in accordance with GLP, and has received certain approval (by one or more reviewers).

(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 4th 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. Judgment 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) In case only minimal symptoms (slight fever, etc.) are reported, the substance shall not be classified based on the data only.

e) Consider all affected organs that are described in reliable information sources (e.g. List 1). However, when descriptions of organs listed in multiple assessment documents based on the same type of tests are the same, consider the commonly listed organs. When a toxic symptom alone is described and the affected organ cannot be identified, indicate as “systemic toxicity”. When the target organ is identified, fundamentally, indication 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] Reliable information sources (e.g. List 2) show evidence that the substance induces toxic effects in humans.

(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 reliable source (e.g. List 1).

(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 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.

(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 3-3-9-2 (UN GHS 4th revised edition tables 3.9.1 and 3.9.2). Vapour inhalation is indicated in the unit of mg/L. However, there are no notes regarding vapour inhalation like for Acute Toxicity in Table 3.1.1, neither in UN GHS 4th revised edition. 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 ppm, 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.

(5) Classification methods for mixtures

Classification of mixtures for specific target organ toxicity (repeated toxicity) shall be basically performed based on the test data of the mixture itself by weight of evidence evaluation of the data as described later in A). If test data of the mixture itself are not available, classification may be performed in accordance with bridging principle as described later in B). In case test data or classification category information of all or part of ingredients of the mixture are available, classification can be performed using concentration limit of each ingredient as described later in C).

A) Classification of mixtures when data are available for the complete mixture

When reliable and good quality evidence from human experience or appropriate studies in animals is available for the mixture, then the mixture can be classified based on the weight of evidence evaluation of this data. Care should be exercised in evaluating data on mixtures that dose, duration, observations or analysis, do not render the results inconclusive.

B) Classification of mixtures when data are not available for the complete mixture

When the mixture itself has not been tested to determine its specific target organ toxicity, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data can be used in accordance with bridging principles (3-2-4). This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without necessity for additional testing in animals. For specific target organ toxicity (repeated exposure), "dilution", "batching", "concentration of mixtures of the highest toxicity", "interpolation within one toxicity category", "substantially similar

mixtures", and "aerosols" among bridging principles are applicable, but if the affected organs are limited, the application may be difficult.

C) Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture.

When at least one ingredient of a mixture has specific target organ toxicity (repeated exposure) and information on its toxic ingredients of the mixture (Category and the affected organ) is available:

1) The mixture will be classified as a specific target organ toxicant (repeated exposure) when at least one ingredient has been classified as a Category 1 or Category 2 specific target organ toxicant (repeated exposure) and is present at or above the concentration limit as mentioned in Table 3-3-9-3 for Category 1 and 2 respectively.
2) When a mixture whose ingredients are classified in different categories is classified based on the concentration limits, each ingredient should be considered whether its concentration is applicable to the concentration limit.

D) Mixture should be classified for either or both single and repeated dose toxicity independently.

E) Toxicants affecting more than one organ systems

The potentiation or synergistic interactions should be considered when toxicants affecting more than one organ system are used in combination. If other ingredients in the mixture are known to potentiate its toxic effect, consultation with experts is preferable.

F) Concentration limits of ingredients that would trigger classification of the mixture (*)

Table 3-3-9-3 is identical to Table 3-3-8-3 (concentration limit table for single exposure).

Table 3-3-9-3: Concentration limits of ingredients of a mixture as a specific target organ toxicant that would trigger classification of the mixture as Category 1 or 2

Ingredient classified as:	Concentration limits triggering classification of a mixture as:	
	Category 1	Category 2
Category 1 target organ toxicant	≥ 10%	1.0% ≤ ingredient < 10%
Category 2 target organ toxicant	–	≥ 10%

Note: If a Category 2 specific target organ toxicant is present in the mixture as an ingredient at a concentration of more than 1.0%, even if it is below concentration limit, ingredient information

including classification category information and the concentration or the concentration range must be stated. This principle is also applied to impurities and stabilizing additives that are elements composing chemical substances and the like, other than mixtures. Furthermore, if concentration limits are defined by legal controls, accord to them.

3-3-10 Aspiration Hazard

(1)Definitions

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

【GHS 4th 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 labeling, 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:

Dynamic viscosity(mPa･s) / Density (g/cm^3)＝Kinematic viscosity (mm^2 /s)

3.10.1.6.4 Although the definition of aspiration in 3.10.1.2 includes the entry of solids into the respiratory system, classification according to (b) in table 3.10.1 for Category 1 or for Category 2 is intended to apply to liquid substances and mixtures only.

3.10.1.6.5 *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 Classification JIS

Table 3-3-10-1: 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 ≤20.5 mm^2/s, measured at 40°C.

Note: Examples of chemicals included in Category 1 are certain hydrocarbons, turpentine, and pine oil.

B) Classification criteria in GHS (Reference information)

In GHS classification, in addition to Classification JIS, category 2 is set. Explanation of classification criteria by GHS is as follow.

【GHS 4th revised edition】

Table 3.10.1 *: 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 1); or (b) If it is a hydrocarbon and has a kinematic viscosity ≤20.5 mm^2/s, measured at 40°C.
Category 2: Chemicals	On the basis of existing animal studies and expert judgment

which cause concern owing to the presumption that they cause human aspiration toxicity hazard	that takes into account surface tension, water solubility, boiling point, and volatility, substances, other than those classified in Category 1, which have a kinematic viscosity≤14mm^2/s, measured at 40°C (See note 2).

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 3th 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

* Classification procedures including information gathering can be referred to "3-1 Summary of GHS 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 multiple data exist

Refer to “3-2-2 Order of precedence when multiple data exist”.

C) Comparison with conventional classification systems

EU CLP H304 and EU DSD R65 correspond to Category 1.

D) Guidance concerning data

- A review of the medical literature on chemical aspiration (for example, WHO/IPCS “ICSC card”) 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 4th 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.

  Dynamic viscosity (mPa･s) / Density (g/cm^3) = Kinematic viscosity (mm^2/s)

(4)Guidance for classification and judgment

A) Background of this item and points to be noted

In classification, take the following points into account.

* Determination of “Not classified” should be made carefully except the case that reliable information source (e.g. List 1) denies hazard potential of the substance or provides description that its hazard potential is extremely low. If any question arises, it is preferable that the 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 indicate the evidence.
* As for Aspiration hazard, a substance shall be classified in “Classification not possible” instead of “Not classified” in accordance with Classification JIS from the judgment that the substance does not fall into UN GHS category 1 on the grounds that it falls into UN GHS 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]: Reliable information source (e.g. List 1 or List 2) has a description that the substance caused chemical pneumonia due to accidental aspiration in humans.

(Notes)

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 4th 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^2/s or less at 40°C.

(Notes)

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^2/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 4th 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) In this guidance, "hydrocarbon" means substances consisting of carbon and hydrogen including nonlinear ones, 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^2 = poise(or P)). Use the following conversion formula when appropriate.

1 poise = 0.1Pa・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.

Dynamic viscosity (mPa・s) / Density (g/cm^3) = Kinematic viscosity (mm^2/s)

(5) Classification methods for mixtures

Classification of mixtures for aspiration hazards shall be basically performed based on the test data of the mixture itself by weight of evidence evaluation of the data as described later in A). If test data of the mixture itself are not available, classification may be performed in accordance with bridging principle as described later in B). In case test data or classification category information of all or part of ingredients of the mixture are available,

classification can be performed using concentration limit of each ingredient as described later in C).

A) Classification of mixtures when data on the mixture itself are available

A mixture shall be classified in Category 1 when reliable and good quality evidence from human experience is available.

B) Classification of mixtures when data on the mixture itself are not available

If test data of the mixture itself are not available, classification in accordance with bridging principle (3-2-4) should be considered provided that there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazard of the mixture. This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without necessity for additional testing in animals. For aspiration hazard, "dilution", "batching", "concentration of mixtures of the highest toxicity", "interpolation within one toxicity category", and "substantially similar mixtures" among bridging principles are applicable, but "aerosols" is not applicable.

C) Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

A mixture meeting any of the following criteria is classified in Category 1.

[Decision Criteria 2a]: A mixture which contains ≥ 10% of Category 1 chemical as an ingredient and has a kinematic viscosity ≤ 20.5 mm^2/s, measured at 40°C.

[Decision Criteria 2b]: In case of a mixture which separates into two or more distinct layers, one of which contains ≥ 10% of an ingredient classified in Category 1 and has a kinematic viscosity ≤ 20.5 mm2/s, measured at 40°C.

Reference: Substances with Risk phrase R-65 in EU DSD Classification are exemplified.

- Pentanes (including branched pentanes)
- Heptanes (including branched heptanes)
- Cyclohexane
- Methylcyclohexane
- 1, 4-Dimethylcyclohexane
- Cumene (isopropylbenzene);
- Normal hexane;
- Benzene;
- Octanes (including branched octanes);
- Toluene.

Part4 Environmental Hazards Guidance

4-1 Summary of GHS classification

A. Identification of substances

In classification, a chemical to classify shall be identified first. Items required for identification are shown in Chapter 1-2 in this guidance.

- Judge whether or not classification of the chemical is necessary. (Refer to Chapter 1-2)
- Determine if the chemical is a substance or a mixture (solution).
- If it is a mixture, examine its ingredients composing it.

B. In cases, as hazard and toxicity information, in-house data or existing data are available

(1) When in-house data or existing literature information (data) on the environmental hazards of the chemical are available, classify based on the data.

(2) When a plurality of data are available, the enterprises should probe into and determine the used testing method of the data, the used testing method is one of the testing methods which can be used for GHS classification, which is the most reliable among data.

