GHS Implementation Guidance for Household Consumer Products
1st edition

Japan Soap and Detergent Association (JSDA)
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Contents

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, as JSDA's voluntary standard, 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 placed on the market within Japan.
Household consumer products have diverse compositions and patterns of use. While this guidance showed several examples of Classification and Labeling evaluation of model products to explain the basic procedure for implementing GHS, those examples are not standard classification and labeling cases. On using the guidance, it is intended that every user of this guidance takes note of the concept and confirms data, classifies chemicals, and determines the labeling of chemicals appropriate to the products at its own responsibility.

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 agreement 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 Material Safety Data Sheets (MSDS)[1] 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

[1] It is mentioned as Safety Data Sheet (SDS) in the GHS document

- 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 to ensure comprehensibility

   The GHS includes "special arrangements to take into account the information needs of different target audiences."
   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 warranted labels[2].

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" 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."
   When the data are scientifically robust, data from non-animal test approaches (human experience), similar products (bridging principles), in vitro study using enzymes and cells, SAR/QSAR, 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

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[2] IOMC/ILO/HC6/00.13 "An Option for Consumer Product Labeling Based on the Likelihood of Injury" September 21, 2000
http://www.cleaninginstitute.org/assets/1/AssetManager/hc60013%20IOE%20risk%20based%20labeling%20Rome%20Oct-Nov%202000.pdf

The GHS document says, “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 data of all available information.

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 says, “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 the 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
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 agreed 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 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 Hazard Classification/Labeling Items

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

6.1 Hazard classification/labeling items described in the first revised edition of GHS official text[3]

＜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

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

- substances and mixtures which, in contact with water, emit flammable gases
- oxidizing liquids
- oxidizing solids
- organic peroxides
- corrosive to metals

＜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 Application to Household Consumer Products

The choices of 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) and with the consideration of the current situation of related laws and regulations, and of assessment methodology level. GHS hazard classes and categories to covered and those not to be covered (or pending for decision) in this guidance are shown below. Rationales for the choices of classes and categories are described in Explanation. This Guidance does not cover the following classes and categories among ones described in the GHS official text. Classes and Categories to cover may be changed according to the changes in relevant laws and regulations in Japan and developments of assessment methods.

＜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, 2 of specific target organ toxicity (repeated exposure)
- Category 1 of aspiration hazard

＜Classes and Categories not covered in this Guidance＞

- All the classes of Physical Hazards

- 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 aspiration toxicity

＜Classes and Categories pending in this Guidance＞
- Specific target organ toxicity (single exposure): Whether/how this class is applied or not is pending
- Hazardous to the aquatic environment

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 and environmental 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 based labeling, in addition, 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, hazard statements etc.) as well as the precautionary statements described in the GHS Document.

7.2 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 elements.

The details of the approach to be used for scientifically determining what hazards are to be communicated on the 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 in Japan 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 are determined in consideration of current situations of laws and regulations, and of assessment methods applicability from the viewpoint of assessment methodology level, and may be changed according to the changes in relevant laws and regulations in Japan, GHS implementation situations in other geographies, and developments of assessment methods.[4]

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)	Under discussion
	Specific target organ toxicity (repeated exposure)	1, 2
	Aspiration hazard	1

[4] Refer Explanation for GHS Implementation Guidance for Household Consumer Products first Version, about the hazard endpoints not described in this Annex.

Reference: Classification Criteria and Label Elements

Classification criteria and label elements for the classes and categories to be applied are shown in Tables A1-2 to A1-14. 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	• $LD_{50} \leq 5$ mg/kg bodyweight		DANGER	Fatal if swallowed
2	• $5 < LD_{50} \leq 50$ mg/kg bodyweight		DANGER	Fatal if swallowed
3	• $50 < LD_{50} \leq 300$ mg/kg bodyweight		DANGER	Toxic if swallowed
4	• $300 < LD_{50} \leq 2000$ mg/kg bodyweight		WARNING	Harmful if swallowed

Table A1-3 Acute Toxicity – Dermal

Category	Criteria	Symbol	Signal Word	Hazard Statement
1	• $LD_{50} \leq 50$ 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	• $LC_{50} \leq 100$ 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	• $LC_{50} \leq 0.5$ 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	• $LC_{50} \leq 0.05$ 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	• 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	• Mean value of ≥ 2.3 - ≤ 4.0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or • 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	• Causes irreversible effects on the eye: -- 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	• Causes reversible effects on the eye: -- 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	• Causes reversible effects on the eyes: -- 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	• 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	• 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

Cate-gory	Criteria	Symbol	Signal Word	Hazard Statement
1A	• **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	• **Chemicals which should be regarded as if they induce heritable mutations in the germ cells of humans** (a) Positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals; or (b) Positive result(s) from *in vivo* somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. This supporting evidence may, for example, be derived from mutagenicity/genotoxic tests in germ cells *in vivo*, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or (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	• **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 *in vitro* experiments, obtained from: (a) Somatic cell mutagenicity tests *in vivo*, in mammals; or (b) Other in vivo somatic cell genotoxicity tests which are supported by positive results from *in vitro* mutagenicity assays.		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	• **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	• **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	• **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	• **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	• **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	• **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		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)

	in view of this Category 2 could be the more appropriate classification.			

TableA1-13 Specific Target Organ Toxicity – Repeated Exposure

Category	Criteria	Symbol	Signal Word	Hazard Statement
1	• **Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following repeated exposure** Placing a substance in Category 1 is done on the basis of: (a) reliable and good quality evidence from human cases or epidemiological studies; or, (b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations.		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	• **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 exposur**e Placing a substance in Cateory 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 A1-14 Aspiration Hazard

Category	Criteria	Symbol	Signal Word	Hazard Statement
1	• Chemicals known to cause human aspiration toxicity hazards or to be regarded as if they cause human aspiration toxicity hazard: A substance is classified in Category 1 (a) Based on reliable and good quality human evidence; or (b) If it is a hydrocarbon and has a kinematic viscosity of 20.5 mm^2/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 methodology for determination of the likelihood of injury utilizing the results of hazard classification and exposure assessment, in order to determine 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 compounds
   - It is recommended to comply with the following procedure in classification of compounds.

   (i) If data or other information concerning the compound itself is available, classify the compound based on them (**Figure A2-1** a).
   (ii) If no such data or other information concerning the compound itself is available, use data or other information for similar items. 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 compound 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 compound (product) (**Figure A2-1** b).

3) Determine the hazard category of the substance or compound (product) as necessary, based on a comparative examination of the aforementioned data or other information and the hazard classification standards (**Figure A2-1** c).

The specific classification criteria related to substances or compounds are based on the GHS Official text. **Table A2-1** shows sources of information required for classification.

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 negligible. After that, determine whether the exposure level to the substance or compound to be classified is equivalent to or lower than the level that does not cause harm (**Figure A2-1** e).
   (i) If it can be determined that the exposure level is equivalent to or lower than that not causing significant harm to humans, no hazard would have to be communicated on the label.
   (ii) If comparison of exposure levels reveals a hazard based on the likelihood of injury, only this hazard would have to be communicated on the label.

   Table A2-3 lists information sources of assistance in determination of exposure levels. , the information concerning human experience shown in **TableA2-2** can be used for estimating the relationship between the likelihood of injury and exposure level, as reference. The specific procedure for determination of the likelihood of injury follows that in the GHS Official text.

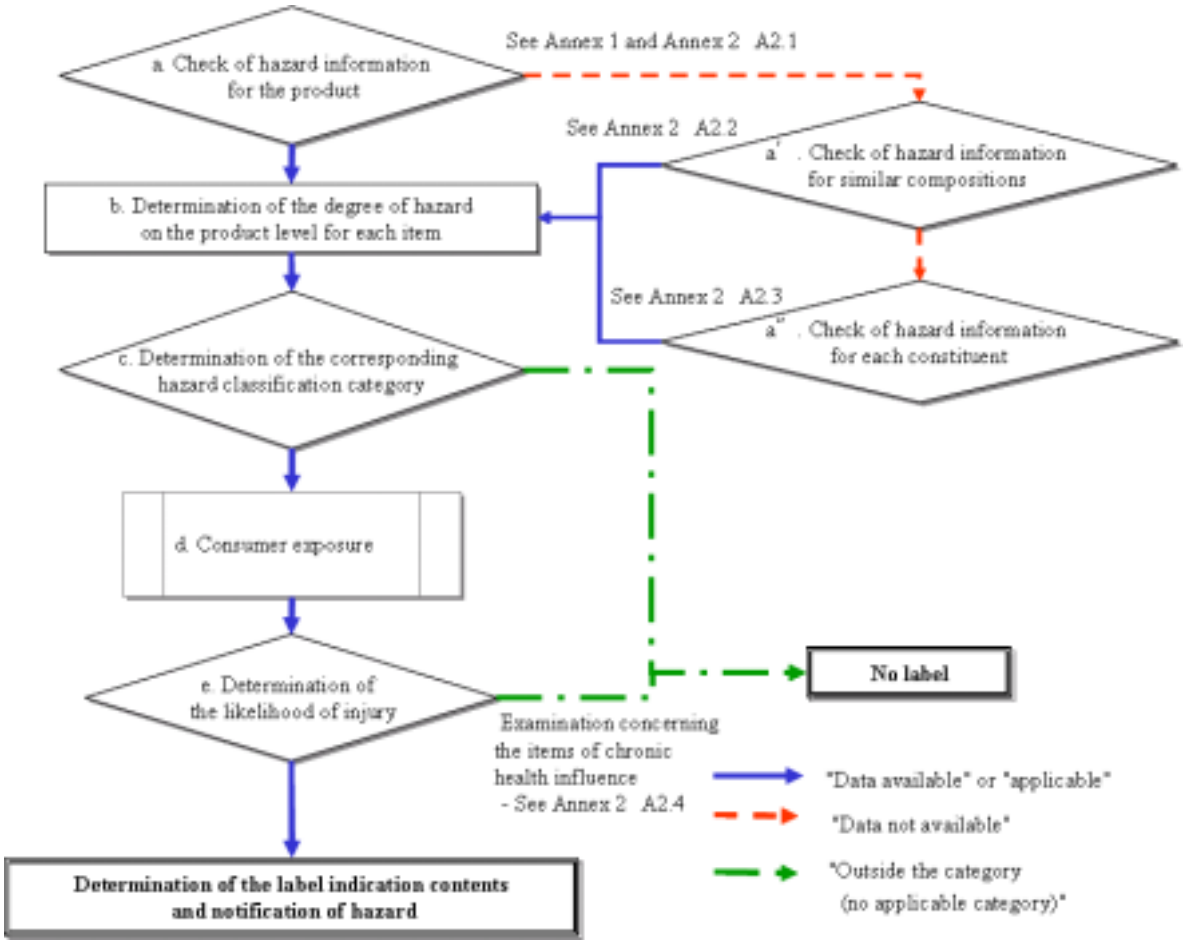

Figure A2-1 Procedure for determination of hazard category requiring notification on the label of household consumer products

