

# **Technical Guidance Document on the GHS Classification**

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## Chapter-1 : Acute Toxicity

This technical guideline was prepared for those who perform classification for the 1,500 substances that are classified by the nation in preparation for implementing GHS domestically. The guideline assumes that the provisional work is carried out with limited time and resources. Therefore, it restricts the search for hazard information exclusively to the specified review documents; offers provisional methods when numerical values for classification criteria cannot be obtained and only qualitative descriptions are available; and presents easy methods which do not require experts in cases where the classification should be decided by an expert review of weight of evidence. Accordingly, note that the guideline does not show general principles to be observed when performing the classification in conformity with the GHS.

As for acute toxicity (fatal effect is the target in this case), the substance is classified in accordance with the main body of the GHS document. However, in the case where plural pieces of information are available, the substance shall be classified as follows.

Notes:

- \*1. When there is no information available for classifying a substance except for the EU Risk phrase, the substance shall be determined as “Classification not possible”.
- \*2. When there is only data for a mixture available for a substance (limited to the case where the substance is mixed/diluted by a solvent or the like without toxicity), GHS classification of the substance as a pure substance is performed by proper estimation from the concentration, and the process of the estimation is described.

### 1-1 Calculation in the case where there are plural descriptions related to acute toxicity:

When there are plural descriptions related to acute toxicity, the following formula is adopted. The description in Priority 1 has higher priority, and even when there are plural descriptions related to acute toxicity in Priority 2, if there is only one description related to acute toxicity in Priority 1, calculation shall be made using only the data of Priority 1.

1. Data shall be adopted by considering the species difference of the animals in Fig. 1.
2. For animals having a gender difference, the value of the gender having a smaller value is adopted as the acute toxicity value in the test, and when there are plural data, the value is used for calculation.
3. When there is no animal data available but there is a report of a human death case, conversion into the intake/exposure amount or the like for the weight of the dead is performed, then this is compared with the reference value of acute toxicity ( $ATE/LD_{50}/LC_{50}$ ) and GHS classification is performed. However, when sufficient information on the intake or the like in the human death case is not available, and the above concept cannot be applied, the substance is classified as “Categories 1 to 5”, and a description that this decision was made

(for example, “a case of death by oral intake is reported but the exposure level is not known”, etc.) is clearly made.

- 1) In the case where the number of data is N (three or more) and respective LD<sub>50</sub> (LC<sub>50</sub>) values are assumed to be x:

$$\text{Average value: } m = (x_1 + x_2 + \dots + x_N)/N$$

$$\text{Unbiased variance: } S^2 = \{(x_1 - \bar{x})^2 + (x_2 - \bar{x})^2 + \dots + (x_N - \bar{x})^2\} / (N - 1),$$

then the acute toxicity value is determined as follows:

$$LD_{50} (LC_{50}) = m - 1.64 \times S \div \sqrt{N}$$

In the case where the number of data is small and the variation in data is large, the formula cannot be applied and the calculated value sometimes becomes smaller than the lowest value of the data. In this case, the calculated value is abandoned, and the lowest value of the data shall be adopted.

- 2) In the case where the number of data is one or two:

The lower value (the value of the data with higher toxicity) is adopted.

Note: The above formula is expedient in this project in which all the acute toxicity values are regarded to have no reason for exclusion and to have equivalent reliability, and are processed semi-statically, and the study of the degree of reliability of the acute toxicity value itself (reliability of the test and evaluation method) is not performed, and is not the standard method of evaluating the acute toxicity.

## 1-2 Considerations in the case of evaluating the acute toxicity LC<sub>50</sub> in inhalation route

- 1) Values for inhalation toxicity are based on a 4-hour test in laboratory animals. Data are adopted based on the following criteria, and converted to the 4-hour test and calculated.
1. If 1-hour and 4-hour data are available, only the data are used, and calculation is performed. (1-hour data is converted to a 4-hour equivalent and calculated.)
  2. If the data corresponding to 1 hour is not available, data of 30 minutes to 24 hours are used, and calculation is performed.
  3. If the data corresponding to 1 and 2 are not available, the substance is determined 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 criteria value or below of Category 1 (determined by ATE/LC<sub>50</sub>) is classified as Category 1 (inhalation).

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

- Gas/vapor:  $D = B \sqrt{A} / \sqrt{C}$
- Dust/mist:  $D = BA/C$

\* In the case of performing GHS classification, enter 4 (hours) for C.

Conversion: When an experimental value is adopted from the 1-hour exposure test, it shall be converted into a 4-hour equivalent by dividing the 1-hour value by 2 in the case of gas and vapor, and by 4 in the case of dust and mist. The experimental values other than 1 hour are not described in the GHS text, but LC<sub>50</sub> in 4 hours necessary for deciding the GHS classification shall be obtained by using the following arithmetic expression.

*Note: The arithmetic expression is applied to this project only for convenience, and shall not be considered to be a general method with a recognized basis for evaluating acute toxicity. The propriety of applying convenient conversion for the above-described arithmetic expression is now under discussion in OECD HCL (WG of mixture gas), and the concept may change in future.*

- 2) In some cases it is not clear whether the adopted data is from the vapor inhalation test or mist inhalation test. In such cases, the substance shall be determined as “Classification not possible” except for the case where the substance is obviously concluded as either one from the physical properties such as vapor pressure and the like. The reason why the decision cannot be made is: “If the test condition is vapor, the substance is determined as Category ○○, and if it is mist, it applies to Category △△, but it cannot be determined whether it is vapor or mist, and so it is determined as “Classification not possible”<sup>6</sup>.
- 3) In some cases even if the substance is mist, LC<sub>50</sub> is described in ppm, or even it is gas, LC<sub>50</sub> is described in mg/L. In the estimation document, only the LC50 value is described, and the test conditions such as temperature are often not described. If accurate conversion cannot be made, conversion shall be done using the formula:

$\text{ppm} \doteq \text{mg/L} \times 1000 \times 24.45 / \text{molecular weight (in the case of converting at 1 atmospheric pressure, 25}^\circ\text{C)}$

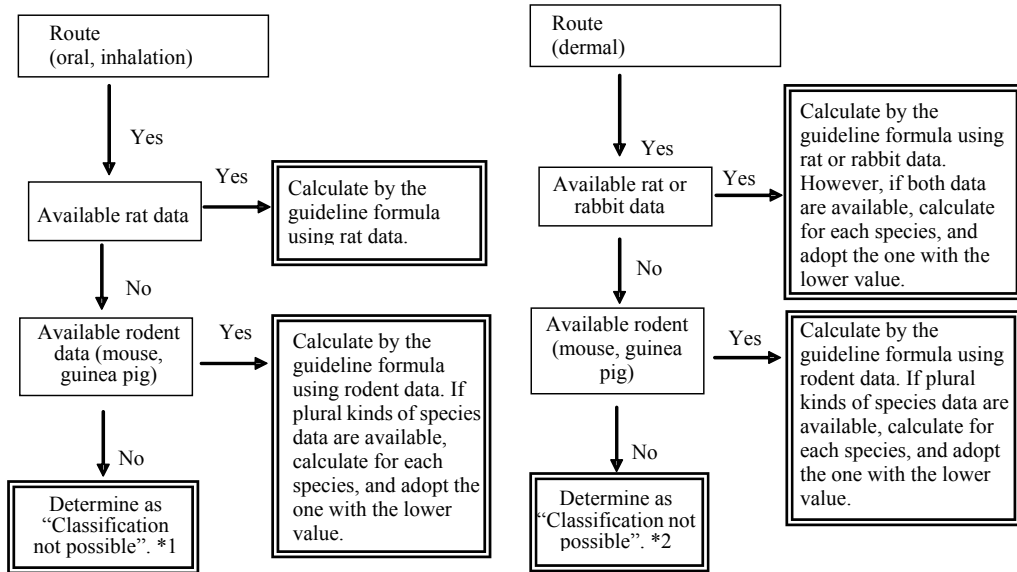
### **1-3 Considerations for handling GHS classification criteria newly added by the committee of the United Nations in December, 2004**

As for GHS, the following two points were revised:

1. Definitions of dust, mist and vapor were added.
2. In inhalation toxicity, if there is evidence indicating corrosiveness of the respiratory tract, estimation related to corrosiveness can be performed.

As for 2 above, if the description mentioning corrosiveness and the fact that the target substance itself is corrosive are specifically known, they must be described as such without fail.

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



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

\*2 Data other than rodent and rabbit data are not adopted for classification, but are described in the input sheet for future reference.

## **Chapter-2 : SKIN CORROSION/IRRITATION**

This technical guideline was prepared for those who perform classification for the 1,500 substances that are classified by the nation in preparation for implementing GHS domestically. The guideline assumes that the provisional work is carried out with limited time and resources. Therefore, it restricts the search for hazard information exclusively to the specified review documents; offers provisional methods when numerical values for classification criteria cannot be obtained and only qualitative descriptions are available; and presents easy methods which do not require experts in cases where the classification should be decided by an expert review of weight of evidence. Accordingly, note that the guideline does not show general principles to be observed when performing the classification in conformity with the GHS.

As for serious skin corrosion, there are clear decision criteria in GHS, and classification shall be made in accordance with the flow of decision logic 3.2.1 of GHS, while referring to the technical advice for the decision method according to the existing test data, as described below.

As for the subdivision of corrosion, classification can be made only when animal testing is conducted with exposed time and observation period to which the decision of corrosion of GHS (GHS Table 3.2.1) can be applied. Therefore, subdivision can be made only in such cases; otherwise, subdivision is not made.

Notes:

- \*1. When there is no information available for classifying a substance except for the EU Risk phrase, the substance shall be determined as “Classification not possible”.
- \*2. When there is only data for a mixture available for a substance, the mixture itself shall be classified, and this shall be stated as such in “Basis”.
- \*3. Regarding “Not classified”, unless there is definitely no hazard or an extremely low hazard is described, a decision of “Not classified” shall be made carefully. If there is any doubt, “Classification not possible” should be chosen due to lack of sufficient information for making a decision.
- \*4. In the case where subdivision cannot be made, “1A-1C” shall be described in “Model GHS Classification”.

### **2-1 Decision by reliable existing exposure experience**

When a substance has an example of corrosion (Category 1A-1C) or irritation (Category 2) in human or animal results, the substance shall be classified as such. (Example: Accidental event, a non-GLP test result, etc.)

### GHS 3.2.1 Definition (extract)

Skin corrosion means the production of irreversible damage to the skin. Namely, it is visible necrosis through the epidermis and into the dermis following the application of a test substance for up to 4 hours.

Skin irritation is the production of irreversible damage to the skin following application of the test substance for up to 4 hours.

## 2-2 Decision based on reliable existing data

### 2-2-1 Decision by in vivo test result

**Corrosion:** (any of Categories 1A, 1B and 1C, or Categories 1A-1C)

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

- 1) Necrosis into the dermis
- 2) Ulcer, bleeding, and bloody scabs in the applied area
- 3) Blanching of the skin, complete areas of alopecia and remaining scars are seen at the end of the observation period of 14 days.
- 4) In the case of erythema/eschar or edema score of 4 or more, the substance is determined as Category 1A-1C (however, in the case where no irreversible lesion is observed, the substance is determined as Category 2).

**Irritation: (Category 2)**

At 24, 48 and 72 hours from application

- 1) Mean value of Draize Score (for each animal) is  $\geq 2.3$  to 4.0 for erythema/eschar or edema in 2 of 3 tested animals)
- 2) Inflammation and alopecia, limited area, hyperkeratosis, hyperplasia, and scaling persist to the end of 14 days after application
- 3) Definite positive effects are recognized in a single animal, but less than the criteria of corrosion (In the case of a pronounced variability of response among animals, with a definite lesion recognized at the end of the observation period in only 1 of 3 tested animals).

Mild irritation: (Category 3)

At 24, 48 and 72 hours after application

- 1) Mean value of Draize Score (for single animal) is  $\geq 1.5$  to 2.3 for erythema/eschar or edema in 2 of 3 tested animals.

### 2-2-2 Decision by comparison with existing classification

- The substance classified as Severe or Corrosive is determined as corrosive (Categories 1A-1C). (However, the substance classified as Severe with no irreversible lesion observed is determined as Category 2.)
- The substance classified as Moderate is determined as irritant (Category 2).

- The substance classified as Mild is determined as mild irritant (Category 3).