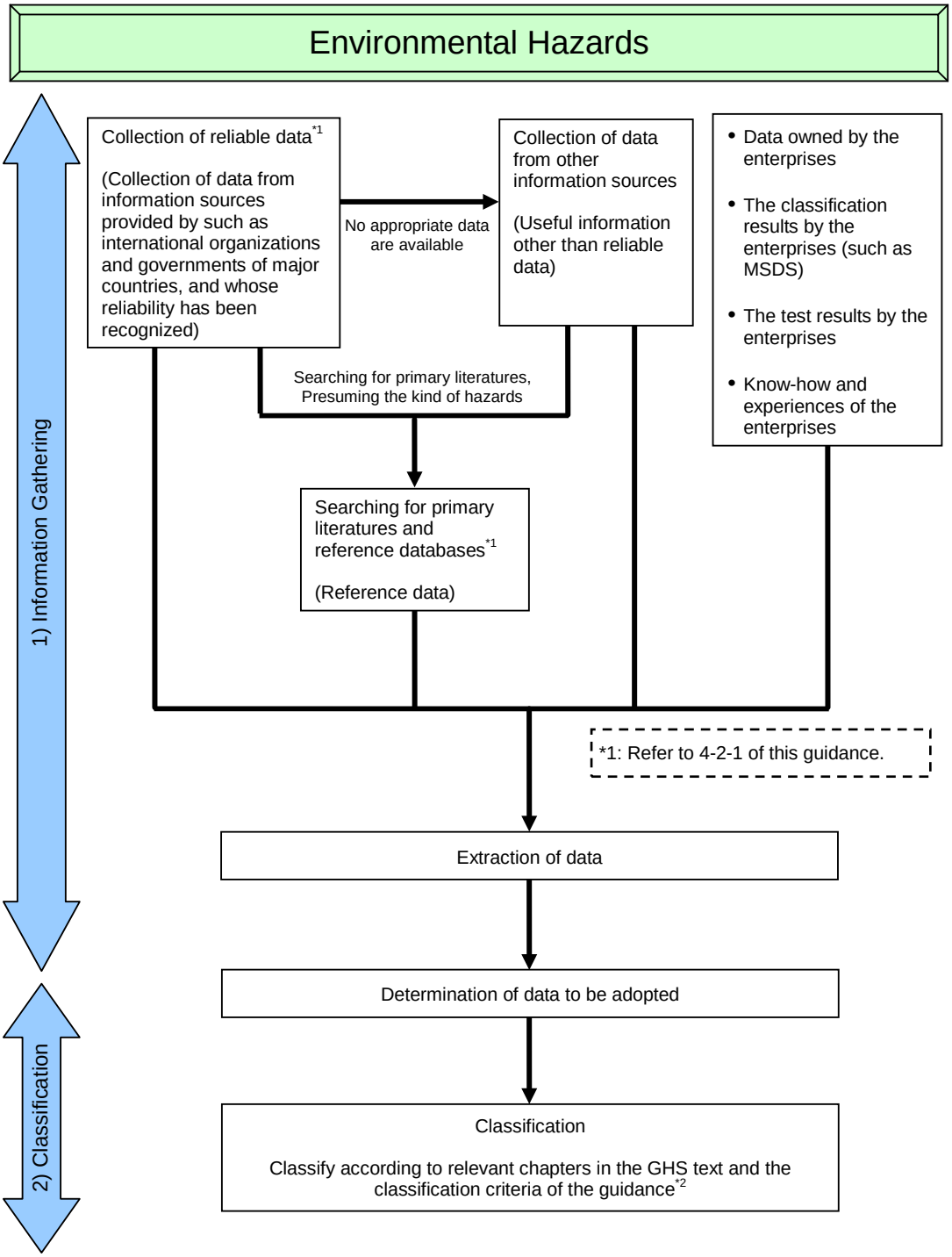
C. Classifying by utilizing existing classifications

(1) In some cases, although no data are available, classification may be completed by utilizing existing classifications (such as SDSs classified by enterprises) as reference.

(2) It is preferable to check the evidence data for such as EU classification (EU CLP classification, etc).

The figure below shows the workflow of GHS classification (environmental hazards).

Figure 4-1-1 GHS Classification workflow (Environmental Hazards)



4-2 Information available for classification

4-2-1 Sources of information available for classification

In UN GHS, available data are reviewed for classification. Available data are as follows. Enterprises are required to review available data exhaustively among below sources of information and to classify on its own judgment. When the following information is not available, it may consult suitable experts in the field regarding matters such as classification methods on its own judgment.

In any cases, any results obtained through execution of the classification with consulting this guidance, including the responsibility for the results, shall belong to the enterprises.

- ✓ Information sources provided by international organizations, governments of major countries, etc., whose reliability has been recognized.
- ✓ Useful information sources other than described above.
- ✓ Data bases of primary literatures for searching and referencing
- ✓ Data owned by the enterprises
- ✓ The classification results by the enterprises (such as SDS)
- ✓ The test results by the enterprises
- ✓ Know-how and experiences of the enterprises

(1) Information sources of test data on aquatic environmental hazards

In “GHS Classification Guidance for the Japanese Government”, obtained information is prioritized from List 1 to List 3 depending on how much its accuracy is confirmed, which represents order of precedence to be applied to classification.

List 1 includes 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 literature 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 (e.g. OECD) and GLP and judged to be valid by reviews of experts in national committees, etc., shall be treated equally.

List 2 includes databases, etc. of summaries of primary documents, which cannot be traced to confirm accuracy of information.

List 3 includes databases for searching primary literatures and reference databases.

Although Lists 1-3 appear in explanation of each classification category, enterprises are entrusted to judge which of them information they have collected belongs to.

In the "GHS Classification Guidance for the Japanese Government", information sources applicable to Lists1-3 are shown to reduce variations in classification results as much as possible and to perform classification work efficiently. In classification, enterprises are required to review available data exhaustively.

For your reference, information sources applicable to List 1 and List 2 that the Japanese government uses for classification are shown below. It should be noted that the order of precedence from List 1 to List 3 is an index to show how much accuracy of the obtained information is confirmed and does not limit the range of data to use by this Lists.

[Reference] The principle for the precedence of information sources in the "GHS Classification Guidance for the Japanese Government"

Upon conducting search for classification, firstly review the assessment documents shown in List 1 and look for information on the relevant substance.

If required information cannot be obtained from sources in List 1, repeat the process with List 2.

The sources of the below lists shall be used for classification, in principle. This does not limit the use of reliable and useful information sources other than those listed here.

It should be noted that if any literature in the list requires confirmation of the reliability, its original should be reviewed. If its reliability is low, the literature shall not be used for classification.

The latest information of the below on-line sites should be obtained, which are updated when appropriate.

List 1:

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

The following information can also be searched at the National Institute for Environmental Studies, “Webkis-plus”, Chemical Safety Database (http://db-out3.nies.go.jp/kis-plus/) and eChemPortal (http://www.echemportal.org/echemportal/substancesearch/page.action?pageID=0), for example.

1-1)	Organisation	Ministry of the Environment (Japan)
	Source	Test for the Ecological Effects of Chemical Substances
	URL	http://www.env.go.jp/chemi/sesaku/02e.pdf
1-2)	Organization	Environmental Risk Assessment Office, Ministry of the Environment (Japan)

	Source	Environmental Risk Assessments for Chemical Substances
	URL	http://www.env.go.jp/chemi/risk/index.html
1-3)	Organization	National Institute of Technology and Evaluation(NITE)
	Source	Initial Risk Assessment
	URL	http://www.safe.nite.go.jp/english/risk/initial_risk.html
	Note	Chemicals Evaluation and Research Institute, Japan(CERI)・National Institute of Technology and Evaluation (NITE) “Hazard Assessment Report” http://www.cerij.or.jp/evaluation_document/hazard_assessment_report_03.html http://www.safe.nite.go.jp/japan/sougou/view/SystemTop_jp.faces?child_flg=child&service_id=APSelectingListsList_jp
1-4)	Organization	OECD
	Source	SIDS Initial Assessment Report (SIAR) Initial Targeted Assessment Report (ITAR)
	URL	Documents created by OECD SIAM (current CoCAM) are firstly published at OECD’s website and then partially at UNEP’s website excluding 1-7). http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=44C0151D-03E8-464F-9BE4-50085BD01218 http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html
	Note	OECD:HPV-SIAP Japanese version Japan Chemical Industry Ecology-Toxicology & Information Center http://www.jetoc.or.jp/safe/siap_top.html
1-5)	Organization	WHO/IPCS
	Source	Environmental Health Criteria(EHC)
	URL	http://www.who.int/ipcs/publications/ehc/en/index.html http://www.inchem.org/pages/ehc.html
	Note	EHC Japanese version: http://www.nihs.go.jp/hse/ehc/index.html It should be noted that a Japanese version is available only of limited volumes.
1-6)	Organization	WHO/IPCS
	Source	Concise International Chemical Assessment Documents (CICAD)
	URL	http://www.inchem.org/pages/cicads.html
	Note	CICAD Japanese version http://www.nihs.go.jp/hse/cicad/cicad.html