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 risk

Subject information	Information sources
Information concerning physical hazards of products	• In-house data
Information concerning physical hazards of ingredients (sources of information on the web)	• In-house data • International Chemical Safety Cards (ICSCs) http://www.inchem.org/pages/icsc.html • U.S. NLM　Household Product Database http://householdproducts.nlm.nih.gov/index.htm • UN Recommendations on the Transport of Dangerous Goods -　Model Regulations Sixteenth revised edition http://www.unece.org/trans/danger/publi/unrec/rev16/16files_e.html
Information concerning physical hazards of ingredients (documents)	• Sax's Dangerous Properties of Industrial Materials - 3 volumes set Edited by: Richard J. Lewis Sr. Wiley-Interscience; 10 edition (January 15, 2000)　ISBN: 0471354074

Table A2-2 Sources of information on hazard

Subject information	Information sources
Hazard information for products	• In-house data
Hazard information for similar compositions	• In-house data • U.S. NLM　Household Product Database http://householdproducts.nlm.nih.gov/index.htm • See information concerning the human experience values for similar compositions
Hazard information for each ingredient (sources of information on the web)	• 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/sheet/yugai_03.htm • NEDO（New Energy and Industrial Technology Development Organization） Initial risk assessment sheet http://www.safe.nite.go.jp/risk/syoki_risk.html

Subject information	Information sources
	• Ministry of the Environment　Initial assessment of the environmental risk of chemical substances http://www.env.go.jp/chemi/risk/index.html • OECD HPV（High Production Volume Chemicals）SIDS Reports, etc. http://cs3-hq.oecd.org/scripts/hpv/ http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html • European chemical Substances Information System http://ecb.jrc.ec.europa.eu/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. NLM　Hazard information for household product constituents http://householdproducts.nlm.nih.gov/ingredients.htm • 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
Hazard information for each ingredient (documents)	• Patty's Toxicology (5th Edition) Volumes 1-8 Edited by: Bingham, Eula; Cohrssen, 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)	• 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 A2-3 Exposure information: reference information concerning amounts, frequency, etc. of product use

Information providers	Information sources
American Cleaning Institute （former The Soap and Detergent Association）	Consumer Product Ingredient Safety Exposure and Risk Screening Methods for Consumer Product Ingredients, 2nd Edition （September 2010） http://www.aciscience.org/docs/Consumer_Product_Ingredient_Safety_v2.0.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/

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 compound, and interaction. As a result, the process of decision-making regarding product similarity becomes more complicated as the number of ingredient types rises. In some cases, it may be necessary to seek the decision of experts. When the propriety of a decision on product similarity cannot be corroborated, the hazard classification process shall proceed through steps such as the examination and acquisition of additional data instead of being confined to bridging principles.

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

The determination of the category of one product by means of hazard information for a similar one requires confirmation that the classification subject (Product B) is on a par with another serving as the source of reference data on hazard classes (Product A in the figure below). 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 Product B and Product A are similar in respect of physicochemical properties, pattern of use, etc.

ii) It must be confirmed that the two are similar in respect of composition, based on ingredients and compounding amounts (proportions).

iii) 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 iii) 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).

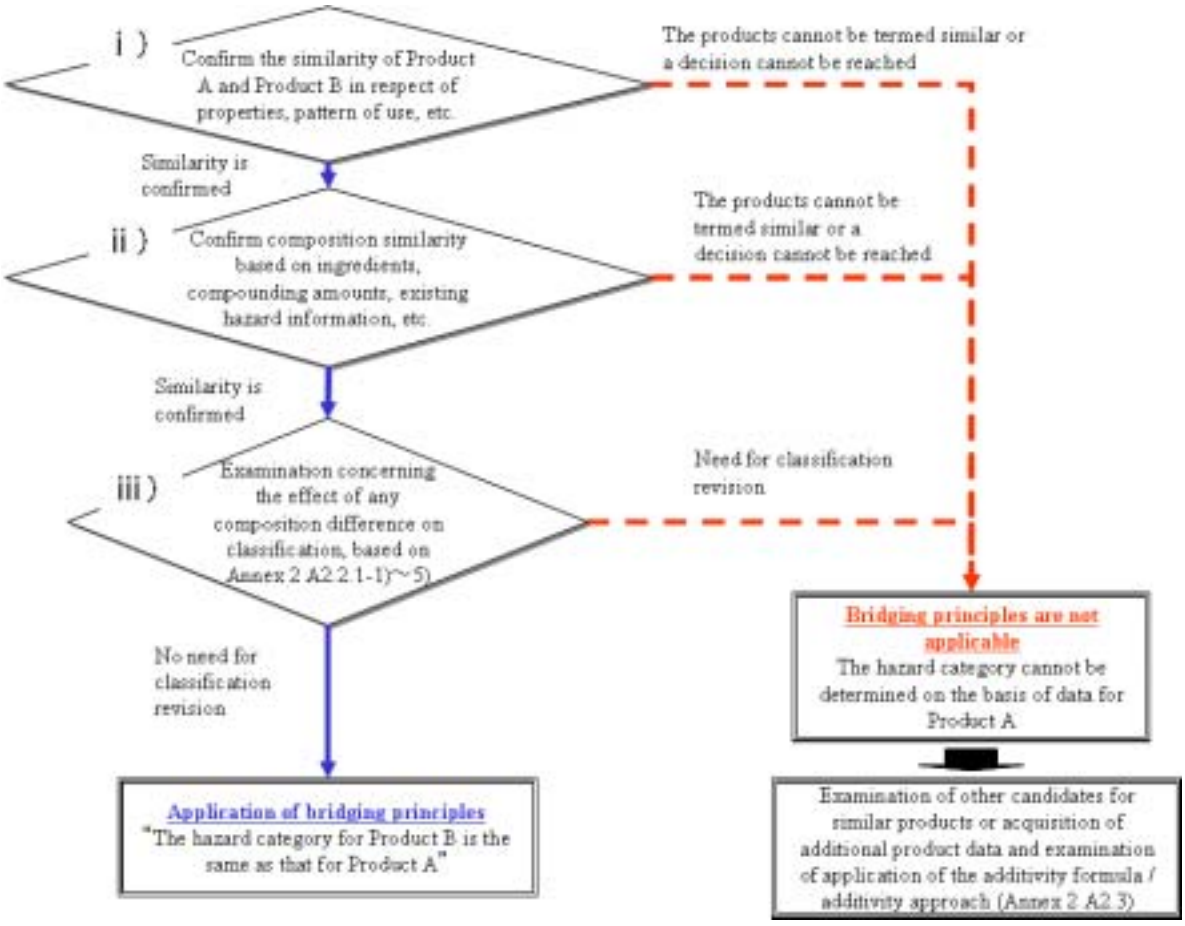

Figure A2-2 Procedure for application of bridging principles

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 totally non-toxic substances, product toxicity may be calculated on the basis of test data for undiluted products. For example, if a product with an LD_{50} concentration of 1,000 mg/kg is diluted with an equal proportion of water, the LD_{50} concentration of the diluted product would be 2,000 mg/kg (calculation examples are presented in **Annex 2 A2.3**).

2) Production batch

The hazard of a production batch of a certain product in terms of toxicity, corrosion, serious eye damage/eye irritation, sensitization, germ cell mutagenicity, carcinogenicity, and reproductive toxicity may be regarded as essentially the same as that of a different batch of the same products produced by or under the control of the same manufacturer. However, this shall not apply if there are circumstances that could conceivably cause a significant difference between the batches, such as a change in their toxicity. In such cases, a 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 the new product is classified in Category 1 and has a higher concentration of ingredients than another product in Category 1, it 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 the three products have the same ingredients, where the products A and B are classified in the same irritation/serious eye damage toxicity category and that 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: A + B, C + B
(b) The concentration of Ingredient B is essentially the same in both products.
(c) The concentration of Ingredient A in Product “A + B” is equal to the concentration of Ingredient C in Product “C + B”.
(d) For ingredients A and C, data concerning toxicity, skin corrosion/irritation serious eye damage/eye irritation are available and have practically the same values.

Based on these assumptions, if Product “A + B” has already been classified on the basis of test data, Product “C + B” may be placed in the same hazard category.

(ii) Respiratory or skin sensitization

The assumptions are as follows.

(a) Two products: A + B, C + B
(b) The concentration of Ingredient B is essentially the same in both products.
(c) The concentration of Ingredient A in Product “A + B” is equal to the concentration of Ingredient C in Product “C + B”.
(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 “A + B” has already been classified on the basis of test data, Product “C + B” may be placed in the same hazard category.

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 a bleach product.

Reference Product A	
Hypochlorite	: 5%
Sodium hydroxide	: 0.9%
Other constituents	: Balance
pH	: 12

Assessment Product B	
Hypochlorite	: 6%
Sodium hydroxide	: 1%
Other constituents	: Balance
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 in respect of product properties, use pattern, etc.
   Both products are used to bleach apparel and fabric in the home.
   Both products basically share the same pattern of use, i.e., dilution of the base liquid to a standard use concentration, soaking of laundry, etc. for a certain time followed by rinsing, and recommended wearing of gloves for use.

2) 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.

3) Confirmation of influence of composition differences on hazard category
   Of the ingredients composing products A and B, that of 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 ingredients" 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%	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 LD_{50} exceeds 2g/kg. 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.
Sodium hydroxide	0.9%	1.0%	Even in the case of substances with a strong toxicity (LD_{50} 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.

The GHS Official Text contains calculation methodology for arriving at the acute toxicity estimate (ATE) for mixtures (Section 3.1.3.6 on classification of mixtures based on ingredients of the mixture (Additivity formula)). If data are available for all ingredients with a compounding proportion of at least 1.0%, this calculation procedure should be applied to confirm that there is no significant difference from the ATE of the product whose toxicity is being estimated from the standard product. Annex 2 A2.3 presents the detailed methodology for ATE application.

[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 contained in the classification in the European Directive of Restriction on Hazardous Substances, is generally classified as a severe skin irritant at concentrations of from 5% to less than 10%, and is not a skin corrosive. 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 test, 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

	Concentration in Product A	Concentration in Product B	Potential to cause serious eye damage/eye irritation of ingredients in Product B, and reasons
Sodium hydroxide	0.9%	1.0%	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.

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 the other items as well, hazard can be inferred from similar products by comparing the contents of the Official Text, differences of ingredients and compounding amounts, 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 Annex2 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, as described below. However, the following points must be borne in mind when utilizing this methodology for hazard classification.

When a product is classified in a category based on the additivity approach, the hazard information may be different from risk of the product in actual use. Using this Annex for classification of products, this possibility must be taken into consideration and the adequacy of the results must be carefully assessed by investigating consumer information for similar products. It may also be noted that the process of applying the additivity approach becomes more complicated as the number of ingredients increases. Classifying products into adequate categories and providing information for consumer protection demand hazard classification approach that is not limited to the additivity formula or additivity approach but instead includes examination and acquisition of additional data as necessary.

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 item.

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 (not classified).

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.