### **2-2-3 Decision by symptom (in the case when no other information is available)**

- When described as Necrosis, the substance is determined as corrosive (Categories 1A-1C).
- When a substance has repeated descriptions of erythema, inflammation, and discoloration, the substance is determined as irritant (Category 2). When a substance has the single description of erythema, inflammation, and discoloration, but as a definite indication, the substance is determined as irritant (Category 2).

### **2-3 Decision by structure-activity correlation or structure-property correlation**

In this project, this shall not be considered at all. However, if there is a description that the substance is determined as applicable by the analysis of the structure-activity correlation in the assessment document of Priority 1, the substance is classified based on the result.

### **2-4 Decision by physico-chemical properties**

In the case of  $\text{pH} \leq 2, \geq 11.5$ , the substance is classified as corrosive (Categories 1A-1C) (determined with buffer capacity also taken into consideration. (Booman et al. (1989) proposed 0.2 meg HCL/g in eye irritation.)

### **2-5 Decision by in vitro testing method:**

If the data of testing based on OECD TG431 (human skin model Epiderm), TG430 (skin electric conductivity test) is available, the substance is classified in accordance with the decision criteria with which it is validated at each of the tests. The other in vitro tests are not considered.

## **Chapter-3 : SERIOUS EYE DAMAGE/EYE IRRITATION**

This technical guideline was prepared for those who perform classification for the 1,500 substances that are classified by the nation in preparation for implementing GHS domestically. The guideline assumes that the provisional work is carried out with limited time and resources. Therefore, it restricts the search for hazard information exclusively to the specified review documents; offers provisional methods when numerical values for classification criteria cannot be obtained and only qualitative descriptions are available; and presents easy methods which do not require experts in cases where the classification should be decided by an expert review of weight of evidence. Accordingly, note that the guideline does not show general principles to be observed when performing the classification in conformity with the GHS.

As for serious eye damage or irritation, there are clear decision criteria in GHS, and classification shall be made in accordance with the flow of decision logic 3.3.1 of GHS, while referring to the technical advice for the decision method according to the existing test data, as described below.

As for the subdivision of irritation, classification can be made only when the test is performed on a rabbit by the Draize method to which the decision of eye irritation of GHS (GHS Table 3.2.2) is applicable, and the observation result in seven days or the recovery term is clearly described. Therefore, subdivision can be made only in such cases; otherwise, subdivision is not made.

Notes:

- \*1. When there is no information available for classifying a substance except for the EU Risk phrase, the substance shall be determined as “Classification not possible”.
- \*2. When there is only data for a mixture available for a substance, the mixture itself shall be classified, and this shall be stated as such in “Basis”.
- \*3. Regarding “Not classified”, unless there is definitely no hazard or an extremely low hazard is described, a decision of “Not classified” shall be made carefully. If there is any doubt, “Classification not possible” should be chosen due to lack of sufficient information for making a decision.
- \*4. In the case where subdivision cannot be made, “1A-1C” shall be described in “Model GHS Classification”.

### **3-1 Decision by reliable existing exposure experience:**

In the case where a substance has a case example of serious eye damage (Category 1) or irritancy (Category 2A-2B) in a human or animal experience, the substance shall be classified as such. In the case where a substance has a case example of skin corrosion in a human or animal experience, the substance shall be classified as a substance leading to serious eye damage (Category 1). (Example: An accidental event, a non-GLP test result, etc.)

#### GHS 3.3.1 Definition (extract)

Serious eye damage is the production of tissue damage in the eye, or serious physical decay of vision, following application of the 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 application of the test substance to the anterior surface of the eye, which are fully reversible within 21 days of application.

### **3-2 Decision based on reliable existing data:**

#### **3-2-1 Decision by in vivo test (Draize test) result**

##### **Decision criteria of 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 average values of the scores following grading at 24, 48 and 72 hours after installation of the test material are 3 or more in corneal opacity, and more than 1.5 in iritis

##### **Decision criteria of irritant (reversible effects) (Category 2A, 2B, or 2A-2B):**

- In the Draize test conducted using 3 animals, the average values of the scores following grading at 24, 48 and 72 hours after installation of the test material in two or more animals are 1 or more in corneal opacity, 1 or more in iritis, 2 or more in conjunctival redness and 2 or more in conjunctival edema.
- The effects are fully reversed within an observation period of 21 days.
- The substance is classified as mildly irritating to the eye (Category 2B) when the above description applies to the substance and the effect reverses within 7 days.

#### **3-2-2 Decision by existing classification:**

- The substance which is classified as Severe or Corrosive (very strong irritation or corrosiveness corresponding to AOI 80 or more) is classified as Category 1 (however, when irreversible lesion is not observed, the substance is determined as irritating to the eye (Category 2A)).
- The substance which is classified as Moderate (strong irritation corresponding to AOI 30–80) is classified as Category 2A.
- The substance which is classified as Mild is classified as Category 2B.

### **3-3 Decision by structure-activity correlation or structure-property correlation:**

In this project, this shall not be considered at all. However, if there is a description that the substance is determined as applicable by the analysis of the structure-activity correlation in the assessment document of Priority 1, the substance is classified based on the result.

**3-4 Decision by physico-chemical properties:**

In the case of  $\text{pH} \leq 2, \geq 11.5$ , the substance is classified as Category 1 (determined with buffer capacity taken into consideration (Booman et al. (1989) proposed 0.2 meg HCL/g in eye irritation).

**3-5 Decision by in vitro testing method:**

No internationally recognized method is available yet, and therefore it shall not be considered in this project.

## Chapter-4 : SENSITIZATION

This technical guideline was prepared for those who perform classification for the 1,500 substances that are classified by the nation in preparation for implementing GHS domestically. The guideline assumes that the provisional work is carried out with limited time and resources. Therefore, it restricts the search for hazard information exclusively to the specified review documents; offers provisional methods when numerical values for classification criteria cannot be obtained and only qualitative descriptions are available; and presents easy methods which do not require experts in cases where the classification should be decided by an expert review of weight of evidence. Accordingly, note that the guideline does not show general principles to be observed when performing the classification in conformity with the GHS.

Notes:

- \*1. When there is no information available for classifying a substance except for the EU Risk phrase, the substance shall be determined as “Classification not possible”.
- \*2. When there is only data for a mixture available for a substance, the mixture itself shall be classified, and this shall be stated as such in “Basis”.
- \*3. Regarding “Not classified”, unless there is definitely no hazard or an extremely low hazard is described, a decision of “Not classified” shall be made carefully. If there is any doubt, “Classification not possible” should be chosen due to lack of sufficient information for making a decision.

### 4-1 Classification Procedure

#### 4-1-1 Respiratory Sensitization

Substances applicable to Decision Criteria 1 or Decision Criteria 2 are determined as Category 1.

**Decision Criteria 1: If there is evidence that the substance induces respiratory hypersensitivity by inhalation and exposure to humans, and if the substance is concluded as positive in any assessment document of Priority 1 (“is concluded” does not mean “is suggested”, or “has the possibility”, but is definitely stated to be obviously positive)**

#### Exclusion Rule

When the substance is applicable to Decision Criteria 1, and when it is proved that the substance induces asthma in only those who have bronchial hypersensitivity, the substance is determined as “Not classified”.

**Decision Criteria 2: If the substance is listed by the following academic societies**

Japanese Society of Occupational Allergy Special Committee (2004) “Guideline (proposal) on the Prevention of Occupational Allergy Disease”, Japanese Society of Occupational Allergy Journal 12(1): pp. 95–97

**\* As there is no animal test currently recognized internationally, it is only used for reference in this project, and is not used as a basis for deciding the GHS classification.**

#### **4-1-2 Skin Sensitization**

Substances applicable to any of Decision Criteria 1 to Decision Criteria 4 are classified as Category 1.

**Decision Criteria 1: If there is evidence that the substance induces hypersensitivity by skin contact in humans, and if the substance is concluded as positive in any assessment document of Priority 1**

**Decision Criteria 2: If there is an epidemiological study report showing allergic contact dermatitis caused by the substance, or if there are two or more case reports of allergic contact dermatitis from separate medical institutions, of Priority 1 or Priority 2**

**Decision Criteria 3: If a substance is listed by the following academic societies**

Japanese Society of Contact Dermatitis lists substances having skin sensitization from actual case reports in humans.

[http://www.fujita-hu.ac.jp/JSCD/all\\_folder/text\\_folder/contents\\_06.html#1](http://www.fujita-hu.ac.jp/JSCD/all_folder/text_folder/contents_06.html#1)

**Decision Criteria 4: If a positive result is obtained in the following animal tests**

○ Positive Decision Criteria

The case of using adjuvant: 30% of animals or more react

The case of not using adjuvant: 15% of animals or more react

\* The ratio of sensitized animals is often not clear. If the substance is clearly concluded to include skin sensitization in Priority 1 with the test as the basis even though the ratio is unknown, the substance is determined as Category 1.

\* As for Priority 2, if the animal test was performed by the testing method shown below, the ratio of sensitized animals is clear, and the substance is concluded as positive in skin sensitization, then the substance shall be classified as Category 1. In all other cases, the substance shall be classified as “Classification not possible” even if the test was carried out.

- Animal tests on skin sensitization (approved by OECD)

OECD guideline	Name of test	Animal	Adjuvant use/nonuse
406	Maximization Test (Magnusson and Kligman)	Guinea pig	Used
406	Buehler Test	Guinea pig	Not used
429	LLNA (Local Lymph Node Assay)	Mouse	Not used

- Other typical animal tests on skin sensitization are cited.

Name of test	Animal	Adjuvant use/nonuse
Mouse Ear Swelling Test (MEST)	Mouse	Not used
Adjuvant and Patch Test	Guinea pig	Used
Draize Test	Guinea pig	Not used
Freund's Complete Adjuvant Test	Guinea pig	Used
Open Epicutaneous Test	Guinea pig	Not used
Optimization Test	Guinea pig	Used
Split Adjuvant Test	Guinea pig	Used

## **Chapter-5 : GERM CELL MUTAGENICITY**

This technical guideline was prepared for those who perform classification for the 1,500 substances that are classified by the nation in preparation for implementing GHS domestically. The guideline assumes that the provisional work is carried out with limited time and resources. Therefore, it restricts the search for hazard information exclusively to the specified review documents; offers provisional methods when numerical values for classification criteria cannot be obtained and only qualitative descriptions are available; and presents easy methods which do not require experts in cases where the classification should be decided by an expert review of weight of evidence. Accordingly, note that the guideline does not show general principles to be observed when performing the classification in conformity with the GHS.

Notes:

- \*1. When determination by the technical guideline is difficult, an expert's decision shall be sought.
- \*2. When there is no information available for classifying a substance except for the EU Risk phrase, the substance shall be determined as "Classification not possible".
- \*3. When there is only data for a mixture available for a substance, the mixture itself shall be classified, and this shall be stated as such in "Basis".
- \*4. Regarding "Not classified", unless there is definitely no hazard or an extremely low hazard is described, a decision of "Not classified" shall be made carefully. If there is any doubt, "Classification not possible" should be chosen due to lack of sufficient information for making a decision.

As for germ cell mutagenicity, the substances shall be classified in accordance with the flow of the determination theory of the GHS system with reference to the GHS text and the following technical guideline.

In the present GHS classification project, if only in vitro mutagenicity test data is available, the substance shall be determined as "Classification not possible" in principle (refer to 2. Item 5)).

### **5-1 Data Used for Classification and Explanation**

- 1) The GHS classification primarily concerns chemicals that cause mutation in germ cells in humans that can be transmitted to progeny. In this guideline, to facilitate understanding, the terminology "heritable mutagenicity" is used in addition to "germ cell mutagenicity". "Germ cell mutagenicity" refers to an effect that induces mutagenicity/genotoxicity in germ cells, and "heritable mutagenicity" refers to an effect that the mutagenicity admitted in the germ cell induces gene mutation or chromosomal aberration. In the GHS text, the term "heritable mutagenicity" is not used, and as the corresponding phrase, "to induce heritable mutations in germ cells of humans" is used.