		It should be noted that a Japanese version is available only of limited volumes.
1-7)	Organization	EU European Chemicals Bureau (ECB)
	Source	EU Risk Assessment Report:EU RAR
	URL	http://esis.jrc.ec.europa.eu/
1-8)	Organization	Environment Canada/ Health Canada
	Source	Assessment Report Environment Canada: Priority Substance Assessment Reports
	URL	http://www.ec.gc.ca/substances/ese/eng/psap/final/main.cfm (Abstract only on the web site)
1-9)	Organization	Australia NICNAS
	Source	Priority Existing Chemical Assessment Reports
	URL	http://www.nicnas.gov.au/publications/car/pec/default.asp
1-10)	Organization	European Center of Ecotoxicology and Toxicology of Chemicals (ECETOC)
	Source	Technical Report TR91(Aquatic Hazard Assessment II)(TR91)
	URL	http://www.ecetoc.org/technical-reports
	Note	http://www.ecetoc.org/publications (list only)
1-11)	Organization	WHO/FAO
	Source	Pesticide Data Sheets(PDSs)
	URL	http://www.inchem.org/pages/pds.html
1-12)	Organization	United States Environmental Protection Agency (EPA)
	Source	Pesticides “Regeneration Eligibility Decision”
	URL	http://www.epa.gov/pesticides/reregistration/status.htm

List 2:

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

2-1)	Organization	AQUIRE
	Source	Aquatic Toxicity Information Retrieval (AQUIRE)
	URL	http://cfpub.epa.gov/ecotox/
	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: http://www.jaici.or.jp/stn/dbsummary/db.html

2-2)	Organization	EU European Chemicals Bureau (ECB)
	Source	International Uniform Chemical Information Database (IUCLID) IUCLID CD-ROM (Update Version Edition 2 - 2000)
	URL	http://esis.jrc.ec.europa.eu/index.php?PGM=dat
2-3)	Organization	National Library of Medicine(NLM)
	Source	Hazardous Substance Data Bank(HSDB)
	URL	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB
2-4)	Organization	German Chemical Society-Advisory Committee on Existing Chemicals of Environmental Relevance
	Source	BUA Report (BUA)
	URL	http://www.hirzel.de/bua-report/download.html
	Note	Full report can not be available from web site.

List 3:

These are databases for searching primary literature and reference databases. In case data are available in List 1 or 2, these databases should be referred to for confirmation of the data reliability and so on, if appropriate.

If it is impossible to evaluate the reliability of individual ingredients of a product even if hazard information of the product is available from existing SDSs, etc., it should be avoided to use the data.

3-1) Database for primary literatures

- Pub-Med/NLM(For original literature)
  http://www.ncbi.nlm.nih.gov/sites/entrez?db=ncbisearch
- NLM TOXNET(Online database including original literature)
  http://toxnet.nlm.nih.gov/index.html
- JICST of Japan Science and Technology Agency (J DreamII online database)
  http://pr.jst.go.jp/db/db.htm

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.htmll
- Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA)
  "GESTIS-database on hazardous substances" (GESTIS):
  http://gestis-en.itrust.de/nxt/gateway.dll/gestis_en/000000.xml?f=templates$fn=default.htm$3.0
- Ministry of the Environment Government: Chemical Substances Fact Sheets

http://www.env.go.jp/chemi/communication/factsheet.html

- 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
- Chemicals Evaluation and Research Institute, Japan(CERI) ”Chemical Substance Hazard Data”:
  http://www.cerij.or.jp/evaluation_document/Chemical_hazard_data.html
- 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 (6th edition, 2012)”: http://www.sciencedirect.com/science/book/9781437778694
- 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/icstart.html
  (ICSC Japanese version: http://www.nihs.go.jp/ICSC/)
- EU European Chemicals Bureau (ECB) “The N-CLASS Database on Environmental Hazard Classification (N-Class)”:
  http://apps.kemi.se/nclass/default.asp
  Database jointly developed by ECB and The Nordic Council of ministers, which provides information about N(R50-53) in EU hazardous substances list

3-3) EU classification

http://esis.jrc.ec.europa.eu/index.php?PGM=cla (searchable from “SEARCH ANNEX VI”)

- Classification based on Table 3-1, Annex VI of EU CLP regulations (hereinafter abbreviated as “EU CLP classification". R-phrases shall be referred to as EU DSD classification) can be referred to for GHS classification

Fundamentally, classification shall be performed based on quality, reliability, and consistency of the evidence obtained from the information source using the weight of evidence, and expert judgment where appropriate.

In this guidance, classification based on the Annex VI, Table 3-1 of EU CLP regulations is referred to as EU CLP classification, and R-Phrase 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.

(2) Information sources of data on bioaccumulation and rapid degradability

Like in "(1) Information sources of test data on aquatic environmental hazards ", in “GHS Classification Guidance for the Japanese Government, information sources applicable to Lists 1 to 3 are provided to reduce variations in classification results as much as possible and to perform classification work efficiently. In classification, enterprises are required to review available data exhaustively.

For your reference, information sources applicable to List 1 and List 2 that the Japanese government uses for classification are shown below. It should be noted that the order of precedence of List 1 and List 2 is an index to show how much accuracy of the obtained information is confirmed and does not limit the range of data to use by this Lists.

[Reference] Information sources in the "GHS Classification Guidance for the Japanese Government"

List 1:

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

1-1)	Source	Japan CHEmicals Collaborative Knowledge database
	URL	http://www.safe.nite.go.jp/jcheck/
1-2)	Source	PHYSPROP Database(SRC,2005)
	URL	http://www.syrres.com/esc/physprop.htm
	Note	Measured values and estimate values are listed. Use only measured values for judgment in classification as List 1. It is preferable that estimate value is added for reference.

List 2:

Useful information sources of assessment documents other than those in List 1 described in "(2) Information sources of data on bioaccumulation and rapid degradability ".

2-1)	Source	AQUIRE(Aquatic Toxicity Information Retrieval) (AQUIRE)
	URL	http://cfpub.epa.gov/ecotox/
	Note	Database on chemical substances and aquatic toxicity established by EPA in 1981. It is now included in the Ecotox database. Search by “Accumulation”

		and refer to BCF for the results.
2-2)	Organization	EU European Chemicals Bureau (ECB)
	Source	International Uniform Chemical Information Database (IUCLID) IUCLID CD-ROM (Update Version Edition 2 - 2000)
	URL	http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html
	Note	See items, Biodegradation and Bioaccumulation
2-3)	Organization	National Library of Medicine(NLM)
	Source	Hazardous Substance Data Bank(HSDB)
	URL	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB

(3) Information sources of data on hazards on ozone layer

List 1:

Confirm substances to control with Annexes of Montreal Protocol.

Organization	UNEP
Source	Montreal Protocol on Substances that Deplete the Ozone Layer
URL	http://ozone.unep.org/new_site/en/Treaties/treaty_text.php?treatyID=2
Note	Japanese version: http://www.meti.go.jp/policy/chemical_management/ozone/files/law_ozone/law_ozone_laws/Montreal_Protocol.pdf#search='http%3A%2F%2Fwww.meti.go.jp%2Fpolicy%2Fchemical_management%2Fozone%2Ffiles%2Flaw_ozone%2Flaw_ozone_laws%2FMontreal_Protocol.pdf'

4-3 Classification of Hazardous to the Aquatic Environment

UN GHS defines “Hazardous to the aquatic environment” and “Hazardous to the ozone layer” as environmental hazards, which are stipulated in Chapters 4.1 and 4.2 of the UN GHS 3rd revised edition, respectively. Classification JIS has reflected its update. 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” of UN GHS 4th revised edition. GHS classification shall be performed by referring to them.

4-3-1 Aquatic toxicity

(1)Definitions

Definitions by UN GHS are used in this guidance.

【GHS 4th 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°) 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

Categories for substances hazardous to the aquatic environment and the categories for substances considered long-term hazardous to the aquatic environment are shown in Table 4-3-1-1 and Figure 4-3-1-1, respectively.

The criteria for classification of a substance into categories Chronic 1 to 3 follow a tiered approach where the first step is to see if available information on chronic toxicity and degradability merits long-term hazard classification. In absence of adequate chronic toxicity data, the subsequent step is to combine acute toxicity data and environmental fate data (degradability and bioaccumulation data) and classify the substance according to the most stringent outcome.

Table 4-3-1-1: Categories for substances hazardous to the aquatic environment (Note 1)

a) Acute (short-term) aquatic hazard (Note 2)

Category: Acute 1 is assigned based on any of the following:	
96 hr LC_{50} (for fish)	≤1 mg/L and/or
48 hr EC_{50} (for crustacea)	≤1 mg/L and/or
72 or 96 hr ErC_{50} (for algae or other aquatic plants)	≤1 mg/L (Note 3)
Category: Acute 2 is assigned based on any of the following:	
96 hr LC_{50} (for fish)	>1 but ≤10 mg/L and/or
48 hr EC_{50} (for crustacea)	>1 but ≤10 mg/L and/or
72 or 96 hr ErC_{50} (for algae or other aquatic plants)	>1 but ≤10 mg/L
Category: Acute 3 is assigned based on any of the following:	
96 hr LC_{50} (for fish)	>10 but ≤100 mg/L and/or
48 hr EC_{50} (for crustacea)	>10 but ≤100 mg/L and/or
72 or 96 hr ErC_{50} (for algae or other aquatic plants)	>10 but ≤100 mg/L

b) Chronic (long-term) aquatic hazard: non-rapidly degradable substances for which there are adequate chronic toxicity data available

Category Chronic 1 is assigned based on any of the following:	
Chronic NOEC or EC_x (for fish)	≤ 0.1 mg/L and/or
Chronic NOEC or EC_x (for crustacea)	≤ 0.1 mg/L and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	≤ 0.1 mg/L
Category Chronic 2 is assigned based on any of the following:	
Chronic NOEC or EC_x (for fish)	≤ 1 mg/L and/or
Chronic NOEC or EC_x (for crustacea)	≤ 1 mg/L and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	≤ 1 mg/L

c) Chronic (long-term) aquatic hazard: rapidly degradable substances for which there are adequate chronic toxicity data

Category Chronic 1 is assigned based on any of the following:	
Chronic NOEC or EC_x (for fish)	≤ 0.01 mg/L and/or
Chronic NOEC or EC_x (for crustacea)	≤ 0.01 mg/L and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	≤ 0.01 mg/L
Category Chronic 2 is assigned based on any of the following:	
Chronic NOEC or EC_x (for fish)	≤ 0.1 mg/L and/or
Chronic NOEC or EC_x (for crustacea)	≤ 0.1 mg/L and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	≤ 0.1 mg/L

Category Chronic 3 is assigned based on any of the following:

Chronic NOEC or EC_x (for fish)	≤ 1 mg/L and/or
Chronic NOEC or EC_x (for crustacea)	≤ 1 mg/L and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	≤ 1 mg/L

d) Chronic (long-term) aquatic hazard: substances for which adequate chronic toxicity data are not available

Category Chronic 1 is assigned based on any of the following (Note1):

96 hr LC_{50} (for fish)	≤ 1 mg/L and/or
48 hr EC_{50} (for crustacea)	≤ 1 mg/L and/or
72 or 96 hr ErC_{50} (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_{ow} ≥ 4).