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

Here:
- Ci = concentration of Ingredient i
- i is n counting from 1 when there are n ingredients
- ATEi = 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 of 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 at all is contained in the product at a concentration of 1% or greater

In this case, it is concluded that a definitive ATE cannot be allocated 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 correction processing for the additivity formula shown in A2.3.1-1).

$$\frac{100-\left(\sum Cunknown\ \ if\ >10\%\right)}{ATEmix}=\sum_{n}\frac{Ci}{ATEi}$$

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 TableA2-4, for calculation using this value.
The inhalation toxicity value is based on 4 hours 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.

TableA2-4 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 5< Category 2 ≤50 50< Category 3 ≤300 300< Category 4 ≤2000 2000< Category 5 ≤5000	0.5 5 100 500 2500
Dermal (mg/kg of body weight)	0< Category 1 ≤50 50< Category 2 ≤200 200< Category 3 ≤1000 1000< Category 4 ≤2000 2000< Category 5 ≤5000	5 50 300 1100 2500
Gas (ppmV)	0< Category 1 ≤100 100< Category 2 ≤500 500< Category 3 ≤2500 2500< Category 4 ≤ 20000 Category 5 (see the footnote)	10 100 700 4500
Vapor (mg/l)	0< Category 1 ≤0.5 0.5< Category 2 ≤2.0 2.0< Category 3 ≤10.0 10.0< Category 4 ≤20.0 Category 5 (see the footnote)	0.05 0.5 3 11
Dust/mist (mg/l)	0< Category 1 ≤0.05 0.05< Category 2 ≤0.5 0.5< Category 3 ≤1.0 1.0< Category 4 ≤5.0 Category 5 (see the footnote)	0.005 0.05 0.5 1.5

Note: The GHS Official Text does not stipulate values to serve as Category 5 standards for acute inhalation toxicity.

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 A2-5. If the combined concentration of such ingredients exceeds the cutoff value/limit concentration forming the classification standard, classify the product as corrosive/irritant.

Table A2-5 Relationship between concentration 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	≥5%	<5%, ≥1%
Skin Category 2		≥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 A2-6.

Table A2-6 Relationship between concentration of ingredients for which the additivity approach cannot be applied and product category

Ingredient	Concentration	Mixture category: skin
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 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, the test may be implemented 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 in 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 A2-7 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 influence	Reversible eye influence
	Category 1	Category 2
Eye or skin Category 1	≥3%	<3%, ≥1%
Eye Category 2/2A		≥10%
(10×Eye Category 1)+ Eye Category 2/2A		≥10%
Eye Category 1+ Skin Category 1	≥3%	<3%, ≥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 A2-7 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 A2-7 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 A2-7: classify in accordance with Table A2-8.

Table A2-8 Relationship between concentration of ingredients for which the additivity approach cannot be applied and product category

Ingredient	Concentration	Mixture category: eye
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 a ingredient even at a concentration above the general cutoff levels indicated in Table A2-7 or Table A2-84. 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, the test may be implemented for 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 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 bleach product

This section describes the process of classification of a bleach 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.

Hypochlorite	: 6%
Sodium hydroxide	: 1%
Other constituents	: Balance
pH	: Over 11.5

Of the ingredients composing bleach of the composition noted above, that of 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 ingredients 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 hypochlorite and sodium hydroxide 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 sodium hypochlorite and sodium hydroxide.

- ✧ Sodium hypochlorite: 5,800 mg/kg (oral LD_{50} value in testing with mice)
- ✧ Sodium hydroxide: 325 mg/kg (oral LD_{50} value in testing with rabbits)

The other ingredients, i.e., the surfactant and balance 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 2,000mg/kg (not classified) may also be ignored. For this reason, sodium hypochlorite may also be excluded as a subject of the ATE calculation. For the purpose of example, however, a calculation was made of the oral LD_{50} value for both sodium hypochlorite and sodium hydroxide based on the additivity formula A2.3.1-1).

The formula, $\frac{100}{ATEmix} = \sum_n \frac{Ci}{ATEi}$ can be converted into $ATEmix = \frac{100}{\sum_n \frac{Ci}{ATEi}}$

Then,

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

The ATE calculation value indicates that the oral LD_{50} value exceeds 2,000 mg/kg on the product level. As such, it may be concluded that the product does not belong in the category of acute oral toxicity.

Acute oral toxicity on the product level 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 sodium hypochlorite and sodium hydroxide 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
- Sodium hypochlorite: 10 - 11 in a 5% solution and 11.2 in a 15% solution [5]
- Sodium hydroxide: about 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 testing 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 corrosiveness/irritation

Use the information sources noted in A3.2 of Annex 3 to obtain data for the corrosion/irritation of each ingredient, and classify each on that basis, as far as possible.

✧ Sodium hypochlorite: corresponds to Category 1. The data serving as grounds are as follows.
Classification as a corrosive substance (R34) at a concentration of at least 10%[6]

✧ Sodium hydroxide: corresponds to Category 1. The data serving as grounds are as follows.
Appearance of serious tissue destruction and mortality in all dermal layers at a concentration of at least 8% [7]

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

Because the composition (bleach) contains bases 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

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[5] SODIUM HYPOCHLORITE, Workplace Environmental Exposure Level Guide (1991), American Industrial Hygiene Association

[6] Annex I of Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labeling of dangerous substances (http://ecb.jrc.ec.europa.eu/legislation/)

[7] OECD SIDS SODIUM HYDROXIDE(CAS No.1310-73-2) : SIDS Initial Assessment Report For SIAM 14(Paris, 26-28 March 2002)

considered one that contains at least 1% acids and bases, 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

As shown in A3.2.3 of Annex 3, placement of the compound (bleach) in Category 2 for skin corrosion/irritation would presumably be appropriate as viewed from the standpoint of providing consumers with suitable information, based on data from animal test with the product and information concerning human experience. Therefore, it would not be appropriate to study the prospect of GHS indication using the results of classification based on the aforementioned additivity approach as grounds.

If there is a difference between the concentration in the data obtained and that in the product composition in respect of the degree of skin corrosion/irritation, the results of classification based on the methodology using the additivity approach/cutoff values may be different from the realities, as noted above. Therefore, the classification should be made using data from animal test using the product and information concerning human experience, instead of application of the methodology using the additivity approach/cutoff values, as far as possible. In addition, if it is difficult to make a proper classification based on the existing data alone, it would be advisable to conduct an "in vitro" ("in vivo" if the conditions can be met) in accordance with the assessment stage noted in the Official Text, and to determine the category based on the test results. If there is no choice but to utilize the additivity approach and cutoff value, it is necessary to collect data on corrosion/irritation at a concentration close to that in the product for each ingredient and to obtain a decision from experts on matters including ingredient interaction.

3) Serious eye damage/eye irritation

The product concentrations of sodium hypochlorite and sodium hydroxide 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
- ✧ Sodium hypochlorite: 10 - 11 in a 5% solution and 11.2 in a 15% solution [8],
- ✧ Sodium hydroxide: about 13 in a 1% solution

Because the product has a 1% content of a substance with a pH of 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 testing of similar products, it would be advisable to proceed to the second step instead of concluding the classification work at this stage. It should be noted that the aforementioned classification result is thought to be proper in the case of this composition, even considering information concerning human experience of use of similar products.

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

Use the information sources noted in A3.2 of Annex 3 to obtain data for the serious eye damage/irritation of each ingredient, and classify each on that basis, as far as possible. Although the result of the classification in Item (1) above is thought to be proper, the data and classification results for each ingredient are shown below for the purpose of example.

- ✧ Sodium hypochlorite: corresponds to Category 1. The data serving as grounds are as follows.
  Classification as a corrosive substance (R34) at a concentration of at least 10 % [6]

- ✧ Sodium hydroxide: corresponds to Category 1. The data serving as grounds are as follows.
  Classification as a corrosive substance (R34) at a concentration of at least 5 % [6]

(iii) Determine the category on the product level based on the category of each ingredient determined in the second step.
Because the composition (bleach) contains bases 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 composition could be considered one that has the contents of at least 1% acids and bases, although it is not the subject of additivity calculation for reason of other corrosive

[8] SODIUM HYPOCHLORITE, Workplace Environmental Exposure Level Guide (1991), American Industrial Hygiene Association

(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. This result matches that of the classification based on data from animal test with the product and human experience information indicated in A3.2 of Annex 3.

As noted in connection with skin corrosion/irritation, in the case of serious eye damage/eye irritation as well, the classification should be made using data from animal test with the product and information concerning human experience, instead of application of the methodology using the additivity approach/cutoff values, as far as possible, in order to supply consumers with more accurate information. In addition, if it is difficult to make a proper classification based on the existing data alone, it would be advisable to conduct an "in vitro" ("in vivo" if the conditions can be met) in accordance with the assessment stages noted in the GHS Official Text, and to determine the category based on the test results. If there is no choice but to utilize the additivity approach and cutoff value, it is necessary to collect data on corrosion/irritation at a concentration close to that in the product for each ingredient and to obtain a decision from experts on matters including ingredient interaction.

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.

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 each ingredient to be classified.
The pH in the model is in the range of 2 - 11.5, and this suggests the product does not belong in Category 1.

(ii) Determine the 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 intensive 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 synthetic 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 model 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 model (dishwashing detergents) outside any category of skin corrosion/irritation based on information concerning human experience would presumably be appropriate even as viewed from the standpoint of providing consumers with suitable information. In similar models 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 each ingredient to be classified.

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 eye irritation study at one 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 2A, as it did not exhibit corrosiveness even if it caused a strong reaction.

* 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%[28], 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 2.

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

As shown in A3.1 of Annex 3, placement of the model (dishwashing detergents) in Subcategory 2B for serious eye damage/eye irritation based on information concerning human experience would presumably be appropriate even as viewed from the standpoint of providing consumers with suitable information. In similar models 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.

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 hazards during safety training, 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 indications, efforts must be made to avoid providing too much or too little information and incorporate data 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 actually cause injury under condition of use and make examinations to determine the appropriate labeling. The work on the GHS has not addressed harmonization of this type of approach. Therefore, specific procedures to apply this approach would have to be developed and applied by the competent authority (GHS Official Text, A5.1.2). In Japan, GHS Inter-ministerial Committee (held on 11 January 2007) recognized it as 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."[9] Furthermore, as a guidance document based on this concept, "Guidance on Risk Assessment of Consumer Products to Determine GHS Labeling"[10] was approved at the 28th GHS Inter-ministerial Committee (held on 17 April 2008) and posted on the website of NITE (National Institute of Technology and Evaluation). This Annex 2-4 presents a detailed description of the procedure for determining the contents of consumer product labels in accordance with the likelihood of injury, and is positioned as "additional guidance" to provide a more concrete indication of risk assessment approach for the consumer products Japan Soap and Detergent Association (JSDA) members handle. The content of this guidance is based on the current state of knowledge. The content of this guidance is based on the current state of knowledge, and depending on the development of national level and international level discussions in this area, the contents may need to be modified in future.

