

NOTE:

This is an old version of the Guidance.

DRAFT

**GHS Implementation Guidance for Household
Consumer Products**

- Human health hazards -

Japan Soap and Detergent Association

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1 Purpose

Household consumer products such as soap and detergent are indispensable to the lives of consumers. It is important, for the companies who are involved in the production and sales of those products, to properly inform consumers of hazard information and information on safe handling of these products so as to prevent any injury that may be caused as a result of product use.

The purpose of this guidance is to outline the basic concept and approach for implementation of the GHS, based on the GHS document adopted by the United Nations, in order to ensure appropriate hazard classification and labeling of household consumer products.

Household consumer products have diverse compositions and patterns of use. This guidance shows several examples of Classification and Labeling evaluation of example products to explain the basic procedure for implementing GHS. This guidance, it is intended to provide every user with an understanding of the concepts and use of data to classify chemicals and products, focusing on human health hazard labeling of consumer products.

2 Purpose and Background of GHS

The Globally Harmonized System of Classification and Labeling of Chemicals (GHS) is an initiative to enable and promote a common and consistent approach to the classification and labeling of chemicals and mixtures of chemicals for physical, health and environmental hazards. The work was mandated by the United Nations Conference on Environment and Development in 1992. Over a ten year period Governments and Stakeholders worked together to develop the system. The system was built on the already existing systems within governments for hazard classification and hazard communication. The GHS was formally adopted by the United Nations Economic and Social Council in July 2003. The GHS is a voluntary approach to chemical hazard classification and labeling that governments are encouraged to adopt and implement as part of the Sound Management of Chemicals.

3 Key Elements of GHS

The GHS consists of two main parts as described below.

1) Hazard Classification:

Classification based on the intrinsic properties of the chemicals and mixtures.

2) Hazard Communication:

Container labels and Safety Data Sheets (SDS) are the means of Hazard Communication, and either one or both of these approaches are used. Labeling of the product container is the hazard communication tool employed for household consumer products.

4 Basic Principles to Apply in Implementation of GHS

The major objectives of the GHS are to:

- Enhance protection of human health and the environment
- Provide a internationally recognized framework for governments without systems
- Reduce the need for testing and evaluation of chemicals
- Facilitate international trade

Basic principles for classification and labeling described in the GHS document are:

- 1) Focus on providing information that meets the differing information needs of users and to ensure comprehensibility

The GHS includes “special arrangements to take into account the information needs of different target audiences.” (GHS document 1.4.10.2)

It is reported that cluttered, difficult to read labels, containing superfluous warnings that are outside the experience of typical consumers reduces the likelihood of consumers’ understanding of and adherence to labels¹.

- 2) Application of the Building Block Approach

Taking into account that different target audiences have differing hazard information needs, the GHS document describes the application of the GHS as the following: “While the full range is available to everyone, the full range does not have to be adopted when a country or an organization uses GHS for the purpose of covering a certain effect....As long as the hazards covered by a sector or a system are consistent with the GHS criteria and requirements, it will be considered appropriate implementation of the GHS.” (excerpted from 2nd edition of GHS document 1.1.3.1.5.3)

With these points in view, the realization of product labeling that will help promote consumer protection is desired.

- 3) Maximum use of existing data without mandated test methods

One of the central objectives of the GHS is to “reduce the need for testing and evaluation of chemicals” and mixtures, (GHS document 1.1.1.4(c)) particularly animal testing, and the GHS does not require additional testing of chemical substances or mixtures. Furthermore, the GHS document says “The GHS is based on currently available data.” (GHS document 1.1.2.5(b)(ii)) When the data are scientifically robust and appropriate for evaluation of health effects in humans, data from non-animal test approaches (human experience), similar products (bridging principles), *in vitro* study using enzymes and cells, SAR/QSAR, or *in silico* approaches may be used for classification.

- 4) Precedence of human experience over other information

The GHS document says “Generally, data of good quality and reliability in humans will have precedence over other data.” (GHS document 1.3.2.4.9.3) This is a critical concept, especially in determining appropriate labeling for household consumer products.

- 5) Use of a weight-of-evidence approach in classification decision

The GHS document states, “For some hazard classes, classification results directly when the data satisfy the criteria. For others, classification of a substance or a mixture is made on the basis of the total weight of evidence. This means that all available information bearing on the determination of toxicity is considered together, including the results of valid *in vitro* tests, relevant animal data, and human experience such as epidemiological and clinical studies and well-documented case reports and observations.” (GHS document 1.3.2.4.9.1) As mentioned, it is important to consider the weight and credibility of the evidence, taking into account the reliability and consistency of all available data and information.

¹ IOMC/ILO/HC6/00.13 “An Option for Consumer Product Labeling Based on the Likelihood of Injury” September 21, 2000

6) Consideration of risk, especially when determining the hazard labeling for chronic endpoints

The GHS document says “competent authorities may authorize consumer labeling systems providing information based on the likelihood of harm (risk-based labeling).” (GHS document 1.4.10.5.5.2) Based on this concept, Annex 5 (“CONSUMER PRODUCT LABELLING BASED ON THE LIKLIHOOD OF INJURY”) A.5.1.1 describes “Where this exposure assessment and determination of likelihood of injury reveal that the potential for harm to occur as a result of the expected exposures is insignificant, chronic health hazards may not be included on the product label for consumer use.”

7) Protection of Confidential Business Information

The GHS document states, “The competent authority should protect the confidentiality of the information in accordance with applicable law and practice.” (GHS document 1.4.8.3(c))

5 Classification approach

“Hazard classification” within the context of the GHS is based on the intrinsic hazardous properties of the product. However, a weight of evidence approach is taken in classifying the product. That means that all information is taken into consideration, including human information, animal data and valid *in vitro* data.

Most of the current hazard labeling systems make use of ethically obtained human data or available human experience, such as information collected by the manufacturing company and information provided by organizations with product accident databases. Application of the GHS should not prevent the use of such data. For classification purposes, reliable epidemiological data and experience on the effects on humans (e.g. occupational data, data from accident databases, clinical studies, consumer comment data) will have precedence over other data.

Specific sources of hazard information based on human experience of product use are exemplified in Annex 2 A2.1.3.

5.1 Principles of Classification

Hazard classification process consists of 3 steps.

- 1) identification of the relevant data regarding the hazards of a substance or a mixture,
- 2) subsequent review of those data to ascertain the hazards associated with the substance or mixture, and
- 3) making a decision on whether the substance or mixture will be classified as a hazardous substance or mixture and the degree of hazard, where appropriate, by comparison of the data with classification criteria.

The specific classification criteria for substances and mixtures are elaborated in Parts 2 and 3 of the UN GHS document.

5.2 Classification process for mixtures

Additionally, the recommended process of classification of mixtures is based on the following sequence:

- 1) Where data are available for the complete mixture, the classification of the mixture will always be based on those data.
- 2) Where data are not available on the mixture itself, the data gained from a similar mixture can be used for the classification. Bridging principles can be applied as elaborated in the GHS document.
- 3) If data are not available for the mixture, classification can be done by making use of data for each of the ingredients or other means as elaborated in the GHS document.

6 GHS Classification/Labeling of Hazards

The GHS document includes the following classification/labeling hazards. However, the GHS is a flexible and variable system that allows application of the building block approach to meet the needs of the target audience. Consequently, not all the hazards listed below are applicable to consumer products. The specific hazards and classification criteria applied to household consumer products are described in Annex 1 and listed below in 6.2.

6.1 Classification/labeling of hazards described in the second revised edition of GHS official text²

The following classes and categories are in the 2nd revised edition of GHS official text.

< Physical Hazards >

- explosives
- flammable/combustible gases
- flammable Aerosols
- oxidizing gases
- high-pressure gases
- flammable liquids
- flammable solids
- self-reactive substances and mixtures
- pyrophoric liquids
- pyrophoric solids
- self-heating substances and mixtures
- substances and mixtures which, in contact with water, emit flammable gases
- oxidizing liquids
- oxidizing solids
- organic peroxides
- corrosive to metals

² based on ST/SG/AC.10/30/Rev.2(July 2007)

<Health Hazards>

- acute toxicity – oral exposure, dermal exposure, inhalation exposure (gases, vapours, dusts and mists)
- skin corrosion/irritation
- serious eye damage/eye irritation
- respiratory or skin sensitization
- germ cell mutagenicity
- carcinogenicity
- reproductive toxicity
- specific target organ toxicity (single exposure)
- specific target organ toxicity (repeated exposure)
- aspiration toxicity

<Environmental Hazards>

- hazardous to the aquatic environment (acute and chronic toxicity)

6.2 Hazards Applicable to Household Consumer Products

This guidance focus on human health hazards, and the choices of these hazard classes and categories are made with the primary purpose of properly communicating hazard information useful for “the appropriate protective measures to be implemented” (GHS official text 1.1.1.1) by consumers and with the consideration of the current situation of related laws and regulations, and of assessment methodology level. GHS hazard classes and categories to be covered and those not to be covered in this guidance are shown below.

<Human health hazard classes and categories covered in this guidance>

- Categories 1, 2, 3, 4 of acute toxicity (all exposure routes)
- Categories 1, 2 of skin corrosion/irritation
- Categories 1, 2A, 2B of serious eye damage/irritation
- Category 1 of respiratory or skin sensitization
- Categories 1A, 1B, 2 of germ cell mutagenicity
- Categories 1A, 1B, 2 of carcinogenicity
- Categories 1A, 1B, 2 of reproductive toxicity
- Categories 1, 3 of specific target organ toxicity (single exposure)
- Categories 1, 2 of specific target organ toxicity (repeated exposure)
- Category 1 of aspiration hazard

<Human health hazard classes and categories not covered in this guidance>

- Category 5 of acute toxicity (all exposure routes)
- Category 3 of skin corrosion/irritation
- Effects on or via lactation in reproductive toxicity
- Category 2 of specific target organ toxicity (single exposure)
- Category 2 of aspiration toxicity

7 Hazard Information Labeling

The primary objective of the GHS for classification and labeling is to enhance protection of human health and the environment through harmonized classification and communication of hazard information. To achieve this goal, the globally harmonized communication system needs to responsibly alert consumers to health hazards likely to cause injury during normal use, foreseeable misuse and accidental exposures. In order for consumers to take action to protect themselves, it is necessary to provide information on hazards that may actually cause injury under use on the label in an easily comprehensive manner. Identifying relevant information that needs to be put on the label by employing risk-based labeling for chronic and repeated exposure endpoints will also be beneficial in increasing the effectiveness of warnings communicated and leading to enhanced consumer protection. Additionally, the GHS does not prescribe specific precautionary statements, but provides examples and allows flexibility in the choice of language for precautionary statements. Further, the GHS permits the use of supplemental labeling.

The following outlines the application of classification and labeling principles. Further details are provided in Annex 2.

7.1 Labeling Approach for Acute Endpoints

For acute endpoints, hazard communication will be based on hazard classification. Once the product is classified for specific hazard classes and categories, the hazards for which it is classified will be communicated on the label using the standardized GHS communication elements (pictogram/symbol, signal words, and hazard statements). Other non-standardized required label elements (e.g., product identifier, supplier identification, precautionary statements) are described in the GHS Document.

7.2 Labeling Approach for Chronic/repeat exposure endpoints

For health effects caused by chronic or repeated exposure (such as carcinogenicity, reproductive toxicity and specific target organ toxicity), the communication will be based on those hazards that are identified as likely to occur during recommended use and foreseeable use of the products. Labeling of household consumer products for chronic/repeat exposure endpoints is a 3-step process:

Step 1: Classify using the GHS criteria

Step 2: Determine the risk/likelihood of adverse effects under use conditions

Step 3: Communicate Health Effects that are likely to occur during use on the label using the GHS communication elements.

The details of the approach to be used for scientifically evaluating these hazards to be communicated on a label are provided in Annex 2 A2.4. The approach is based on knowledge about how the product is used and the likelihood that harm will occur under those use conditions.

The label elements and the general format of the label will conform to those outlined in the GHS document.

Annex 1

Classes and Categories

Annex 1 Classes and Categories

In this Annex, GHS hazard classes and categories to be applied to household consumer products are listed. The choices of hazard classes and categories are made with the primary purpose of properly communicating hazard information which is useful to consumers as the users of household consumer products. (Ref: Chapter 4. “Basic Principles to Apply in Implementation of GHS” of this Guidance)

The adoption of classes and categories is determined in consideration of current laws and regulations and available assessment methods, and may be changed according to the changes in relevant laws and regulations, GHS implementation situations in other geographies, and further development of assessment methods.

The health hazard classes and categories applied at the present time are shown in Table A1-1.

Table A1-1 Health hazard classes and categories applied

| | Hazard class | Category |
|----------------|--|------------|
| Health hazards | Acute toxicity – oral | 1, 2, 3, 4 |
| | Acute toxicity – dermal | 1, 2, 3, 4 |
| | Acute toxicity – gases | 1, 2, 3, 4 |
| | Acute toxicity – vapours | 1, 2, 3, 4 |
| | Acute toxicity – dusts and mists | 1, 2, 3, 4 |
| | Skin corrosion/irritation | 1, 2 |
| | Serious eye damage/irritation | 1, 2A, 2B |
| | Respiratory or skin sensitization | 1 |
| | Germ cell mutagenicity | 1A, 1B, 2 |
| | Carcinogenicity | 1A, 1B, 2 |
| | Reproductive toxicity | 1A, 1B, 2 |
| | Specific target organ toxicity (single exposure) | 1, 3 |
| | Specific target organ toxicity (repeated exposure) | 1, 2 |
| | Aspiration hazard | 1 |

Reference: Classification Criteria and Label Elements

Classification criteria and standardized label elements for the classes and categories to be applied are shown in Tables A1-2 to A1-15. Generally criteria shown here are applied for classification and labeling. However, this should be undertaken in the context of the principles found in the main body of this Guidance, especially with respect to the consideration of risk, the precedence of human experience and the use of available data. Additionally, further guidance on the application of the criteria may be found in the official GHS text (ST/SG/AC.10/30/Rev.2).