Category Chronic 2 is assigned based on any of the following:

96 hr LC_{50} (for fish)	> 1 but ≤ 10 mg/L and/or
48 hr EC_{50} (for crustacea)	> 1 but ≤ 10 mg/L and/or
72 or 96 hr ErC_{50} (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 ≥ 500 (or, if absent, the log K_{ow} ≥ 4).

Category Chronic 3 is assigned based on any of the following:

96 hr LC_{50} (for fish)	> 10 but ≤ 100 mg/L and/or
48 hr EC_{50} (for crustacea)	> 10 but ≤ 100 mg/L and/or
72 or 96 hr ErC_{50} (for algae or other aquatic plants)	> 10 but ≤ 100 mg/L

and the substance is not rapidly degradable and/or the experimentally determined BCF is ≥ 500 (or, if absent, the log K_{ow} ≥ 4) (Note 4 and Note 5)

e) "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} ≥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 degradation in the environment.

Note 1: The organic fish, Crustacea and algae are tested as surrogate species covering a range of trophic levels and taxa, and the test methods are highly standardized. Data on other organisms may also be considered, however, provided they represent equivalent species and test endpoints.

Note 2: When classifying substances as Acute 1 and/or Chronic 1 it is necessary at the same time to indicate an appropriate M factor (*2) to apply the summation method (*1).

Note 3: Where the algal toxicity ErC_{50} [=EC_{50} (growth rate)] falls more than 100 times below the next most sensitive species and results in a classification based solely on this effect, consideration by experts should be used to decide whether this toxicity is representative of the toxicity to aquatic plants. Classification should be based on ErC_{50}. In circumstances where the basis of EC_{50} is not specified and no ErC_{50} is recorded, classification should be based on the data.

Note4: Lack of rapid degradability is based on either a lack of ready biodegradability or other evidence of lack of rapid degradation. When no useful data on degradability are available, either experimentally determined or estimated data, the substance should be regarded as not rapidly degradable.

Note 5: Potential to bioaccumulate, based on an experimentally derived BCF≥500 or, if absent, a log K_{ow}≥4, provided log K_{ow} is an appropriate descriptor for the bioaccumulation potential of the substance. Measured log K_{ow} values take precedence over estimated values and measured BCF values take precedence over log K_{ow} values.

(*1: A method of classifying hazardous mixture by summing up its ingredients classified.

(*2: A coefficient to add weight in applying the summation method to classification of a mixture containing ingredients with high toxicity.)

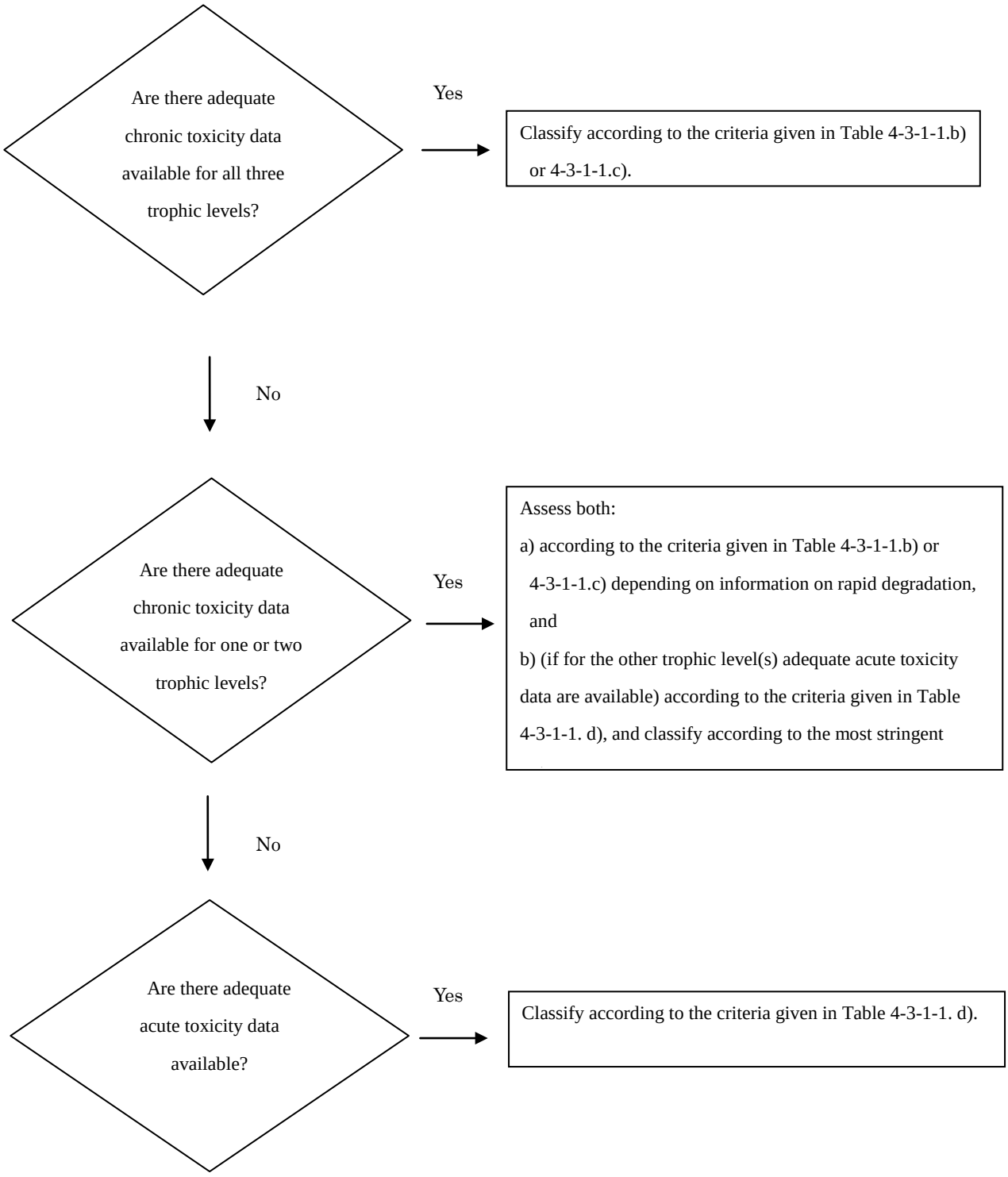


Figure 4-3-1-1 Categories for substances long-term hazardous to the aquatic environment

From the above, classification scheme for substances hazardous to the aquatic environment is shown in Table 4-3-1-2.

Table 4-3-1-2 Classification scheme for substances hazardous to the aquatic environment

<table>
<tr><td colspan="4">Classification categories</td></tr>
<tr><td rowspan="3">Acute hazard
(Note 1)</td><td colspan="3">Long-term hazard (Note 2)</td></tr>
<tr><td colspan="2">Adequate chronic toxicity data available</td><td rowspan="2">Adequate chronic toxicity data not available
(Note 1)</td></tr>
<tr><td>Non-rapidly degradable substances
(Note 3)</td><td>Rapidly degradable substances
(Note 3)</td></tr>
<tr><td>Category: Acute 1
L(E)C50≤1.00 mg/L</td><td>Category: Chronic 1
NOEC or ECx≤0.1 mg/L</td><td>Category: Chronic 1
NOEC or ECx≤0.01 mg/L</td><td>Category: Chronic 1
L(E)C50≤1.00 mg/L and lack of rapid degradability and/or BCF≥500 or, if absent log Kow≥4</td></tr>
<tr><td>Category: Acute 2
1.00 mg/L＜L(E)C50≤ 10.0 mg/L</td><td>Category: Chronic 2
0.1 mg/L＜ NOECorECx ≤1 mg/L</td><td>Category: Chronic 2
0.01 mg/L＜ NOECorECx ≤0.1 mg/L</td><td>Category: Chronic 2
1.00 mg/L＜L(E)C50≤ 10.0 mg/L and lack of raid degradability and/or BCF≥500 or, if absent $logK_{ow}$≥4</td></tr>
<tr><td>Category: Acute 3
10.0 mg/L＜L(E)C50≤ 100 mg/L</td><td></td><td>Category: Chronic 3
0.1 mg/L＜ NOECorECx ≤1 mg/L</td><td>Category: Chronic 3
10.0 mg/L＜L(E)C50≤ 100 mg/L and lack of rapid degradability and/or BCF≥500 or, if absent $logK_{ow}$≥4</td></tr>
<tr><td></td><td colspan="3">Category: Chronic 4 (Note 4)
Example: (Note 5)
No acute toxicity and lack of rapid degradability and BCF≥500 or if absent $logK_{ow}$≥4, unless NOECs＞1 mg/L</td></tr>
</table>

Note 1: Acute toxicity band based on L(E)C50(mg/L) values in mg/L for fish, crustacean and/or algae or other aquatic plants (or QSAR estimation if no experimental data).