For targeted consumer products in this guidance, exposure assessment is applied to determine necessity of indicating label elements and what information ought to be included in the label in this type of approach. For consumer products*, which contain a chemical having chronic health hazards, found to be classified in any hazardous category of the GHS classification standards, manufacturers can determine the necessity and content of the labeling based on evaluation as to whether or not there is a likelihood of injury (or Risk**) in actual use of the product. To make such determinations, manufacturers acquire data for assumptive exposure in normal use and foreseeable misuse/accidents. Next, they conduct risk assessment with referring to these exposure data to determine, in accordance with a risk-based approach, the need for indicating GHS label elements for chronic health hazard in the product 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) in the product under the anticipated exposure conditions is below a certain level. In such cases, it is not necessary to include information concerning chronic health effect on the GHS label of the product. This kind of phased approach for risk assessment may be applied in determining classification of health effects items (e.g.

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[9] 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_interministrial080218set.doc

[10] GUIDANCE ON A CONSUMER PRODUCT RISK ASSESSMENT FOR GHS LABELLING , April, 2008
http://www.safe.nite.go.jp/english/ghs/pdf/guidance_e.pdf

carcinogenicity, reproductive toxicity, specific target organ toxicity [repeated exposure]) induced by chronic or repeat exposure to the product.

* Products handled by the Japan Soap and Detergent Association rarely contain ingredients that are classified into one of the categories of items that will cause chronic effects on health under the GHS classification. Granted that the product has such component chemicals, usually, only one component falls under such categories. 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 procedure for risk assessment on the product based on the results of assessment of the hazard 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 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 exposure concentration (quantity) based on a semi-quantitative calculation and the TDI (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 to be indicated on consumer product labels.

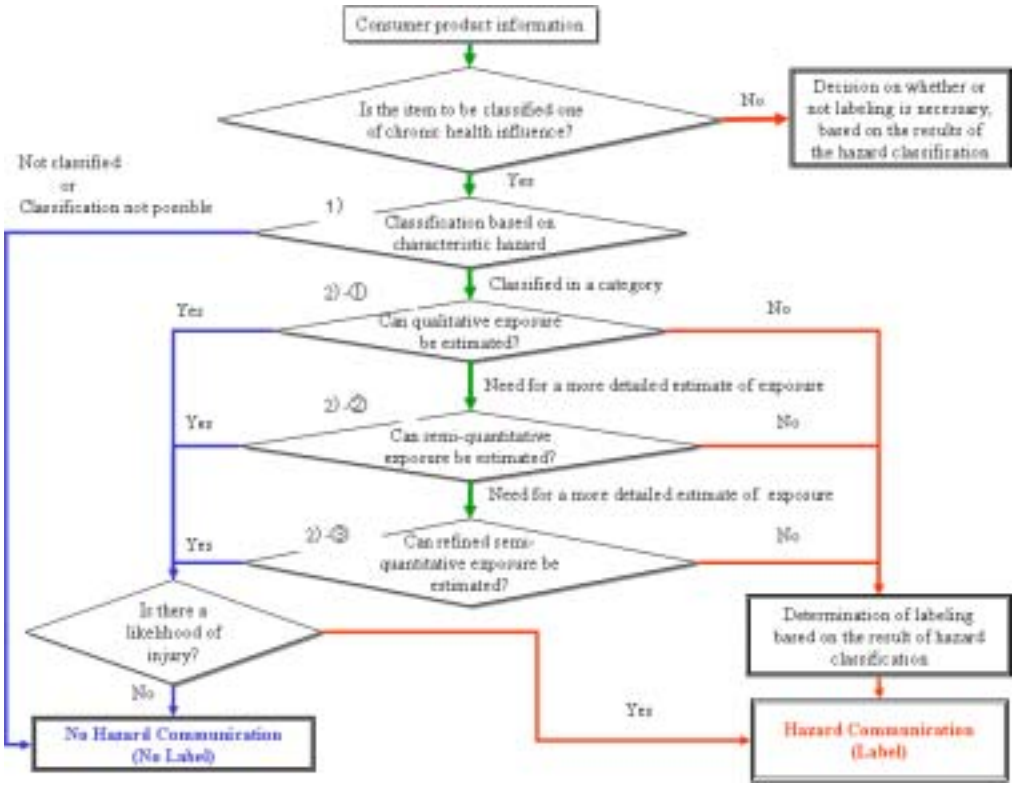

Figure A2-3: Major steps for determination of label based on the likelihood of injury

1) Classification based on characteristic hazard

The methodology begins with the determination of whether or not the consumer product satisfies the GHS classification criteria regarding intrinsic hazards.
Consumer products containing one or more hazardous items classified in GHS category must be classified according to those criteria. However, for the items such as 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 make indication accordingly.
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 in 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 negligible 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 qualitative assessment.
The task in this step is to determine whether or not the use of the product will lead to no or negligible exposure and, therefore, negligible likelihood of injury (risk).

If there is no exposure or it is negligible, 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 class or category of chronic health effect, however, there is evidence that these substances are not released from the product.
- The likelihood of chronic health effect can be negated because the chemical substances that have such effect if inhaled are enclosed in a non-sprayable liquid matrix or in non-inhalable or nonfriable capsules comprising the product.

In contrast, when it is found that exposure may not be negligible, a determination is made of the GHS elements indicated in label based on the intrinsic hazards of the product's component chemicals. However, a more accurate exposure assessment can be made by the approach described in Section (ii) below.

(ii) Semi-quantitative exposure assessment based on assumption

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 many 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 of the exposure level estimated on the basis of this assumption and the product hazard. If it is concluded that the risk to consumers is low, GHS label elements onto the product regarding the hazard is 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 accurate exposure data are not available or there is no need for accurate exposure assessment.

(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 consumer's actual use of products can be obtained from use tests conducted during product development, data being contained 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 product can be obtained from the Technical Guidance Document (TGD) or Guidance on Risk Assessment of Chemicals[11] following European Regulations and Directives and documents published by the US Environmental Protection Agency (EPA).[12] The US Soap and Detergent Association (SDA) also announce guidance information regarding exposure assessment.[31]
The major factors to be considered in estimation of 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, and use concentration of the product)
- Potential of systemic absorption

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 more detailed assessment must 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 based on assumption" 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 based on assumption
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.

[11] 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.ec.europa.eu/home.php?CONTENU=/DOCUMENTS/TECHNICAL_GUIDANCE_DOCUMENT/

[12] USEPA Exposure Factors Handbook http://www.epa.gov/ncea/efh/

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:

$$D_{exposure} = Q_{product}/BW$$

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. "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 considered.

Oral exposure

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

- Supposable intake of the chemical substance in their normal use, 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:

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

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

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

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

  Here, V_{oral}, w_p, and C_{oral} represent the amount of the product ingested daily (cm^3/day), the weight fraction of the chemical in the product, and average concentration of the chemical in the product (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 the product ingested is the total amount of absorption into the body via gastrointestinal tract ($f_{oral} = 1$).

- 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, this may also 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 dermal route (D_{dermal}: expressed as mass of the chemical per mass body weight per day) are shown below: Calculation on an assumption that the total amount of the chemical contacting the skin is absorbed into the body; and calculation considering dermal permeability coefficient of the chemical

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

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

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.

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

Here, V_{dermal}, w_p, C_{dermal} represent the volume of the product (cm^3/day) applied to the skin per day, 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 a high estimate of the systemic exposure by assuming that the total amount of the product contacting the skin is absorbed into the body ($f_{dermal} = 1$).

BW: body weight (kg)

If model calculation values or measured values are available for the f_{dermal} level of the product or the product's component chemicals, 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

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

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

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

- 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.

- Vr: daily human ventilation rate (m^3/day)
  Typical daily adult human ventilation rate is 20 m^3/day (EU, 2006).[13] Calculation of prolonged exposure to the chemical via inhalation requires 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.

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

  Here, $Q_{inhalation}$ 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)

[13] European Commission. 2006 Technical Guidance Document, edition 2, Part I, Human Health. http://ecb.jrc.ec.europa.eu/home.php?CONTENU=/DOCUMENTS/TECHNICAL_GUIDANCE_DOCUMENT/

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

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 category of the GHS chronic health hazards [e.g., reproductive toxicity, specific target organ toxicity (repeated exposure) and carcinogenicity] and the possibilities of exposure that cannot be negligible, the need for 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 comparison of the estimated level of consumer exposure and the tolerable daily intake (TDI). The succeeding sections present guidance concerning determination of TDI, virtually safe dose (VSD), and other items in the classes of 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 the uncertainty factor. For these classes, 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[14,15]. As described above, it is the common practice to use 100 as the default value for the uncertainty factor. In

[14] How to manage uncertainties, ISBN: 978-4621079058

[15] 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)

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).[16, 17] 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 response[18]. 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. Normally lowest NOAEL among appropriate NOAELs is used as base for determining the TDI.

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 test data, the TDI is calculated by dividing the NOAEL by the factor of 10 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 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 lowest LOAEL among appropriate LOAELs is used as base 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 test data, the TDI is calculated by dividing the LOAEL 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 depending on whether or not the concerned chemical has a hereditary toxicity.

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

In the field of consumer products for home use, manufacturers ordinarily do not deliberately compound products with substances that are genotoxic. However, there have been reports revealing the raised suspicions that product's ingredient which has long been in use shows carcinogenicity in animals. There consequently may arise occasions requiring

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

[17] 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

[18] IPCS Environmental Health Criteria 170 http://www.inchem.org/documents/ehc/ehc/ehc170.htm

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, but an international consensus has not yet been built on the procedure for assessment of the risk of genotoxic and carcinogenic substances. In risk assessment within Japan as well, matters in this field have not gone beyond the level of proposal for future discussion.

Usually, even at very low levels of exposure, genotoxic carcinogens are generally considered to have a carcinogenic potential corresponding with that level. In such cases, an estimate is made of the dose response relationship at low doses utilizing various multistage linear models that take T25[19,20], LED_{10} [21] or other values as the point of departure (POD), in order to obtain the virtually safe dose (VSD; at which the carcinogenic probability is no higher than 10^{-5} or 10^{-6}), and implement risk management on the basis of this VSD. Linear multi-stage model has been widely used to estimate carcinogenic potential at low doses. U.S. EPA published "Guidelines for Carcinogen[22]"in March 2005 and recommends simple linear extrapolation approach that determine 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 areas 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 of carcinogenicity risk assessment.

(Supplemental information) Estimated VSD has uncertainty derived from the extrapolation model used. In order to eliminate such uncertainty and prioritize chemicals for evaluation and testing, in 2005, EFSA, WHO, ILSI proposed an approach of MOE (Margin of exposure), where MOE is calculated by dividing $BMDL_{10}$ (lower limit of a one sided 95% confidence limit on the BMD for 10% incidence of tumors; same as LED_{10}) or T25 by estimated human exposure.[23,24] However, approaches and methods to assess the risks of specific substances or products based on the calculated MOE have not been established. Thus, approaches for carcinogenicity risk assessments, regardless of the presence of genotoxicity, continue to be subject of discussion of genotoxic and improvement from various viewpoints. Paying particular attention to the progress of studies, it is desired to do risk assessment using extrapolation models and uncertainty factor, etc. which are considered most appropriate.

* 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

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[19] T25 is a simplified carcinogenic potency index that the chronic daily dose in mg per kg bodyweight which will give 25% of the animals tumours in carcinogenicity tests performed in accordance with OECD Guidelines.

[20] 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)

[21] LED10 : 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.