Table A1-2 Acute Toxicity – Oral




| Category | Criteria | Symbol | Signal Word | Hazard Statement |
|----------|--|--|-------------|----------------------|
| 1 | <ul style="list-style-type: none">• $LD_{50} < 5$ mg/kg bodyweight |  | DANGER | Fatal if swallowed |
| 2 | <ul style="list-style-type: none">• $5 < LD_{50} \leq 50$ mg/kg bodyweight |  | DANGER | Fatal if swallowed |
| 3 | <ul style="list-style-type: none">• $50 < LD_{50} \leq 300$ mg/kg bodyweight |  | DANGER | Toxic if swallowed |
| 4 | <ul style="list-style-type: none">• $300 < LD_{50} \leq 2000$ mg/kg bodyweight |  | WARNING | Harmful if swallowed |

Table A1-3 Acute Toxicity – Dermal





| Category | Criteria | Symbol | Signal Word | Hazard Statement |
|----------|---|--|-------------|------------------------------|
| 1 | • $LD_{50} < 50$ mg/kg bodyweight |  | DANGER | Fatal in contact with skin |
| 2 | • $50 < LD_{50} \leq 200$ mg/kg bodyweight |  | DANGER | Fatal in contact with skin |
| 3 | • $200 < LD_{50} \leq 1000$ mg/kg bodyweight |  | DANGER | Toxic in contact with skin |
| 4 | • $1000 < LD_{50} \leq 2000$ mg/kg bodyweight |  | WARNING | Harmful in contact with skin |

Table A1-4 Acute Toxicity – Inhalation: Gases





| Category | Criteria | Symbol | Signal Word | Hazard Statement |
|----------|-----------------------------------|--|-------------|--------------------|
| 1 | • $LC_{50} < 100$ ppmV |  | DANGER | Fatal if inhaled |
| 2 | • $100 < LC_{50} \leq 500$ ppmV |  | DANGER | Fatal if inhaled |
| 3 | • $500 < LC_{50} \leq 2500$ ppmV |  | DANGER | Toxic if inhaled |
| 4 | • $2500 < LC_{50} \leq 5000$ ppmV |  | WARNING | Harmful if inhaled |

Table A1-5 Acute Toxicity – Inhalation: Vapors





| Category | Criteria | Symbol | Signal Word | Hazard Statement |
|----------|---------------------------------|--|-------------|--------------------|
| 1 | • $LC_{50} < 0.5$ mg/L |  | DANGER | Fatal if inhaled |
| 2 | • $0.5 < LC_{50} \leq 2.0$ mg/L |  | DANGER | Fatal if inhaled |
| 3 | • $2.0 < LC_{50} \leq 10$ mg/L |  | DANGER | Toxic if inhaled |
| 4 | • $10 < LC_{50} \leq 20$ mg/L |  | WARNING | Harmful if inhaled |

Table A1.6 Acute Toxicity – Inhalation: Dusts and Mists





| Category | Criteria | Symbol | Signal Word | Hazard Statement |
|----------|----------------------------------|--|-------------|--------------------|
| 1 | • $LC_{50} < 0.05$ mg/L |  | DANGER | Fatal if inhaled |
| 2 | • $0.05 < LC_{50} \leq 0.5$ mg/L |  | DANGER | Fatal if inhaled |
| 3 | • $0.5 < LC_{50} \leq 1.0$ mg/L |  | DANGER | Toxic if inhaled |
| 4 | • $1.0 < LC_{50} \leq 5$ mg/L |  | WARNING | Harmful if inhaled |

Table A1-7 Skin Corrosion/Irritation



| Category | Criteria | Symbol | Signal Word | Hazard Statement |
|----------|---|--|-------------|---|
| 1 | <ul style="list-style-type: none">• Produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least 1 of 3 tested animals after exposure up to a 4 hour duration; typified by ulcers, bleeding, bloody scabs and, by the end of observation at 14 days, by discoloration due to blanching of the skin, complete areas of alopecia and scars. |  | DANGER | Causes severe skin burns and eye damage |
| 2 | <ul style="list-style-type: none">• Mean value of $\geq 2.3 - \leq 4.0$ for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or• Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or• In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above. |  | WARNING | Causes skin irritation |

Table A1-8 Serious Eye Damage/Irritation



| Category | Criteria | Symbol | Signal Word | Hazard Statement |
|----------|---|--|-------------|-------------------------------|
| 1 | <ul style="list-style-type: none"> • Causes irreversible effects on the eye: <ul style="list-style-type: none"> -- at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or -- at least in 2 of 3 tested animals, a positive response of corneal opacity ≥ 3 and/or iritis > 1.5, calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material. |  | DANGER | Causes serious eye damage |
| 2A | <ul style="list-style-type: none"> • Causes reversible effects on the eye: <ul style="list-style-type: none"> -- at least in 2 of 3 tested animals a positive response of corneal opacity ≥ 1 and/or iritis ≥ 1, and/or conjunctival redness ≥ 2, and/or conjunctival oedema (chemosis) ≥ 2, calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and -- which fully reverses within an observation period of normally 21 days |  | WARNING | Causes serious eye irritation |
| 2B | <ul style="list-style-type: none"> • Causes reversible effects on the eyes: <ul style="list-style-type: none"> -- at least in 2 of 3 tested animals a positive response of corneal opacity ≥ 1 and/or iritis ≥ 1, and/or conjunctival redness ≥ 2, and/or conjunctival oedema (chemosis) ≥ 2, calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and -- which fully reverses within an observation period of normally 7 days | no symbol | WARNING | Causes eye irritation |

Table A1-9 Respiratory or Skin Sensitization



| Category | Criteria | Symbol | Signal Word | Hazard Statement |
|--------------------------------|--|--|--------------------|---|
| Respiratory Sensitization 1 | <ul style="list-style-type: none">• There is evidence in humans that the substance can induce specific respiratory hypersensitivity; and/or• There are positive results from an appropriate animal test. |  | DANGER | May cause allergic or asthmatic symptoms or breathing difficulties if inhaled |
| Skin Sensitization 1 | <ul style="list-style-type: none">• There is evidence in humans that the substance can induce sensitization by skin contact in a substantial number of persons; or• There are positive results from an appropriate animal test. |  | WARNING | May cause an allergic skin reaction |

Table A1-10 Germ Cell Mutagenicity




| Category | Criteria | Symbol | Signal Word | Hazard Statement |
|----------|--|--|-------------|---|
| 1A | <ul style="list-style-type: none"> • Chemicals known to induce heritable mutations in germ cells of humans Positive evidence from human epidemiological studies. |  | DANGER | May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard) |
| 1B | <ul style="list-style-type: none"> • Chemicals which should be regarded as if they induce heritable mutations in the germ cells of humans <ol style="list-style-type: none"> (a) Positive result(s) from <i>in vivo</i> heritable germ cell mutagenicity tests in mammals; or (b) Positive result(s) from <i>in vivo</i> somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. This supporting evidence may, for example, be derived from mutagenicity/genotoxic tests in germ cells <i>in vivo</i>, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or (c) Positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people. |  | DANGER | May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard) |
| 2 | <ul style="list-style-type: none"> • Chemicals which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans Positive evidence obtained from experiments in mammals and/or in some cases from <i>in vitro</i> experiments, obtained from: <ol style="list-style-type: none"> (a) Somatic cell mutagenicity tests <i>in vivo</i>, in mammals; or (b) Other <i>in vivo</i> somatic cell genotoxicity tests which are supported by positive results from <i>in vitro</i> mutagenicity assays. |  | WARNING | Suspected of causing genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard) |

Table A1-11 Carcinogenicity









| Category | Criteria | Symbol | Signal Word | Hazard Statement |
|----------|---|--|-------------|--|
| 1A | <ul style="list-style-type: none"> Known to have carcinogenic potential for humans; the placing of a chemical is largely based on human evidence. |  | DANGER | May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard) |
| 1B | <ul style="list-style-type: none"> Presumed to have carcinogenic potential for humans; the placing of a chemical is largely based on animal evidence. Based on strength of evidence together with additional considerations, such evidence may be derived from human studies that establish a casual relationship between human exposure to a chemical and the development of cancer (known human carcinogen). Alternatively, evidence may be derived from animal carcinogenicity (presumed human carcinogen). In addition, on a case by case basis, scientific judgment may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals. |  | DANGER | May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard) |
| 2 | <ul style="list-style-type: none"> Suspected human carcinogens The placing of a chemical in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the chemical in Category 1. Based on strength of evidence together with additional considerations, such evidence may be from either limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies. |  | WARNING | Suspected of causing cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard) |

Table A1-12 Reproductive Toxicity

| Category | Criteria | Symbol | Signal Word | Hazard Statement |
|----------|--|--|-------------|--|
| 1A | <ul style="list-style-type: none"> • Known human reproductive toxicant The placing of the substance in this category is largely based on evidence from human. |  | DANGER | May damage fertility or the unborn child (state specific effect if known)(state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard) |
| 1B | <ul style="list-style-type: none"> • Presumed human reproductive toxicant The placing of the substance in this category is largely based on evidence from experimental animals. Data from animal studies should provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate. |  | DANGER | May damage fertility or the unborn child (state specific effect if known)(state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard) |
| 2 | <ul style="list-style-type: none"> • Suspected human reproductive toxicant This category includes substances for which there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects, and where the evidence is not sufficiently convincing to place the substance in Category 1. For instance, deficiencies in the study may make the quality of evidence less convincing, and in view of this Category 2 could be the more appropriate classification. |  | WARNING | Suspected of damaging fertility or the unborn child (state specific effect if known)(state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard) |

TableA1-13 Specific Target Organ Toxicity – Single Exposure

| Category | Criteria | Symbol | Signal Word | Hazard Statement |
|----------|---|---|-------------|--|
| 1 | <ul style="list-style-type: none"> Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following single exposure Placing a substance in Category 1 is done on the basis of: <ol style="list-style-type: none"> reliable and good quality evidence from human cases or epidemiological studies; or, observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. |  | DANGER | Causes damage to organs (state all organs affected, if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard) |
| 3 | <ul style="list-style-type: none"> Transient target organ effects There are target organ effects for which a substance/mixture may not meet the criteria to be classified in Category 1. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function. This category only includes narcotic effects and respiratory tract irritation. |  | WARNING | May cause respiratory tract irritation or May cause drowsiness or dizziness |

TableA1-14 Specific Target Organ Toxicity – Repeated Exposure

| Category | Criteria | Symbol | Signal Word | Hazard Statement |
|----------|---|--------|-------------|--|
| 1 | <ul style="list-style-type: none"> Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following repeated exposure Placing a substance in Category 1 is done on the basis of: <ol style="list-style-type: none"> reliable and good quality evidence from human cases or epidemiological studies; or, observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. | | DANGER | Causes damage to organs (state all organs affected, if known) through prolonged or repeated exposure (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard) |
| 2 | <ul style="list-style-type: none"> Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure Placing a substance in Category 2 is done on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. In exceptional cases human evidence can also be used to place a substance in Category 2. | | WARNING | May cause damage to organs (state all organs affected, if known) through prolonged or repeated exposure (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard) |

Table A1-15 Aspiration Hazard

| Category | Criteria | Symbol | Signal Word | Hazard Statement |
|----------|--|--------|-------------|--|
| 1 | <ul style="list-style-type: none"> Chemicals known to cause human aspiration toxicity hazards or to be regarded as if they cause human aspiration toxicity hazard: A substance is classified in Category 1 <ol style="list-style-type: none"> Based on reliable and good quality human evidence; or If it is a hydrocarbon and has a kinematic viscosity of 20.5 mm²/s or less, measured at 40° C. | | DANGER | May be fatal if swallowed and enters airways |

Annex 2

Procedure for Determination of Classification and Labeling

Annex 2 Procedure for Determination of Classification and Labeling

This Annex presents a methodology for determination of hazards and, for chronic endpoints, the likelihood of injury utilizing the results of hazard classification and exposure assessment, in order to determine the hazard to be indicated on the labels of household consumer products. The following sections set forth the major procedure for determining whether or not it is necessary to communicate the specific hazard information concerning such products.

A2.1 General Procedure for Hazard Classification and Its Labeling

A2.1.1 Determination of hazard classification

- 1) Specification of data and other information concerning the hazard of substances and mixtures
 - It is recommended to comply with the following procedure in classification of mixtures.
 - (i) If data or other information concerning the mixture itself is available, classify the mixture based on them (**Figure A2-1 a**).
 - (ii) If no such data or other information concerning the mixture itself is available, use data or other information for similar mixtures. The bridging principles noted in the GHS Official Text may be applied (**Figure A2-1 a'**).
 - (iii) If no data or other information concerning the mixture itself is available, make the classification using data or other information concerning each of the ingredients, in accordance with the methodology detailed in the GHS Official Text (**Figure A2-1 a''**).
- 2) Examine the aforementioned data or other information, and determine the hazard related to the substance or mixture (product) (**Figure A2-1 b**).
- 3) Determine the hazard category of the substance or mixture (product) as necessary, based on a comparative examination of the aforementioned data or other information and the hazard classification criteria (**Figure A2-1 c**).

The specific classification criteria related to substances or mixtures are based on the GHS Official text. **Table A2-1 and A2-2** show sources of information that can be used for classification of hazards.

A2.1.2 Determination of the likelihood of injury

For chronic health hazards in household consumer products (e.g., specific target organ toxicity due to repeated exposure (STOT), reproductive toxicity, and carcinogenicity), a decision on the need for labeling can be made on the basis of the results of an assessment of the likelihood of injury. The related major procedure is as follows.

- 1) Determine the pattern of exposure to the household consumer product to be classified (users, method of use, etc.) (**Figure A2-1 d**)
- 2) Determine the exposure level that causes no harm to humans or only a level of harm that may be insignificant. After that, determine whether the exposure level to the substance or mixture to be classified is equivalent to or lower than the level that does not cause harm or only poses an insignificant probability of causing harm (**Figure A2-1 e**).
 - (i) If the exposure level is equivalent to or lower than the level not causing harm to humans, that hazard would not be communicated on the label.
 - (ii) If the exposure level reveals a likelihood of injury, this hazard would have to be communicated on the label.

This assessment should be done for each chronic hazard for which a consumer product is classified.

Table A2-2 lists information sources of assistance in determination of exposure levels. The hazard and exposure information from the sources in Tables A2-1 and A2-2 allow for assessment of the likelihood of injury due to a chronic health hazard.