Note 2: Substances are classified in the various chronic categories unless there are adequate

chronic toxicity data available for all three trophic levels above the water solubility on above 1mg/L. (“Adequate” means that the data sufficiently cover the endpoint of concern. Generally this would mean measured test data, but in order to avoid unnecessary testing it can, on a case-by-case basis, also be estimated data, e.g. (Q)SAR, or for obvious cases expert judgment).

Note3: Chronic toxicity band based on NOEC (mg/L) or equivalent Cx (mg/L) values (usually x=10%) for fish or crustacea.

Note 4: The system also introduces a “safety net” classification (referred to as category Chronic 4) for use when the data available do not allow classification under the formal criteria but there are nevertheless some grounds for concern.

Note 5: For poorly soluble substances for which no acute toxicity has been demonstrated at the solubility limit, and are both not rapidly degraded and have a potential to bioaccumulate, this category should apply unless it can be demonstrated that the substance does not require classification for aquatic long-term hazards.

(3) Items on information sources and data

A) Data availability

Most information sources (shown in 4-2) 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.

Even if EU classification results which are similar to GHS classification are available as reference information, they cannot be directly used in GHS classification since classification criteria for chronic aquatic toxicity in EU classification are different from those 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_{50} (lethal)
- Crustacea: 24 or 48 hour EC_{50}(immobile), LC_{50}(lethal)
- Daphnia: 24 or 48 hour EC_{50} (immobile), LC_{50} (lethal)
- Decapoda, Amphipoda, Mysidacea: 24, 48, or 96 hour EC_{50} (immobile), LC_{50} (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* sp). 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 $LC_{50,}$ and IC_{50} (50% inhibition concentration), with EC_{50}.

UN GHS states that where no experimental data are available, validated QSARs for aquatic toxicity may be used in the classification process. Although estimates which enterprises consider accurate and highly reliable may be used for classification on its own responsibility, it is preferable to use expert judgment.

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. Even if the test is conducted according to GLP, if an expert judged that there is a doubt about the applied test procedure 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 4th 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 4th 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.

It is required for aquatic toxicity test because of its characteristics that a testing substance should be dissolved in aqueous medium where bioavailable exposure concentration is stably maintained during the test period.

Standard test methods and test conditions to be applied to individual organism groups are shown below.

In the below reliable data (e.g. List 1), if a test result is in accordance with the below test guidelines, etc., but the organism species, or other test conditions are different, expert judgment shall be used to decide adoption of the data.

- Fish: In tests using fish, 96 hour LC_{50} is used which is according to OECD test guideline 203 or corresponding test methods.
- Crustacea: In tests using crustacea, 48 hour EC_{50} according to OECD test guideline 202 (Daphnia Acute Immobilization test) or corresponding test methods should be the standard test. If 48 hour EC_{50} is not available, 24 hour EC_{50} (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_{50} 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_{50} (not

immobile but lethal) may be adopted. As for useful information sources (e.g. List 2), expert judgment should be used.

- Tests using Algae, Cyanobacteria (Cyanophyceae), and higher aquatic plants: OECD test guideline 201 (revised in 2006) is a growth inhibition test for Algae and Cyanobacteria (Cyanophyceae). Algae growth inhibition test is a chronic test, where EC_{50} is regarded as acute toxicity data for classification purpose. This EC_{50} is generally obtained based on the reduction of growth rate (Growth rate method: hereinafter abbreviated to as ErC). It should be noted that in case only EC_{50} from decrease in biomass (called area method/biomass method and abbreviated as EbC) at the completion of the test is available or calculation method to obtain EC_{50} is not clearly identified, these data may be used. Data with exposure time longer than 96 hours shall not be used.
- Other higher aquatic plants: OECD test guideline 221 (approved in 2006) showing a growth inhibition test method using a higher plant, Lemna, and acute EC_{50} according to US EPA850.4400 may be utilized. As in the case of Algae, ErC_{50} (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 3rd revised edition, chronic aquatic toxicity categories are agreed to be categorized based on chronic aquatic toxicity values.

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 (varies depending on the kind of fish), NOEC (hatching success rate, growth (length and weight changes), and survival rate, etc.)
- Crustacea (daphnia and mysidacea): 7 days or more (21 days in *Daphnia magna*, 7 days in *Ceriodaphnia dubia*, and 28 days in *Americamysis bahia*). NOEC (litter size of normal individual in *Daphnia magna*, cumulative mortality rate, length, and number of eggs per female in *Americamysis bahia*)
- Algae (or other aquatic plants):

- Algae: 72 or 96 hours, NOEC (growth inhibition)
- Other aquatic plants: 7 or 14 days, NOEC (growth inhibition)

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 4th 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 4th 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, judgment by experts shall be sought for a final decision.

For individual species, see below. As for reliable data (e.g. List 1) without indication of accordance with the test guidelines below, data shall be adopted in which organism species, exposure time, and endpoint corresponds to those stipulated in the test guidelines.

■ Fish:

Chronic or long-term toxicity tests using fish shall be conducted according to OECD Test Guideline 210 (Fish early life stage) (Note 1), Fish Life Cycle Test (US EPA 850.1500), or equivalent (one- or two-generation test).

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 (length and weight changes),

time to first brood and number of offspring produced per female in OECD Test Guideline 210. In US EPA850.150, they are influence on reproduction (number of eggs and frequency of spawning), mortality rate, behavior, physiologic and pathological effects.

(Note 1) OECD test guideline 210 is sub-chronic test, but the test results, which can be a good index for chronic toxicity, may be used as chronic aquatic toxicity data.)

■ Crustacea:

Chronic toxicity tests using crustacea shall be conducted in accordance with OECD Test Guideline 211 (Daphnia magna Reproduction Test), US EPA OPPTS 850.1050 (Mysid chronic toxicity test), or their equivalent (NOECs of 21 days for Daphnia, NOECs of 7 days or more for Ceriodaphnia).

Endpoints are time to first brood and normal cumulative number of offspring (reproductive output).

■ Algae (or other aquatic plants):

Chronic tests using Algae, OECD Test Guideline 201 (2006 revision) is a growth inhibition test for algae and cyanobacteria (cyanophyceae). In principle, growth inhibition (NOEC) by growth rate method is used for an endpoint.

When it is not clear whether growth rate method or other method is used for concluding NOECs, the NOECs may be tentatively used.

Most often used other aquatic plants are *Lemna gibba* and *Lemna minor*. Expert judgment should be used to decide if obtained NOEC can be treated the same as other chronic toxicity data of algae.

3) Data on bioaccumulation and rapid degradability

a) Requirements for usable data

Data on bioaccumulation (BCF, log K_{ow}), 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) 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 K_{ow}s values are not available, or they are considered to be not reliable, estimation of log K_{ow}s obtained by validated method[20] such as QSAR cannot be used as an evidence of classification but written in as reference information, preferably.

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 ($K_{ow)}$

When test results described above are not available, test results (K_{ow}) from OECD Test Guideline 123 and the corresponding tests may be adopted under an expert's judgment.

ii) Data on rapid degradability

Both biotic and abiotic degradability (for example, hydrolysis) must be taken into account. In case BOD degradability rate exceeds 60% or TOC degradability rate exceeds 70% in the ready biodegradability test, 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 results by use of biodegradability prediction software[21] cannot be used as an evidence of classification but it is preferable that the results are written in as reference information. The prediction results can be utilized only for a decision that the substance is not rapidly degradable.

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.

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[20] An example of Log K_{ow} (bio degradability) prediction software:
http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm

[21] An example of biodegradability prediction software: BIOWIN (EPI Suite)
http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm

OECD Test Guidelines 302A, 302B, 302C, 303A, 303B, 304A, 306, 307, 308, 309, 310, and 311

C) Order of precedence when multiple data exist

1) When reliable information sources (e.g. 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 a) 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 a) and b) 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 reliable information sources (e.g. List 1) are not available:

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, judgment 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

Consistency with EU CLP classification is as follows:

Category: acute 1= EU CLP・H400

Category: Chronic 1 = EU CLP H410

Category: Chronic 2 = EU CLP H411

Category: Chronic 3 = EU CLP H412

Category: Chronic 4 = EU CLP H413

The definitions of EU DSD classification are almost in accord with GHS categories and presumed to be classified as follows:

Category: acute 1 = EU R50 (and R50/53)

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

The definitions of R50, 51, and 52 correspond with Categories: Acute 1, Acute 2, and Acute 3 of (acute) aquatic environmental hazards in GHS classification, respectively. Unlike GHS, the differences are that Crustacea is limited to Daphnia, and that the testing time for algae is fixed at 72 hours in EU DSD. The requirement for R53 is log K_{ow}≥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[22] 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.

(4) Outline of classification methods for mixtures

A) Classification methods for mixtures

[22] For R-Phrase, see Appendix.

(1) The classification system for mixtures covers all classification categories which are used for substances, meaning categories Acute 1 to 3 and Chronic 1 to 4. In order to make use of all available data for purposes of classifying the aquatic environmental hazards of the mixture, the following assumption is applied where appropriate.

(2) The “relevant ingredients” of a mixture are those which are present in a concentration ≥0.1% (w/w) for ingredients classified as Acute and/or Chronic 1 and ≥1% (w/w) for other ingredients, unless there is a presumption (e.g. in the case of highly toxic ingredients) that an ingredient present at a concentration < 0.1% can still be relevant for classifying the mixture for aquatic environmental hazards.

B) Tiered approach for classification

The approach for classification of aquatic environmental hazards is tiered, and is dependent upon the type of information available for the mixture itself and for its ingredients. Process of tiered approach is shown in Figure 4-3-1-2.