- 2) In GHS, “mutagenicity tests” and “genotoxicity tests” are properly used. “Mutagenicity tests” correspond to the tests with chromosomal aberration, the structure of chromosome or numeral chromosome aberration as the indicator, and “genotoxicity tests” correspond to the tests with other factors, such as DNA damage and DNA repair, as the indicator. There are many kinds of mutagenicity tests or genotoxicity tests, and GHS gives the tests used as criteria for determining whether the substances are those which induce heritable mutagenicity in humans or not. Table 1 shows the test data as the basis for classification with some tests added in addition to the examples of GHS.
- 3) At the starting point of the determination tree of GHS 3.5.5.1, “Decision Logic of Substances 3.5.1”, “Does the substance have data on mutagenicity?” is written, and the data on mutagenicity here means mutagenicity tests or genotoxicity tests in vivo which are generally used in principle, and are usually available as the data set including tests in vitro.
- 4) Although a number of mutagenicity or genotoxicity test results including tests in vitro have been reported for many chemicals, few tests in vivo on mammalian germ cells have been reported.
- 5) Data on humans are variable, but data obtained by monitoring a human exposed to a certain chemical (for example, chromosome analysis of human peripheral lymph corpus) often does not clearly show the effect of the chemical itself, and so the use of such data is extremely limited. In epidemiologic data, contradicting results are sometimes obtained, but when positive information (desirably plural pieces of information) is contained in the epidemiologic data adopted in the evaluation document of Priority 1, the information is adopted providing no other refuting information is found.
- 6) There are more chemicals for which only in vitro test data has been obtained than chemicals for which data sets of in vivo and in vitro tests have been obtained. It is usually difficult to determine the presence or absence of the possibility of heritable mutagenicity of humans from only the results of in vitro test data.
- 7) A sperm malformation test using rodents is not used for classification in principle, since sperm malformation is sometimes due to effects on materials other than genetic material.
- 8) Various tests using drosophila (X-linked recessive fatality test, bristle spot test, etc.) are not used for classification in principle since the body dynamics and reproductive and developmental processes of chemicals differ between insects and mammals. However, when no other in vivo mutagenicity/genotoxicity test data is available, and a positive result is obtained especially in the X-linked recessive fatality test using drosophila, experts shall judge the pros and cons of its use and the GHS classification category.
- 9) There are a number of in vitro genotoxicity tests (comet test using mammalian cultured cells, UDS test using mammalian cultured cells, DNA repair test (Rec-assay) using grass bacillus, umu test using Salmonella typhimurium, SOS test using colon bacillus,

chromosome aberration including aneuploidy test using yeast/gene conversion, etc.) and the host-mediated test (host-mediated assay), but these test results are not used for classification.

10) Various routes of administration are used for in vivo mutagenicity/genotoxicity tests, and provided the appropriateness of the routes of administration is logically explained, any route of administration may be used.

## 5-2 Decision Criteria Related to Classification

Examples of the test results corresponding to the respective GHS categories are shown below and the classification flow is shown in Appendix 1 to facilitate classification. This flow basically gives priority to a positive result in each test. A negative result is sometimes caused by only one indicator out of a number of indicators, and is sometimes caused by a test not being performed properly, and its accuracy is difficult to evaluate.

### 1) Category 1A: In the case of epidemiological evaluation in germ cells of humans

When human heritable mutagenicity is recognized by a human epidemiological study, the substance is classified as Category 1A. However, at present, the existence of such a substance is not confirmed.

### 2) Category 1B: In the case where vivo mutagenicity test data is available, and information suggesting mutagenicity of germ cells

Positive results have been obtained in many test methods including in vivo tests, and substances which should be considered to show heritable mutagenicity in humans are determined as Category 1B. Specifically, the following cases apply:

2-1) Positive results in **Heritable mutagenicity tests in germ cells using mammals** (dominant lethal test using rodents, mutual translocation test using mice, specific locus test using mice, etc.)

2-2) Positive results in **Mutagenicity tests in germ cells using mammals** (chromosome aberration test using mammalian spermatogonia, micronucleus test using mammalian sperm cells, gene mutation test in germ cells using transgenic mice/rats, etc.)

2-3) In the case where the substance is positive in the **somatic cell mutagenicity test using mammals** (chromosome aberration test using mammalian bone marrow cells, micronucleus test using mammalian red blood cells, mouse spot test, etc.), **and** there is some evidence that the substance may show mutagenicity in germ cells. For example, a positive result in in vivo genotoxicity tests using germ cells (Sister Chromatid Exchanges (SCE) test using mammalian spermatogonia, an unscheduled DNA synthesis (UDS) test using mammalian testis, etc.), evidence of exposure of the substance showing activity or metabolite to germ cells, etc.

2-4) In the case where there are **positive results showing mutagenicity in human germ cells** though no evidence of influence on the next generation. For example, an

increase in the frequency of occurrence of heteroploidy in human sperm to which the substance is exposed, etc.

**3) Category 2: In the case where in vivo mutagenicity/genotoxicity data is available, but there is no direct information suggesting mutation of germ cells**

The substances which are suspected of inducing human heritable mutagenicity are determined as Category 2. For example, the following cases apply:

- 3-1)** Positive results in **somatic cell mutagenicity tests using mammals** (chromosome aberration test using mammalian bone marrow cells, micronucleus test using mammalian red blood cells, mouse spot test, etc.)
- 3-2)** In the case of positive results in **somatic cell genotoxicity tests using mammals** (Unscheduled DNA Synthesis (USD) test using mammalian liver, Sister Chromatid Exchanges (SCE) using mammalian bone marrow, etc.), **and** positive results in a **mutagenicity test in vitro** (chromosome aberration test using mammalian cultivated cells, gene mutation test using mammalian cultivated cells, reverse mutation test using bacteria, etc.)
- 3-3)** In the case where exceptionally, a strong positive result in the in vitro mutagenicity test with plural indicators is obtained even though no test data is available, and the substance shows (strong) similarity in chemical structure to the known germ cell mutagenicity substance (Category 1, namely, the heritable mutagenicity substance) (Refer to 2. Item 5), seek the decision of the expert.

**4) (Not classified): In the case where in vivo mutagenicity test data is available, and the substance is negative**

The substances which are not classified as Category 1A, 1B or Category 2 though the data necessary for classification (basically, in vivo mutagenicity) is available are determined as “Not classified”. For example, the following cases apply:

- 4-1)** When the substance is negative in human heritable epidemiology data, heritable mutagenicity test, or in vivomutagenicity test (somatic cells or germ cells)

**5) Cannot be classified (Classification not possible): When mutagenicity data necessary for classification is not available**

- 5-1)** It is difficult to estimate human heritable mutagenicity from only the results of in vitro mutagenicity tests. Accordingly, when only in vitro mutagenicity test data is available, the substance is determined as “Classification not possible” in principle.
- 5-2)** Exceptionally, substances showing strong positivity in the mutagenicity test of plural indicators (for example, a chromosome aberration test using mammalian cultivated cells, and a reverse mutation test using bacteria) are sometimes properly classified as Category 2, and therefore, the decision of an expert should be sought.
- 5-3)** When the substance is negative in the in vivo genotoxicity test, but negative data of in vivo mutagenicity is not available. This is because even if it has the negative support

of in vitro mutagenicity, this is not determined as sufficient information to clearly deny (namely, “Not classified”) the mutagenicity effect in vivo (resultantly, germ cells).

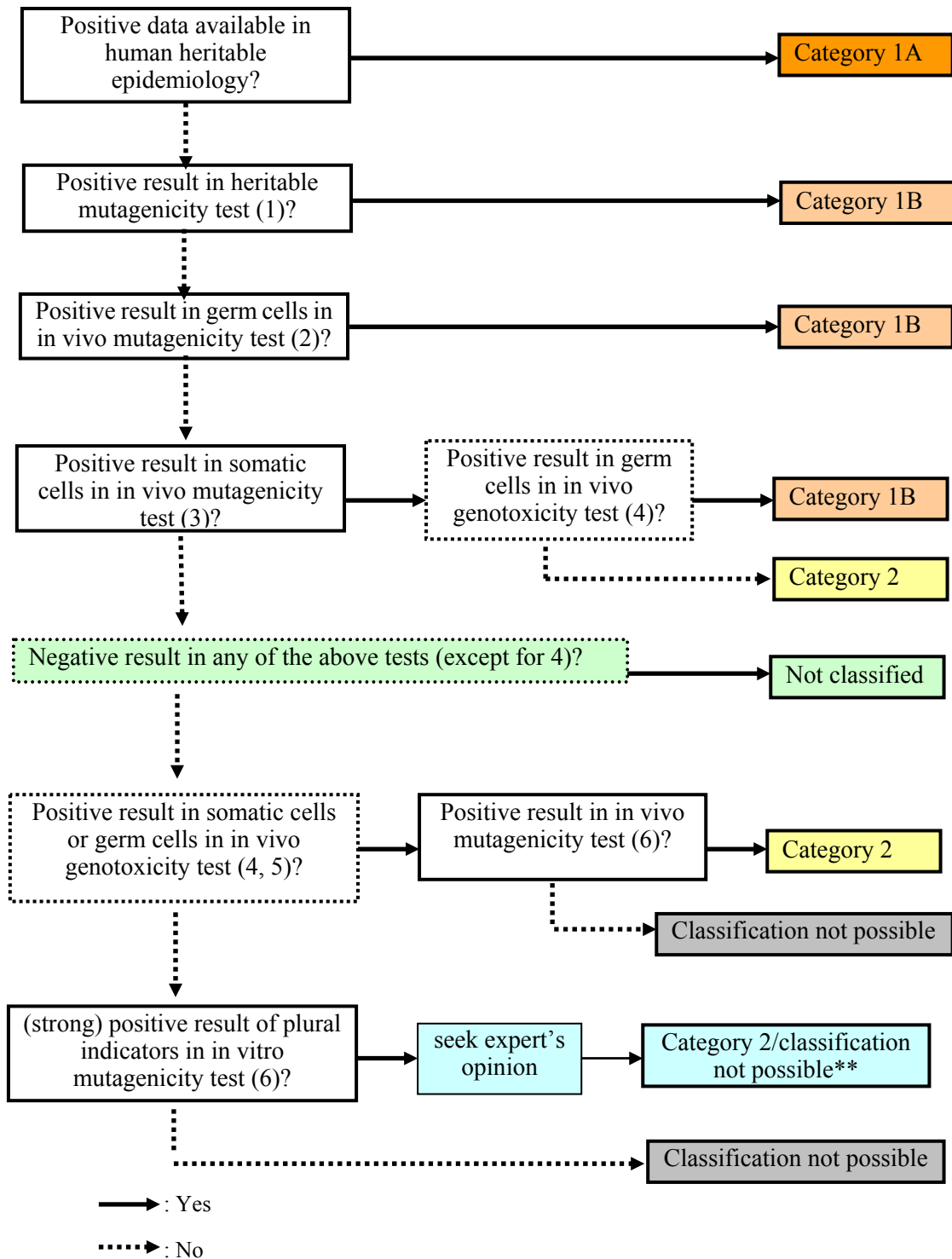
**Table 5-1 Test data as the basis of GHS classification (\*: Added to GHS examples)**

<p><b>(1) Examples of in vivo heritable mutagenicity test using germ cells</b> dominant lethal test using rodents mutual translocation test using mice specific locus test using mice</p> <p><b>(2) Examples of in vivo mutagenicity test using germ cells</b> chromosome aberration test using mammalian spermatogonia micronucleus test using mammalian sperm cells germ cell gene mutation test using transgenic mice/rats* analysis of heteroploidy in human sperm</p> <p><b>(3) Examples of in vivo mutagenicity test using somatic cells</b> chromosome aberration test using mammalian bone marrow cells mouse spot test micronucleus test using mammalian red blood cells chromosome/micronucleus analysis in human peripheral lymph corpuscles (human monitoring analysis)* chromosome aberration test using mammalian peripheral lymph corpuscles* gene mutation test in somatic cells using transgenic mice/rats*</p> <p><b>(4) Examples of in vivo genotoxicity test using germ cells</b> Sister Chromatid Exchanges (SCE) test using mammalian spermatogonia Unscheduled DNA Synthesis (UDS) test using mammalian testis cells (covalent) bond test with mammalian germ cell DNA and adduct formation test* DNA damage test in mammalian germ cells (comet test, dissolution test for alkali, etc.)*</p> <p><b>(5) Example of in vivo genotoxicity test using somatic cells</b> Unscheduled DNA Synthesis (UDS) test using mammalian liver Sister Chromatid Exchanges (SCE) test using mammalian bone marrow cells (covalent) bond test with mammalian somatic cells DNA and adduct formation test* DNA damage test in mammalian somatic cells (comet test, dissolution test for alkali, etc.)*</p> <p><b>(6) Example of in vitro mutagenicity test</b> chromosome aberration test using mammalian cultivated cells micronucleus test using mammalian cultivated cells* gene mutation test using mammalian cultivated cells reverse mutation test using bacteria</p>
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**Tests not used for classification in principle:** Sperm malformation test using rodents (refer to 1. Item 7)), various tests using drosophila (refer to 1. Item 8))

**Tests not used for classification:** **In vitro genotoxicity tests (comet test using mammalian cultivated cells, UDS test using mammalian cultivated cells, DNA repair test using grass bacillus (Rec-assay), umu test using Salmonella typhimurium, SOS test using colon bacillus, various tests using yeast, etc.), and host-mediated assay (refer to 1. Item 9))**

## Appendix 1 Germ Cell Mutagenicity Classification Flow in GHS



\* Number of each test corresponds to each test number.