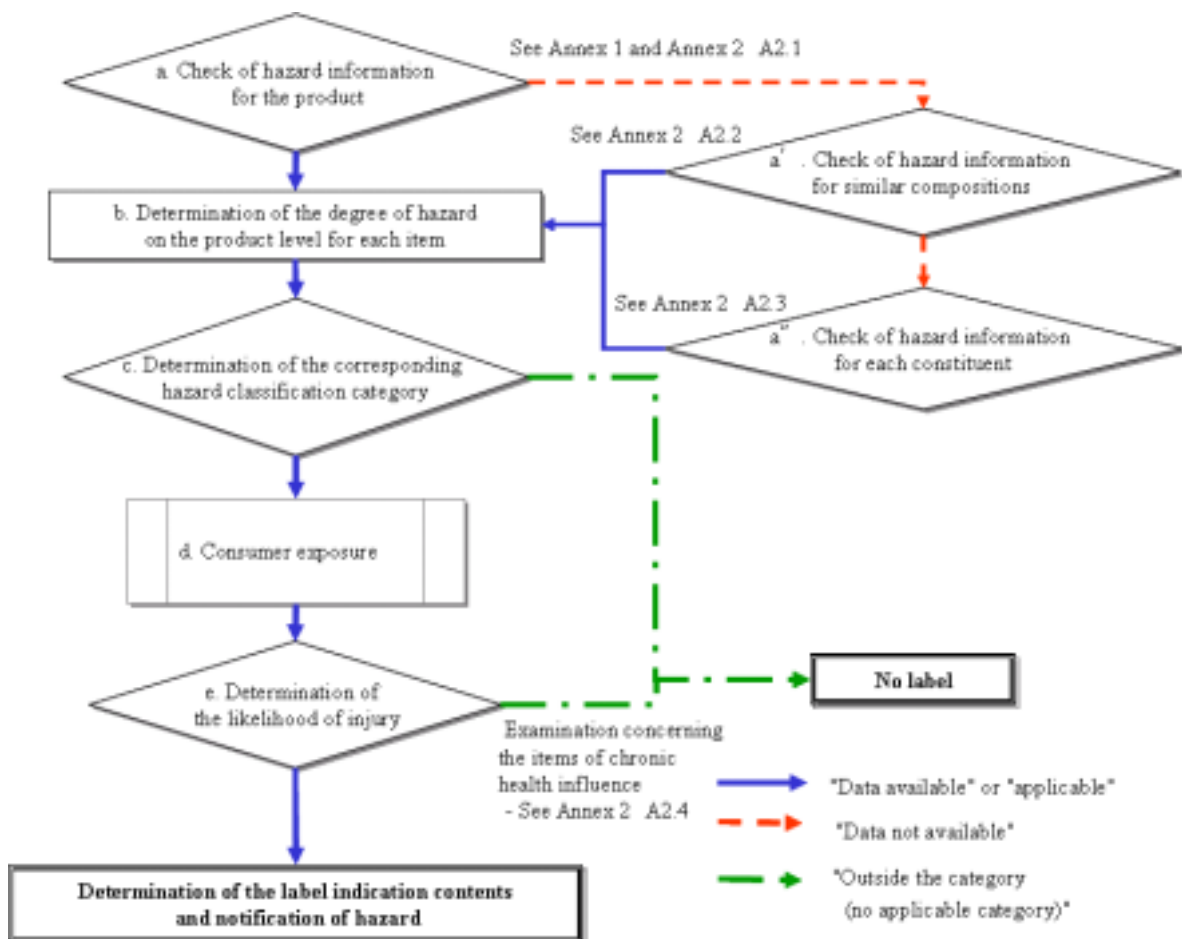


Figure A2-1 Procedure for determination of hazard category requiring notification on the label of household consumer products

A2.1.3 Sources of information useful for check of hazard information and decisions on the likelihood of injury

The tables below list sources of information useful for checking hazard information that could provide the grounds for classification and decisions on the likelihood of injury that determine whether or not labeling is necessary.

Table A2-1 Sources of information on hazard

| Subject information | Information sources |
|--|--|
| Hazard information for products | <ul style="list-style-type: none"> ▪ In-house data |
| Hazard information for similar compositions | <ul style="list-style-type: none"> ▪ In-house data ▪ See information concerning the human experience values for similar compositions |
| Hazard information for each ingredient (sources of information on the web) | <ul style="list-style-type: none"> ▪ In-house data ▪ International Chemical Safety Cards (ICSC) Japanese Version http://www.nihs.go.jp/ICSC/ ▪ UN Recommendations on the Transport of Dangerous Goods. Model Regulations. (Rev.14) online - http://www.unece.org/trans/danger/publi/unrec/rev14/14files_e.html ▪ NITE (National Institute of Technology and Evaluation): CHRIP (Chemical Risk Information Platform) http://www.safe.nite.go.jp/english/db.html ▪ CERI (Chemicals Evaluation and Research Institute): Safety assessment sheet http://www.cerij.or.jp/db/date_sheet_list/list_sideindex_cot.html ▪ NEDO (New Energy and Industrial Technology Development Organization) Initial risk assessment sheet http://www.safe.nite.go.jp/english/risk/initial_risk.html ▪ OECD HPV (High Production Volume Chemicals) SIDS Reports, etc. http://cs3-hq.oecd.org/scripts/hpv/ http://www.chem.unep.ch/irptc/sids/OECD/SIDS/sidspub.html ▪ European Chemicals Bureau (ECB) Risk assessment sheet http://ecb.jrc.it/ESIS/ ▪ U.S. NTP (National Toxicology Program) Websites for retrieval of test results http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm ▪ IARC (International Agency for Research on Cancer) Monographs http://monographs.iarc.fr/ ▪ U.S. EPA State of assessment under the HPV Challenge Program http://cfpub.epa.gov/hpv-s/ ▪ IPCS (WHO International Programme on Chemical Safety) INCHEM http://www.inchem.org/ ▪ HERA Risk assessment reports http://www.heraproject.com/RiskAssessment.cfm |

Table A2-1 Sources of information on hazard (continued)

| Subject information | Information sources |
|--|---|
| Hazard information for each ingredient (documents) | <ul style="list-style-type: none"> ▪ Patty's Toxicology (5th Edition) Volumes 1-8 Edited by: Bingham, Eula; Cohrsen, Barbara.; Powell, Charles H., John Wiley & Sons (2001) ISBN : 0471319430 ▪ Sax's Dangerous Properties of Industrial Materials - 3 volume set Edited by: Richard J. Lewis Sr. Wiley-Interscience; 10 edition (January 15, 2000) ISBN: 0471354074 |
| Information concerning human experience (Items to be considered) | <ul style="list-style-type: none"> ▪ Japan Poison Information Center http://www.j-poison-ic.or.jp/homepage.nsf ▪ U.S. CPSC (Consumer Product Safety Commission) http://www.cpsc.gov/ ▪ AAPCC (American Association of Poison Control Centers) http://www.aapcc.org/ |

Table A2-2 Exposure information: reference information concerning amounts, frequency, etc. of product use

| Information providers | |
|---|---|
| The Soap and Detergent Association | Exposure and risk screening method for consumer product ingredients April 2005 http://www.cleaning101.com/files/Exposure_and_Risk_Screening_Methods_for_Consumer_Product_Ingredients.pdf |
| Holland RIVM (National Institute for Public Health and the Environment) | ConsExpo. (Software: free of charge) http://www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp |
| Japan Chemical Industry Association | Risk Manager (Software: fee-based) http://chemrisk.org/contents/code/riskmanager |
| Advanced Industrial Science and Technology Research Institute of Science for Safety and Sustainability (RISS) | Exposure Factors Handbook http://unit.aist.go.jp/riss/crm/exposurefactors/ |
| Human and Environmental Risk Assessment on Ingredients of Household Cleaning Products | HERA Risk assessment reports http://www.heraproject.com/RiskAssessment.cfm |

A2.2 Bridging principles

When tests have not been conducted for classification of the product in question but sufficient data are available for the hazard of its ingredients and similar products, these data may be utilized in accordance with the bridging principles described below. This makes it possible to make maximum use of data that are applicable for reaching a decision on product hazard. However, product similarity must be determined for each hazard class, with consideration of the hazard of each ingredient, concentration in the mixture, and interaction. As a result, the process of decision-making regarding product similarity becomes more complicated as the number of ingredient types rises.

A2.2.1 Determination of hazard category based on hazard information for similar products

The determination of the hazard category of one product by means of hazard information for a similar one requires confirmation that the classification subject (Product B) is similar to another serving as the source of reference data on hazard classes (Product A). The basic rules for confirmation are termed "bridging principles."

The following conditions must be met to properly reach a decision that a given product belongs in the same hazard category as a similar one based on bridging principles.

- i) It must be confirmed that the two are similar in respect of composition, based on ingredients and their concentrations in the product (proportions).
- ii) It must be confirmed that any differences of composition do not affect the classification.

The following sections present the main points concerning the hazard classes for application of bridging principles as noted in Item ii) above. Reference must also be made to more detailed descriptions contained in Chapter 3 of the GHS Official Text (i.e., 3.1.3.5, 3.2.3.2, 3.3.3.2, 3.4.3.2, 3.5.3.2, 3.6.3.2, 3.7.3.2, 3.8.3.3, 3.9.3.3, and 3.10.3.2).

1) Dilution

The new product may be classified as equivalent to the existing product if it is diluted with a substance that belongs to a category of toxicity, corrosion or irritation that is no higher than that of the ingredient with the lowest degree of hazard as regards toxicity, corrosion, and serious eye damage and irritation, and said substance is not anticipated to have an effect on the degree of hazard of other ingredients in the same regard.

The new product also may be classified in the same way as the existing one if it is not a sensitizing substance itself and is diluted with a dilution agent that is not anticipated to have an effect on the sensitizing effect of other ingredients.

The new product may be classified in the same way as the existing one if it is diluted with a dilution agent that is not anticipated to have an effect on the germ cell mutagenicity or reproductive toxicity of the other ingredients.

The new product may be classified in the same way as the existing one if it is diluted with a dilution agent that is not anticipated to have an effect on the carcinogenicity of the other ingredients.

The following calculation may be performed for acute toxicity:

If the product is diluted with water or other similar substances, product toxicity may be calculated on the basis of test data for undiluted products. For example, if a product with an LD₅₀ concentration of 1,000 mg/kg is diluted with an equal proportion of water, the LD₅₀ concentration of the diluted product would be 2,000 mg/kg (calculation examples are presented in **Annex 2 A2.3**).

2) Production batch

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

3) Concentration of products with a high degree of toxicity, skin corrosion/irritation, serious eye damage/eye irritation, and sensitization

(i) Acute toxicity

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

(ii) Skin corrosion/irritation

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

(iii) Serious eye damage/eye irritation

If a tested product classified in the highest subcategory for serious eye damage is concentrated, a more concentrated product should be classified in the highest serious eye damage category without additional testing. In the event that a tested product classified in the highest subcategory for skin/eye irritation is

concentrated and does not contain serious eye damage ingredients, a more concentrated product should be classified in the highest irritation category without additional testing.

4) Interpolation within a single hazard category

For three products that have the same ingredients, where the products A and B are classified in the same irritation/serious eye damage toxicity category and Product C has a concentration of toxicologically active ingredients which is intermediate to those of products A and B, Product C is assumed to be in the same irritation/serious eye damage category as products A and B.

5) Essentially similar products

- (i) Acute toxicity, skin corrosion/irritation, serious eye damage/eye irritation, germ cell mutagenicity, carcinogenicity, reproductive toxicity, specific target organ toxicity (single exposure/repeated exposure)

The assumptions are as follows.

- (a) Two products: (i) A + B, (ii) C + B
- (b) The concentration of Ingredient B is essentially the same in both products.
- (c) The concentration of Ingredient A in Product (i) is equal to the concentration of Ingredient C in Product (ii).
- (d) For ingredients A and C, data concerning toxicity, skin corrosion/irritation serious eye damage/eye irritation are available and are substantially equivalent.

Based on these assumptions, if Product (i) has already been classified on the basis of test data, Product (ii) may be placed in the same hazard category. If Product (i) has not been classified, Product (ii) also would not be classified.

- (ii) Respiratory or skin sensitization

The assumptions are as follows.

- (a) Two products: (i) A + B, (ii) C + B
- (b) The concentration of Ingredient B is essentially the same in both products.
- (c) The concentration of Ingredient A in Product (i) is equal to the concentration of Ingredient C in Product (ii).
- (d) Ingredient B is a sensitizing substance, but ingredients A and C are not.
- (e) Ingredients A and C are anticipated not to exert an influence on the sensitization effect of B.

Based on these assumptions, if Product (i) has already been classified on the basis of test data, Product (ii) may be placed in the same hazard category. If Product (i) has not been classified, Product (ii) also would not be classified.

A2.2.2 Decision on similarity and example of application of bridging principles (items of short-term influence in the case of bleach)

This section describes the process of decision on similarity and application of bridging principles in the case of the classes of acute toxicity, skin corrosion/irritation, and serious eye damage/eye irritation, for an example bleach product.

| Reference Product A | Assessment Product B |
|---|---|
| Hypochlorite : 5% | Hypochlorite : 6% |
| Sodium hydroxide : 0.9% | Sodium hydroxide : 1% |
| Water and Other constituents : Balance | Water and Other constituents : Balance |
| pH : 12 | pH : >11.5 |

The data for Product A and its ingredients may serve as the basis for an inference of the toxicity and irritation degree of Product B and its classification.

1) Confirmation of similarity of composition

The two products are thought to have similar compositions, seeing that both consist mainly of hypochlorite and sodium hydroxide, and have a potential of hydrogen (pH) exceeding 11.5. The balance is mainly water. Other constituents are <1%.

2) Confirmation of influence of composition differences on hazard category

Of the ingredients composing products A and B, since the balance consists mainly of water, there is no apprehension about a difference in its proportion affecting the toxicity or irritation intensity of the other ingredients. The "other constituents" other than water have a concentration of less than 1% and are not of the type that must be taken into consideration under the GHS provisions. Judging from the general characteristics of each ingredient, there is no apprehension about a change in the toxicity or irritation intensity of the other ingredients at a concentration of less than 1%.

As such, determination of the classification of Product B based on the data for Product A would merely require examination as to whether or not the difference between the two in respect of the concentrations of hypochlorite and sodium hydroxide would change the toxicity or irritation intensity on the product level. Here, examples are provided for acute toxicity, skin corrosiveness/irritation, and serious eye damage/eye irritation.

[Acute toxicity]

| | Concentration in Product A | Concentration in Product B | Acute toxicity of ingredients in Product B, and reasons |
|------------------|----------------------------|----------------------------|--|
| Hypochlorite | 5.0% | 6.0% | <p>In testing of acute oral toxicity in mice using a product with an effective chlorine concentration of 6%, it has been confirmed that the oral LD₅₀ exceeds 2 g/kg.</p> <p>Therefore, it may be concluded that, even with a 1% increase in hypochlorite concentration, there would not be a significant influence as regards acute toxicity.</p> |
| Sodium hydroxide | 0.9% | 1.0% | <p>Even in the case of substances with a strong toxicity (LD₅₀ concentration of no more than 10mg/kg), an approximately 0.1% difference in sodium hydroxide concentration would not have a significant influence on the acute oral toxicity value. Therefore, it may be concluded that, even with a 0.1% increase in sodium hydroxide concentration, there would not be a significant influence as regards acute oral toxicity.</p> |

[Skin corrosion/irritation]

| | Concentration in Product A | Concentration in Product B | Skin corrosion/irritation of ingredients in Product B, and reasons |
|------------------|----------------------------|----------------------------|---|
| Hypochlorite | 5.0% | 6.0% | Sodium hypochlorite is generally classified as a severe skin irritant at concentrations of from 5% to less than 10%, and is not a skin corrosive at these product concentrations. Therefore, there would be no concern about a significant influence on the skin on the product level as a result of a 1.0% increase in the hypochlorite concentration. |
| Sodium hydroxide | 0.9% | 1.0% | There are no skin irritation data from testing with animals at concentrations under 1.0%. As the result of eye irritation testing, concentrations in the range of 0.2 - 1.0% are reportedly not irritating. Therefore, there would be no concern about a significant influence on the skin on the product level as a result of a 0.1% increase in the sodium hydroxide concentration. |

[Serious eye damage/eye irritation]

| | Concentration in Product A | Concentration in Product B | Potential to cause serious eye damage/eye irritation of ingredients in Product B, and reasons |
|------------------|----------------------------|----------------------------|--|
| Hypochlorite | 5.0% | 6.0% | Testing of eye irritation with eye drops at a sodium hypochlorite concentration of 5% and sodium hydroxide concentration of 1% reportedly confirmed damage to the cornea on the 21st day. Therefore, Product A would be classified in Category 1. Because Product B has a composition in which the main ingredients of Product A are increased slightly, it would be classified in Category 1, like Product A. |
| Sodium hydroxide | 0.9% | 1.0% | |

The results of the comparison of compositions noted above indicate that Product B would have about the same toxicity as Product A for the classes of acute toxicity, skin

corrosion/irritation, and serious eye damage/eye irritation. Therefore, the hazard category and label indication of Product B can be determined on the basis of the classification results for Product A.