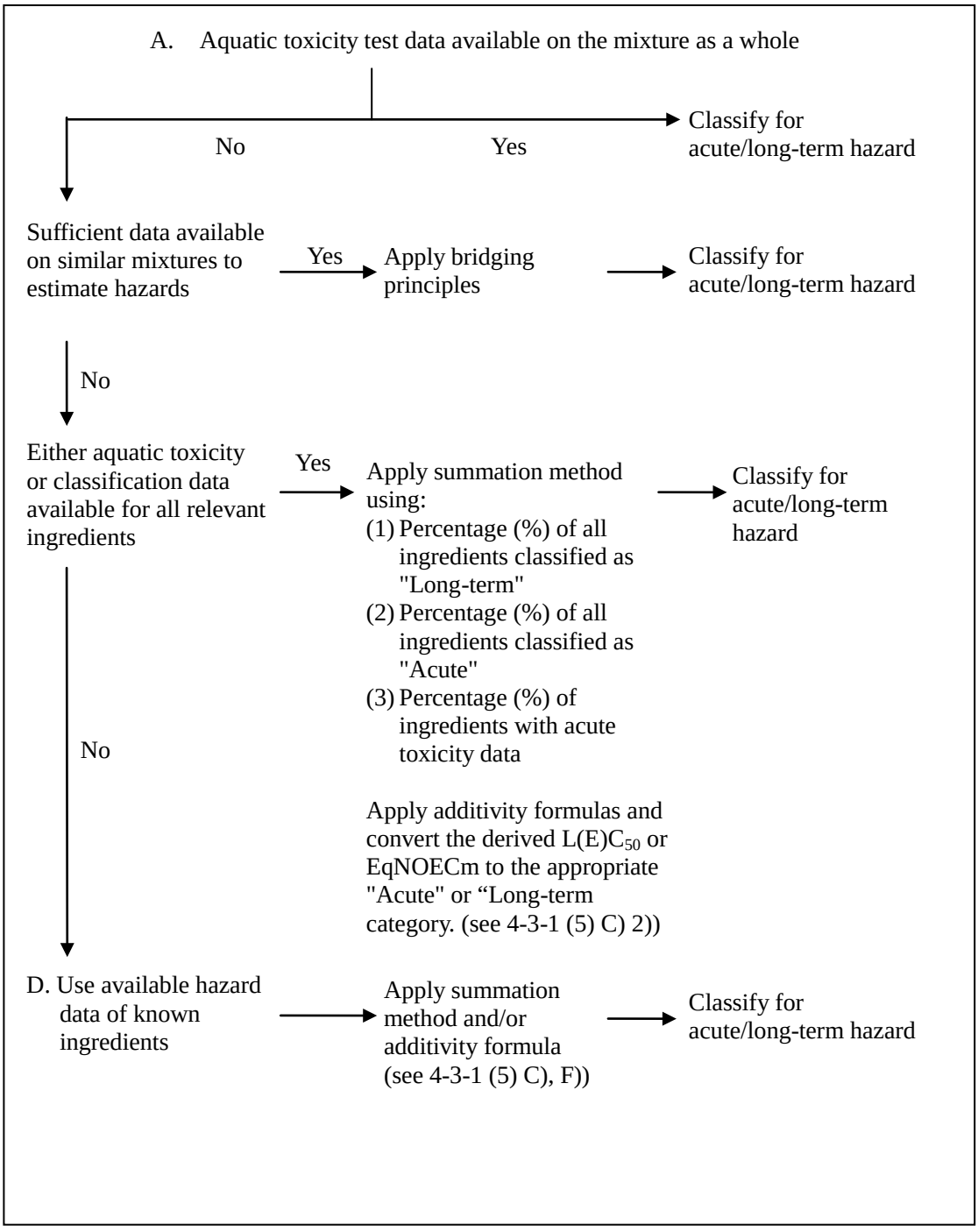
Elements of the tiered approach include

a) classification based on data of tested mixtures,

b) classification based on bridging principles, and

c) classification based on the use of "summation of classified ingredients" and/or "additivity formula".

Figure 4-3-1-2 Tiered approach for classification of mixtures for aquatic environmental hazards



(5) Classification methods for mixtures

Classification procedures are explained in accordance with Figure 4-3-1-2.

A) Classification of mixtures when data on the aquatic toxicity are available for the complete mixture

1) Classification for categories Acute 1, 2 and 3

When there are adequate acute toxicity test data LC_{50} or EC_{50}) available for the mixture as a whole showing $L(E)C_{50} \leq 100$ mg/L , the mixture shall be classified in Acute 1, 2 or 3.

When there are acute toxicity test data (LC_{50}(s) or EC_{50}(s)) available for the mixture as a whole showing $L(E)C_{50} > 100$ mg/L, or above the water solubility, the mixture at the trophic level as the data are obtained at least shall be classified as “not classified” for acute toxicity.

2) Classifications for categories Chronic 1, 2 and 3

When there are adequate chronic toxicity data (ECx or NOEC) available for the mixture as a whole showing ECx or NOEC of the tested mixture ≤ 1 mg/L, classify the mixture as Chronic 1, 2 or 3 in accordance with Table 4-3-1-1 c) (rapidly degradable) if the available information allows the conclusion that all relevant ingredients of the mixture are rapidly degradable.

Classify the mixture as Chronic 1, 2 or 3 in all other cases in accordance with Table 4-3-1-1 b) (non-rapidly degradable).

Where there are adequate chronic toxicity data (ECx or NOEC) available for the mixture as a whole showing Cx(s) or NOEC(s) of the tested mixture > 1 mg/L or above the water solubility, no need to classify (Not classified) for long-term hazard, unless there are nevertheless reasons for concern.

In classifying a mixture for long-term hazard, additional information about degradability or in some cases bioaccumulation is required, but interpretation of such data is generally too difficult to be used.

3) Classification for Category Chronic 4

Although a mixture is not classified according to 1) or 2), but if there are nevertheless reasons for concern, classify the mixture as Chronic 4 (safety net classification) in accordance with Table 4-3-1-1 e).

B) Classification of mixtures when aquatic test data are not available for the complete mixture

When data are not available for the complete mixture, consider classification with bridging principles (Dilution, Batching, Concentration of mixtures which are classified with the most severe classification categories, Interpolation within one toxicity category, and Substantially similar mixtures, refer to "3-2-4 Bridging principles").

C) Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

1) Summation of concentrations of classified ingredients

The classification of a mixture is based on summation of the concentrations of its classified ingredients. The summation method to which the percentage of ingredients classified as "Acute" or "Chronic" hazard is fed straight are described in D) 2).

2) Classification of mixtures made of a combination of both ingredients that are classified and those for which adequate test data are available;

Mixtures can be made of a combination of both ingredients that are classified (Acute 1, 2, 3 and/or Chronic 1, 2, 3, 4) and those for which adequate test data are available. When adequate toxicity data are available for more than one ingredient in the mixture, the combined toxicity of those ingredients may be calculated using the additivity formula (4-2-1) depending on the nature of the toxicity data.

a) Based on acute aquatic toxicity

$$\frac{\sum C_i}{L(E)C_{50m}} = \sum_{i=1}^{n} \frac{C_i}{L(E)C_{50i}} \qquad \text{.....} \quad \text{formula (4-2-1)}$$

Where:

C_i = concentration of ingredient i (weight percentage)

$L(E)C_{50i}$ = LC_{50} or EC_{50} for ingredient i (mg/L)

n = number of ingredients, and i is running from 1 to n

$L(E)C_{50m}$ = $L(E)C_{50}$ of the part of the mixture with test data

The calculated toxicity shall be used to assign that portion of the mixture an acute hazard category which is then subsequently used in applying the summation method;

b) Based on chronic aquatic toxicity

$$\frac{\sum \mathrm{Ci} + \sum \mathrm{Cj}}{\mathrm{EqNOEC_m}} = \sum_{\mathrm{n}} \frac{\mathrm{Ci}}{\mathrm{NOECi}} + \sum_{\mathrm{n}} \frac{\mathrm{Cj}}{0.1 \times \mathrm{NOECj}} \quad \text{---formula 4-2-1}$$

where:

C_i = concentration of ingredient i (weight percentage) covering the rapidly degradable ingredients;

C_j = concentration of ingredient j (weight percentage) covering the non-rapidly degradable ingredients;

$NOEC_i$ = NOEC (or other recognized measures for chronic toxicity) for ingredient i covering the rapidly degradable ingredients, in mg/L;

$NOEC_j$ = NOEC (or other recognized measures for chronic toxicity) for ingredient j covering the non-rapidly degradable ingredients, in mg/L;

n = number of ingredients, and i and j are running from 1 to n;

$EqNOEC_m$ = equivalent NOEC of the part of the mixture with test data;

The calculated equivalent toxicity may be used to assign that portion of the mixture a long-term hazard category, in accordance with the criteria for rapidly degradable substances (Table 4-3-1-1 c), which is then subsequently used in applying the summation method.

The equivalent toxicity thus reflects the fact that non-rapidly degrading substances are classified one hazard category level more “severe” than rapidly degrading substances.

If a mixture is classified in more than one way, the method yielding the more conservative result should be used.

3) Adopt the highest toxicity value in case toxicity data of multiple trophic levels (classification group) are available.

When applying the additivity formula for part of the mixture, it is preferable to calculate the toxicity of this part of the mixture using for each ingredient toxicity values that relate to the same taxonomic group (i.e. fish, crustacean or algae) and then to use the highest toxicity (lowest value) obtained (i.e. use the most sensitive of the three groups). However, when toxicity data for each ingredient are not available in the same taxonomic group, the toxicity value of each ingredient should be selected in the same manner that toxicity values are selected for the classification of substance, i.e. the higher toxicity (from the most sensitive test organism) is used. The calculated acute and chronic toxicity may then be used to classify this part of the mixture as Acute 1, 2 or 3 and/or Chronic 1, 2 or 3 using the same criteria described for substances.