\*\* Classified as either “Category 2” or “Classification not possible” in accordance with expert’s decision.

## Chapter-6 : CARCINOGENICITY

This technical guideline was prepared for those who perform classification for the 1,500 substances that are classified by the nation in preparation for implementing GHS domestically. The guideline assumes that the provisional work is carried out with limited time and resources. Therefore, it restricts the search for hazard information exclusively to the specified review documents; offers provisional methods when numerical values for classification criteria cannot be obtained and only qualitative descriptions are available; and presents easy methods which do not require experts in cases where the classification should be decided by an expert review of weight of evidence. Accordingly, note that the guideline does not show general principles to be observed when performing the classification in conformity with the GHS.

Notes:

- \*1. When decision by the technical guideline is difficult, an expert's decision shall be sought.
- \*2. When there is only data for a mixture available for a substance, the mixture itself shall be classified, and this shall be stated as such in "Basis".
- \*3. Regarding "Not classified", unless there is definitely no hazard or an extremely low hazard is described, a decision of "Not classified" shall be made carefully. If there is any doubt, "Classification not possible" should be chosen due to lack of sufficient information for making a decision.

### 6-1 Substances for which GHS classification can be decided without an expert's decision

For substances classified in accordance with the following, it is considered that the GHS classification can be decided without an expert's decision.

- 1) Substances already evaluated by the following agencies are subjected to GHS classification in accordance with the correspondence table of Table 1. Though the assessment of IARC is given priority, if a substance has plural assessment documents and its decision category differs among them, then the substance is classified in accordance with the latest assessment documents in principle. However, if the latest assessment documents have plural decision categories and GHS classification cannot be made (for example, EPA, NTP, etc.), then classification shall be properly made with reference to the past evaluation documents (an expert's decision is sought as necessary).

Example: When a substance is determined as K/L in the EPA classification (1998), and as 2A in the IARC classification (1998), it is determined as 1B in the GHS classification.

(Reference document: "Carcinogenicity assessment of chemical substances and their classification criteria (sixth version)", JETOC special data No. 190 (2004))

- International Agency for Research on Cancer (IARC)
- Japan Society for Occupational Health

- American Conference of Governmental Industrial Hygienists (ACGIH)
- US Environmental Protection Agency (EPA)
- US National Toxicology Program (NTP)
- European Union (EU)

**Table 6-1 Correspondence table of GHS classification and classifications of other agencies (Carcinogenicity)**

GHS	IARC	Japan Society for Occupational Health	ACGIH	EPA 1986	EPA 1996	EPA 2005	NTP	EU
1A	1	1	A1	A	K/L	CaH	K	1
1B	2A	2A	A2	B1		L	R	2
2	2B	2B	A3	B2		S		3
Not classified	3		A4	C, D	CBD	I		
	4		A5	E	NL	NL		

\* When carcinogenicity classification is performed in accordance with Table 1, data may not be entered into other items such as toxicity information or epidemiological/occupational exposure.

- 2) When a substance is definitely determined as “Classification not possible” due to the absence of information under Table 1 and inadequacy of other hazard information

## 6-2 Substances requiring expert’s decision

As for substances that are difficult to determine and that cannot be determined in accordance with 1) and 2) above, all the descriptions regarding carcinogenicity cited in the assessment documents shall be gathered and an expert’s decision shall be sought.

- 1) In Priority 1 (except for the assessment documents cited in 1. 1)), descriptions related to carcinogenicity, or descriptions suggesting carcinogenicity
- 2) In Priority 2 and Priority 3, only the descriptions shown below. The rule of 2) does not prevent those who implement classification from presenting the documents and descriptions which they consider to be materials as a basis for making a decision.
  - Description made in a section clearly categorized as “carcinogenic” (for example, the category of Carcinogenicity in “RTECS”)
  - Description confirming the occurrence of a tumor after conducting histopathological inspection in a long-term administration test in animals (or a description clearly mentioning the presence or absence, or suggestion of carcinogenicity or tumor)
  - Epidemiological studies in human groups

## **Chapter-7 : REPRODUCTIVE TOXICITY**

This technical guideline was prepared for those who perform classification for the 1,500 substances that are classified by the nation in preparation for implementing GHS domestically. The guideline assumes that the provisional work is carried out with limited time and resources. Therefore, it restricts the search for hazard information exclusively to the specified review documents; offers provisional methods when numerical values for classification criteria cannot be obtained and only qualitative descriptions are available; and presents easy methods which do not require experts in cases where the classification should be decided by an expert review of weight of evidence. Accordingly, note that the guideline does not show general principles to be observed when performing the classification in conformity with the GHS.

The classification results of reproductive toxicity shall be checked by an expert except for that of “Classification not possible”.

Notes:

- \*1. When there is no information available for classifying a substance except for the EU Risk phrase, the substance shall be determined as “Classification not possible”.
- \*2. For all the assessment documents in Priority 1, the presence and absence of descriptions related to the examined substance shall be checked without fail. If there are a number of similar descriptions, not all of the descriptions of the assessment documents need be transferred to the CERI input sheet.
- \*3. Regarding “Not classified”, unless there is definitely no hazard or an extremely low hazard is described, a decision of “Not classified” shall be made carefully. If there is any doubt, “Classification not possible” should be chosen due to lack of sufficient information for making a decision.

### **7-1 Definitions and General Considerations**

#### **“Reproductive Toxicity”**

Regarding reproductive toxicity, GHS covers the toxicity for sexual function and fertility of adult males and females, and development of offspring.

#### **“Adverse effect on sexual function or fertility”**

Any effect of chemicals that could interfere with sexual function or fertility. This includes alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete reproduction and transport, reproductive cycle normality, fertility and parturition, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive system.

#### **“Adverse effect on development of offspring”**

In its broadest sense, development toxicity includes any effect which interferes with normal development of the conceptus, either before or after birth. However, for the purpose of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure.

## **7-2 Decision Logic and Classification of Substances**

### **1) Decision Logic of Substances**

Decisions are taken for substances in accordance with “Globally Harmonized System of Classification and Labeling of Chemicals (GHS)” (temporary translation of liaison conference of the ministry concerned, April 2004, p. 184, 3.7.5 Decision logic for reproductive toxicity).

### **2) Classification**

**In principle, information shall be collected in accordance with the classification manual produced by the authorities concerned, and substances shall be classified in accordance with the collected data.**

#### **Substance determined as “Classification not possible”**

A substance is determined as “Classification not possible” when data on reproduction toxicity regarding the substance is not available.

#### **Substances to be classified**

##### **Category 1A: Substances known to have adverse effect on human sexual function, fertility or development of offspring**

(Determination criteria)

Substance which is clearly described as recognized to have reproductive toxicity in humans in the information of Priority 1.

\* When other substances are considered to fall under Category 1A, an expert’s decision shall be sought.

\* When the substance is applicable to the following [Substance requiring caution on classification], and information sufficiently proving that the substance falls under Category 1A is not obtained as a result of investigating documents based on the classification manual, an expert’s decision shall be sought.

##### **Category 1B: Substance presumed to have adverse effect on human sexual function, fertility or development of offspring**

(Determination Criteria)

Substances which meet the following two conditions. However, substances corresponding to “Not classified” are excluded.

(1) Substance for which it is described that clear reproduction toxicity \*(excluding small changes in sperm measurement items, incidence of spontaneous defects in fetus, variant/ossification retardation, fetal/pup body weight, and postnatal developmental assessments) is manifested when taken at a dosage which does not indicate general toxicity (not only maternal toxicity, but also effects except for reproduction toxicity on female and male parental animals; the same shall apply hereinafter) in parental animals in animal experiments in the information of Priority 1.

\*The reproduction toxicity here means reproduction toxicity defined in 1. Namely, it means effects on parental sexual function and fertility, and development. The same applies in this guideline.

**Category 2: Substances suspected to have toxicity for human reproduction/development**

(Determination Criteria)

Substances which meet any of the following conditions in the information of Priority 1 or Priority 2. However, substances corresponding to “Category 1” and “Not classified” are excluded.

(1) Substance for which it is described that clear reproduction toxicity (excluding small changes in sperm measurement items, incidence of spontaneous defects in fetus, variant/ossification retardation, fetal/pup body weight, postal developmental assessments) is manifested when taken at a dosage with which general toxicity in parental animals is manifested in animal experiments.

(2) Substance for which it is described that clear reproduction toxicity (excluding small changes in sperm measurement items, incidence of spontaneous defects in fetus, variant/ossification retardation, fetal/pup body weight, postal developmental assessments) is manifested, though descriptions regarding general toxicity in parental animals in animal experiments are not available.

(Special case)

A substance for which it is described that clear reproduction toxicity (excluding small changes in sperm measurement items, incidence of spontaneous defects in fetus, variant/ossification retardation, fetal/pup body weight, postal developmental assessments) is manifested when taken at a dosage with which general toxicity in parental animals is not manifested in animal experiments, in Priority 2 is determined as having no evidence (ground) reliable enough to be classified as Category 1B, and so is classified as Category 2 in this guideline.

(3) Substance which is reported as being related to reproduction toxicity in humans, but is not sufficiently proven (substance not classified as Category 1A)\*

\*This includes the case for which it is described that reproduction toxicity is recognized in

humans in the information of Priority 2.

**Not classified: Substances which are clearly determined to have no reproduction/development toxicity**

(Determination criteria)

When it is clear from proper reproduction toxicity test results that the substance has no reproduction toxicity, the substance is determined as “Not classified”. In addition, when a substance falls under the following conditions, the substance is determined as “Not classified”.

- (1) Substances for which adverse effects on reproduction function, fertility or development are reported, but which are considered to be induced as non-specific secondary effects of other toxicity effects, are determined as “Not classified”.
- (2) Substances for which reproduction toxicity manifestation is proved to be caused by a mechanism peculiar to the animal which manifests reproduction toxicity, or substances for which reproduction toxicity is not manifested in humans due to significant differences in toxicokinetics, are determined as “Not classified”.
- (3) Substances which are of low toxicological importance or only induce minimum effects (small changes in semen measurement items, incidence of spontaneous defects in fetus, variant/ossification retardation, fetal/pup body weight, postal developmental assessments) are also determined as “Not classified”.

**\* Cautions in Classification**

- (1) When exposure of reproductive organs to the test substance is at unrealistically high levels in the test using administration routes such as intravenous injection or intraperitoneal injection, or when local damage is caused to reproductive organs such as by irritation, the test results are not used as the basis of classification. Adverse effects on reproduction seen only at extremely high doses (for example, doses that induce prostration, severe inappetence, and high mortality) in animal tests are not used as the basis for classification, unless information of, for example, toxicokinetics indicating that humans are more susceptible than animals is available, suggesting that classification is appropriate.
- (2) When a substance is determined as insufficient to make a final decision though information regarding reproduction toxicity is available, the substance is determined as “Classification not possible” because sufficient information is unavailable for GHS classification. An expert’s decision shall be sought as necessary.

**EFFECTS ON OR VIA LACTATION**

When a description regarding effects on or via lactation is found, it shall be noted under [Special Case], and an expert’s decision shall be sought.

The expert judges whether the substance has effects on or via lactation from the special knowledge based on GHS.