For other hazards as well, hazard can be inferred from similar products by comparing the contents of the Official Text, differences of ingredients and their concentrations, and known hazard information. However, it is advisable to consult experts as necessary regarding the interpretation of hazard information for individual ingredients, which must take account of the weight of evidence in some cases.

A2.3 Additivity formula and additivity approach

In some cases, the product itself has not been tested to determine its classification and there are no similar products enabling application of bridging principles (see Annex 2 A2.2), but there are sufficient data for the individual ingredients. In such cases, the product can be classified using the additivity formula or additivity approach.

The GHS Official Text defines classification methodology using the additivity formula for acute toxicity and using additivity approach for skin corrosion/irritation and serious eye damage/eye irritation. The following sections present principles and examples of application of each methodology for each hazard endpoint.

A2.3.1 Acute toxicity: classification using the additivity formula

1) When data are available for all ingredients

The following guidelines should be followed in making acute toxicity estimates (ATE) for ingredients in order to accurately classify the product and perform only one calculation for all systems, divisions, and categories.

- Include ingredients whose acute toxicity is known and which are classified in a category of GHS acute toxicity.
- Ignore ingredients that may be considered not acutely toxic (e.g., water and sugar).
- Ignore ingredients that do not exhibit acute toxicity in a concentration of 2,000 mg/kg of body weight in testing at the oral limit dose.

As a general rule, determination of hazard category for products must take account of ingredients that are contained in a concentration of at least 1% (w/w for solids, liquids, dusts, mists, and vapors, and v/v for gases) as classification subjects. Ingredients contained in a concentration of less than 1 %, however, must present no possibility of affecting the acute toxicity classification on the product level. It is especially vital to bear this in mind when classifying products that have not undergone testing and contain ingredients in Category 1 or Category 2.

The product ATE for oral, dermal, and inhalation toxicity is determined in accordance with the following additivity formula utilizing the ATEs for each ingredient included in the product.

$$\frac{100}{ATE_{mix}} = \sum_n \frac{C_i}{ATE_i}$$

Here:

C_i = concentration of Ingredient i

n ingredients and i is running from 1 to n

ATE_i = acute toxicity estimate for Ingredient i

2) When data are not available for one or more ingredients

The additivity formula noted in A2.3.1-1 may be applied when ATEs are not available for individual ingredients but there are conversion values forecast from available information noted below.

Here, the following assessments may be applied.

- (i) Extrapolation among oral, dermal, and inhalation ATEs. Such an evaluation could require appropriate pharmacodynamic and pharmacokinetic data;
- (ii) Evidence from human exposure that indicates toxic effects but does not provide lethal dose data;
- (iii) Evidence from any other toxicity test/assays available on the substances that indicates acute effects but does not necessarily provide lethal dose data; or
- (iv) Data from closely analogous substances, using structure activity relationships.

This methodology generally requires substantial supplemental technical information and highly trained and experienced experts. If such information is not available, the classification may be made in accordance with Item A2.3.1-5.

3) When an ingredient without any useable information is contained in the product at a concentration of 1% or greater

In this case, it is concluded that a definitive ATE cannot be assigned to the product. In this case, the product should be classified based on the known ingredients only, with the additional statement that X% of the product consists of ingredient(s) with unknown toxicity.

4) When the total concentration of ingredients with unknown acute toxicity is equivalent to no more than 10% of the product

Classification using the additivity formula shown in A2.3.1-1).

5) When the total concentration of ingredients with unknown acute toxicity is equivalent to more than 10% of the product

The total concentration percentage of the unknown ingredients may be adjusted through the following adjustment of the additivity formula shown in A2.3.1-1).

$$\frac{100 - \left(\sum C_{unknown} \text{ if } > 10\% \right)}{ATE_{mix}} = \sum_n \frac{C_i}{ATE_i}$$

When experimentally obtained acute toxicity range values (or acute toxicity hazard categories) are available, a conversion can be made to the acute toxicity point estimates in accordance with the following Table A2-3, for calculation using this value.

The inhalation toxicity value is based on a 4 hour test in laboratory animals. When experimental values are taken from tests using 1 hour exposure, they can be converted to a 4 hour equivalent by dividing the 1 hour value by a factor 2 for gases and vapors and by 4 for dusts and mists.

TableA2-3 Table for conversion from the acute toxicity range estimates (or categories) obtained experimentally to acute toxicity point estimates for each type of exposure route

| | Classification category experimentally obtained acute toxicity range estimate | Converted Acute Toxicity point estimate |
|----------------------------------|---|---|
| Oral (mg/kg of body weight) | 0 < Category 1 ≤ 5 | 0.5 |
| | 5 < Category 2 ≤ 50 | 5 |
| | 50 < Category 3 ≤ 300 | 100 |
| | 300 < Category 4 ≤ 2000 | 500 |
| Dermal (mg/kg of body weight) | 0 < Category 1 ≤ 50 | 5 |
| | 50 < Category 2 ≤ 200 | 50 |
| | 200 < Category 3 ≤ 1000 | 300 |
| | 1000 < Category 4 ≤ 2000 | 1100 |
| Gas (ppmV) | 0 < Category 1 ≤ 100 | 10 |
| | 100 < Category 2 ≤ 500 | 100 |
| | 500 < Category 3 ≤ 2500 | 700 |
| | 2500 < Category 4 ≤ 20000 | 4500 |
| Vapor (mg/l) | 0 < Category 1 ≤ 0.5 | 0.05 |
| | 0.5 < Category 2 ≤ 2.0 | 0.5 |
| | 2.0 < Category 3 ≤ 10.0 | 3 |
| | 10.0 < Category 4 ≤ 20.0 | 11 |
| Dust/mist (mg/l) | 0 < Category 1 ≤ 0.05 | 0.005 |
| | 0.05 < Category 2 ≤ 0.5 | 0.05 |
| | 0.5 < Category 3 ≤ 1.0 | 0.5 |
| | 1.0 < Category 4 ≤ 5.0 | 1.5 |

A2.3.2 Dermal corrosion/irritation: classification using the additivity approach

1) When data are available for all or only some of the product ingredients

The classification is made through the following stages for ingredients contained in the product in a concentration of 1% (w/w for solids, liquids, dusts, mists, and vapors, and v/v for gases) or greater.

- (i) Confirm that there is no possibility related to classification of skin corrosion/irritation in a concentration range of less than 1% for the ingredients. If there is concern about skin corrosion/irritation in such a concentration range, make the classification in accordance with A2.3.2-2).
- (ii) For ingredients with a confirmed skin corrosion or irritation effect, check the following Table A2-4. If the combined concentration of such ingredients exceeds the cutoff value/limit concentration forming the classification standard, classify the product as corrosive or irritant.

Table A2-4 Relationship between concentrations of ingredients classified as skin Category 1 or 2 and product category

| Sum of ingredients classified as: | Concentration triggering classification of a product as: | |
|-----------------------------------|--|------------------------|
| | Skin corrosive | Skin irritant |
| | Category 1 | Category 2 |
| Skin Category 1 | $\geq 5\%$ | $< 5\%$ and $\geq 1\%$ |
| Skin Category 2 | | $\geq 10\%$ |

2) When the products to be classified contain specific types of ingredients, such as acids, bases, inorganic salts, aldehydes, phenols, and surfactants

Some acids, bases, inorganic salts, aldehydes, phenols, and surfactants are corrosive or irritant at concentrations of less than 1%. In such cases, corrosion/irritation intensity cannot be classified in accordance with the methodology described in A2.3.2-1) (which is premised on a lack of influence by ingredients in concentrations of less than 1%). Instead, make the classification in accordance with one of the standards in items i) - iv) below, based on the information for ingredient pH and toxicity.

- (i) Mixtures, including strong acids or strong bases: use the pH value as the classification standard
- (ii) When a classification cannot be made by the methodology in accordance with Table A2-5 and the product contains corrosive ingredients at a concentration of at least 1%: place in Category 1.
- (iii) When a classification cannot be made by the methodology in accordance with Table A2-5 and the product contains corrosive ingredients at a concentration of at least 3%: place in Category 2 (or 3).

- (iv) Other products that cannot be classified by the methodology in accordance with Table A2-5: classify in accordance with Table A2-5.

Table A2-5 Relationship between concentration of ingredients for which the additivity approach cannot be applied and product category

| Ingredient | Concentration | Mixture category: skin |
|---|---------------|------------------------|
| Acids pH ≤ 2 | $\geq 1\%$ | Category 1 |
| Bases pH ≥ 11.5 | $\geq 1\%$ | Category 1 |
| Other corrosive (Category 1) ingredients for which the additivity calculation is not applicable | $\geq 1\%$ | Category 1 |
| Other irritating (Category 2) ingredients for which the additivity calculation is not applicable, including acids and bases | $\geq 3\%$ | Category 2 |

There may be reliable data indicating a lack of irritating or corrosive influence on the skin by an ingredient even at a concentration above the general cutoff levels indicated in Table A2-5 or Table A2-6. In this case, make the classification of the mixture based on those data. Conversely, if there are data indicating the presence of an irritating or corrosive effect even at a concentration of less than 1% (corrosive) or 3% (irritant), the product is to be classified in accordance with these data. If it is anticipated that the ingredients do not have an irritating or corrosive effect on the skin, testing may be considered for the product as a whole.

A2.3.3 Serious eye damage/irritation: classification using the additivity approach

1) When data are available for all or only some of the product ingredients

The classification is made through the following stages for ingredients contained in the product at a concentration of at least 1% (w/w for solids, liquids, dusts, mists, and vapors, and v/v for gases).

- (i) Confirm that there is no possibility related to classification of skin corrosiveness or irritation in a concentration range of less than 1% for ingredients with a concentration of less than 1%. If there is apprehension about an influence on skin corrosion or irritation in such a concentration range, make the classification in accordance with A2.3.3-2).
- (ii) For ingredients with a confirmed corrosiveness or irritation effect, check the following table. If the combined concentration of such ingredients exceeds the cutoff value/limit concentration forming the classification standard, classify the product as corrosive/irritant.

Table A2-6 Relationship between concentration of ingredients in skin Category 1 or eye Category 1 or 2 and product category

| Classification based on combined ingredient concentrations | Ingredient concentration for mixture classification | |
|--|---|-----------------------|
| | Irreversible eye effect | Reversible eye effect |
| | Category 1 | Category 2 |
| Eye or skin Category 1 | ≥3% | <3% and ≥1% |
| Eye Category 2/2A | | ≥10% |
| (10×Eye Category 1)+ Eye Category 2/2A | | ≥10% |
| Eye Category 1+ Skin Category 1 | ≥3% | <3% and ≥1% |
| 10×(Skin Category 1×Eye Category 1)+ Eye Category 2A/2B | | ≥10% |

2) When the products to be classified contain specific types of ingredients, such as acids, bases, inorganic salts, aldehydes, phenols, and surfactants

Some acids, bases, inorganic salts, aldehydes, phenols, and surfactants exhibit a corrosive or irritating effect even at a concentration of less than 1%. In such cases, corrosiveness/irritation intensity cannot be classified in accordance with the methodology described in A2.3.3-1) (which is premised on a lack of influence by ingredients in concentrations of less than 1%). Instead, make the classification in accordance with one of the standards in items i) - iv) below, based on the information for ingredient pH and toxicity.

- (i) Mixtures including strong acids or strong bases: use the pH value as the classification standard
- (ii) When a classification cannot be made by the methodology in accordance with Table A2-6 and the product contains corrosive ingredients at a concentration of at least 1%: place in Category 1.
- (iii) When a classification cannot be made by the methodology in accordance with Table A2-6 and the product contains corrosive ingredients at a concentration of at least 3%: place in Category 2.
- (iv) Other products that cannot be classified by the methodology in accordance with Table A2-6: classify in accordance with Table A2-8.

Table A2-7 Relationship between concentration of ingredients for which the additivity approach cannot be applied and product category

| Ingredient | Concentration | Mixture category: eye irritation/corrosion |
|---|---------------|--|
| Acids pH ≤ 2 | ≥1% | Category 1 |
| Bases pH ≥ 11.5 | ≥1% | Category 1 |
| Other corrosive (Category 1) ingredients for which the additivity calculation is not applicable | ≥1% | Category 1 |
| Other irritating (Category 2) ingredients for which the additivity calculation is not applicable, including acids and bases | ≥3% | Category 2 |

There may be reliable data indicating a lack of reversible or irreversible influence on the eye by an ingredient even at a concentration above the general cutoff levels indicated in Table A2-6 or Table A2-7. In this case, make the classification of the product based on those data. If it is anticipated that the ingredients do not have an irritating or corrosive effect on the skin, that conclusion may be applied to the product as a whole. Conversely, if there are data indicating the presence of an irritating or corrosive effect even at a concentration of less than 1% (corrosive) or 3% (irritant), the product is to be classified in accordance with these data.

A2.3.4 Example of classification using the additivity formula and additivity approach

This section intends to show how to apply the additivity approach in case that no human experience nor animal data are available. This section describes the process of application of the additivity formula and additivity approach related to acute toxicity, skin corrosion/irritation, and serious eye damage/eye irritation.

A2.3.4.1 Example of classification of a product

This section describes the process of classification of a product with the composition shown below based on the additivity formula and approach, with respect to acute toxicity, skin corrosion/irritation, and serious eye damage/eye irritation.

| | |
|---------------------------------|-------------|
| Ingredient A | : 6% |
| Ingredient B | : 1% |
| Water and Other constituents | : Balance |
| pH | : Over 11.5 |

Of the ingredients composing the composition noted above, the balance consists mainly of water, and there is no apprehension about a difference in its proportion affecting the toxicity or irritation intensity of the other ingredients. The “other constituents” other than water have a concentration of less than 1% and are not of the type that must be taken into consideration under the GHS provisions. Judging from the general characteristics of each ingredient, there is no apprehension about a change in the toxicity or irritation intensity of the other ingredients at a concentration of less than 1%.