[22] Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001B, March 2005. US EPA. http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.PDF

[23] Risk assessment of substances that are both genotoxic and carcinogenic. Report of an International Conference organized by EFSA and WHO with support of ILSI Europe.e http://rivm.openrepository.com/rivm/bitstream/10029/5535/1/barlow.pdf

[24] EFSA/WHO INTERNATIONAL CONFERENCE WITH SUPPORT OF ILSI EUROPE ON RISK ASSESSMENT OF COMPOUNDS THAT ARE BOTH GENOTOXIC AND CARCINOGENIC （ISBN 92-9199-028-0） http://www.efsa.europa.eu/en/home/publication/efsawho2006.htm

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.

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

Determination of the likelihood of injury (risk) for items of chronic health effect must take account of both hazard and data from qualitative/semi-quantitative based on assumption/refined semi-quantitative exposure assessment, as described in A2.4.1-2) (i)-(iii) and –A2.4.2-1) and 2).

1) Determination of the likelihood of injury (-risk)
   To determine that the likelihood of injury (risk) for chronic health effect is low at any step of exposure assessment, the exposure needs to be negligible [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 GHS label elements.

   (i) Qualitative exposure assessment

   In case that the consumer exposure is nil or negligible.

   (ii) Semi-quantitative exposure assessment based on assumption

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

   (iii) Refined semi-quantitative exposure assessment

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

2) Determination of labeling based on the likelihood of injury (risk)
   If it is decided that the likelihood of injury (risk) is negligible 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 a model for a synthetic 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 animal data for the product
  No animal data for the model compositions is available; therefore, the model product cannot be classified in any category of reproductive toxicity.

- Classification based on human experience
  No information on human exposure to the model compositions is available; therefore, the model products cannot be classified in any category of reproductive toxicity.

- 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 babies[25]. Therefore, ethanol would be classified as Category 1, and this model formula, 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%[26]) of those classified as Category 1. The ingredients other than ethanol would not be considered reproductive toxicity substances[27,28,29,30].

Because ethanol is a Category 1 ingredient, the model would be placed in Category 1 in a classification of reproductive toxicity 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 coming with use of a synthetic dishwashing detergent.

(i) Qualitative exposure assessment
The first task is to determine whether use of the product entails absolutely no exposure or only exposure on a level that can be negligible, such that the likelihood of injury (risk) may also be

[25] International Agency for Research on Cancer (IARC) – Summaries & Evaluations ALCHOHOL DRINKING (Group 1)VOL.:44(1988)
[26] As of September 2007, Japanese Government had not decided the use of cut-off values/concentration limits triggering classification of a mixture. In this case, "0.1%" is tentatively used as the cut-off value.
[27] 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/RiskAssessment.cfm
[28] 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/RiskAssessment.cfm
[29] The Risk Assessment of Human Health Effects and Environmental effects of Surfactant, Japan Soap and Detergent Association, July, 2001
[30] Toxicity of Detergent and its Assessment, edition by Food Chemistry Division, Environmental Sanitation Department, MHLW, 1983

negligible. The reproductive toxicity deriving from ethanol is recognized in the aforementioned case of excessive and consecutive 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 synthetic 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 synthetic dishwashing detergent include systemic exposure through oral intake and dermal absorption, and accidental exposure to the eye via splashes or spills with 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 negligible in an assessment of chronic human health effect.

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 synthetic dishwashing detergent indirectly, through ingestion of food that has come into contact with the detergent residue on dish, and that is washed in a bowl of water including the detergent.

Dermal exposure

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

(ii) Semi-quantitative exposure assessment based on assumption

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. Nevertheless, this approach often leads to overestimation of the exposure level and risk assessment results that are divorced from reality. 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 US SDA, and this could serve as footing 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 within the body through each route (oral and dermal), and addition of these levels for calculation of the total exposure. This calculation employs the model computation formula and default values for calculating exposure levels stipulated in "Exposure and Risk Screening Methods for Consumer Product Ingredients" (April 2005; US SDA) [31] and HERA Risk Assessment of Alcohol Ethoxysulphates (DRAFT)[32]. As a rule, the default values in "Exposure and Risk Screening Methods for Consumer Product Ingredients"[31] 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 researches considering variation in usage of the product or consumer's average physical size in USA and

[31] Exposure and risk screening methods for consumer product ingredients（April 2005）
http://www.aciscience.org/docs/Exposure_and_Risk_Screening_Methods.pdf

[32] HERA Risk Assessment of Alcohol Ethoxysulphates, AES DRAFT
http://www.heraproject.com/RiskAssessment.cfm

Japan. In such cases, the reference cited in which the values used as a basis for calculation is provided.

AIHC: American Industrial Health Council
AISE: International Association for Soaps, Detergents and Maintenance Products
APC: All Purpose Cleaners
PCPC: Personal Care Products Council (Formerly CTFA)
D4: Octamethylcyclotetrrasiloxane 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: CTFA's Safety and Regulatory Toxicology Committee
TGD: EU Technical Guidance Document (2003)

Oral exposure

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

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

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

C': Product concentration in the residual liquid on dish
= Product use concentration (4g)[33] / the amount o water used per use (5000cm^3)[34]
=0.008 (g/cm^3)=0.8 (mg/cm^3)
The values used for calculating C' are determined on the basis that there is no rinsing process during dishwashing in EU or US. Hence, this calculation does not take account of dilution of the synthetic dishwashing detergent due to rinsing. In Japan, C' would be lower than that of EU or US, because rinsing process is included in Japanese's dishwashing behavior.

Ta': Amount of water containing the detergent on dish after rinse = 5.5×10^{-5}(mL/cm^2)[31]

Sa: Area of dish contacting food = 5400 (cm^2/day) [31]
The amount of daily use of dishes (area of dish contacting food) is put at 3,700 cm^2 (assuming 120 cm^2 each for 10 dishes and 50 cm^2 each for 50 dishes[35]) in "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. Here, however, the much conservative values calculated by the US SDA were utilized.

CF: Conversion factor =1 (cm^{3}water/1 mL water)

BW: Body weight = 55.5 kg (a pregnant Japanese woman) [36]

[33] In-house data
[34] Human and Environmental Risk Assessment LAS Linear Alkylbenzene Sulphonate (CAS No. 68411-30-3) Version 2.0 May, 2004 http://www.heraproject.com/RiskAssessment.cfm
[35] Atsushi Nishida, Research Concerning the Safety of Food Detergents, Food Sanitation Research , 40, 1-25
[36] 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

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

Of the level of systemic exposure to synthetic dishwashing detergent accompanying indirect exposure through dish noted above, 5% would be occupied by ethanol, that is,

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

Synthetic dishwashing detergent that complies with the provisions of the enforcement regulations of the 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 washing[37]. Table A2-9 shows the residual levels of aminoxide detergent.

[37] Volume 1 (on detergents containing aminoxides) published in September 1991 of the report on basic research concerning the safety of food-use detergents conducted under the MHLW program of scientific research in 1989, Shokusen

Table A2-9 Residual level of aminoxide detergent on food products after washing and daily intake of food products

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

*1: Revision of Table 43 "Daily Intake Levels", p.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, 2002[38]

Publicly known information is not yet available regarding the residual level of ethanol after washing vegetables and fruit with synthetic dishwashing detergent. For this reason, it was decided to consider it equivalent with the residual level of surfactant, and to calculate the level of ethanol intake through vegetables and fruit based on the highest levels in Table A2-9.

It was assumed that the daily intake levels of vegetables and fruit are 263 and 256 grams, respectively.

[1.4 (μg/g) x 263 (g/person/day)] + [0.24 (μg/g) x 256 (g/person/day)]
= 430.48 (μg/person/day)

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

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

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

$$\text{Oral exposure to ethanol accompanying use of synthetic dishwashing detergent} \fallingdotseq 0.0080(\text{mg/kg/}day)$$

Dermal exposure

The daily systemic exposure to synthetic 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".

$$\text{Dermal systemic exposure to ethanol in synthetic dishwashing detergent per day} = \frac{CA \times PC \times F_l \times FQ \times CF \times Kp \times T}{BW}$$

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

The following figures 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; US SDA.) [31]

CA: Body surface area in contact with the detergent = 1980 (cm^2) *3
PC: Concentration of product in contact with the skin = 0.1 (g/cm^3) *4
F_1: 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 woman[36]

*3 Appendix II of the European TGD, Page 237, notes the figure of 731 cm^2 for the surface area of a female hand. Here, however, the much conservative values provided by the US Soap and Detergent Association are utilized.

*4 Use of the higher concentration in the case of application of synthetic dishwashing detergent directly to the sponge (non-concentrated type: 0.1 g/cm^3; concentrated type: 0.05 g/cm^3) [39].

*5 Here, much conservative figure stipulated in the following source is utilized[40]
-- "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).
-- "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

$$\text{Dermal systemic exposure to synthetic dishwashing detergent per day} = \frac{(1980\times0.1\times0.05\times0.8\times10^{-3}\times1000\times0.75)\times3}{55.5} \fallingdotseq 0.3211(\text{mg/kg/}day)$$

Above exposure assessment rests on a scenario on the safe side by applying the higher figure for each value recognized in the conditions closer to actual use of detergent.

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

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

For the items provided with insufficient exposure data, the calculation is made based on the conservative exposure rate from the worst case scenario, therefore, the above total exposure is larger than the actual rate. If more accurate data is available with further assessment, it is possible to obtain more refined exposure rate.

3) Determination of the likelihood of injury

[39] In-house data
[40] 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"

The presence or absence of risk of manifestation of reproductive toxicity arising from ethanol contained in synthetic 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 unconscious 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 tentative 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, the lowest is 2,000 mg/kg/day[41]. The tentative TDI can be calculated by dividing this value by 100 [intraspecies differences (10) x interspecies differences (10)].

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

It is known that intake of about one glass per day of alcoholic beverage generally has no adverse effect on human fetuses[25]. Newman et al. reported that it is 28.5mL (22.49g , when the specific gravity of ethanol is 0.789[42]) per day as the threshold for alcohol intake during pregnancy with an effect on fetuses or new-borns[43]. If a pregnant woman (body weight of 55.5 kg[36]) 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:

$$\text{Ethanol intake by a pregnant woman accompanying intake of alcoholic beverages} = \frac{22.49 \times 1000}{55.5} \fallingdotseq 405.16\,(\text{mg/kg/}d\text{ay})$$

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]:

$$\text{Tentative human TDI} = \frac{405.16}{100} = 4.05(\text{mg/kg/}d\text{ay})$$

The levels calculated above may be summarized as follows：
Systemic ethanol exposure accompanying use of synthetic dishwashing detergent
= 0.3291 (mg/kg/day) ≒ 0.33 (mg/kg/day)
Tentative TDI based on NOAEL from animal study =20 (mg/kg/day)
Tentative human TDI based on human LOAEL = 4.05 (mg/kg/day)

The total amount of ethanol exposure deriving from dermal exposure to synthetic 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, likelihood is considered very little 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 item.

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[41] Rat offspring sired by males treated with alcohol. Alcohol. 1993 May-Jun;10(3):237-42.(OECD SIDS data)
[42] NITE CHRIP(http://www.safe.nite.go.jp/japan/db.html
[43] Effects of alcohol in pregnancy., Med J Aust (1980). Vol.2 No.