D) Summation method

1) Rationale

In case of ingredient classification categories Acute 1/Chronic 1 to Acute 3/Chronic 3, the underlying toxicity criteria differ by a factor of 10 in moving from one category to another. Ingredients with a classification in a high toxicity band may therefore contribute

to the classification of a mixture in a lower band. The calculation of these classification categories therefore needs to consider the contribution of all ingredients classified Acute 1/Chronic 1 to Acute 3/Chronic 3 together.

When a mixture contains ingredients classified as Acute 1 or Chronic 1, attention should be paid to the fact that such ingredients, when their acute toxicity is well below 1 mg/L and/or chronic toxicity is well below 0.1 mg/L (if non rapidly degradable) and 0.01 mg/L (if rapidly degradable) contribute to the toxicity of the mixture even at a low concentration. Active ingredients in pesticides often possess such high aquatic toxicity but also some other substances like organometallic compounds. Under these circumstances the application of the normal concentration limits may lead to an "under-classification" of the mixture. Therefore, multiplying factors "M" should be applied to account for highly toxic ingredients, as described in 3).

2) Classification procedure

In general, a more severe classification for mixtures overrides a less severe classification, e.g. a classification with Chronic 1 overrides a classification with Chronic 2. As a consequence the classification procedure is already completed if the result of the classification is Chronic 1. A more severe classification than Chronic 1 is not possible, therefore it is not necessary to undergo the further classification procedure.

3) Summation method

I. Classification for categories Acute 1, 2 and 3

1) Consideration of Acute 1

- First, pick up all ingredients classified as Acute 1 and sum their concentrations (in%). In summing, the concentrations (in %) of Acute 1 shall be multiplied by M (toxicity multiplying factor; Table 4-3-1-4) determined by its L(E)C_{50}.
- If the sum of the concentrations (in %) of these ingredients is ≥ 25%, the mixture is classified as Acute 1, and the classification process is completed.
- If the sum is < 25%, go to "2) Consideration of Acute 2".

2) Consideration of Acute 2

- Pick up all ingredients of the mixture classified as Acute 1 and Acute 2, and sum their concentrations (in %) multiplied by weight and M. In summing, the concentrations (in %) of all ingredients classified as Acute 1 is multiplied by 10 and M (toxicity multiplying factor; Table 4-3-1-4) determined by its L(E)C_{50}.
- If the sum of the concentrations (in %) of these ingredients is ≥ 25%, the mixture is classified as Acute 2, and the classification process is completed.
- If the concentrations (in %) of these ingredients is < 25%, go to "3) Consideration of Acute 3".

3) Consideration of Acute 3

- Pick up all ingredients classified as Acute 1, 2, and 3 and sum their concentrations (in %). In summing, the sum of the concentrations (in %) of all ingredients classified as Acute 1 is multiplied by 100 and M (toxicity multiplying factor; Table 4-3-1-4) determined by its L(E)C_{50} , the sum of the concentrations (in%) of all ingredients classified as Acute 2 is multiplied by 10 and the sum of contents of Acute 3 is as-is.
- If the sum of the concentrations (in %) of these ingredients is ≥ 25%, the mixture is classified as Acute 3, and the classification process is completed.

The above calculating method is summarized in Table 4-3-1-3, and M (toxicity multiplying factor) is summarized in Table 4-3-1-4.

Table 4-3-1-3 Classification of a mixture for acute hazards based on summation of the concentrations of classified ingredients

Sum of the concentrations (in%) of ingredients classified as:	Mixture is classified as:
Acute 1 x M[a] ≥ 25%	Acute 1
(M x 10 x Acute 1) + Acute 2 ≥ 25%	Acute 2
(M x 100 x Acute 1) + (10 x Acute 2) + Acute 3 ≥ 25%	Acute 3
Note [a)]: For explanation of M; toxicity multiplying factor; see Table 4-3-1-4	

Table 4-3-1-4 M (toxicity multiplying factor) for ingredients with highly acute toxicity of mixtures

L(E)C_{50} value	M: toxicity multiplying factor
$0.1 < L(E)C_{50} \leq 1$	1
$0.01 < L(E)C_{50} \leq 0.1$	10
$0.001 < L(E)C_{50} \leq 0.01$	100
$0.0001 < L(E)C_{50} \leq 0.001$	1 000
$0.000\ 01 < L(E)C_{50} \leq 0.000\ 1$	10 000
(continue in factor 10 intervals)	

II. Classification for categories Chronic 1, 2, 3 and 4

1) Consideration of Chronic 1

- First, pick up all ingredients classified as Chronic 1 and sum their concentrations (in %). In summing, the concentrations (in %) of Chronic 1 shall be multiplied by M (toxicity multiplying factor; Table 4-3-1-6) determined by its L(E)C_{50}.
- If the sum of the concentrations (in %) of these ingredients is ≥ 25%, the mixture is classified as Chronic 1, and the classification process is completed.

- If the sum is < 25%, go to "2) Consideration of Chronic 2".

2) Consideration of Chronic 2

- Pick up all ingredients of the mixture classified as Chronic 1 and Chronic 2 and sum their concentrations (in %) multiplied by weight and M. In summing, the concentrations (in %) of all ingredients classified as Chronic 1 is multiplied by 10 and M (toxicity multiplying factor; Table 4-3-1-6) determined by its L(E)C_{50}.
- If the sum of the concentrations (in%) of these ingredients is ≥ 25%, the mixture is classified as Chronic 2, and the classification process is completed.
- If the concentrations (in %) of these ingredients is < 25%, go to "3) Consideration of Chronic 3".

3) Consideration of Chronic 3

- Pick up all ingredients classified as Chronic 1, 2, and 3 and sum their concentrations (in %). In summing, the sum of the concentrations (in %) of all ingredients classified as Chronic 1 is multiplied by 100 and M (toxicity multiplying factor; Table 4-3-1-6) determined by its L(E)C_{50} , the sum of the concentrations (in%) of all ingredients classified as Chronic 2 is multiplied by 10, and the sum of contents of Chronic 3 is as is.
- If the sum of the concentrations (in %) of these ingredients is ≥ 25%, the mixture is classified as Chronic 3. If the concentrations (in %) of these ingredients is < 25%, go to "4) Consideration of Chronic 4".

4) Consideration of Chronic 4

- If the mixture cannot be classified as any of Chronic 1, 2 or 3, classifying the mixture in Chronic 4 shall be considered. If the sum of the concentrations (in%) of the all ingredients classified in Chronic 1, 2, 3, and 4 is ≥ 25%, the mixture shall be classified as Chronic 4.

The calculating method for chronic toxicity is shown in Table 4-3-1-5

Table 4-3-1-5: Classification of a mixture for chronic hazards based on summation of the concentrations of classified ingredients

Sum of the concentrations (in %) of ingredients classified as:		Mixture is classified as:
Chronic 1 x M[a]	≥ 25%	Chronic 1
(M x 10 x Chronic 1) + Chronic 2	≥ 25%	Chronic 2
(M x 100 x Chronic 1) + (10 x Chronic 2) + Chronic 3	≥ 25%	Chronic 3
Chronic 1 + Chronic 2 + Chronic 3 + Chronic 4	≥ 25%	Chronic 4
Note [a)]: For explanation of M; toxicity multiplying factor; see Table 4-3-1-6		

Table 4-3-1-6 M (toxicity multiplying factor) for ingredients with high chronic toxicity of mixtures

Chronic toxicity	M factor	
NOEC value	Non-rapidly degradable ingredients	Rapidly degradable ingredients
0.01＜NOEC≤0.1	1	—
0.001＜NOEC≤0.01	10	1
0.0001＜NOEC≤0.001	100	10
0.000 01＜NOEC≤0.000 1	1000	100
0.0000 01＜NOEC≤0.0000 1	10000	1000
(continue in factor 10 intervals)		

E) Mixtures with highly toxic ingredients

Acute 1 or Chronic 1 ingredients with acute toxicities well below 1 mg/L and/or chronic toxicities well below 0.1mg/L 8if non-rapidly degradable) or 0.01mg/L (if rapidly degradable) may influence the toxicity of the mixture and should be given increased weight in applying the summation method. When a mixture contains ingredients classified as Acute or Chronic 1, the tiered approach described in “D) 3) Summation method I, Acute toxicity” and “D) 3) Summation method II, Chronic toxicity” should be applied using a weighted sum by multiplying the concentrations of Acute 1 and Chronic 1 ingredients by a factor, instead of merely adding up the percentage. This means that the concentration of “Acute 1” in the left column of Table 4-3-1-3 and the concentration of “Chronic 1” in the left column of Table 4-3-1-5 are multiplied by the appropriate multiplying factor (M). The M factors to be applied to these ingredients are defined using the toxicity value, as summarized in Table 4-3-1-4 and Table 4-3-1-6. Therefore, in order to classify a mixture containing Acute/Chronic 1 ingredients, the classifier needs to be informed of the value of the M factor in order to apply the summation method. Alternatively, the additivity formula (4-2-1) may be used when toxicity data are available for all highly toxic ingredients in the mixture and there is

convincing evidence that all other ingredients, including those for which specific acute and/or chronic toxicity data are not available, are of low or no toxicity and do not significantly contribute to the environmental hazard of the mixture.
If a mixture is classified in more than one way, the method yielding the more conservative result should be used.