Therefore, the examination of classification based on the additivity formula or additivity approach would focus on the hazard influence of Ingredients A and B in each of the categories of acute toxicity, skin corrosion/irritation, and serious eye damage/eye irritation.

1) Acute toxicity

The following data are available for the acute oral toxicity of ingredient A and B.

- ✧ Ingredient A: 5,800 mg/kg (oral LD₅₀ value in testing with mice)
- ✧ Ingredient B: 325 mg/kg (oral LD₅₀ value in testing with rabbits)

The other ingredients may be ignored as far as toxicological effect is concerned. In addition, ingredients that do not exhibit acute toxicity in testing of oral limit dose at a concentration of 2,000 mg/kg (not classified) may also be ignored.

The formula.

$$\frac{100}{ATE_{mix}} = \sum_n \frac{C_i}{ATE_i} \quad \text{can be converted into} \quad ATE_{mix} = \frac{100}{\sum_n \frac{C_i}{ATE_i}}$$

Then,

| |
|--|
| $\begin{aligned} \text{ATE on the product level} &= \frac{100}{(6/5800 \text{ mg / kg}) + (1/325 \text{ mg / kg})} \\ &= 24390 \text{ mg / kg} = 24.39 \text{ g / kg} \end{aligned}$ |
|--|

The ATE calculation value indicates that the oral LD₅₀ value exceeds 2,000 mg/kg on the product level. As such, it may be concluded that the product should not be classified for acute oral toxicity.

| |
|--|
| Acute oral toxicity of the product based on the additivity formula: not classified |
|--|

If there is no information about the toxicity of other ingredients, and those ingredients make up no more than 10% of the product taken together, the calculation would include a concentration correction based on the equation in A2.3.1-5.

2) Skin corrosion/irritation

The product concentrations of Ingredients A and B are each higher than the cutoff values. For this reason, the classification would be made in accordance with the description in A2.3.2-2 if the additivity approach is applied. The following procedure is to be applied in classification of products that contain acids or bases.

- (i) Check the pH of each ingredient to be classified
 - Ingredient A: pH 10 - 11 in a 5% solution and pH 11.2 in a 15% solution
 - Ingredient B: about pH 13 in a 1% solution

Because the product has a 1% content of a substance with a pH of over 11.5, its skin corrosion/irritation may be placed in Category 1, based on the description in A2.3.2-2 (i).

The classification work may be concluded at this stage. Nevertheless, categorization based on pH values alone often yield results that are different from the realities of the corrosion/irritation that can be caused by the finished product. If it is thought that the classification results based only on pH value do not reflect the actual product hazard in light of information from human use of similar products, it would be advisable to proceed to the second step instead of concluding the classification work at this stage.

(ii) Determine the hazard category for each ingredient to be classified, based on the data for corrosiveness/irritation

✧ Ingredient A: corresponds to Category 1. The data serving as grounds are as follows.

In this case we will assume it have been classified as a corrosive substance at a concentration of at least 10%

✧ Ingredient B: corresponds to Category 1. The data as grounds are as follows. Appearance of serious tissue destruction and mortality in all dermal layers at a concentration of at least 8% would lead to a classification of corrosive for this substance.

(iii) Determine the category on the product level based on the category of each ingredient determined in the second step.

Because the product contains corrosive substances in excess of the cutoff values, the category would be determined in accordance with the contents of Table A2-6. The classification results of the second step indicate that the composition could be considered one that has a content of at least 1% corrosive substances, although it is not the subject of additivity calculation by reason of other corrosive (Category 1) ingredients. Therefore, its skin corrosion/irritation on the product level would correspond to Category 1.

| |
|---|
| Skin corrosion/irritation of the product based on the additivity approach: Category 1 |
|---|

3) Serious eye damage/eye irritation

The product concentrations of Ingredient A and B are each higher than the cutoff values. For this reason, the classification would be made in accordance with the description in A2.3.3-2 of Annex 2 if the additivity approach is applied. The following procedure is to be applied in classification of products that contain acids or bases.

(i) Check the pH of each ingredient to be classified

✧ Ingredient A: pH 10 - 11 in a 5% solution and pH 11.2 in a 15% solution,

✧ Ingredient B: about pH 13 in a 1% solution

Because the product has a 1% concentration of a substance with a pH over 11.5, its degree of serious eye damage/eye irritation may be placed in Category 1, based on the description in A2.3.3-2 (i) of Annex 2.

| |
|--|
| Serious eye damage/eye irritation based on the additivity approach: Category 1 |
|--|

The classification work may be concluded at this stage. Nevertheless, categorization based on pH values alone often yield results that are divorced from the realities of the corrosion/irritation that can be caused by the finished product. If it is thought that the classification results based only on pH value do not reflect the actual product hazard in light of information from human use of similar products, it would be advisable to proceed to the second step instead of concluding the classification work at this stage.

(ii) Determine the category for each ingredient to be classified, based on the data for serious eye damage/irritation

✧ Ingredient A: corresponds to Category 1. The data serving as grounds are as follows.

Classification as a corrosive substance at a concentration of at least 10%

✧ Ingredient B: corresponds to Category 1. The data serving as grounds are as follows.

Classification as a corrosive substance at a concentration of at least 5%

(iii) Determine the hazard category of the product based on the hazard category of each ingredient determined in the second step.

Because the mixture contains corrosive substances in excess of the cutoff values, the category would be determined in accordance with the contents of Table A2-6 of Annex 2. The classification results of the second step indicate that the product could be considered one that has the content of at least 1% corrosive substances, although it is not the subject of additivity calculation for reason of other corrosive (Category 1) ingredients. If classified on the basis of the existing assessment results for each ingredient, it would fall in Category 1 on the product level in terms of serious eye damage/irritation.

A2.3.4.2 Example of classification of a dishwashing detergent

This section describes the process of classification of a dishwashing detergent with the composition shown below based on the additivity approach, with respect to skin corrosion/irritation and serious eye damage/irritation. The additivity approach may not be the best approach to use first for addressing skin and eye effects, but in a case where there is no human experience information or available animal test data, this example shows how it might be employed.

| | |
|--------------------------------------|-------|
| Anionic surfactants ^{*1} | : 20% |
| Amphoteric surfactants ^{*2} | : 5% |
| Nonionic surfactants ^{*3} | : 5% |
| Ethanol | : 5% |
| Water | : 65% |

*1: Alkylether sulfonates (AES) 10%, alkyl sulfonates (AS) 10%

*2: Alkylamine oxide (AO) 5%

*3: Polyoxyethylene alkylether (AE) 5%

1) Skin corrosion/irritation

(i) Check the pH of the mixture or of each ingredient to make a classification decision.

The pH in the example is in the range of 2 - 11.5, and this suggests the product does not belong in Category 1.

- (ii) Determine the hazard category for each ingredient to be classified, based on the data for corrosion/irritation

Use the information sources noted in A3.1 of Annex 3 to obtain data for the corrosion/irritation of each ingredient, and classify each on that basis, as far as possible.

* AES

Closed patch study (in conformance with OECD 404) of base liquid (90% concentration) yielded average scores of 2.33 for erythema and 2.78 for edema. Because the reaction had completely subsided 14 days later, it was concluded that the substance was a moderate irritant. At a 10% concentration, its irritation was found to be from mild to moderate. As such, a solution with a 10% concentration of AES would probably be placed in Category 2.

* AS

AS is considered to have an irritation effect of from moderate to severe at a concentration of 10%, but is not regarded as a corrosive. Therefore, a 10% solution of AS would presumably be placed in Category 2.

* AO

AO is considered not to have a significant irritating effect at a concentration of 5%. To judge from these data, there would be no need to take account of AO in a classification with respect to skin corrosion/irritation.

* AE

AE is generally used in detergents for dishwashing and reportedly has a mild-to-moderate irritating effect at a concentration of 10%. In addition, it has a primary irritation index (PII) value of 1.0 for skin at a concentration of 60%. At a concentration of 5%, it would probably not exhibit corrosive effects even if it causes a strong reaction, and should presumably be left in Category 2.

* Ethanol

Ethanol reportedly does not irritate the skin. There would be no need to take account of it in a classification with respect to skin corrosion/irritation.

- (iii) Determine the category on the product level based on the category of each ingredient determined in the second step.

As noted in above, AES, AS, and AE each belong in Category 2 in terms of irritation. Based on the classification in accordance with the EU Council Directive 67/548/EEC each surfactant exhibits no corrosiveness. Example A consequently would not be placed in Category 1.

Therefore, in classification based on the additivity approach, the example product would be placed in Category 2 for skin corrosion/irritation.

| |
|---|
| Skin corrosion/irritation of the product based on the additivity approach: Category 2 |
|---|

As shown in A3.1 of Annex 3, placement of the example product (dishwashing detergents) outside any category of skin corrosion/irritation based on information concerning human experience is more appropriate. In similar products as well, precedence should be accorded to classification based on human experience if it is possible to make a classification on that basis, even if the classification based on the additivity approach places the product in Category 2.

2) Serious eye damage/irritation

(i) Check the pH of the product or of each ingredient to make a classification decision.

The pH in the model is in the range of 2 - 11.5, and this suggests the product does not belong in Category 1 as far as pH is concerned.

(ii) Determine the category for each ingredient to be classified, based on the data for corrosiveness/irritation.

Use the information sources noted in A3.1 of Annex 3 to obtain data for the corrosiveness/irritation of each ingredient, and classify each on that basis, as far as possible.

* AES

AES is said to be a mild to moderate irritant at a concentration in the range of 1 - 10 %. In an eye irritation study of one substance in the range of 2 - 10%, AES caused iritis and minor conjunctivitis. Both conditions, however, reportedly cleared up within two days. Therefore, at a 10% concentration, it would probably be placed in Category 2B, as it did not exhibit corrosiveness.

* AS

AS is considered to be a moderate irritant at a concentration of 10%. Therefore, a 10% solution of AS would presumably be placed in Category 2A.

* AO

AO is considered not to show a significant eye irritation potential at a concentration of 5%. To judge from these data, there would be no need to take account of AO in such a classification.

* AE

AE would probably not show an eye irritation potential on a par with a category at a concentration of 5%³, and there would be no need to take account of it in such a classification.

* Ethanol

In a 27% aqueous solution, ethanol has a minimal eye irritation potential (MAS = 2.7, recovery on the day after eye drops), and there would be no need to take account of it in such a classification at a concentration of 5%.

- (iii) Determine the category on the product level based on the category of each ingredient determined in the second step.

As noted in Section (ii) above, AES and AS, the main surfactants in the model, each belong in Category 2A in terms of irritation. It would correspond to “Other irritant” (Category 2) ingredients for which additivity does not apply, including acids and bases, as noted in Table 3.3.4 of the GHS Official Text.

Therefore, its serious eye damage/eye irritation would correspond to Category 2A.

| |
|---|
| Serious eye damage/eye irritation of the product based on the additivity formula: Category 2A |
|---|

As shown in A3.1 of Annex 3, placement of the example product (dishwashing detergents) in Subcategory 2B for serious eye damage/eye irritation based on information concerning human experience is appropriate. In similar products as well, precedence should be accorded to classification based on human experience if it is possible to make a classification on that basis, even if the classification based on the additivity approach places the product in Category 2A.

³ Human and Environmental Risk Assessment on ingredients of household cleaning Products (HERA), Alcohol Ethoxylates, May 2007 http://www.heraproject.com/files/34-F-HERA-AE-HH+ENV%20Final%20Draft%20Report_01-05-07.pdf

Annex A2.4 Approach for determination of consumer product labeling regarding chronic effects on human health based on the likelihood of injury (risk)

Of the hazards subject to GHS classification and labelling, this text (A2.4) applies to chronic effects on human health [e.g., carcinogenicity, reproductive toxicity, and specific target organ toxicity (repeated exposure)].

Unlike the case of work environments, where factory workers, for example, can all be fully provided with information on avoiding or minimizing hazards during safety training in addition to the SDS and label, the label is the sole source of information on product hazard in the case of consumer products used by the general public. As a result, in such situations, efforts must be made to avoid providing too much or too little information and incorporate data or information that are necessary and sufficient to enable consumers to use products properly and avoid their dangers. To this end, it is necessary to clearly ascertain the likelihood that the product will cause injury under condition of use and to determine the appropriate labeling on the basis of that likelihood. The work on the GHS has not addressed harmonization of this type of approach. Therefore, specific procedures for manufacturers to use in applying this approach would have to be adopted by the competent authority (GHS Official Text, A5.1.2). In Japan, the GHS Inter-ministerial Committee (held on 11 January 2007) recognized it is appropriate to determine the contents of labels regarding chronic effects on human health posed by consumer use based on the results of risk assessments on hazardous chemicals. Its concept was officially announced in a document entitled “Outlook on Assessment of Risk of Exposure to Consumer Products to Determine GHS Labeling.”⁴

In this guidance for consumer products, exposure assessment is applied to determine the necessity of indicating label elements and information that needs to be included on the label in this type of approach. For consumer products* containing a chemical(s) having chronic health hazards included in GHS for classification, manufacturers can determine the necessity and content of the labeling based on an evaluation as to whether or not there is a likelihood of injury (or Risk**) due to use of the product. To make such determinations for chronic endpoints, manufacturers acquire data for exposure in normal use and foreseeable misuse. Next, they conduct a risk assessment referring to these exposure data to determine, in accordance with a risk-based approach, the need for indicating GHS label elements for a chronic health hazard on the product label and the advisable preventive measures. It may happen that the studies of the exposure data and of health hazards information reveal that the likelihood of injury (risk) of the product under the anticipated exposure conditions is below a certain level. In such cases, it is not necessary to include information concerning the chronic health effect on the GHS label of the product. This kind of phased approach for risk assessment may be applied in determining classification for health effects items (e.g. carcinogenicity, reproductive toxicity, specific target organ toxicity [repeated exposure]) induced by chronic or repeat exposure to the product.

* Consumer cleaning products rarely contain ingredients that are classified into more than one of the hazard categories of chronic health effects under the GHS. Therefore, the procedure of risk assessment taking account of the effects of two or more constituents (i.e., additive and synergic action) are excluded from the scope of this guidance. The guidance presents a procedure for risk assessment on the product based on the results of an assessment of the hazard and exposure of single constituents.