Descriptions in A2.4 were reviewed by the following experts:

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Annex 3

Examples of Classification and Labeling Evaluation

Annex 3: Examples of Classification and Labeling Evaluation

The main body of this document outlines the principles to follow in determining the classification and labeling of consumer products. Annex 1 contains the specific categories and classes to address. Annex 2 describes evaluation approaches and steps to determine classification and labeling.

This Annex provides examples to illustrate how those principles and approaches for classification and labeling may be applied. A3.1, A3.2, A3.3 are to illustrate evaluation approaches to determine classification and labeling using specific information examples on model formulations, and are not intended to suggest that every formulation within these product categories will bear the same classification or label elements. Formulations within a product category vary and the information sets available also vary. Consequently, each formulation, and the information available about it, must be considered separately.

Examples of information used for classification evaluation are listed below.

- Human experience with the subject formulation
- Human experience with similar formulations
- Data from animal testing of the subject formulation
- Data from animal testing of similar formulations
- Data from human experience with individual ingredients within the subject formulation
- Data from animal testing of individual ingredients within the subject formulation

A3.1 and A3.3 also show how to determine label elements, once the classification has been determined, based on the consideration of the likelihood of harm when determining the labeling related to the chronic endpoints.

A3.1 Dishwashing Detergent

This Annex document shows the procedures of classifying into a hazard category a model of typical formula for commercial dishwashing detergent in accordance with the guidance, along with some examples of the classification. The classification here is on a typical formula, and any marketed products different from the typical product in composition or intended or actual usage shall be considered for classification separately.

A3.1.1 The model formula for dishwashing detergent

Anionic surfactant*1	: 20%
Amphoteric surfactant*2	: 5%
Nonionic surfactant*3	: 5%
Ethanol	: 5%
Water	: 65%

*1: Consists of 10% of an Alcohol ethoxysulphates (AES) and 10% of an Alcohol sulphates (AS)
*2: Amine oxide（AO）5%
*3: Alcohol ethoxylates（AE）5%

A3.1.2 General usages of dishwashing detergent

Dishwashing detergent is used to clean dishware. Generally, dishware is soaked and washed in the detergent solution of the standard concentration or sponged with the undiluted detergent, and thereafter rinsed with water.

A3.1.3 Hazard category and statement

1) Acute toxicity

Acute oral toxicity

In an acute oral toxicity study on mice, each of six brands of commercial dishwashing detergent (hereinafter referred to as “compact detergent”), each of which contains 37 to 48% of surfactant, such as AES, AE, AO, or AOS(Alpha Olefin Sulphonate) , demonstrated an LD 50 of no less than 10 g/kg[44]. These results suggested that the compact detergent had low toxicity following single oral administration. With regard to two brands of traditional type of dishwashing detergent, which contain approximately 20% of surfactant, no death was found in the group of 10 g/kg dosage. Consequently, the lethal dose of the commercial

[44] Kanagawa Prefectural Institute of Public Health. “The Oral Toxicity of Compact Detergents for Dishwashing”, The Annual Research Report; No.27, 1997.

dishwashing detergent is estimated to be more than 2 g/kg, and generally not classified into any hazard category as acute oral toxicity.

The composition of commercially available dishwashing detergent is generally as shown below. Because the similarity of the model formula can be confirmed, bridging principles may be applied (see A2.2 of Annex 2).
Therefore, the model formula is not classified into any hazard category as regards acute oral toxicity.

Classification: None
Label : No label

*General composition of commercial dishwashing detergent

Anionic surfactant	:	15-25%
Amphoteric surfactant	:	6-10%
Nonionic surfactant	:	4-7%
Ethanol	:	4-7%
Others	:	15-20%
Water	:	Balance (The remainders adjusted)

Acute dermal toxicity

There are no available acute dermal toxicity data on the model formula. In addition, there are no sufficient LD50 values available for individual components. Nevertheless, it is possible to use the classification results for acute oral toxicity, as described below.

In dermal exposure, the rate of absorption into the body is no higher than in oral exposure, and the LD50 value is therefore generally higher than in oral exposure. Such being the case, as commercial dishwashing detergent fall into no hazard category of acute oral toxicity, it is thought that they also was not classified into any hazard category as regards acute dermal toxicity.

As noted above, bridging principles may be applied because the similarity between the model formula and the commercially available dishwashing detergent can be confirmed (see A2.2 of Annex 2).
Therefore, the model formula was not classified into any hazard category as regards acute dermal toxicity.

Classification: None
Label : No label

Acute inhalation toxicity

In respect of this class, there are no animal test data and no human experience information available for the model formula and commercial dishwashing

detergent. In addition, it is impossible to obtain sufficient data on the LD50 values for the ingredients.
Therefore, classification of the model formula was not possible with respect to acute inhalation toxicity.

Classification: None
Label : No label

2) Skin corrosion/irritation

There has been a report of the results of patch testing for four hours with human subjects for a household product with a composition 30% anionic surfactant, 4% nonionic surfactant, 7% ethanol, 2% potassium chloride, and 54% water (liquid detergent, pH=7.0). In these data, the primary irritation index (PII) was 0.1, indicating that the irritation effect was negligible[45]. The 4-hour patch test study of the dishwashing detergent referred was also conducted with human skin of the upper arms (n=10 to 12), reporting a PII of 0.4[46].
These results indicate that, if any, the irritating effect on humans by commercially available dishwashing detergent and products with a surfactant content of about 30% is so slight that it may be ignored.

As for those data from human experiences with commercial dishwashing detergent, the Hospital report of monitoring of health hazards associated with household products [47], issued by the Ministry of Health, Labour, and Welfare (MHLW), reported some cases related to the skin exposure, all of which were with eczema alone but with no evident symptom of irritation. Furthermore, published literatures also have not reported any irreversible skin lesion caused by commercial dishwashing detergent.

Therefore, commercial dishwashing detergent was generally not classified in any hazard category as regards skin corrosion/irritation.

As noted above, bridging principles may be applied because the similarity between the model formula and the commercially available dishwashing can be confirmed (see A2.2 of Annex 2).
Therefore, the model formula was not classified into any hazard category as regards skin corrosion/irritation.

Classification: None
Label : No label

3) Serious eye damage/eye irritation

The manufacturer's information of human experiences with commercial dishwashing detergent revealed no case with serious eye damage, but reported

[45] G. A. Nixon, et al, Toxicology and Applied Pharmacology, 31, 481-491, 1975
[46] G. A. Nixon, et al, Regulatory Toxicology and Pharmacology, 12,127-136, 1990
[47] Ministry of Health, Labour and Welfare (1995-2006) Hospital report of monitoring of health hazards associated with household products, http://www.nihs.go.jp/mhlw/chemical/katei/monitor(new).html

some cases with ocular hyperemia or swelling related to exposure to a droplet of detergent, which were reversible within seven days, as far as the outcomes were followed up.
Consequently, based on the human exposure experiences, commercial dishwashing detergent was classified into the Hazard Category 2B.

As noted above, bridging principles may be applied because the similarity between the model formula and the commercially available dishwashing detergent can be confirmed (see A2.2 of Annex 2).

Therefore model formula was classified into the Hazard Category 2B as regards serious eye damage/eye irritation.

Classification: Category 2B
Label : following labeling is needed

Symbol	None
Signal word	Warning
Hazard statement	Causes eye irritation
Precautionary statement	Refer to Labeling Guidance[48]

4) Respiratory or skin sensitization

Respiratory sensitization

In respect of this class, there are no animal test data and no human experience information available for the model formula and commercial dishwashing detergent and the ingredients.
Therefore, classification of the model formula was not possible with respect to acute inhalation toxicity.

Classification: None
Label : No label

Skin sensitization

Any ingredients in the model formula were not classified in terms of skin sensitization. Consequently, the present model formula does not classified into any hazard category as regards skin sensitization.

Classification: None
Label : No label

5) Germ cell mutagenicity

[48] GHS Labelling Preparation Guidance for Household Consumer Products（Draft）2nd version (July, 2008)

It is reported that all components of the model formula are not genotoxin[49,50,51,52,53]. Therefore the model formula was not classified into any hazard category as regards the germ cell mutagenicity.

Classification: None
Label : No label

6) Carcinogenicity

None of the surface-active agents used are considered carcinogenic substances[26, 27, 28, 29].

In addition, standard animal testing indicates that ethanol was not a carcinogenic substance[54, 55].

In the IARC classified "intake of alcoholic beverages and ethanol in alcoholic beverages" is classified into Group 1[56]. In OECD-HPV program, on the other hand, the carcinogenic scenarios of intake of "alcoholic beverage" are not considered to have any concern with occupational exposure and consumer exposure. As a consequence, ethanol is not classified as regards carcinogenicity[53].

In light of these information, the model formula is not classified into any hazard category as regards carcinogenicity.

Classification: None
Label : No label

7) Reproductive toxicity

Excessive and continual oral ingestion of ethanol in a pregnant mother is known to affect fetal development[54, 56]. The animal studies reported reproductive toxicity by ethanol intake and the results are also referred in OECD-SIDS[53]. In light of these information, ethanol may be classified into the Category 1A . The model formula was classified into the Category 1, because of its content of 5% of ethanol, higher than the cut-off values of ethanol for the Category 1(1A) .

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[49] Human and Environmental Risk Assessment on ingredients of household cleaning Products (HERA), Alcohol Ethoxysulphates Human Health Risk Assessment Draft, January, 2003. http://www.heraproject.com/RiskAssessment.cfm

[50] 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/RiskAssessment.cfm

[51] The Risk Assessment of Human Health Effects and Environmental effects of Surfactant, Japan Soap and Detergent Association, July, 2001 http://www.heraproject.com/RiskAssessment.cfm

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

[53] SIDS INITIAL ASSESSMENT PROFILE, Ethanol (SIAM 19, 19-22 October 2004)

[54] OVERVIEW OF THE HEALTH ISSUES RELATED TO ALCOHOL CONSUMPTION, 2nd EDITION ILSI（http://www.ilsi.org/Europe/Publications/R1999Over_Heal.pdf)

[55] The effects of long-term oral administration of ethanol on Sprague-Dawley rats － a condensed report, Toxicology 96（1995）133-145

[56] International Agency for Research on Cancer (IARC) - Summaries & Evaluations ALCOHOL DRINKING(Group 1) VOL.: 44, 1988

Other components of the model formula are considered negative for reproductive toxicity[49, 50, 52, 57].

As regards reproductive toxicity, a decision on label can be made on the basis of the results of an assessment of the likelihood of injury to consumers as shown in A2.4 of Annex 2.
As described in detail in A2.4 of Annex 2, in the event of use of a dishwashing detergent with an ethanol content of 5%, the intake of ethanol per kilogram of body weight per day would be 0.3291 mg/kg/day[58]. The tolerable daily intake (TDI) tentatively calculated on the basis of data contained in highly reliable review documents is equivalent to about 4.05 mg/kg/day for human and 20 mg/kg/day for animals[59]. As a result, the total exposure to ethanol accompanying oral and dermal exposure to a dishwashing detergent would be lower than both the tentative TDI based on human information and the TDI based on animal test. Considering the actual use of the product as a dishwashing detergent, it is consequently thought that the ethanol contained in it would hold very little likelihood of injury to consumers. Therefore, based on risk assessment, labeling is not required.