### **SUBSTANCES REQUIRING CAUTIONS IN CLASSIFICATION**

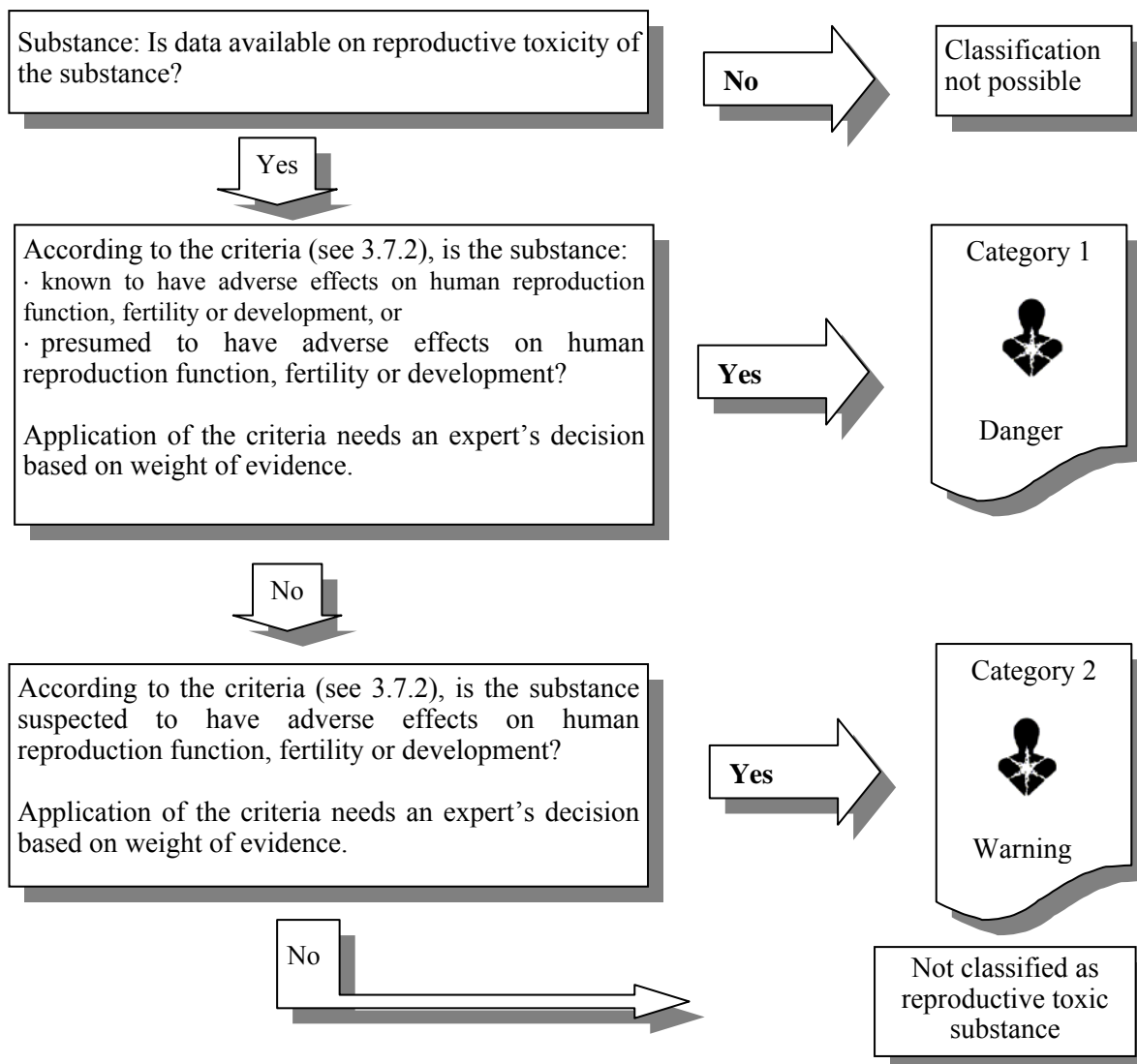
Document 1 shown at the end of this guideline for reference cites the following teratogens in humans: alcohol, anticancer agents (aminopterin, busulfan, chlorambucil, methotrexate, cytarabine, cyclophosphamide, mechlorethamine), androgenic hormones, antithyroid drugs, aminoglycoside antibiotics, coumarine anticoagulants, diethylstilbestrol, methyl mercury, PCBs, thalidomide, anticonvulsants (hydantoin, primidone, carbamazepine, diones, valproic acid), penicillamine, lithium, cocaine, retinoic acids, ACE inhibitors, toluene, and tetracyclines (Schardein, 2000, Table 1-18). Substances applicable to these may be classified as “Category 1A”, and so information shall be especially carefully collected in accordance with the classification manual produced by the authorities concerned.

Document 1 shows the list of substances considered to indicate 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 shall be studied especially carefully in accordance with the classification manual produced by the authorities concerned, and efforts should be made to collect sufficient information in order to make a decision.

### **References**

1. Schardein JL, Chemically Induced Birth Defects – 3<sup>rd</sup> edition, Marcel Dekker, New York, 2000
2. Shepard TH, Lemire RJ, Catalog of Teratogenic Agents, 11<sup>th</sup> edition, Johns Hopkins Univ. Press, Baltimore, 2004

### 3.7.5 DECISION LOGIC OF REPRODUCTIVE TOXICITY



## **Chapter-8 : SPECIFIC TARGET ORGAN/SYSTEMIC TOXICITY (SINGLE EXPOSURE)**

This technical guideline was prepared for those who perform classification for the 1,500 substances that are classified by the nation in preparation for implementing GHS domestically. The guideline assumes that the provisional work is carried out with limited time and resources. Therefore, it restricts the search for hazard information exclusively to the specified review documents; offers provisional methods when numerical values for classification criteria cannot be obtained and only qualitative descriptions are available; and presents easy methods which do not require experts in cases where the classification should be decided by an expert review of weight of evidence. Accordingly, note that the guideline does not show general principles to be observed when performing the classification in conformity with the GHS.

Notes:

- \*1. When there is no information available for classifying a substance except for the EU Risk phrase, the substance shall be determined as “Classification not possible”.
- \*2. When there is only data for a mixture available for a substance (limited to the case where the substance is mixed/diluted by a solvent or the like without toxicity), GHS classification of the substance as a pure substance is performed by proper estimation from the concentration, and the process of the estimation is described.
- \*3. Regarding “Not classified”, unless there is definitely no hazard or an extremely low hazard is described, a decision of “Not classified” shall be made carefully. If there is any doubt, “Classification not possible” should be chosen due to lack of sufficient information for making a decision.
- \*4. When an affected organ can be identified, the applicable category as well as the affected organ given in parentheses shall be described in “GHS classification”. When the organ cannot be identified, “systemic toxicity” shall be described in parentheses. (Example of “GHS classification”: Category 1 (liver, kidney, blood), or Category 1 (systemic toxicity))
- \*5. Substances which are classified as Category 1 or 2 and also satisfy the conditions of Category 3 (substance having temporary effect on a specific organ such as a respiratory tract irritation substance or anesthetic substance) are also classified as Category 3, and applicability to both shall be described. (Example of “GHS classification”: Category 1 (liver, kidney, blood), Category 3 (respiratory tract irritation))
- \*6. When a substance is classified into different categories for the affected organs, the category shall be described for each of the affected organs. (Example of “GHS classification”: Category 1 (liver, kidney), Category 2 (blood), Category 3 (respiratory tract irritation))

## **8-1 Classification Procedure**

### **1) Substances applicable to Decision Criteria 1a or Decision Criteria 1b are determined as Category 1.**

#### **Decision Criteria 1a: Evidence of inducement of toxic effects on humans is found in Priority 1.**

Notes:

- 1) As for toxic effects, the GHS text and the following [reference] shall be carefully read.
- 2) Organs that are obviously known to be secondarily affected shall be excluded from the description. When the secondary effects are difficult to determine, all the organs affected shall be cited.
- 3) In the human case, guidance values are not considered.
- 4) Effects on the respiratory system by site of contact are applicable here, and are determined as Category 1 (pneumoconiosis, etc.). However, the site of contact in other than the respiratory tract, such as irritation/inflammation reaction in the digestive system in the case of oral administration of a corrosive/irritant substance, is considered to apply to other toxicity items such as skin corrosion, etc., and is not classified into the specific target organ.
- 5) When only a slightly toxic symptom (slight fever, languor, etc.) is described, the substance is determined as “Not classified”.
- 6) All organs that have the effects described in Priority 1 shall be written. However, when the descriptions of the organs in plural assessment documents based on the same test differ, the commonly described organs shall be described. When only a toxic symptom is described and the affected organ cannot be identified, the substance is described as systemically toxic. When the target organ is identified, the toxic symptom need not be described.
- 7) When the affected organ can be identified, the applicable category as well as the affected organ given in parentheses are described in “GHS classification”. When the organ cannot be identified, “systemic toxicity” is described in parentheses. (Example of “GHS classification”: Category 1 (liver, kidney, blood), or Category 1 (systemic toxicity))

#### **Decision Criteria 1b: Animal tests that satisfy the following conditions:**

- (1) Animal species do not matter.
- (2) Exposure amount is clear and within the range of the guidance value of Category 1.
- (3) Test that is described in Priority 1 or an OECD TG test in Priority 2, and a GLP compliance test, and receives some degree of approval (review by plural persons).

Notes:

- 1) As for toxic effects, the GHS text and the following [reference] shall be carefully read.

- 2) Organs that are obviously known to be secondarily affected shall be excluded from the description. When the secondary effects are difficult to determine, all the organs affected shall be cited.
- 3) Effects on the respiratory system by site of contact are applicable here, and are determined as Category 1 (pneumoconiosis, etc.). However, the site of contact in other than the respiratory tract, such as irritation/inflammation reaction in the digestive system in the case of oral administration of a corrosive/irritant substance, is considered to apply to other toxicity items such as skin corrosion, etc., and is not classified into the specific target organ.
- 4) When only a slightly toxic symptom (slight fever, languor, etc.) is described, the substance is determined as “Not classified”.
- 5) All organs that have the effects described in Priority 1 shall be written. However, when the descriptions of the organs in plural assessment documents based on the same test differ, the commonly described organs shall be described. When only a toxic symptom is described and the affected organ cannot be identified, the substance is described as systemically toxic. When the target organ is identified, the toxic symptom need not be described.
- 6) As for conversion of exposure amount, the technical guideline of acute toxicity shall be used (except for the criteria regarding dealing of species difference).
- 7) When the affected organ can be identified, the applicable category as well as the affected organ given in parentheses are described in “GHS classification”. When the organ cannot be identified, “systemic toxicity” is described in parentheses. (Example of “GHS classification”: Category 1 (liver, kidney, blood), or Category 1 (systemic toxicity))

**2) Substances applicable to Decision Criteria 2a or Decision Criteria 2b are determined as Category 2.**

**Decision Criteria 2a: Evidence of inducement of toxic effects on humans is found in Priority 2.**

Notes:

In conformity with Decision Criteria 1a, Notes (1) to (7)

**Decision Criteria 2b: Animal tests that satisfy the following conditions:**

- (1) Animal species do not matter.
- (2) Exposure amount is clear and within the range of the guidance value of Category 2. (When plural documents are available, the decision is made with that with the minimum exposure amount.)
- (3) Tests that are described in Priority 1 or Priority 2

Exception: In case of a test for which the animal species does not matter, has a clear exposure amount within the range of the guidance value of Category 1, but is described in only Priority 2 and does not apply to the condition of Decision Criteria 1b ③ (that does not satisfy the condition that the test is an OECD TG test in Priority 2, and a GLP compliance test, and receives some degree of approval (review by plural persons)), then substances with such test results are exceptionally classified as Category 2, and “The substance is applicable to Category 1 judging from the guidance value, but does not satisfy the Decision Criteria 1b ③ with the data in Priority 2, and therefore, classified as Category 2 in accordance with the technical guideline” shall be described in the special remarks.

Notes:

1. In conformity with Decision Criteria 1b, Notes (1) to (7)

**3) Substances applicable to Decision Criteria 3 shall be determined as Category 3.**

**Decision Criteria 3: Human evidence or an animal test that satisfies all the following conditions:**

- (1) When toxicity applying to the criteria of respiratory tract irritation or classification criteria of narcotics for only a short period after exposure.
- (2) The effect is considered to be reversible.
- (3) Described in Priority 1 or Priority 2.

Notes:

- 1) The definition of Category 3 (temporary effect on a specific organ) is “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”. GHS presently puts the classification criteria into Category 3 for respiratory tract irritation and narcotic effect, and substances applicable to these two effects are classified as Category 3 for the present. If there is any irreversible effect other than these effects, such an effect shall be described in the special remarks in the present classification work, but shall not form the basis of classification.
- 2) In the case of respiratory irritation, when a more serious organ/systemic effect including the respiratory system is observed, the substance is classified as Category 1 or 2. As for the narcotic effect, if the effect of a substance is not essentially temporary, the substance is classified as Category 1 or 2.
- 3) When a substance applies to both Category 1 (or Category 2) and Category 3, the fact that the substance is applicable to both categories shall be described.

- 4) Whether it is a respiratory irritation substance or narcotic effect substance shall be clearly described. (Example of “GHS classification”: Category 3 (respiratory irritation))

Other notes:

Care should be taken since the specific toxicities described as follows are handled separately in GHS, and therefore are not included in the specific target organ/systemic toxicity (single exposure) handled here.