** Risk:

In the general sense, risk is defined as the degree of hazard, as exemplified by “a function of the probability of occurrence of a certain endpoint and the significance of that endpoint” (National Institute of Advanced Industrial Science and Technology, CRM) and “the combination of the probability of occurrence of harm and the degree of that harm” (ISO/IEC Guide 51, 1999). In

⁴ Outlook on Risk Assessment for Consumer Products Based on Exposure for GHS Labeling (Unofficial Provisional Translation)
http://www.meti.go.jp/policy/chemical_management/int/files/ghs/risk_based_label_interministerial080218set.doc

assessment of risk to human health, however, it is not the ordinary practice to make a quantitative assessment taking account of the severity of the endpoint to be assessed. The degree of risk is instead estimated through comparison between the daily exposure (quantity) based on a semi-quantitative calculation and the Tolerable Daily Intake (TDI) (or, where available for food and food additives, the Acceptable Daily Intake (ADI)). In this guidance, we therefore adopted “the likelihood of adverse effect,” definition in *Casarett & Doull's Toxicology, 6th ed.: The Basic Science of Poisons, Klaassen, Curtis D., 2004* as one reflecting the characteristics of risk assessment to human health.

A2.4.1 General approach

The following sections set forth an integrated approach, utilizing the hazard classification and exposure results, for determination of hazard labeling to be indicated on consumer product labels.

1) Classification based on characteristic chronic health hazard

The methodology begins with the determination of whether or not the consumer product satisfies the GHS classification criteria regarding intrinsic chronic health hazards.

Consumer products containing one or more hazardous ingredients classified in GHS category must be classified according to the criteria for that endpoint. However, for the hazards such as sensitization, germ cell mutagenicity, carcinogenicity, reproductive toxicity, and specific target organ toxicity (repeated exposure), the approach noted below shall be utilized to determine the risk of injury to consumers and the appropriate labeling.

The next step for determining the GHS label elements to be applied to the consumer product is to determine the likelihood of injury (risk) posed by the chronic health effect for which the consumer product is classified. This step contains many important items:

- Identification of the possibility of consumer exposure to the product
- Estimation of the level of exposure that does not cause any chronic health effect or poses only a insignificant risk of such effect
- Determination of whether the level of exposure to the classified substance or mixture is equivalent to or below the level which poses no chronic health effect
- Determination of the chronic health effect which has influence on the likelihood of injury (risk)

The likelihood of injury (risk) shall be determined by comparison of the exposure level obtained from the exposure assessment utilizing the tiered approach presented below, and the Tolerable Daily Intake (TDI) value calculated based on human or animal testing data. If values have been established for the Acceptable Daily Intake (ADI) of the substance in question in use for food additives or other purposes, these values can be used to determine the likelihood of injury (or examine a risk).

2) Exposure assessment

(i) Qualitative exposure assessment

The first step in exposure assessment consists of a qualitative assessment.

The task in this step is to determine whether or not the use of the product will lead to no or insignificant exposure and, therefore, insignificant likelihood of injury (risk).

If there is no exposure or it is insignificant, hazard communication is not required. The following may be cited as cases in which there is no exposure.

- The product contains chemical substances that are classified into a certain classes or categories of chronic health effects, however, there is evidence that these substances are not released from the product.

- The likelihood of chronic health effects can be disregarded because the chemical substances that have such effects if inhaled are enclosed in a non-sprayable liquid matrix or in non-inhalable or non-friable capsules in the product.

In contrast, when it is found that exposure may not be insignificant, a determination is made of the GHS communication elements to appear on the label based on the intrinsic hazards of the product. Alternatively, a more accurate exposure assessment can be made by the approach described in Section (ii) below.

(ii) Semi-quantitative exposure assessment

Next step is a semi-quantitative exposure assessment to develop an approximate conservative assessment of exposure.

One approach to semi-quantitative exposure assessment is to assume consumer exposure to the entire product in the prescribed container every day, and absorption of the total amount of the product's component substance or mixture into the body on a continuous basis throughout the consumer's life. Such assumptions are extremely unrealistic for almost all consumer products. Nevertheless, some consumer products are designed for consumption of the entire amount in a single use or in a day.

After that, a comparison is made between the exposure level estimated on the basis of this assumption and the dose at which the hazard would produce an effect. If it is concluded that the risk to consumers is low, GHS label elements regarding the hazard are not required. If it is concluded that the risk is significant, a more accurate assessment can be made according to the following step before making a final decision on the labeling.

It should be noted that GHS label elements shall be applied to the product when exposure data are insufficient to make a refined assessment or the manufacturer decides to label for the chronic hazard rather than proceed to do further analysis.

(iii) Refined semi-quantitative exposure assessment

Refined semi-quantitative assessment of exposure can yield estimates that are closer to the realities by incorporating information and numerical data from the standard use scenario for the product in question (for amount of product daily use, exposure routes, etc).

In this step, a variety of data sources are available to help exposure assessment. Information on consumers' actual use of products can be obtained from use tests conducted during product development, data possessed by manufacturers, the results of investigative research by administrative agencies, data from the Japan Poison Information Center, and consumer comments. Furthermore, much numerical exposure data related to consumer products can be obtained from the Technical Guidance Document (TGD) or Guidance on Risk Assessment of Chemicals⁵ following European Regulations and Directives and documents published by the US Environmental Protection Agency (EPA).⁶ The Soap and Detergent Association (SDA) in the U.S. has also published guidance information regarding exposure assessment.²³

The major factors to be considered in estimating exposure to consumer products and their ingredients are as follows:

- Routes of exposure (oral, dermal, inhalation)
- Frequency and duration of exposure
- Product use (e.g., amount of product used, concentration of hazardous ingredients in the product, use concentration of the product)
- Potential of systemic absorption

⁵ EU Technical Guidance Document in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market (Edition 2) <http://ecb.jrc.it/Technical-Guidance-Document/>

⁶ USEPA, Exposure Factors Handbook, <http://www.epa.gov/ncea/efh/>

If it is found that the exposure level calculated (see A2.4.2) on the basis of this information is sufficiently low so as to assure that humans are not harmed as a result of consumer product use, there would be no need for hazard communication on the product label. If this is not the case, a manufacturer can label for the chronic hazard or a more detailed assessment can be made of exposure and risk before making a final decision on the need for hazard communication on the product label.

A2.4.2 Guidance for determination of exposure level and TDI

1) Procedure for calculation of estimated values for consumer exposure based on “Semi-quantitative exposure assessment” or “Refined semi-quantitative exposure assessment”

This section provides guidance for calculation of estimated values for consumer exposure for consumer products through the execution of assumption-based or refined semi-quantitative assessments.

- (i) Calculation of estimated consumer exposure by semi-quantitative exposure assessment
As noted in A2.4.1-2) (ii), in this step of exposure assessment, a determination is made of the amount of daily consumer exposure based on a worst-case scenario for product use.

For this level of assessment, the daily systemic exposure (D_{exposure} ; expressed as mass of chemical per unit mass of body weight per day) is calculated from:

$$D_{\text{exposure}} = Q_{\text{product}} F1/BW$$

where " Q_{product} " indicates total amount of the product's ingredients. At this tier, it is assumed that the entire product is taken into the body every day. "F1" refers to the concentration of the substance in the product (%). "BW" refers to the average body weight of an adult.

- (ii) Calculation of estimated consumer exposure by refined semi-quantitative exposure assessment

In this step of exposure assessment, the total exposure level in the body is calculated by specifying the foreseeable routes of exposure during product use and calculating the exposure levels over each. The following gives an account of the basic approach for calculating the exposure level over each route (oral, dermal, and inhalation). It is not necessary to calculate the exposure level for the routes in which no possibility of exposure during actual use of the product is expected to occur.

Oral exposure

The following case must be taken into account as regards chronic oral exposure to consumer products:

- Possible intake of the chemical substance resulting from normal use of the product, such as oral ingestion of the chemical in the product upon transfer of the product to food or drinks, directly or indirectly, during or after use.

The calculation procedures for estimating the daily systemic exposure from oral exposure are shown below. The rate of transfer to food and drinks are also considered in accordance with the usage of the consumer product.

The equation for estimating the daily systemic exposure through oral routes (D_{oral}) is as follows:

$$D_{\text{oral}} = Q_{\text{oral}} f_{\text{oral}}/BW$$

- Q_{oral} : the amount of the chemical in the product ingested daily (mg/day)

The Q_{oral} value can be calculated using the following equation.

$$Q_{\text{oral}} = w_p V_{\text{oral}}, \text{ or, } Q_{\text{oral}} = C_{\text{oral}} V_{\text{oral}}$$

Here, V_{oral} , w_p , and C_{oral} represent the amount of the product ingested daily (cm^3 products/day for liquids and gm of product/day for solids), the weight fraction of the chemical in the product for solids, and the average concentration of the chemical in the product for liquids (mg/cm^3), respectively.

- f_{oral} : fraction of the product absorbed through the gastrointestinal tract into body

Normally, gastrointestinal absorption factors are rarely indicated for consumer products. For this reason, generally, it is assumed that the total amount of absorption into the body via gastrointestinal tract is the total amount of the product ingested ($f_{\text{oral}} = 1$).

- BW: body weight (kg)

Depending on the product type and application, Q_{oral} may need to be modified, taking account of the effects of product dilution. In addition, if there are calculated or measured values of f_{oral} for the product or chemical, they may be used to refine the estimate of the D_{oral} .

Dermal exposure

Two calculation procedures for estimating the daily systemic exposure to a product via the dermal route (D_{dermal} : expressed as mass of the chemical per mass body weight per day) are shown below. The calculation is based on an assumption that the total amount of the chemical contacting the skin is absorbed into the body. A calculation may also be done considering the dermal permeability coefficient of the chemical, if such data are available.

- Calculation based on an assumption that the total amount of the chemical contacting skin is absorbed into the body

$$D_{\text{dermal}} = Q_{\text{dermal}} f_{\text{dermal}} / \text{BW}$$

Q_{dermal} : the amount of the chemical in the product contacting the skin each day (mg/day)

The Q_{dermal} value can be calculated using the following equation.

$$Q_{\text{dermal}} = w_p V_{\text{dermal}}, \text{ or } Q_{\text{dermal}} = C_{\text{dermal}} V_{\text{dermal}}$$

Here, V_{dermal} , w_p , C_{dermal} represent the volume of the product (cm^3/day) applied to the skin per day (presumed to be a liquid product), the weight fraction of the chemical in the product, and the average concentration of the chemical in the product (mg/cm^3), respectively. V_{dermal} can be calculated based on the thickness of the product layer on the skin and the surface area of skin exposed to the product.

f_{dermal} : fraction of the product that is absorbed through the skin

The f_{dermal} highly depends on specific exposure conditions. For this reason, it is the usual practice to make an initial high estimate of the

systemic exposure by assuming that the total amount of the product contacting the skin is absorbed into the body ($f_{\text{dermal}} = 1$).

BW: body weight (kg)

If model calculation values or measured values are available for the f_{dermal} of the product or the product's component chemicals exhibiting chronic hazards, these values may be used to refine the estimate of the D_{dermal} . Apart from the calculation methods noted above, D_{dermal} (total daily exposure from dermal exposure to the product) can also be estimated using the dermal permeability coefficient of the chemical and exposure duration as shown below.

- Calculation considering dermal permeability coefficient of the chemicals

$$D_{\text{dermal}} = (CA \times PC \times F_1 \times FQ \times CF \times Kp \times T) / BW$$

CA: body surface area in contact with the detergent (cm^2)

PC: concentration of product in contact with the skin (g/cm^3)

F1: concentration of the substance in the product (%)

FQ: frequency of use (times/day)

CF: conversion factor (mg/g)

Kp: dermal permeability coefficient of the substance (cm/h)

T: exposure time (h).

(Conforming to the equations stipulated in HERA Risk Assessment of Alcohol Ethoxysulphates, AES DRAFT [<http://www.heraproject.com/files/1-HH-04-HERA%20AES%20HH%20web%20wd.pdf>], 4.1.3.4 Direct skin contact from hand dishwashing)

Inhalation exposure

Inhalation exposure can occur with the use of product from which a mist, dust or gas is released in the forms of particulates or aerosols. To estimate the daily systemic exposure due to inhalation of a mist, dust or gas released into the air during product use ($D_{\text{inhalation}}$, expressed as mass of chemical per body mass per day), the following equation is used:

$$D_{\text{inhalation}} = C_{\text{air}} t V_r / BW$$

- t: fraction of the day that the person would be exposed to the chemical via inhalation.

The fraction of the day that the person would be exposed to the chemical (t) may include, as appropriate, single or multiple uses of the product.

- V_r : daily human ventilation rate (m^3/day)
Typical daily adult human ventilation rate is $20 \text{ m}^3/\text{day}$ (EU, 2006).⁷
Calculation of prolonged exposure to the chemical via inhalation requires

⁷ European Commission. 2006 Technical Guidance Document, edition 2, Part I, Human Health. http://ecb.jrc.it/documents/TECHNICAL_GUIDANCE_DOCUMENT/EDITION_2/tgdpart1_2ed.pdf

adjustment to daily human ventilation rate considering diurnal fluctuation of activity level.

- C_{air} : concentration of the chemical in the air (mg/m^3)

C_{air} can be calculated using the following equation.

$$C_{\text{air}} = Q_{\text{inhalation}} w_p / V$$

Here, $Q_{\text{inhalation}}$ indicates the amount of product released into the air per day (mg/day), while w_p is the weight fraction of the chemical in the product, and the V represents the volume of air (in m^3) immediately surrounding the user.

BW: body weight (kg)

If data of the respirable fraction of the chemical in the air ($f_{\text{respirable}}$) are available, then multiplying C_{air} by $f_{\text{respirable}}$ also may provide a further refined exposure estimate.

Total systemic exposure

The total systemic exposure is the sum of the oral, dermal, and inhalation exposures.

2) Determination of Tolerable Daily Intake (TDI) or Virtually Safe Dose (VSD)

If the consumer product is classified in any of the GHS chronic health hazard categories [e.g., sensitization, germ cell mutagenicity, reproductive toxicity, specific target organ toxicity (repeated exposure) and carcinogenicity] and the possibilities of exposure are not insignificant, the need for a label indication, and the contents if such indication is necessary, can be determined on the basis of the likelihood of injury. The likelihood of injury is determined based on a comparison of the estimated level of consumer exposure and the tolerable daily intake (TDI). The succeeding sections present guidance concerning determination of TDI or virtually safe dose (VSD) for sensitization, germ cell mutagenicity, reproductive toxicity, specific target organ toxicity (repeated exposure), and carcinogenicity.

(i) Reproductive toxicity and specific target organ toxicity (repeated exposure)

For reproductive toxicity and specific target organ toxicity (repeated exposure), the TDI is determined by dividing the no observed adverse effect level (NOAEL) or, if the NOAEL cannot be determined, the lowest observed adverse effect level (LOAEL) by an uncertainty factor. For these endpoints, the exposure level is expressed in terms of the mass of chemical per unit of body weight per day (e.g., milligrams of chemical per kilogram of body weight per day). The uncertainty factor applied to the NOAEL or LOAEL to calculate the TDI differs depending on the type of the information used as the basis of its calculation. The following factors must be considered in establishing the uncertainty factor.