Classification: Category 1
Label : No label based on consideration of likelihood of injury (risk).

8) Specific target organ toxicity (repeated exposure)

Based on various reviews such as OECD-SIDS, neither surfactant nor ethanol used in the model formula is classified[49,50,60,61,62]. Therefore, the model formula is not classified into any hazard category as regards specific target organ toxicity (repeated exposure).

Classification: None
Label : No label

9) Aspiration hazard

In respect of this class, there are no human experience information available for the model formula and commercial dishwashing detergent.
Therefore, classification of the model formula was not possible with respect to aspiration hazard.

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[57] Initial Risk Assessment Report No21 N,N-Dimethyldodecylamine N-oxide (CAS RN:1643-20-5) http://www.safe.nite.go.jp/english/db.html, http://www.safe.nite.go.jp/risk/files/pdf_hyoukasyo/166riskdoc.pdf

[58] Exposure and risk screening methods for consumer product ingredients, April, 2005. Calculation is based on the exposure data from the U.S. organization (ed.key US Soap and Detergent Association)

[59] A2.4 of Annex 2 :Approach for determination of consumer product Labeling regarding chronic effects on human health based on the likelihood of injury

[60] Human and Environmental Risk Assessment on ingredients of household cleaning Products (HERA), Alcohol Ethoxylates, Version 1.0, May 2007. http://www.heraproject.com/RiskAssessment.cfm

[61] Final Drafts of SIDS Documents Category Amine Oxides

[62] OECD SIDS ETHANOL (CAS No. 64-17-5) : SIDS Initial Assessment Report For AIAM 19 (Berlin, Germany, 19 – 22 October 2004)

Classification: None
Label : No label

TableA3-1 Example of Classification and Labeling Evaluation for a Dishwashing Detergent

Hazard Class		Information used for Classification	Other information	Classification	Consideration of Likelihood of Injury	label-ing	Sym-bol	Signal word/ Hazard statement	Precautionary statement
Acute toxicity	Oral exposure	LD_{50} of similar commercial product does not meet the GHS criteria.		None		No label			
	Skin exposure	No lethal cases in human experience with similar commercial products.		None		No label			
	Inhalation exposure	No sufficient information	Inhalation exposure very unlikely. No inhalation exposure cases in human experience.	None		No label			
Skin corrosion/ irritation		PII in human patch test with similar commercial products are not more than 0.4 (negligible response).	No clear irritation cases but only eczema cases in human experience	None		No label			
Severe eye damage/eye irritation		Human experience with similar commercial products shows hyperemia and swelling with rapid recovery.		Category 2B		Label	No symbol	Warning/Causes eye irritation	Refer to Labeling Guidance
Respiratory or skin sensitization		Respiratory: Adequate data not available. Skin: Sensitization not identified on ingredients.		None		No label			
Germ cell mutagenicity		Ingredients are not genetic toxicant and do not have germ cell mutagenicity.		None		No label			
Carcinogenicity		No carcinogen contained.		None	N/A	No label			
Reproductive toxicity		Ethanol: excessive oral ingestion by pregnant female is known to affect fetus development.		Category 1A	Consideration shows no likelihood of injury for consumers.	No label			
STOT (repeated exposures)		All ingredients do not meet GHS criteria.	Human health risks of ingredients are reported to be very low.	None	N/A	No label			
Aspiration hazard		No adequate data available.		None		No label			

Note: This table summarizes an evaluation example for determining classification and labeling example of a dishwashing detergent model formula described in A3.1.

A3.2 Laundry Chlorine Bleach

This annex shows which hazard class and category a typical laundry chlorine bleach is classified in and how the classification is reasoned.
The classification is on a typical marketed product, and any products different from the typical product in composition or intended or actual usage shall be considered on separately.

A3.2.1 Typical formulae for laundry chlorine bleach

Sodium hypochlorite : 6.0%
Sodium hydroxide : 1.0%
Others : Balance
（pH>11.5）
（Free alkaline component of the composition: approx. 0.9% sodium hydrate）

A3.2.2 General usages of laundry chlorine bleach

The bleach of the present composition is intended for use in household laundry.
Typically, the laundry is soaked for a certain period of time in the bleach diluted to the standard concentration, and then rinsed. The user is recommended to wear gloves when handling the bleach.

A3.2.3 Hazard classification and labeling

1) Acute toxicity

Acute oral toxicity

An acute oral toxicity study of a similar composition of laundry chlorine bleach with of 6% available chlorine in male mice revealed the LD_{50} of 12.2 mL/kg, which is over 2 g/kg. The study reported no fatal case in the mice group of 10 mL/kg administration.
These data suggested that any composition similar to (but not identical with) the present typical composition would not have an LD_{50} level lower than 2 g/kg.

Therefore the typical formula is not classified into any hazard category as regards acute oral toxicity.

Classification: None
Label : No label

Acute dermal toxicity

There are no available acute dermal toxicity data on the present composition. In addition, there are no sufficient LD50 values available for individual components. Nevertheless, it is possible to use the classification results for acute oral toxicity, as described below.

In dermal exposure, the rate of absorption into the body is no higher than in oral exposure, and the LD50 value is therefore generally higher than in oral exposure. As mentioned above, acute oral toxicity of laundry chlorine bleach revealed the LD50 of 12.2 mL/kg, and laundry chlorine bleach is not classified in any hazard categories in terms of acute oral toxicity. Therefore, laundry chlorine bleach is not classified in any hazard categories in terms of acute dermal toxicity, either.
Furthermore "Hospital report of monitoring of health hazards associated with household products 2004[47] reported an accidental exposure case where a baby was poured an estimated more than 100 mL of undiluted chlorine bleach over his head, and presented only with redness and congestion of the face and had no abnormal condition found in the medical examination the next day.
Consequently, this composition is not classified into any hazard category with regards acute dermal toxicity in light of the information about acute oral toxicity of the laundry chlorine bleach with similar composition and human experience.

Classification: None
Label : No label

Acute inhalation toxicity

In respect of this class, there are no animal test data and no human experience information available for this composition and the laundry chlorine bleach with similar composition. In addition, it is impossible to obtain sufficient data on the LD50 values for the ingredients. Therefore, classification of this composition is not possible with respect to acute inhalation toxicity.

Classification: None
Label : No label

2) Skin corrosion/irritation

Classification based on physicochemical properties

Laundry chlorine bleach has the pH of higher than 11.5 generally, which corresponds to the Hazard Category 1 (See Fig. 3.2.4, the GHS official text). However, if reliable data on the components of a mixture are available and deny the possibility of skin corrosion/irritation, then such data may be used in hazard classification of the mixture (See the GHS official text 3.2.3.3.5). With regard to laundry bleaches, hazard classification based on physicochemical data is not made because the animal data and human experience information are available.

Classification based on animal data

The animal studies of the laundry chlorine bleach of a composition (with the available chlorine concentration of 6%) similar to the present typical composition demonstrated severe skin irritation, but revealed no skin corrosion[63].
A literature published by the manufacturer in 1990[64] reported that a 4-hour closed patch test of hypochlorite bleach in rabbits showed the primary skin irritation index (PII) of 3.6 and corrosive effects were not observed.
Consequently, chlorite laundry bleach was classified into the Hazard Category 2.

[63] In-house data
[64] Evaluation of Modified Methods for Determining Skin Irritation: Regulat. Toxicol. Pharmacol, 1990, Vol.12, p.127-136.

Classification: Category 2
Label : following labeling is needed

Symbol	
Signal word	Warning
Hazard statement	Causes skin irritation
Precautionary statement	Refer to Labeling Guidance[48]

3) Serious eye damage/eye irritation

Classification based on physicochemical properties

As in the case of skin corrosion/irritation, there is information available from both animal and human testing, and there is no need for classification on the basis of physicochemical properties (product pH).

Classification based on test data and human experience

In testing commissioned by the Conference on Detergent and Bleach Safety with samples (with a sodium hydroxide concentration of 1% and sodium hypochlorite concentration of 5%), the maximum average score (n=3) for irritation among the rinsed-off groups was 27.7 (consisting of 15.0 for the cornea, 3.3 for the iris, and 9.3 for the conjunctiva 24 hours after instillation of the sample). The maximum average score (n=3) among the unrinsed groups was 47.7 (consisting of corresponding figures of 30.0, 5.0, and 12.7). In addition, even on the 21st day after instillation, opaque cornea, conjunctiva redness, and iris congestion were observed in about one-third of the rinsed-off group, and opaque cornea, conjunctiva redness, swelling, and secretion were observed in about two-thirds of the unrinsed group[65]. It may also be noted that there have been reports of several cases of irreversible effects resulting from accidental exposure of the human eye to laundry chlorine bleach of a similar composition[64].

In light of the above, it would presumably be appropriate to classify the product in Category 1 as regards eye irritation.

Classification: Category 1
Label : following labeling is needed

[65] The Conference on Detergent and Bleach Safety (1996)

Symbol	
Signal word	Danger
Hazard statement	Causes severe eye damage
Precautionary statement	Refer to Labeling Guidance[48]

4) Respiratory or skin sensitization

- Respiratory sensitization

In respect of this class, there are no animal test data and no human experience information available for this composition and the laundry chlorine bleach with similar composition, and the ingredients. Therefore, classification of the model formula is not possible with respect to respiratory sensitization.

Classification: None
Label : No label

- Skin sensitization

It is reported that both sodium hypochlorite and sodium hydroxide are negative in skin sensitization[66,67]. Therefore, the model formula is not classified into any hazard category as regards skin sensitization..

Classification: None
Label : No label

Because classification of the model formula is not possible with respect to respiratory sensitization and the laundry chlorine bleach is not classified in any hazard categories in terms of skin sensitization, it does not require any label for respiratory or skin sensitization under the GHS criteria.

5) Germ cell mutagenicity

In vitro and in vivo studies of sodium hypochlorite, sodium hydroxide, and other components of the present composition reported negative results for mutagenicity[66,67]. Therefore, the model formula is not classified into any hazard category as regards germ cell mutagenicity.

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[66] Technical task force hypochlorite Benefit and safety aspects of hypochlorite formulated in domestic products Scientific dossier （AISE, 1997）

[67] OECD SIDS SODIUM HYDROXIDE(CAS No.1310-73-2) : SIDS Initial Assessment Report For SIAM 14 (Paris, 26-28 March 2002) http://www.inchem.org/documents/sids/sids/NAHYDROX.pdf

Classification: None

Label : No label

6) Carcinogenicity

(After obtaining expert opinions in respect of principles of classification for mixtures and decision logic flowcharts, the contents mentioned are settled.)
As for sodium hypochlorite, one of the main components of the present composition, the International Agency for Research on Cancer (IARC) classifies it in Group 3 "Not classifiable as to carcinogenicity to humans[エラー! ブックマークが定義されていません。]" because the appropriate animal studies were not demonstrated carcinogenicity of this substance[66,68]. However, there are no available carcinogenicity test data for sodium hydroxide. Therefore, classification of this composition is not possible with respect to carcinogenicity.