- acute lethal/toxicity
- skin corrosion/irritation
- serious eye damage/eye irritation
- skin and respiratory sensitization
- germ cell mutagenicity
- carcinogenicity
- reproductive toxicity

## **Chapter-9 : SPECIFIC TARGET ORGAN/SYSTEMIC TOXICITY (REPEATED EXPOSURE)**

This technical guideline was prepared for those who perform classification for the 1,500 substances that are classified by the nation in preparation for implementing GHS domestically. The guideline assumes that the provisional work is carried out with limited time and resources. Therefore, it restricts the search for hazard information exclusively to the specified review documents; offers provisional methods when numerical values for classification criteria cannot be obtained and only qualitative descriptions are available; and presents easy methods which do not require experts in cases where the classification should be decided by an expert review of weight of evidence. Accordingly, note that the guideline does not show general principles to be observed when performing the classification in conformity with the GHS.

Notes:

- \*1. When there is no information available for classifying a substance except for the EU Risk phrase, the substance shall be determined as “Classification not possible”.
- \*2. When there is only data for a mixture available for a substance (limited to the case where the substance is mixed/diluted by a solvent or the like without toxicity), GHS classification of the substance as a pure substance is performed by proper estimation from the concentration, and the process of the estimation is described.
- \*3. Regarding “Not classified”, unless there is definitely no hazard or an extremely low hazard is described, a decision of “Not classified” shall be made carefully. If there is any doubt, “Classification not possible” should be chosen due to lack of sufficient information for making a decision.
- \*4. When an affected organ can be identified, the applicable category as well as the affected organ given in parentheses shall be described in “GHS classification”. When the organ cannot be identified, “systemic toxicity” shall be described in parentheses. (Example of “GHS classification”: Category 1 (liver, kidney, blood), or Category 1 (systemic toxicity))
- \*5. When a substance is classified into different categories for the affected organs, the category shall be described for each of the affected organs. (Example of “GHS classification”: Category 1 (liver, kidney), Category 2 (blood))

### **9-1 Classification Procedure**

**1) Substances applicable to Decision Criteria 1a or Decision Criteria 1b are determined as Category 1.**

**Decision Criteria 1a: Evidence of inducement of toxic effects on humans is found in Priority 1.**

Notes:

- 1) As for toxic effects, the GHS text and the following [reference] shall be carefully read.
- 2) Organs that are obviously known to be secondarily affected shall be excluded from the description. When the secondary effects are difficult to determine, all the organs affected shall be cited.
- 3) In the human case, guidance values are not considered.
- 4) Effects on the respiratory system by site of contact are applicable here, and are determined as Category 1 (pneumoconiosis, etc.). However, the site of contact in other than the respiratory tract, such as irritation/inflammation reaction in the digestive system in the case of oral administration of a corrosive/irritant substance, is considered to apply to other toxicity items such as skin corrosion, etc., and is not classified into the specific target organ.
- 5) When only a slightly toxic symptom (slight fever, languor, etc.) is described, the substance is determined as “Not classified”.
- 6) All organs that have the effects described in Priority 1 shall be written. However, when the descriptions of the organs in plural assessment documents based on the same test differ, the commonly described organs shall be described. When only a toxic symptom is described and the affected organ cannot be identified, the substance is described as systemically toxic. When the target organ is identified, the toxic symptom need not be described.
- 7) When the affected organ can be identified, the applicable category as well as the affected organ given in parentheses are described in “GHS classification”. When the organ cannot be identified, “systemic toxicity” is described in parentheses. (Example of “GHS classification”: Category 1 (liver, kidney, blood), or Category 1 (systemic toxicity))

**Decision Criteria 1b: Animal tests that satisfy the following conditions:**

- (1) Animal species do not matter.
- (2) Exposure amount is clear and within the range of the guidance value of Category 1.
- (3) A test that is described in Priority 1 or an OECD TG test in Priority 2 and a GLP compliance test, and receives some degree of approval (review by plural persons).

(Animal tests)

- A standard animal test is a 28-day, 90-day or lifetime test (up to 2 years) in rats and mice, and includes hematological examination, clinical chemistry examination, and detailed macroscopic and histopathological examination.
- Data of a repeated-dose study conducted using animal species other than rats or mice shall be referred to.
- Attention shall be paid to the fact that the other long-term exposure tests, such as a

carcinogenicity test, neurotoxicity test or reproductive toxicity test, can provide evidence of specific target organ/systemic toxicity that is used for deciding the classification.

Notes:

- 1) As for toxic effects, the GHS text and the following [reference] shall be carefully read.
- 2) Organs that are obviously known to be secondarily affected shall be excluded from the description. When the secondary effects are difficult to determine, all the organs affected shall be cited.
- 3) Effects on the respiratory system by site of contact are applicable here, and are determined as Category 1 (pneumoconiosis, etc.). However, the site of contact in other than the respiratory tract, such as irritation/inflammation reaction in the digestive system in the case of oral administration of a corrosive/irritant substance, is considered to apply to other toxicity items such as skin corrosion, etc., and is not classified into the specific target organ.
- 4) When only a slightly toxic symptom (slight fever, languor, etc.) is described, the substance is determined as “Not classified”.
- 5) All organs that have the effects described in Priority 1 shall be written. However, when the descriptions of the organs in plural assessment documents based on the same test differ, the commonly described organs shall be described. When only a toxic symptom is described and the affected organ cannot be identified, the substance is described as systemically toxic. When the target organ is identified, the toxic symptom need not be described.
- 6) In repeated exposure, a substance having repeated exposure data or the like for 14 days or more (in the case of inhalation exposure, one exposure time is 1 hour or more) shall be considered. When comparing the exposure amount with the guidance value, the guidance value is corrected (inverse proportion calculation by the number of exposure days and exposure time per day) by comparing the number of days and exposure time per day with the conditions of the guidance value (90 days, 6 hours/day). However, in the case of repeated exposure data for more than 90 days, only the exposure time per day is corrected, and correction by the number of days is not performed.
- 7) When the affected organ can be identified, the applicable category as well as the affected organ given in parentheses are described in “GHS classification”. When the organ cannot be identified, “systemic toxicity” is described in parentheses. (Example of “GHS classification”: Category 1 (liver, kidney, blood), or Category 1 (systemic toxicity))

**2) Substances applicable to Decision Criteria 2a or Decision Criteria 2b are determined as Category 2.**

**Decision Criteria 2a: Evidence of inducement of toxic effects on humans is found in Priority 2.**

Notes:

In conformity with Decision Criteria 1a, Notes (1) to (7)

**Decision Criteria 2b: Animal tests that satisfy the following conditions:**

- (1) Animal species do not matter.
- (2) Exposure amount is clear and within the range of the guidance value of Category 2.  
(When plural documents are available, the decision is made with that with the minimum exposure amount.)
- (3) Tests that are described in Priority 1 or Priority 2

Exception: In case of a test for which the animal species does not matter, has a clear exposure amount within the range of the guidance value of Category 1, but is described in only Priority 2 and does not apply to the condition of Decision Criteria 1b ③ (that does not satisfy the condition that the test is an OECD TG test in Priority 2, and a GLP compliance test, and receives some degree of approval (review by plural persons)), then substances with such test results are exceptionally classified as Category 2, and “The substance is applicable to Category 1 judging from the guidance value, but does not satisfy the Decision Criteria 1b ③ with the data in Priority 2, and therefore, classified as Category 2 in accordance with the technical guideline” shall be described in the special remarks.

Notes:

1. In conformity with Decision Criteria 1b, Notes (1) to (7)

Other notes:

Care should be taken since the specific toxicities described as follows are handled separately in GHS, and therefore are not included in the specific target organ/systemic toxicity (single exposure) handled here.

- acute lethal/toxicity
- skin corrosion/irritation
- serious eye damage/eye irritation
- skin and respiratory sensitization
- germ cell mutagenicity
- carcinogenicity
- reproductive toxicity

## **Chapter-10 : ASPIRATION RESPIRATORY HAZARD**

This technical guideline was prepared for those who perform classification for the 1,500 substances that are classified by the nation in preparation for implementing GHS domestically. The guideline assumes that the provisional work is carried out with limited time and resources. Therefore, it restricts the search for hazard information exclusively to the specified review documents; offers provisional methods when numerical values for classification criteria cannot be obtained and only qualitative descriptions are available; and presents easy methods which do not require experts in cases where the classification should be decided by an expert review of weight of evidence. Accordingly, note that the guideline does not show general principles to be observed when performing the classification in conformity with the GHS.

Notes:

- \*1. When there is no information available for classifying a substance except for the EU Risk phrase, the substance shall be determined as “Classification not possible”.
- \*2. When there is only data for a mixture available for a substance, the mixture itself shall be classified, and this shall be stated as such in “Basis”.
- \*3. Regarding “Not classified”, unless there is definitely no hazard or an extremely low hazard is described, a decision of “Not classified” shall be made carefully. If there is any doubt, “Classification not possible” should be chosen due to lack of sufficient information for making a decision.

### **10-1 Classification Procedure**

#### **1) Substances applicable to Decision Criteria 1a or Decision Criteria 1b are determined as Category 1.**

**Decision Criteria 1a: Data of Priority 1 or Priority 2 contains descriptions stating that the substances cause chemical pneumonia by aspiration.**

Notes:

- 1) Kinematic viscosity is not considered.
- 2) Liquids and solids, not gases, are subject to classification, since the hazard relates to aspiration of liquids/solids rather than aspiration of suspended matter in the gas phase. Therefore, aerosol/dust/mist substances are determined by adding the properties of the substance and the performance, etc. of the container in which the substance is provided (spray can, etc.) by referring to GHS text 3.10.1.6.4. Substances which are aspirated into the respiratory tract/respiratory system while suspended in the gas phase do not need to be classified.

**Decision Criteria 1b: The substance is a hydrocarbon, and its kinematic viscosity is 20.5 mm<sup>2</sup>/s or less at 40°C.**

Notes:

- 1) The presence or absence of human evidence is not considered.
- 2) Viscosity depends on temperature, and in the case of a liquid, viscosity generally becomes lower as the temperature increases. Therefore, in the case of a liquid, if the kinematic viscosity is 20.5 mm<sup>2</sup>/s at room temperature, the liquid substance is determined as Category 1. However, the temperature dependency of viscosity of liquids is generally not linear, and so it is desirable to confirm the viscosity of the substance at 40°C by using chemical engineering references, or to estimate using an empirical formula recognized in an individual substance.
- 3) Liquids and solids, not gases, are subject to classification, since the hazard relates to aspiration of liquids/solids rather than aspiration of suspended matter in the gas phase. Therefore, aerosol/dust/mist substances are determined by adding the properties of the substance and the performance, etc. of the container in which the substance is provided (spray can, etc.). Substances which are aspirated into the respiratory tract/respiratory system while suspended in the gas phase do not need to be classified.
- 4) Hydrocarbon consists of carbon and hydrogen in the present project. Non-straight-chain hydrocarbon shall be included here. Halogen replacer, etc. shall not be included.

**2) Substances applicable to Decision Criteria 2a or Decision Criteria 2b are determined as Category 2.**

**Decision Criteria 2a: Substances described in Note 2 in 3.10.1 in GHS Table**

**Decision Criteria 2b: Substances having animal data indicating harmful effects such as chemical pneumonia when exposed to the respiratory tract/respiratory system in the data of Priority 1 or Priority 2, which have a kinematic viscosity of 14 mm<sup>2</sup>/s or less, measured at 40°C (substances falling under Category 1 are excluded)**

Notes:

- 1) Even when a report of animal testing exists, if the kinematic viscosity is unknown, the substance shall be determined as “Classification not possible”.
- 2) The kinematic viscosity is not described in documents dealing with toxicity information, and is considered to be described in some documents on physico-chemical properties. Therefore, information shall be searched in conformity with the classification manual.

General notes regarding kinematic viscosity:

- 1) Viscosity is described in cgs units in many cases. ( $\text{dyn} \cdot \text{s}/\text{cm}^2 = \text{poise (or P)}$ ). Use the following conversion formula where necessary:

$$1 \text{ poise} = 0.1 \text{ Pas}$$

- 2) Classification criteria refer to kinematic viscosity. The formula for converting viscosity and kinematic viscosity is shown below; care is required because both SI units and CGS units are used in the formula.

$$\text{viscosity (mPas)} / \text{density (g/cm}^3\text{)} = \text{kinematic viscosity (mm}^2\text{/s)}$$

## **Chapter-11 : ANNEXES**

This technical guideline was prepared for those who perform classification for the 1,500 substances that are classified by the nation in preparation for implementing GHS domestically. The guideline assumes that the provisional work is carried out with limited time and resources. Therefore, it restricts the search for hazard information exclusively to the specified review documents; offers provisional methods when numerical values for classification criteria cannot be obtained and only qualitative descriptions are available; and presents easy methods which do not require experts in cases where the classification should be decided by an expert review of weight of evidence. Accordingly, note that the guideline does not show general principles to be observed when performing the classification in conformity with the GHS.