- Intraspecies differences: variable susceptibilities in the human population
- Interspecies differences: species specificity (animals vs. human beings)
- LOAEL-to-NOAEL extrapolation
- Differences of exposure route
- Differences of exposure duration in animal studies, etc.

For reproductive toxicity and specific target organ toxicity, the TDI can be obtained by dividing the NOAEL derived from animal studies or human information by the appropriate uncertainty factor. Typically, international organizations and national administrative authorities use an uncertainty factor of 100 (interspecies difference of 10 x intraspecies difference of 10) as default. When a NOAEL is not available, an LOAEL derived from animal studies or human information can be used to calculate the TDI. An additional safety factor is included if an LOAEL is used to adjust the uncertainty accompanying extrapolation from the LOAEL to the NOAEL. In this case, it is the normal practice to use an uncertainty factor of up to 10.

In addition, there have been various international discussions about uncertainty factors, but these discussions have not reached an agreement on an absolute value^{8,9}. As described above, it is the common practice to use 100 as the conservative default value for the uncertainty factor. In some cases, however, an uncertainty factor with a value lower than 100 could be applied when it is judged to be appropriate (e.g., when data for TK (toxicokinetics) and TD (toxicodynamics) are available for the substance).^{10,11} In some instances, it may be appropriate to apply an additional uncertainty factor to account for incomplete dataset or severity of the response especially when there is a shallow dose response¹². An additional factor also applies for cases in which the exposure routes or exposure duration in animal studies differ from those of the exposure scenario applied in the assessment. In cases such as making extrapolations from acute to chronic toxicity or from oral to inhalation exposure, it would be advisable to apply uncertainty factors appropriate for each assessment case. Development of the discussion on this field will make it possible to apply uncertainty factors more scientifically.

TDI based on NOAEL

In a study based on administration of doses, the NOAEL is the highest dose at which no significant increase in the frequency of an adverse effect is observed as compared to the control group. When the NOAEL can be obtained from multiple studies, the TDI may be determined through use of the NOAEL value thought to be the most appropriate considering items such as the observed toxicity symptoms, exposure duration, and dose response relationship. If the NOAEL is based on animal test data, the TDI is calculated by dividing the NOAEL by the aforementioned uncertainty factor of 100. If the NOAEL is based on human experience data, the TDI is calculated by dividing the NOAEL by the factor of 10 to account for the difference in responses among humans.

TDI based on LOAEL

In a study based on administration of doses, the LOAEL is the lowest dose at which a significant increase in the frequency of an adverse effect is observed as compared to the control group. When the LOAEL can be obtained from multiple studies, the TDI may be determined through use of the LOAEL value thought to be the most appropriate considering items such as the observed toxicity symptoms, exposure duration, and dose response relationship. Normally the lowest LOAEL among appropriate LOAELs is used as the basis for determining the TDI.

If the LOAEL is based on animal test data, the TDI is calculated by dividing the LOAEL by 1000 (i.e., the product of the aforementioned uncertainty factor of 100 and the factor of 10 for uncertainty accompanying extrapolation of the NOAEL from the LOAEL). If the LOAEL is based on human experience data, the TDI is calculated by dividing the LOAEL

⁸ How to manage uncertainties, ISBN: 978-4621079058

⁹ A National and International Debate on Default Uncertainty Factors vs. Data-Derived Uncertainty Factors, Human and Ecological Risk Assessment, Volume 8, Number 4, pp.895-911 (2002)

¹⁰ Derivation of Assessment Factors for Human Health Risk Assessment (No. TR 086), ECETOC, February, 2003

¹¹ CHEMICAL-SPECIFIC ADJUSTMENT FACTORS FOR INTERSPECIES DIFFERENCES AND HUMAN VARIABILITY: GUIDANCE DOCUMENT FOR USE OF DATA IN DOSE/CONCENTRATION-RESPONSE ASSESSMENT http://whqlibdoc.who.int/publications/2005/9241546786_eng.pdf

¹² IPCS Environmental Health Criteria 170 <http://www.inchem.org/documents/ehc/ehc/ehc170.htm>

by 100 (i.e., the product of the factor of 10 for human individual variation and the factor of 10 for the uncertainty accompanying extrapolation of the NOAEL from the LOAEL).

(ii) Carcinogenicity

In assessment of the risk of carcinogenicity, there are two modes of calculation for the Virtually Safe Dose (VSD) and NOAEL (or LOAEL). The selection of mode is dependent on whether or not the concerned chemical exhibits genotoxicity.

* If the substance does not show genotoxicity (with a threshold value)

The method consists of specification of the NOAEL or LOAEL and calculation of the TDI by the same procedure as described under A2.4.2-2) (i) above on reproductive toxicity and specific target organ toxicity (repeated exposure). Application of this method for carcinogenic substances is preconditioned on acquisition of reliable data evidencing their mechanism of non-genotoxic carcinogenicity.

** If the chemical shows genotoxicity (without a threshold value)

In the field of consumer products for home use, manufacturers ordinarily do not deliberately formulate products with substances that are genotoxic. However, there have been reports raising suspicions that some products' ingredients, which have long been in use, show carcinogenicity in animals. There consequently may arise occasions requiring tentative risk assessment at a stage preceding elucidation of the carcinogenic mechanism. In this case, the standard procedure is to make the assessment on the assumption that there is no threshold value for the carcinogenic effect of the substance. However, an international consensus has not yet been built on the procedure for assessment of the risk of substances that are both genotoxic and carcinogenic.

Usually, genotoxic carcinogens are generally considered to have a carcinogenic potential, even at very low levels of exposure. In such cases, an estimate is made of the dose response relationship at low doses utilizing various multistage linear models that take $T25^{13,14}$, LED_{10}^{15} or other values as the point of departure (POD), in order to obtain the virtually safe dose (VSD; the dose at which the carcinogenic probability is no higher than 10^{-5} or 10^{-6}), and implement risk management on the basis of this VSD. A linear multistage model has been widely used to estimate carcinogenic potential at low doses. U.S. EPA published "Guidelines for Carcinogen Risk Assessment"¹⁶ in March 2005 and recommends a simple linear extrapolation approach that determines the slope factor derived from the line drawn from POD (e.g. LED_{10} based on benchmark dose method (BMD)) to zero. Genotoxic carcinogenicity risk assessment requires multifaceted examinations of factors including the implications for the mode of action, selection of extrapolation models corresponding with the mode of action, and type of exposure to the substance. As such, it is advisable to make the assessment on a case-by-case basis, through a procedure including discussion with experts on carcinogenicity risk assessment.

¹³ $T25$ is a simplified carcinogenic potency index that expresses the chronic daily dose in mg per kg bodyweight which will produce tumors in 25% of animals in carcinogenicity tests performed in accordance with OECD Guidelines.

¹⁴ A simplified carcinogenic potency index: Description of the system and study of correlations between carcinogenic potency and species/site specificity and mutagenicity: Dybing et al., PHARMACOL TOXICOL, VOL.80. PAGE 272-279 (1997)

¹⁵ LED_{10} : Lower limit on Effective Dose 10. Curve fitting in the observed range provides the effective dose corresponding to the lower 95% limit on a dose associated with a 10% response.

¹⁶ Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001B, March 2005. US EPA.
<http://www.epa.gov/IRIS/cancer032505.pdf>

A2.4.3 Determination of labeling based on the likelihood of injury

Determination of the likelihood of injury (risk) for chronic health effect endpoints must take account of both hazard and data from qualitative or semi-quantitative exposure assessment, as described in A2.4.1-2) (i)-(iii) and –A2.4.2-1) and 2). The steps are as follows:

1) Determination of the likelihood of injury (risk)

To determine that the likelihood of injury (risk) for a chronic health effect is low at any step of exposure assessment, the exposure needs to be insignificant [as described in A2.4.1-2) (i)] or to be no higher than the TDI [as described in A2.4.1-2) (ii) and (iii)].

In any of the following three cases, it may be concluded that there is little likelihood of injury (risk), and consequently no need to indicate such a chronic hazard on a GHS label.

(i) Qualitative exposure assessment

In case that the consumer exposure is insignificant.

(ii) Semi-quantitative exposure assessment

The exposure level estimated in accordance with a semi-quantitative assessment based on assumptions is compared with the determinations of Tolerable Daily Intake (TDI) or Virtually Safe Dose (VSD), calculated as described in A2.4.2-2. The likelihood of injury (risk) may be deemed insignificant if the estimated exposure level is no higher than the TDI or VSD for the chronic health effect.

(iii) Refined semi-quantitative exposure assessment

The exposure level estimated in accordance with a more accurate semi-quantitative assessment is compared with the determination of tolerable daily intake (TDI) or virtually safe dose (VSD), calculated as described in A2.4.2-2. The likelihood of injury (risk) may be deemed insignificant if the estimated exposure level is no higher than the TDI or VSD for the chronic health effect.

2) Determination of labeling based on the likelihood of injury (risk)

If it is decided that the likelihood of injury (risk) is insignificant as a result of the studies described in A2.4.3-1, there is no need to communicate the chronic health effect for which product is classified on the label. If this is not the case, it is necessary either to communicate the hazard on the product label or to make a more detailed exposure assessment and investigation of the likelihood of injury (risk), followed by another decision on whether or not labeling is needed.

A2.4.4 Cases of classification and labeling based on the likelihood of injury (risk)

This section presents examples of classification and the labeling determination process for *reproductive toxicity* based on the likelihood of injury (risk), utilizing an example hand dishwashing detergent containing ethanol.

| | |
|-------------------------------------|-------|
| Anionic surfactants ^{*1} | : 20% |
| Amphoteric surfactant ^{*2} | : 5% |
| Nonionic surfactant ^{*3} | : 5% |
| Ethanol | : 5% |
| Water | : 65% |

*1: Alkylether sulfonates (AES) 10%, alkyl sulfonates (AS) 10%

*2: Alkylamine oxide (AO) 5%

*3: Polyoxyethylene alkyl ether (AE) 5%

1) Classification based on the intrinsic hazardous properties of the product

- Classification based on human experience

No human experience information addressing reproductive toxicity is available for the example product; therefore, it cannot be classified in any category of reproductive toxicity based on human experience.

- Classification based on animal data for the product

No animal data addressing reproductive toxicity is available for the example product; therefore, it cannot be classified in any category of reproductive toxicity based on animal test data.

- Classification based on the cut-off value utilizing information on ingredients

It is known that excessive and consecutive oral consumption of ethanol in alcoholic beverages during pregnancy affects babies¹⁷. Therefore, ethanol would be classified as Category 1, and this example product, which has an ethanol content of 5%, would be classified as Category 1 because the concentration of the ingredient exceeds the cut-off value (0.1%¹⁸) of those classified as Category 1. The ingredients other than ethanol would not be considered reproductive toxicant^{19,20,21,22}.

Because ethanol is a Category 1 ingredient, the example product would be placed in Category 1 in a classification of reproductive toxicity hazard based on the cut-off value utilizing the information on ingredient contents.

2) Exposure assessment

In accordance with Annex 5 of the GHS Official Text, labeling on consumer products can be determined on the basis of the likelihood of injury to consumers. In advance of determining the likelihood of injury, an estimate is made of the exposure level to ethanol resulting from the use of the dishwashing detergent.

(i) Qualitative exposure assessment

¹⁷ International Agency for Research on Cancer (IARC) – Summaries & Evaluations ALCOHOL DRINKING (Group 1) VOL.:44(1988)

¹⁸ In this example, 0.1% is used as the cut-off value although the GHS provides an option to use 0.3% as a cut-off.

¹⁹ Human and Environmental Risk Assessment on ingredients of household cleaning Products (HERA), Alcohol Ethoxysulphates Human Health Risk Assessment Draft, Jan 2003 <http://www.heraproject.com/files/1-HH-04-HERA%20AES%20HH%20web%20wd.pdf>

²⁰ Human and Environmental Risk Assessment on ingredients of household cleaning Products (HERA), Alkyl Sulphate Human Health Risk Assessment Draft, July 2002 <http://www.heraproject.com/files/3-HH-04-%20HERA%20AS%20HH%20web%20wd.pdf>

²¹ The Risk Assessment of Human Health Effects and Environmental Effects of Surfactant, Japan Soap and Detergent Association, July, 2001

²² Toxicity of Detergent and its Assessment, edition by Food Chemistry Division, Environmental Sanitation Department, MHLW, 1983

The first task is to determine whether use of the product entails absolutely no exposure or only exposure on a level that can be insignificant, such that the likelihood of injury (risk) may also be insignificant. The reproductive toxicity deriving from ethanol is recognized in the aforementioned case of excessive and repeated oral consumption in the form of alcoholic beverages during pregnancy. Such hazard would presumably not arise in repeated dermal exposure or indirect oral exposure to the dishwashing detergent containing ethanol. However, this section sets forth the process of exposure assessment and determination of the likelihood of injury (risk), for the purpose of providing an example of risk assessment procedure.

The conceivable cases of human exposure to dishwashing detergent include systemic exposure through incidental oral intake and dermal absorption, and accidental exposure to the eye via splashes or spills of the product. Of these, the case of exposure to the eye via splashes or spills would be a temporary one accompanying accidents as opposed to one of repeated ocular exposure to the detergent on a daily basis. As such, the likelihood of injury (risk) accompanying ocular exposure may be insignificant in an assessment of chronic human health effects.

As for oral and dermal exposure, the following cases are estimated to occur repeatedly as long as the dishwashing detergent is used.

Oral exposure

There may be a risk of oral ingestion of dishwashing detergent indirectly, through ingestion of food that has come into contact with the detergent residue on dishes, or is washed with water in a bowl previously cleaned using the detergent.

Dermal exposure

There may be a risk of absorption of dishwashing detergent ingredients into the body through the skin, if dishes are washed with the bare hands using the detergent after every meal.

Inhalation exposure

Significant inhalation exposure may not be expected.

(ii) Semi-quantitative exposure assessment

This step would ordinarily consist of a calculation of the exposure level based on the assumption that consumers are exposed to the entire amount of product in a given container every day and that all of the product or the ingredients are absorbed into the body. For this product, this approach leads to overestimation of the exposure level and risk assessment results that are divorced from reality. However, it is a very simple assessment which, if it estimates that the exposure is below the TDI, can demonstrate that labeling for this hazard is unwarranted, or a more detailed analysis is necessary. Information has already been compiled on items such as the standard use amount and concentration of dishwashing detergent in the exposure assessment guidance at the U.S. SDA, and this could serve as the basis for a more accurate quantitative assessment of exposure. As a result, it was decided to omit the assessment process in this step and proceed to the next step, i.e., refined quantitative assessment of exposure.