F) Classification of mixtures with ingredients without any useable information

In the event that no useable information on acute and/or chronic aquatic hazard is available for one or more relevant ingredients, it is concluded that the mixture cannot be attributed (a) definitive hazard category(ies). In such a case, the mixture should be classified based on the known ingredients only, with the additional statement that: "x% of the mixture consists of ingredient(s) of unknown hazards to the aquatic environment".

G) Examples of classification of mixtures

Example 1) Classification of a mixture for Acute/ Chronic categories when category information of its ingredients is available

Ingredient information

Ingredient	% (weight)	Acute (Multiplying factor: M)	Chronic (Multiplying factor: M)
Ingredient A	0.01	Acute 1 M:10	Chronic 1 M:10
Ingredient B	1.0	Acute 2	Chronic 2
Ingredient C	25.0	Not classified	Chronic 4
Ingredient D	73.99	Not classified	Not classified

(i) Classification of a mixture for acute hazards

1) Applicability to Category Acute 1

Acute 1 ingredient→Ingredient A；0.01%

(0.01%×10) ＝0.1% ＜ 25%

Therefore, it is not classified in Acute 1.

2) Applicability to Category Acute 2

Acute 1 ingredient→Ingredient A；0.01%

Acute 2 ingredient→Ingredient B；1.0%

（0.01%×10×10) ＋1.0%＝2.0% ＜ 25%

Therefore, it is not classified in Category Acute 2.

3) Applicability to Category Acute 3

Acute 1 ingredient→Ingredient A ; 0.01%

Acute 2 ingredient→Ingredient B ; 1.0%

（0.01%×10×100) ＋ (1.0%×10) ＝20% ＜ 25%

Therefore, it is not classified in Category Acute 3.

From the above, the mixture is not classified as acute hazard.

(ii) Classification of a mixture for long-term hazards

1) Applicability to Category Chronic 1

Chronic 1 ingredient→Ingredient A ; 0.01%

(0.01%×10) ＝0.1% ＜ 25%

Therefore, it is not classified in Chronic 1.

2) Applicability to Category Chronic 2

Chronic 1 ingredient→Ingredient A ; 0.01%

Chronic 2 ingredient→Ingredient B ; 1.0%

(0.01%×10×10) ＋1.0%＝2.0% ＜ 25%

Therefore, it is not classified in Chronic 2

3) Applicability to Category Chronic 3

Chronic 1 ingredient→Ingredient A ; 0.01%

Chronic 2 ingredient→Ingredient B ; 1.0%

(0.01%×10×100) ＋ (1.0%×10) ＝20% ＜ 25%

Therefore, it is not classified in Chronic 3.

4) Applicability to Category Chronic 4

Chronic 1 ingredient→Ingredient A ; 0.01%

Chronic 2 ingredient→Ingredient B ; 1.0%

Chronic 4 ingredient→Ingredient C ; 25.0%

0.01%＋1.0%＋25.0%＝26.01% ＞ 25%

Therefore, it is classified in Chronic 4.

Example 2) Classification of a mixture in Long-term category when test data and category information of the ingredients are available

Ingredient information

Ingredient	% (weight)	Chronic toxicity data	NOEC or ECx	Rapid degradability	Chronic category
Ingredient X	15	NOEC (Fish: 28days)	4.1	Applicable	－
		NOEC (Crustacea: 21 days)	0.13		
Ingredient Y	5	NOEC (Algae)	0.8	N/A	－
Ingredient Z	80	－			Chronic 3

(Step 1) Application of summation formula based on chronic hazard data

1) Application of formula 4-2-2 to ingredients with chronic hazard data

EqNOECm ＝ 20/((15/0.13)+5/(0.1×0.8))＝0.11 mg/L

EqNOECm of part (20% portion) of a mixture with chronic hazard data is 0.11 mg/L.

2) In 1), the concentration of ingredients with non-rapid degradability is calculated by multiplying a coefficient: 0.1. Comparing with criteria for rapid degradability, part (20% portion) of the mixture is judged to be Chronic 3.

(Step 2) Application of summation method

Ingredient information taking into account Step 1

Ingredient	% (weight)	Chronic category
Result of application of summation method to part of mixture with chronic hazard data	20	Chronic 3
Ingredient Z	80	Chronic 3

1) Applicability to Category Chronic 1
   Chronic 1 ingredient→ None
   Therefore, it is not classified in Chronic 1
2) Applicability to Category Chronic 2
   Chronic 1 ingredient or Chronic 2 ingredient→ None
   Therefore, it is not classified in Chronic 2.
3) Applicability to Category Chronic 3

Chronic 1 ingredient or Chronic 2 ingredient→ None

Chronic 3 ingredient→Result with summation formula applied: 20%, Ingredient Z: 80％

20%＋80%＝100% ＞ 25%

Therefore, it is classified in Chronic 3

4-3-2 Hazardous to the ozone layer

(1) Definitions

Definitions of hazardous to the ozone layer in UN GHS are as follows, and they are adopted in this guidance.

【UN GHS 4th revised edition】 (4.2.1)

Ozone Depleting Potential (ODP) is an integrative quantity, distinct for each halocarbon source species, that represents the extent of ozone depletion in the stratosphere expected from the halocarbon on a mass-for-mass basis relative to CFC-11. The formal definition of ODP is the ratio of integrated perturbation to total ozone, for a differential mass emission of a particular compound relative to an equal emission of CFC-11.

Montreal Protocol is the Montreal Protocol on Substances that Deplete the Ozone Layer as either adjusted and/or amended by the Parties to the Protocol.

(2) Classification criteria

A) Classification criteria according to Classification JIS

Chemicals shall be classified as hazardous to the ozone layer, Category 1 according to the following classification criteria:

"Any of the controlled substances listed in Annexes to the Montreal Protocol; or any mixture containing at least one ingredient listed in the Annexes to the Montreal Protocol, at a concentration ≥ 0.1%"

B) Classification criteria in UN GHS (reference information)

Classification JIS and UN GHS classification adopts the same classification criteria.

(3) Items on information sources and data

A) Requirements for data to be collected and utilized

Information about the controlled substances listed in the Annexes to the Montreal Protocol is available on the following website.

http://ozone.unep.org/new_site/en/Treaties/treaty_text.php?treatyID=2

http://www.env.go.jp/earth/ozone/montreal/Montreal_protocol.pdf

The chemical (a substance or mixture) shall be classified as Category 1 if it contains such a controlled substance at a concentration above 0.1%.

B) Comparison with conventional classification systems

Classification criteria in EU CLP and EU DSD, classification criteria correspond to those of Classification JIS and UN GHS.

A substance applicable to EU CLP H420 and R59 in EU DSD corresponds to Category 1 of Classification JIS and UN GHS.

(4) Classification of mixtures

Any mixture containing at least one ingredient listed in the Annexes to the Montreal Protocol, at a concentration ≥ 0.1% shall be classified as Category 1.

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 eyes
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 by inhalation, skin contact, and oral exposure
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
R59	Dangerous for the ozone layer
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 breast-fed babies
R65	Harmful: may cause lung damage if swallowed
R67	Vapours may cause drowsiness and dizziness
R68	Possible risk of irreversible effects

Note: Japanese translation was added/corrected in conformity with GHS Classification Guidance for the Japanese Government, 2010 edition.

EU CLP H statements used in this guidance

H300	Fatal if swallowed
H301	Toxic if swallowed
H302	Harmful if swallowed
H304	May be fatal if swallowed and enters airways
H310	Fatal in contact with skin
H311	Toxic in contact with skin
H312	Harmful in contact with skin
H314	Causes severe skin burns and eye damage
H315	Causes skin irritation
H317	May cause an allergic skin reaction
H318	Causes serious eye damage
H319	Causes serious eye irritation
H330	Fatal if inhaled
H331	Toxic if inhaled
H332	Harmful if inhaled
H334	May cause allergy or asthma symptoms or breathing difficulties if inhaled.
H335	May cause respiratory irritation
H336	May cause drowsiness or dizziness
H340	May cause genetic defects; harmful exposure route should be written in if it is conclusively proven that exposure through other route is not harmful.
H341	Suspected of causing genetic defects; harmful exposure route should be written in if it is conclusively proven that exposure through other route is not harmful.
H350	May cause cancer; harmful exposure route should be written in if it is conclusively proven that exposure through other route is not harmful.
H351	Suspected of causing cancer; harmful exposure route should be written in if it is conclusively proven that exposure through other route is not harmful.
H360	May damage fertility or the unborn child; details of effects should be written in, if known. Also, harmful exposure route should be written in if it is conclusively proven that exposure through other route is not harmful.
H361	Suspected of damaging fertility or the unborn child; details of effects should be written in, if known. Also, harmful exposure route should be written in if it is conclusively proven that exposure through other route is not harmful.
H362	May cause harm to breast-fed children
H370	Causes damage to organs; all names of organs likely to be affected should be written in, if known. Also, harmful exposure route should be written in if it is conclusively proven that exposure through other route is not harmful.

H371	May cause damage to organs; all names of organs likely to be affected should be written in, if known. Also, harmful exposure route should be written in if it is conclusively proven that exposure through other route is not harmful.
H372	Causes damage to organs through prolonged or repeated exposure; all names of organs likely to be affected should be written in, if known. Also, harmful exposure route should be written in if it is conclusively proven that exposure through other route is not harmful.
H373	May cause damage to organs through prolonged or repeated exposure; all names of organs likely to be affected should be written in, if known. Also, harmful exposure route should be written in if it is conclusively proven that exposure through other route is not harmful.
H400	Very toxic to aquatic life
H410	Very toxic to aquatic life with long lasting effects.
H411	Toxic to aquatic life with long lasting effects.
H412	Harmful to aquatic life with long lasting effects
H413	May cause long lasting harmful effects to aquatic life
H420	Destructive to the ozone layer and harmful to human health and the environment