This chapter is a special collection of matters that must be added in two or more items in common due to necessity in classification.

**Simplified Conversion Table of Concentration in Diet to Dose per Body Weight in  
Animal Tests**

• (added on August 31, 2005)  
•

When only the description of the concentration in the diet is available in an animal test report, and when the dose per body weight is found from the concentration in the diet, it shall be obtained in accordance with the following conversion table (quoted from Environmental Health Criteria, No. 104, 1990, p. 113). In this case, there is no need for further conversion in consideration of the body weight of the animal used.

APPROXIMATE RELATION OF PARTS PER MILLION IN THE DIET TO MG/KG BODY WEIGHT PER DAY<sup>a</sup>

Animal	Weight (kg)	Food consumed per day (g) (liquids omitted)	Type of diet	1 ppm in food = (mg/kg body weight per day)	1 mg/kg body weight per day = (ppm of diet)
Mouse	0.02	3		0.15	7
Chick	0.4	50		0.125	8
Rat (young)	0.1	10	Dry	0.1	10
Rat (old)	0.4	20	laboratory	0.05	20
Guinea-pig	0.75	30	chow diet	0.04	25
Rabbit	2	60		0.03	33
Dog	10	250		0.025	40
Cat	2	100		0.05	20
Monkey	5	250	Moist, semi-	0.05	20
Dog	10	750	solid diets	0.075	13
Man	60	1500		0.025	40
Pig or sheep	60	2400	Relatively	0.04	25
Cow (maintenance)	500	7500	dry grain	0.015	65
Cow (fattening)	500	15000	forage	0.03	33
Horse	500	10000	mixture	0.02	50

<sup>a</sup> Lehman, A.J. (1954) Association of Food and Drug Officials Quarterly Bulletin, 18: 66. The values in this table are average figures, derived from numerous sources.

Example: What is the value in ppm and mg/kg body weight per day of 0.5% substance X mixed in the diet of a rat?

Solution: I. 0.5% corresponds to 5000 ppm.

II. From the table, 1 ppm in the diet of a rat is equivalent to 0.050 mg/kg body weight per day. Consequently, 5000 ppm is equivalent to 250 mg/kg body weight per day (5000 × 0.050).

**Reference Value Regarding Vapor Inhalation in Acute Toxicity Classification**  
**(added on November 30, 2005)**

Since in the classification of acute toxicity, the criteria for vapor inhalation are easily misunderstood when using only the reference to Table 3.1.1 of the United Nations GHS document, classification needs to be performed by considering note (c) of Table 3.1.1 and the text paragraph 3.1.2.6.2 of the same document (Temporary translation by the authorities concerned, the version of April 2004).

Note (c) attached to the column of “vapor” in Table 3.1.1 states, “For some chemicals, the test atmosphere (Note by the producer of the technical guideline: This means the phase including the test substance in the inhalation chamber containing the animal, upon implementing the inhalation test) will not just be a vapor but will consist of a mixture of liquid and vapor phase. For other chemicals, the test atmosphere may consist of a vapor which is near the gaseous phase. In these latter cases, classification should be based on ppmV as follows: Category 1 (100 ppm), Category 2 (500 ppm), Category 3 (2500 ppm), and Category 4 (5000 ppm). (Note by the producer of the technical guideline: “should be based on ppmV” in the English text suggests that classification should be made based on ppm concentration).” This instructs that the reference value is set in mg/l in the column of vapor inhalation of the main body of the Table, since the test described as conducted as “vapor” actually has “inclusion of mist” in some cases, and in this case the concentration cannot be indicated accurately unless indicated in mg/l, but when the test is conducted with vapor that is completely gasified, classification is made with the reference value shown in ppm. The values shown here are the same as the classification reference values of gas. In the text paragraph 3.1.2.6.2, the same gist is repeatedly stated.

In accordance with Note (c) of Table 3.1.1 and the gist of the text paragraph 3.1.2.6.2, classification on acute toxicity in the case of “inhalation” is performed as follows.

1. The category reference value (ppm) of Gas is applied to Gas (translated as “kitai” in Japanese) by the definition of GHS.
2. When an inhalation experiment is conducted at the concentration of the saturated vapor pressure or more with the vapor generating from liquid, the substance is determined as “mist”, and the Category reference value of “mist/dust” is applied.
3. When an inhalation experiment is conducted at the concentration of the saturated vapor pressure or less with the vapor generating from liquid, the substance is handled as “vapor”. When handled as “vapor”, there are cases where mist is estimated to be included and where

mist is hardly included in accordance with GHS, and therefore categorization is performed based on the following (A) to (D) accordingly.

- (A) When mist is estimated to be included, categorization is performed based on the reference value in the unit of mg/l shown in the row of “vapor” in the Table.
- (B) When mist is considered to be hardly included, categorization is performed based on the reference value in the unit of ppm shown in Note (c) in Table 3.1.1 (the same value as gas).
- (C) When the ATE (LC50) value obtained in a test is between the saturated vapor pressure concentration of the substance and the value of the concentration corresponding to 90% of the saturated vapor pressure concentration, the substance is determined to be in the state of “vapor with mist included” in consideration of the possibility of mist inclusion, and (A) is applied. In the case of a lower concentration than this, it is determined as “vapor with mist hardly included”, and (B) is applied.
- (D) When the description in a document is in mg/l, the aforementioned method is applied by converting it into ppm from the molecular weight and temperature. When the temperature during the inhalation test is not described, the unit conversion is performed by assuming that the temperature is 25°C and the volume of gas of 1 mol is 24.45 liters.

- 4. When it is described that the test is conducted definitely with “mist”, it is treated as mist.
- 5. Since it is assumed that vapor generating from solid is inhaled, the vapor which is generated from solid (other than gas/liquid) is treated as “vapor” when it is clearly indicated as “vapor” or the inhalation concentration is indicated in units of ppm. However, when the concentration is the saturated vapor pressure concentration or more, there is the possibility of inclusion of dust. GHS has no special definition for this, and so the following is specially described: “Doubtful description as vapor because it exceeds the saturated vapor pressure; the possibility of dust inclusion is high”. In the case where the concentration corresponds to the saturated vapor pressure or less, and there is no clear indication of vapor or dust, classification is not generally possible. In this case, it is desirable to specially describe “Category ○○ if it is vapor, Category ○○ if it is dust”.

(Related matter) Dealing with Vapor Inhalation Guidance Value in the Classification of Specific Target Organ/Systemic Toxicity (Single Exposure and Repeated Exposure)

As for the classification of specific target organ/systemic toxicity (single exposure and repeated exposure), the “guidance values” which are used for categorization based on animal data are shown in Table 3.8.1, Table 3.9.1 and Table 3.9.2, and all of them are in units of mg/l for vapor inhalation. However, the note regarding vapor inhalation for Table 3.1.1 of acute toxicity is

not made, and there is no description in the GHS text. Therefore, in this project, regarding specific target organ/systemic toxicity (single exposure and repeated exposure), the toxicity manifestation concentration at the time of vapor inhalation is investigated in mg/l, and is evaluated by comparing it with the value shown in the Table. If the original data is given in ppm, the unit is converted into mg/l and a comparison is made.

If the concentration is that of saturated vapor pressure or more, the value is treated as that of mist (or dust) by referring to the case of acute toxicity.

## **EVALUATION OF ANALOGOUS COMPOUND**

**(added on December 10, 2005)**

Regarding hazard data for metals, salts, anhydrides, hydrates, isomers, etc. differing in molecular species, data are searched, collected and evaluated targeting the substances identified by CAS number in principle. This is because even analogous substances may differ in solubility, intracorporeal absorption, biological activity, etc., due to differences in their molecular species, and so the manifestation of health hazards is likely to differ.

In some cases, sufficient information is provided for an analogous substance even though sufficient hazard data is not obtained for the target substance; when such substance is handled in the classification project, “As for health hazard, IDXXXX, name of substance, CAS: ZZZZ-ZZ-Z shall also be referred to” or the like is described to clearly indicate the existence of another reference substance. This can be done by describing it in the first item of hazard to health, namely, in the “classification basis” column of “acute toxicity (oral)” in the GHS classification list. When the classification target substance is a chemical substance (identified in CAS) including plural isomers such as a racemic modification, and having less information as mistura (for example, a racemic modification), but having information for each isomer, the substance is classified by using the data of the isomer and “based on the data of XXX isomer” or the like is described in the “classification basis” column as a “note”.

As for carcinogenicity, if the compound is not an analogous compound for the target substance identified by the CAS number, but if it applies to a compound which is evaluated by IARC as “○○ and its compounds”, it is treated as one of the analogous compounds and its carcinogenicity is adopted. Regarding analogous compounds, care should be taken since the evaluation may differ for compounds determined as an excluded substance and inorganic salt/organic salt (refer to the following corresponding examples).

- 1) When evaluation of hazard definitely differs in different states/modes, they are listed.

Example: Carcinogenicity of lead

Model GHS classification Category 1B (inorganic lead)/not classified (organic lead)

Basis IARC (2004)

- 2) When evaluation of hazard is not always definite in different states/modes, a comment is added to the item of “model GHS classification, basis”.

Example: Carcinogenicity of cadmium

Model GHS classification Category 1A

Basis IARC (1993) Note that “as cadmium and its compounds”

**(Related matter) Handling of epidemiological data**

Epidemiological data makes it difficult to judge the appropriateness of treating the substance as one of the target substances. However, if the epidemiological data is obtained by searching the information sources in the range shown in the classification manual in accordance with CAS number, even though the substance identified purely by CAS number is not evaluated, if an evaluation as the substance group including analogous compounds is made, their hazard information can be adopted.

Epidemiological data sometimes cannot be applied to cases where the definition of the category in GHS is quantitative corresponding to the strength of an effect (acute toxicity, etc). The handling of epidemiological data in CMR in which categories are set in accordance with the reliability of evidence is shown below.

Handling of epidemiological data in CMR

- 1) As for human epidemiological data, only the target of evaluation in the evaluation document in Priority 1 is classified in accordance with evaluation in the evaluation document.
- 2) When evaluations differ in the same epidemiological data, if different evaluations are made based on different epidemiological data, the evaluation result of the latest evaluation document is relied upon.
- 3) When only the epidemiological data of evaluation documents other than Priority 1 is available, regarding the appropriateness of classification in accordance with the data, an expert's decision shall be sought as [special comment] in the item of "Model GHS classification basis" of the CERI input form.

## Chapter-12 : List of Abbreviations of GHS Evaluation Documents

- This list shows fixed abbreviations for evaluation data entered in the "GHS classification manual" that is used for GHS classification work.
- These abbreviations are used for entering quoted data names in the "basis" column of "model GHS classification, basis" in a GHS classification sheet and unify the notation for publicly announcing the concerned articles.
- If there are, for information about an evaluation document that is entered in the proper "basis" column, at least the abbreviation, the publication date (the creation date) and also revision of quoted data, enter the version number concerned. If necessary, you may add a material reference number in each document, a document number, the number of volumes, etc.
- The "Examples" column shows how to write basic information in the "basis" column.
- If you cannot confirm the preparation/renewal year for an example online, etc., write the date the information was acquired, such as access on May 2004.
- When basic information is entered in the "basis" column, instead of using an abbreviation, you may mention its name in the manual (or its formal evaluation document name).