(iii) Refined semi-quantitative assessment of exposure

The task in this step is estimation of the exposure level considering each route of exposure (oral and dermal), and addition of these exposures for calculation of the total exposure. This calculation employs the model computation formula and conservatively high default values for calculating exposure levels stipulated in "Exposure and Risk Screening Methods for Consumer Product Ingredients" (April 2005; US SDA)²³ and HERA Risk Assessment of

²³ Exposure and risk screening methods for consumer product ingredients (April 2005)
http://www.cleaning101.com/files/Exposure_and_Risk_Screening_Methods_for_Consumer_Product_Ingredients.pdf

Alcohol Ethoxysulphates (DRAFT)²⁴. As a rule, the default values in "Exposure and Risk Screening Methods for Consumer Product Ingredients"²³ are used for calculating exposure levels. The default values noted here were determined on the basis of the highest exposure levels shown in the review documentation of the following governmental agencies and industrial associations. Some calculations were made based on the values gained in Japanese research considering variation in usage of the product or consumer's average physical size in the USA and Japan. In such cases, the reference provides the values used as a basis for calculation.

AIHC: American Industrial Health Council

AISE: International Association for Soaps, Detergents and Maintenance Products

APC: All Purpose Cleaners

PCPC: Personal Care Products Council

D4: Octamethylcyclotetrasiloxane Exposure Assessment prepared by K.S. Crump Group (1999)

EFH: EPA's Exposure Factors Handbook (U.S. EPA 1997)

EPA: U.S. Environmental Protection Agency

F&H: Face and Hand

HERA: Human & Environmental Risk Assessments (subcommittee within AISE)

SRTC: PCPC's Safety and Regulatory Toxicology Committee

TGD: EU Technical Guidance Document (2003)

Oral exposure

The following equation can be used to calculate the total daily systemic exposure (equivalent to D_{oral}) to the dishwashing detergent through oral exposure.

$$\text{Level of indirect oral exposure to dishwashing detergent per day} = \frac{C' \times Ta' \times Sa \times CF}{BW}$$

The following figures are obtained from a calculation of the total daily systemic exposure to the detergent based on the values stipulated in "Exposure and Risk Screening Methods for Consumer Product Ingredients" (April 2005; U.S. SDA).

C' : Product concentration in the residual detergent on a dish

$$= \text{Product use concentration (4g)}^{25} / \text{the amount of water used per use (5000 cm}^3)^{26}$$

$$= 0.008 \text{ g/cm}^3 = 0.8 \text{ mg/cm}^3$$

The values used for calculating C' are determined on the basis that there is no rinsing process during dishwashing in the EU. Hence, this calculation does not take account of dilution of the dishwashing detergent due to rinsing. In Japan, C' would be lower than that of the EU or U.S., because a rinsing process is included in Japanese dishwashing behavior.

Ta' : Amount of water containing the detergent remaining on the dish after rinse²³ = $5.5 \times 10^{-5} \text{ mL/cm}^2$

Sa : Area of dish contacting food = $5400 \text{ cm}^2/\text{day}$ ²³

The amount of daily use of dishes (area of dish contacting food) is put at $3,700 \text{ cm}^2$ (assuming 120 cm^2 each for 10 dishes and 50 cm^2 each for 50 dishes²⁷) in "Volume 1, Detergents Containing Aminoxides, Report on Basic Research Concerning the Safety of Food-Use Detergents initiated by the Japanese Ministry of Health, Labor and Welfare (MHLW) program of scientific research in 1989", published in

²⁴ HERA Risk Assessment of Alcohol Ethoxysulphates, AES DRAFT

<http://www.heraproject.com/files/1-HH-04-HERA%20AES%20HH%20web%20wd.pdf>

²⁵ In-house data

²⁶ Human and Environmental Risk Assessment. LAS Linear Alkylbenzene Sulphonate (CAS No. 68411-30-3) Version 2.0 May, 2004 <http://www.heraproject.com/files/4-F-E7AA1D19-0072-281E-D42AFC94BEA5BD2F.pdf>

²⁷ Atsushi Nishida, Research Concerning the Safety of Food Detergents, Food Sanitation Research, 40, 1-25

September 1991. Here, however, the very conservative values calculated by the U.S. SDA were utilized.

CF: Conversion factor = 1 cm³ water/1 mL water
 BW: Body weight = 55.5 kg (a pregnant Japanese woman)²⁸

| |
|---|
| Level of indirect oral exposure to dishwashing detergent per day $= \frac{0.8 \times (5.5 \times 10^{-5}) \times 5400 \times 1}{55.5} \doteq 0.0043 \text{ (mg/kg/day)}$ |
|---|

Of the systemic exposure to dishwashing detergent resulting from indirect exposure through the use of dishes noted above, 5% would be occupied by ethanol; that is,

| |
|--|
| Level of exposure to ethanol through indirect oral exposure to dishwashing detergent $= \frac{0.0043 \times 5}{100} = 0.0002 \text{ (mg/kg/day)}$ |
|--|

Dishwashing detergent that complies with the provisions of the enforcement regulations of the Japanese Food Sanitation Law may be used to wash vegetables and fruit. A study has been made of the residual level of surfactant on vegetables and fruit after washing²⁹. Table A2-8 shows the residual levels of amine oxide after washing with amine oxide-containing detergent.

Table A2-8 Residual level of amine oxide on food products after washing with amine oxide-containing detergents and daily intake of food products

| Ingestion route | Residual level* ¹ | Daily intake of foods in each group* ² |
|----------------------------|------------------------------|---|
| Vegetables | 1.4 µg/g | 263 g |
| Fruit, potatoes, and beans | 0.24 µg/g | 256 g |

*1: Based on Table 43 “Daily Intake Levels”, page 55 of “Volume 1, Detergents Containing Aminoxides, Report on Basic Research Concerning the Safety of Food-Use Detergents initiated by the Ministry of Health, Labor and Welfare (MHLW) program of scientific research in 1989”, published in September 1991, Japan Food Detergent Sanitation Association

*2: Use of the total figures for food group intake by women according to the results of the National Nutrition Survey, 2002³⁰

Information is not yet publicly available regarding the residual level of ethanol after washing vegetables and fruit with dishwashing detergent. For this reason, it was decided to consider it equivalent to the residual level of the surfactant, amine oxide, (despite the fact that the ethanol level is probably lower due to evaporation), and to calculate the level of ethanol intake through vegetables and fruit based on the levels in Table A2-9.

Assuming the daily intake levels of vegetables and fruit are 263 and 256 grams, respectively, the total daily systemic exposure is estimated as follows:

$$[1.4 \text{ µg/g} \times 263 \text{ g/person/day}] + [0.24 \text{ µg/g} \times 256 \text{ g/person/day}] \\ = 430.48 \text{ µg/person/day}$$

²⁸ Ministry of Health, Labour and Welfare, Review of Cautions Concerning Intake of Seafood by Pregnant Women and Mercury, 2 November 2005 (Outline) <http://www.mhlw.go.jp/topics/bukyoku/iyaku/syoku-anzen/suigin/dl/051102-1-01.pdf>

²⁹ Volume 1 (on detergents containing amine oxides) published in September 1991: report on basic research concerning the safety of food-use detergents conducted under the MHLW program of scientific research in 1989, Shokusen

³⁰ Summary of the results of the National Nutrition Survey, 2002 <http://www.mhlw.go.jp/houdou/2003/12/h1224-4d.html>

The following values are obtained when this is divided by 55.5 kilograms, the weight of a pregnant woman.

| |
|---|
| <p>Level of ethanol exposure due to intake of vegetables and fruit after washing</p> $= \frac{430.48 \times 10^{-3}}{55.5} \doteq 0.0078 \text{ (mg/kg/day)}$ |
|---|

With the addition of the exposure level to ethanol through vegetables and fruit (about 0.0078 mg/kg/day) to that of indirect exposure to ethanol from dish calculated above (0.0002 mg/kg/day), the total exposure would be about 0.0080 mg/kg/day.

| |
|---|
| <p>Oral exposure to ethanol accompanying use of dishwashing detergent</p> $\doteq 0.0080 \text{ (mg/kg/day)}$ |
|---|

Dermal exposure

The daily systemic exposure to dishwashing detergent through dermal exposure (equivalent to D_{dermal}) can be calculated by utilizing the aforementioned equation “Calculation considering dermal permeability coefficient of the chemicals”.

| |
|---|
| <p>Dermal systemic exposure to ethanol in dishwashing detergent per day</p> $= \frac{CA \times PC \times F_1 \times FQ \times CF \times Kp \times T}{BW}$ |
|---|

The following values are obtained from a calculation of the systemic level of daily exposure to the detergent based on the values stipulated in "Exposure and Risk Screening Methods for Consumer Product Ingredients" (April 2005; U.S. SDA).²³

- CA: Body surface area in contact with the detergent = 1980 cm² *³
- PC: Concentration of product in contact with the skin = 0.1 g/cm³ *⁴
- F₁: Concentration of ethanol in the product = 5%
- FQ: Frequency of use = 3.0 times/day
- CF: Conversion factor = 1,000 mg/g
- Kp: Dermal permeability coefficient of ethanol = 0.8 × 10⁻³ cm/h *⁵
- T: Exposure time = 0.75 h *⁶
- BW: Female body weight = 55.5 kg in the case of a pregnant Japanese woman²⁸

- *3 Appendix II of the European TGD, Page 237, notes the figure of 731 cm² for the surface area of a female hand. Here, however, the very conservative values provided by the US Soap and Detergent Association are utilized.
- *4 Use of the higher concentration in the case of application of dishwashing detergent directly to the sponge (non-concentrated type: 0.1 g/cm³; concentrated type: 0.05 g/cm³)³¹.
- *5 The very conservative figure stipulated in the following source is utilized³²
 -- “Dermal Exposure Assessment: Principles and Applications” EPA/600/8-91/011B, January 1992, Interim Report, p.5-78, <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=12188>
- *6 Use of the figure stipulated in the following source for the maximum time taken to wash dishes by hand.

³¹ Unpublished data by Lion Co.

³² The original is “MECHANISM OF PERCUTANEOUS ABSORPTION. IV. PENETRATION OF NONELECTROLYTES (ALCOHOLS) FROM AQUEOUS SOLUTIONS AND FROM PURE LIQUIDS, SCHEUPLEIN and BLANK, Journal of Investigative Dermatology (1973) 60, 286- 296”

-- "Table of Habits and Practices for Consumer Products in Western Europe", Developed by AISE within the HERA Project in 2002.

http://ec.europa.eu/consumers/cons_safe/news/presentations_chemrisk/rodriguez.pdf

$$\frac{\text{Dermal systemic exposure to dishwashing detergent per day}}{55.5} = \frac{(1980 \times 0.1 \times 0.05 \times 0.8 \times 10^{-3} \times 1000 \times 0.75) \times 3}{55.5} \doteq 0.3211 (\text{mg/kg/day})$$

The above exposure assessment is based on the use of conservatively high scenarios by applying the higher figure for each value compared to conditions closer to actual use of detergent.

Total exposure level to ethanol accompanying use of dishwashing detergent

With the addition of the exposure level to ethanol through dermal exposure (0.3211 mg/kg/day) to that of indirect oral exposure to ethanol (0.0080mg/kg/day), the total exposure to ethanol resulting from the use of dishwashing detergent would be as follows:

$$\text{Total exposure to ethanol accompanying use of dishwashing detergent} = 0.0080 (D_{\text{oral}}) + 0.3211 (D_{\text{dermal}}) \doteq 0.3291 (\text{mg/kg/day})$$

The calculation above is a conservative exposure estimate based on the worst case use scenario. Therefore, the above calculated total exposure is larger than the actual exposure. If more accurate data are available, with further assessment, it is possible to obtain a more refined exposure estimate.

3) Determination of the likelihood of injury

The presence or absence of risk of manifestation of reproductive toxicity arising from ethanol contained in dishwashing detergent would be determined by comparing the level of ethanol exposure accompanying use of such detergent described in 2)-iii) (Refined semi-quantitative assessment of exposure) and the Tolerable Daily Intake (TDI; the tolerable level in the event of unintentional intake of ethanol) based on animal testing data and human experience values.

For ethanol, there are no values for acceptable daily intake (ADI: the acceptable level in the case of conscious human intake of alcoholic beverages) or TDI determined by public institutions such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA). As a result, it was decided to make a calculation of the TDI based on data found in highly reliable review sources such as the Organization for Economic Cooperation and Development Screening Information Data Sets (OECD-SIDS) and International Agency for Research on Cancer (IARC) monographs.

Of the ethanol values confirmed to pose no observed adverse effect level (NOAEL) for rat fertility, NOAEL 2,000 mg/kg/day³³ is applied. The TDI* can be calculated by dividing this value by 100 [intraspecies differences (10) x interspecies differences (10)].

$$\text{TDI * based on NOAEL from animal testing} = \frac{2000}{100} = 20 (\text{mg/kg/day})$$

* TDI calculated by JSDA

It is known that intake of about one glass per day of alcoholic beverage generally has no adverse effect on human fetuses¹⁷. Newman et al. reported 28.5 mL (22.49 g, when the specific gravity of ethanol is 0.789³⁴) per day is the threshold for ethanol intake during pregnancy having an effect on

³³ Rat offspring sired by males treated with alcohol. Alcohol. 1993 May-Jun;10(3):237-42.(OECD SIDS data)

³⁴ NITE CHRIP(<http://www.safe.nite.go.jp/japan/db.html>)

fetuses or new-borns³⁵. If a pregnant woman (body weight of 55.5 kg²⁸) were to have a daily intake of 22.49 grams of alcoholic beverage as ethanol equivalent throughout the term of pregnancy, her ethanol intake per unit of body weight could be calculated as follows:

$$\begin{array}{l} \text{Ethanol intake by a pregnant woman accompanying intake of alcoholic beverages} \\ = \frac{22.49 \times 1000}{55.5} \doteq 405.16 \text{ (mg/kg/day)} \end{array}$$

Because this value represents the LOAEL for ethanol intake of a pregnant woman, human TDI can be calculated by dividing the LOAEL by the uncertainty factor of 100 [intraspecies differences (10-fold) multiplied by 10, the factor for deriving NOAEL]:

$$\text{Human TDI}^* = \frac{405.16}{100} = 4.05 \text{ (mg/kg/day)}$$

* TDI calculated by JSDA

The levels calculated above may be summarized as follows:

Systemic ethanol exposure accompanying use of dishwashing detergent

$$= 0.3291 \text{ mg/kg/day} \cong 0.33 \text{ mg/kg/day}$$

The TDI based on NOAEL from animal study = 20 mg/kg/day

The human TDI based on human LOAEL = 4.05 mg/kg/day

The total amount of ethanol exposure derived from dermal exposure to dishwashing detergent is less than both the provisional TDI based on the LOAEL in human data and the TDI based on the NOAEL obtained from animal testing. Consequently, there is very little likelihood that ethanol in such detergent used under the foreseeable conditions of exposure would cause reproductive toxicity. As such, there is no need for labeling based on the GHS classification criteria for the reproductive toxicity endpoint.

³⁵ Effects of alcohol in pregnancy., Med J Aust., July 12 1980, 2: 5-10