### Dangerous Properties

Name of Manual

Chemicals Evaluation and Research Institute: "Chemicals Hazard Data List"

Abbreviation

No.	Name of Manual	Abbreviation	Example
1	United Nations Recommendations on the Transport of Dangerous Goods (UNRTDG)	UNRTDG	UNRTDG (13th, 2003)
2	International Chemical Safety Cards (IPCS)	ICSC	ICSC (19xx)
3	International Chemical Safety Cards (NIHS)	ICSC (J)	ICSC (J) (19xx)
4	Fire Protection Guide to Hazardous Materials, 13th Ed. (NFPA)	NFPA	NFPA (13th, 2002)
5	Gmelins Handbuch der Anorganischen Chemie	GRN	GRN (19xx)
6	Gmelins Handbook of Inorganic and Organometallic Chemistry 8th Ed.	GRN (E)	GRN (E) (19xx)
7	Beilsteins Handbuch der Organischen Chemie	BRN	BRN (19xx)
8	Beilsteins Handbook of Organic Chemistry 4th ed.	BRN (E)	BRN (E) (19xx)
9	The Merck Index 13th Ed.	Merck	Merck (13th, 2001)
10	International Critical Tables of Numerical Data, Physics, Chemistry and Technology	ICT	ICT (19xx)

11	Physical Constants by the Society of Chemical Engineers	CE Physical Constants	CE Physical Constants (19xx)
12	Ullmanns Encyklopaedie der technischen Chemie	Ullmanns	Ullmanns (19xx)
13	Ullmanns Encyclopedia: Industrial Organic Chemicals	Ullmanns (E)	Ullmanns (E) (19xx)
14	Howard and Meylan, Handbook of Physical Properties of Organic Chemicals	Howard	Howard (1997)
15	Chapman and Hall Chemical Database	Chapman	Chapman (19xx)
16	HODOC File (Handbook of Data on Organic Compounds)	HODOC	HODOC (19xx)
17	Hommel's Handbook of Hazardous Materials	Hommel	Hommel (1991)
18	Bretherick's Handbook of Reactive Chemical Hazards	Bretherick	Bretherick (7th, 19xx)
19	Bretherick's Handbook of Hazardous Materials 5th ed.	Bretherick (J)	Bretherick (J) (5th, 1998)
20	Handbook on Accidental Mixing Hazards of Chemicals (Tokyo Fire Department)	Accidental Mixing Hazards Hb	Accidental Mixing Hazards Hb (2nd ed., 19xx)
21	Weiss's Hazardous Chemicals Data Book	Weiss	Weiss (2nd, 19xx)
22	Renzo's Solvents Safety Handbook	Renzo	Renzo (3rd, 19xx)
23	Handbook of Hazardous Materials B44(Tokyo Fire Department)	Hazardous Materials DB	Hazardous Materials DB (2nd, 19xx)
24	Data Sheet of Road Transport Hazardous Materials (Institute of Safety Engineering)	ISE	ISE (19xx)
25	Dictionary of Organic Compounds (The Society of Synthetic Organic Chemistry)	Dictionary of Organic Compounds	Dictionary of Organic Compounds (1985)
26	Pocketbook of Fluxing Materials (The Society of Synthetic Organic Chemistry)	Pocketbook of Fluxing Materials	Pocketbook of Fluxing Materials (1997)
27	Directive 67/548/EEC - Annex I (EU • Annex I)	EU-Annex I	EU-Annex I (19xx)
28	Directive 67/548/EEC - Annex I (EU • Annex I) (JETOC Document)	JETOC Special Document	JETOC Special Document No.188
29	International Maritime Organization (IMDG Code) Annex - Extreme Measure Guide	IMDG	IMDG (2004)
30	Emergency Response Guide (ERG)	ERG	ERG (2004)
31	First Aid Emergency Response Guide (JCIA)	NAERG (J)	NAERG (J) (19xx)
32	SAX's Dangerous Properties of Industrial Materials	Sax	Sax (11th, 2004)
33	Pesticide Manual	PM	PM (13th, 2003)
34	HSDB: Hazardous Substance Data Bank	HSDB	HSDB (20xx)
35	Verschueren's Handbook of Environmental Data on Organic Chemicals 4th Ed.	Verschueren	Verschueren (4th, 2003)
36	Lange's Handbook of Chemistry 15th Ed.	Lange	Lange (15th, 1999)
37	Lide's CRC Handbook of Chemistry and Physics 84th Ed.	Lide	Lide (84th, 2003)
38	Gangolli's The Dictionary of Substances and their Effects 2nd Ed.	Gangolli	Gangolli (2nd, 1999)

39	SRC PhysProp Database	SRC	SRC (20xx)
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### Toxicity Priority 1

No.	Name of Manual	Abbreviation	Example
1	Chemicals Evaluation and Research Institute: "Chemicals Hazard Data List"	CERI Hazard Data List	CERI Hazard Data List (19xx)
2	Chemicals Evaluation and Research Institute (Germany): Institute of Technology and Evaluation "Hazardous Property Evaluation Documents"	CERI · NITE Hazardous Property Evaluation Documents	CERI · NITE Hazardous Property Evaluation Documents (19xx)
3	United Nations Recommendations on the Transport of Dangerous Goods (UNRTDG)	ICSC (J)	UNRTDG (13th, 2003)
4	EU European Chemicals Bureau (ECB) International Uniform Chemical Information Database (IUCLID)	Ministry of Health, Labor and Welfare Test Report	IUCLID (2000)
5	Ministry of the Environment, Environment Risk Research Office "Environment Risk Assessments of Chemicals", Vol.1, Vol.2, Vol.3	ICSC (J)	EHC (J) 135 (19xx)
6	HSDB: Hazardous Substance Data Bank	SIDS	SIDS (19xx)
7	WHO/IPCS: "Environmental Health Criteria" (EHC)	EHC	EHC 127 (1991)
8	Translated into Japanese "Chemicals Safety Assessments, Vol.1, Vol.2, Vol.3"	EHC (J)	EHC (J) 127 (1991)
9	WHO/IPCS: "Concise International Chemical Assessment Documents (CICAD)" (Concise International Chemical Assessment Documents)	CICAD	CICAD 62 (2004)
10	American Conference of Governmental Industrial Hygienists: ACGIH documentation	ACGIH	ACGIH (7th, 2001)
11	American Conference of Governmental Industrial Hygienists (ACGIH) "TLVs and BELs 2004"	ACGIH-TLV	ACGIH-TLV (2005)
12	Deutsche Forschungsgemeinschaft (DFG): "Occupational Toxicants Critical Data Evaluation for MAK Values and Classification of Carcinogens" Vol. 1 ~20.	DFGOT	DFGOT vol.6 (19xx)
13	Deutsche Forschungsgemeinschaft (DFG): "List of MAK and BAT values"	CERI · NITE Toxicity Assessment Documentation	CERI · NITE Toxicity Assessment Documentation (19xx)
14	EU Risk Assessment Report	EU-RAR	EU-RAR (20xx)
15	Ullmanns Encyclopedia: Industrial Organic Chemicals	CaPSAR	CaPSAR (20xx)
16	Australia NICNAS: Priority Existing Chemical Assessment Reports	NICNAS	NICNAS (20xx)
17	European Center of Ecotoxicology and Toxicology of Chemicals (ECETOC)	ECETOC	ECETOCTR63 (1995) ECETOC JACC (19xx)

18	Patty's Toxicology	PATTY	PATTY (4th, 1995?) PATTY (5th, 2001)
19	IARC Monographs Programme on the Evaluation of Carcinogenic Risk to Humans	IARC	IARC 53 (1990)
20	Bretherick's Handbook of Reactive Chemical Hazards	IRIS	IRIS (20xx)
21	National Toxicology Program (NTP)	N T P	NTP TR500 (20xx) NTP DB (Access on June 2005)
22	Japan Society for Occupational Health, "Recommendation for Allowable Concentration (2004)", Journal of Occupational Health, Vol. 46, pp. 124-148, 2004)	Society for Occupational Health Recommendation	Society for Occupational Health Recommendation (2004)

### Toxicity Priority 2

No.	Name of Manual	Abbreviation	Example
1	Chemicals Evaluation and Research Institute: "Chemicals Hazard Data List"	RTECS	RTECS (19xx)
2	WHO/IPCS: "ICSC Cards (International Chemical Safety Cards)"	ICSC	ICSC (19xx)
3	United Nations Recommendations on the Transport of Dangerous Goods (UNRTDG)	ICSC (J)	UNRTDG (13th, 2003)
4	EU European Chemicals Bureau (ECB) International Uniform Chemical Information Database (IUCLID)	IUCLID	IUCLID (2000)
5	EU 7th Correction Directive Annex I (Latest Edition: 8th Correction Council Directive, 29th Adaptation Directive)	ICSC (J)	EHC (J) 135 (19xx)
6	HSDB: Hazardous Substance Data Bank	HSDB	HSDB (19xx)
7	ATSDR: Toxicological Profile	ATSDR	ATSDR (19xx)
8	Hazardous Substance Fact Sheet (New Jersey Department of Health and Senior Services)	HSFS	EHC (J) 127 (1991)
9	German Chemical Society-Advisory Committee on Existing Chemicals of Environmental Relevance "BUA Report"	BUA	BUA140 (1993)
10	American Conference of Governmental Industrial Hygienists: ACGIH documentation	SITTIG	SITTIG (47th, 2002)
11	American Conference of Governmental Industrial Hygienists (ACGIH) "TLVs and BELs 2004"	DHP	DHP (13th, 2002)

### Toxicity Priority 3

No.	Name of Manual	Abbreviation	Example
1	Chemicals Evaluation and Research Institute: "Chemicals Hazard Data List"	Not Applicable	Enter documentary information (head author, journal title, year of publication, volume, pages) obtained through retrieving
2	NLM TOXNET/TOXLINE	Not Applicable	Id.
3	United Nations Recommendations on the Transport of Dangerous Goods (UNRTDG)	ICSC (J)	UNRTDG (13th, 2003)
4	EU European Chemicals Bureau (ECB) International Uniform Chemical Information Database (IUCLID)	Not Applicable	IUCLID (2000)
5	Institute of Technology and Evaluation "Chemical Risk Information Platform"	ICSC (J)	EHC (J) 135 (19xx)
6	HSDB: Hazardous Substance Data Bank	WebKis-Plus	WebKis-Plus (20xx)
7	GESTIS-database on hazardous substances (BIA)	GESTIS	GESTIS (Access on June 2004)

### Environment Priority 1

No.	Name of Manual	Abbreviation	Example
1	Chemicals Evaluation and Research Institute: "Chemicals Hazard Data List"	Ministry of the Environment Ecological Effect Test	Ministry of the Environment Ecological Effect Test (19xx)
2	Ministry of the Environment, Environment Risk Research Office "Environment Risk Assessments of Chemicals"	Ministry of the Environment Risk Assessments	Ministry of the Environment Risk Assessments Vol.3 (20xx)
3	United Nations Recommendations on the Transport of Dangerous Goods (UNRTDG)	ICSC (J)	UNRTDG (13th, 2003)
4	EU European Chemicals Bureau (ECB) International Uniform Chemical Information Database (IUCLID)	EHC	IUCLID (2000)
5	Translated into Japanese "Chemicals Safety Assessments, Vol.1, Vol.2, Vol.3"	ICSC (J)	EHC (J) 135 (19xx)
6	HSDB: Hazardous Substance Data Bank	CICAD	CICAD62 (2004)
7	EU Risk Assessment Report	EU-RAR	EU-RAR (20xx)
8	Environment Canada: Priority Substance Assessment Report	CaPSAR	EHC (J) 127 (1991)
9	Australia NICNAS Assessment Report	NICNAS	NICNAS (20xx)
10	American Conference of Governmental Industrial Hygienists: ACGIH documentation	ECETOC	ECETOCJACC27 (19xx)

11	American Conference of Governmental Industrial Hygienists (ACGIH) "TLVs and BELs 2004"	PDS	PDS (19xx)
12	Chemicals Evaluation and Research Institute: "Chemicals Hazard Data List"	CERI Hazard Data List	DFGOT vol.6 (19xx)
13	Deutsche Forschungsgemeinschaft (DFG): "List of MAK and BAT values"	CERI • NITE Toxicity Assessment Documentation	CERI • NITE Toxicity Assessment Documentation (19xx)

#### Environment Priority 2

No.	Name of Manual	Abbreviation	Example
1	Chemicals Evaluation and Research Institute: "Chemicals Hazard Data List"	AQUIRE	AQUIRE (19xx)
2	HSDB	HSDB	HSDB (19xx)
3	United Nations Recommendations on the Transport of Dangerous Goods (UNRTDG)	ICSC (J)	UNRTDG (13th, 2003)
4	EU European Chemicals Bureau (ECB) International Uniform Chemical Information Database (IUCLID)	ECBHPV-LPV	IUCLID (2000)
5	EU European Chemicals Bureau (ECB) The N-CLASS Database on Environmental Hazard Classification	ICSC (J)	EHC (J) 135 (19xx)
6	HSDB: Hazardous Substance Data Bank	BUA	BUA244 (2003)

Note: The blank in the Examples column has not been confirmed in the original.