Classification: None
Label : No label

7) Reproductive toxicity

The animal studies of sodium hypochlorite either with gavage administration and drinking water administration reported negative results for reproductive toxicity[66,エラー! ブックマークが定義されていません。]. So this substance is not classified in the hazard categories. As for sodium hydroxide, it is stated in the OECD-HPV SIAR document that the substance will neither reach the fetus nor reach reproductive organs under normal use condition, therefore, the tests for identifying developmental toxicity and reproductive toxicity are not required[67]. Thus, the present composition does not contain any reproductive toxicant at a concentration higher than the cut-off value, and is not classified in the hazard categories. Therefore, the model formula is not classified into any hazard category as regards reproductive toxicity.

Classification: None
Label : No label

8) Specific target organ toxicity (repeated exposure)

(After obtaining expert opinions in respect of principles of classification for mixtures and decision logic flowcharts, the contents mentioned are settled.)
Repeated dose toxicity studies of sodium hypochlorite reported no finding of serious organic damage or dysfunction that may fit for any hazard category in terms of specific target organ toxicity[68,69]. Since no information as for sodium hydroxide is available with regard to specific target organ toxicity, hazard classification of the bleach using the cut-off values is not applicable. Since no data about specific target organ toxicity related to repeated exposures to the present or similar composition, the hazard classification based on animal data or human experiences is not applicable.

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[68] HSDB（Hazardous Substances Data Bank）SODIUM HYPOCHLORITE CASRN: 7681-52-9（Complete Update on 03/05/2003） http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+7681-52-9

[69] Hasegawa R et al; Food Chem Toxicol 24 (12): 1295-302 (1986)

Classification: None
Label : No label

9) Aspiration hazard

In respect of this class, there are no animal test data and no human experience information available for this composition and the similar composition, and the ingredients. Therefore, classification of this composition is not possible.

Classification: None
Label : No label

TableA3-2 Example of Classification and Labeling Evaluation for a Laundry Chlorine Bleach

Hazard Class		Information used for Classification	Other information	Classification	Consideration of Likelihood of Injury	label-ing	Sym-bol	Signal word/ Hazard statement	Precautionary statement
Acute toxicity	Oral exposure	LD50 of similar formula does not meet the GHS criteria.		None		No label			
	Skin exposure	Dermal toxicity not suggested in human experience with similar commercial products.		None		No label			
	Inhalation exposure	No sufficient information		None		No label			
Skin corrosion/irritation		Data from animal testing of similar formula show irritation, and do not show corrosion.		Category 2		Label		Warning/Causes skin irritation	Refer to Labeling Guidance
Severe eye damage/eye irritation		Data from animal testing of similar formula show irreversible effects. Human experience also shows irreversible effects.		Category 1		Label		Danger/Causes severe eye damage	Refer to labeling Guidance
Respiratory or skin sensitization		Respiratory: No sufficient information. Skin: All ingredients negative.	Skin: Sensitization not identified in human exposure cases on similar commercial products.	None		No label			
Germ cell mutagenicity		All ingredients negative.		None		No label			
Carcinogenicity		No sufficient information.		None	N/A	No label			
Reproductive toxicity		No reproductive toxicant contained.		None	N/A	No label			
STOT (repeated exposures)		Sodium hydroxide: No data available	Sodium hypochlorite: does not meet GHS criteria	None	N/A	No label			
Aspiration hazard		No data available.		None		No label			

Note: This table summarizes an evaluation example for determining classification and labeling example of a typical laundry chlorine bleach formula described in A3.2.

A3.3 Laundry Granule Detergent

This Annex document shows an example of classifying and then determining the label for a consumer laundry granule detergent. The classification and labeling here is on a typical formula, and any marketed products different from the typical product in composition or intended or actual use should be considered separately.

A3.3.1 The model formula for the laundry granule detergent

Anionic surfactant (LAS, AS, AES)	15%
Builder (Carbonate, Aluminosilicate)	50%
Silicate	1%
Polymer	5%
Sulfate	25%
Water	5%

A3.3.2 General usages of laundry granule detergent

Laundry granules are used to clean clothing. The laundry granule product is primarily used for machine washing. There is some hand washing of clothing with a diluted solution of laundry granule according to use instruction.

A3.3.3 Classification and labeling of the laundry granule detergent

1) Acute toxicity:

Oral

An acute oral LD_{50} study was conducted in rats with this laundry granule. The oral LD_{50} was determined to be 7.1g/kg. Therefore, the model formula is not classified into any hazard category as regards oral acute toxicity.

Classification: None
Label: No label

Dermal

Acute dermal toxicity data in animals on this formula, similar formulas or the ingredients are not available. However, human experiences from over 25 years of use of detergent formulations with similar composition indicate that these products do not cause lethality or serious adverse effects as a consequence of use. Additionally, it is generally recognized that materials are more toxic via the oral route than the dermal route. Consequently, the dermal LD_{50} would be estimated to be greater than 7.1 g/kg. Therefore, the model formula is not classified into any hazard category as regards dermal acute toxicity.

Classification: None
Label: No label.

Inhalation

Acute inhalation toxicity data in animals are not available on this formula, similar formulas or the ingredients. Therefore, classification is not possible.

Classification: None
Label: No label.

2) Skin Corrosion/Irritation:

Animal or human skin corrosion/irritation data are not available on this formula. However, a 4-hr. single patch study of moistened, neat product in humans is available for a formula that has similar builder and surfactant composition (in-house data). The erythema and edema scores are shown in the following table. These scores are below the GHS classification cut-off values. Therefore, the model formula is not classified into any hazard category as regards skin corrosion/irritation.

Laundry Granule Product
Skin Irritation Study (Human)

Mean Scores of 24, 48, 72 hr Observation

Subject	Erythema	Edema	Clear at end of 72h Observation Period
1	0	0	yes
2	0	0	yes
3	0	0	yes
4	0	0	yes
5	0	0	yes
6	0	0	yes
7	0	0	yes
8	0	0	yes
9	0.33	0	yes
10	0	0	yes
Mean	0.03	0	All clear

Classification: None
Label: No label.

3) Serious Eye Damage/Eye irritation

The only animal data available on this specific product was generated utilizing Low Volume Eye Irritation Test (LVET) method[70,71]. The corneal, conjunctival scores and days to clear are shown in the following table. Responses were minimal and it is

[70] Dose-response studies with chemical irritants in the albino rabbit eye as a basis for selecting optimum testing conditions for predicting hazard to the human eye
Toxicol Appl Pharmacol, VOL.55（1980）, PAGE 501-513

[71] ASTM E1055 - 99(2003) Standard Test Method for Evaluation of Eye Irritation in Albino Rabbits

concluded that this granular laundry product does not warrant classification. Therefore, the model formula is not classified into any hazard category as regards serious eye damage/eye irritation.

Laundry Powder Product
Rabbit Eye Irritation Study (LVET)

Mean Scores 24, 48, 72 hr Observations

Animal	Cornea Opacity	Iris	Conjunctiva Redness	Chemosis
1	0	0	0	0
2	0	0	0.3	0
3	0	0	0.3	0

All eyes were cleared within 2 days.

Classification: None
Label: No label.

4) Respiratory or skin sensitization:

Inhalation

No animal or human respiratory sensitization test data or experience are available for this specific formula, similar formulas or the ingredients. Therefore the product cannot be classified.

Classification: None
Label: No label.

Dermal

Human data are available for the laundry granule formula. A confirmatory human repeat insult dermal sensitization patch test was conducted at a 0.5% (W/V) application concentration for both induction and challenge in 80 subjects. No sensitization was observed. Therefore, the model formula is not classified into any hazard category as regards skin sensitization.

Classification: None
Label: No label.

5) Germ cell mutagenicity:

LAS, AS, and AExS, and are not genotoxic or mutagenic either based on testing of the ingredient or similar ingredients in the chemical group[72,73,74]. Sodium aluminosilicate,

[72] OECD SIDS Linear Alkylbenzene Sulfonate (LAS), SIDS Inisial Assessment Report For SIAM 20 (Paris, France, 19-21 April 2005).
[73] Human and Environmental Risk Assessment on Ingredients of Household Cleaning Products, Alkyl Sulphate Human Health Risk Assessment Draft, December 2002.

sodium carbonate and sodium silicate are not genotoxic based on testing of the chemical or similar chemicals[75,76,77]. The polymers and sodium sulfate in the formula are not mutagenic or genotoxic based on published literature data[78,79]. Therefore, the model formula is not classified into any hazard category as regards germ cell mutagenicity.

Classification: None.
Label: No label.

6) Carcinogenicity:

(After obtaining expert opinions in respect of principles of classification for mixtures and decision logic flowcharts, the contents mentioned are settled.)

7) Reproductive Toxicity:

LAS, AS, AExS, Sodium Aluminosilicate, and sodium silicate are not developmental or reproductive toxicants based on animal data and a weight-of-evidence approach[72,73,74,77]. Sodium carbonate, sodium sulfate, and the polymers are predicted not to be toxic to reproduction based on their chemical properties[76,79,78]. Therefore, the model formula is not classified into any hazard category as regards reproductive toxicity.

Classification: None
Label: No label.

8) Specific Target Organ Toxicity -- Repeated Exposure

Repeat dose toxicity studies have been conducted in various animal species with LAS, AS , AExS , Sodium aluminosilicate. The LOAELs in these studies for the surfactants do not meet the GHS classification criteria.

Oral

The GHS classification guidance cut-off value for oral exposure is 100mg/kg/day or less. Sodium aluminosilicate LOAELs for repeat oral exposure is 110 mg /kg/day, and the LOAELs for the surfactants are all greater than 100mg/kg per day. Therefore, the model formula is not classified into any hazard category as regards specific target organ toxicity - repeated exposure (oral).

Classification: None.
Label: No label.

Inhalation

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[74] Human and Environmental Risk Assessment on Ingredients of Household Cleaning Products, Alcohol Ethoxysulphate Human Health Risk Assessment Draft, January 2003. http://www.heraproject.com/RiskAssessment.cfm

[75] Human and Environmental Risk Assessment on Ingredients of Household Cleaning Products, Zeolite A Version 3.0, January 2004. http://www.heraproject.com/RiskAssessment.cfm

[76] Human and Environmental Risk Assessment on Ingredients of Household Cleaning Products, Sodium Carbonate Edition 2.0, April 2005. http://www.heraproject.com/RiskAssessment.cfm

[77] OECD SIDS Soluble Silicate, SIDS Initial Assessment Report For SIAM 18 (Paris, France, 20-23 April 2004)

[78] Human and Environmental Risk Assessment on Ingredients of Household Cleaning Products, Polycarboxylate used in detergents, September 2007. http://www.heraproject.com/RiskAssessment.cfm

[79] OECD SIDS Sodium Sulfate (CAS 7757-82-6), SIDS Initial Assessment Report For SIAM20 (Paris, France, 19-22 April 2005)

The LOAEL for aluminosilicate via inhalation exposure is 1mg/m^3/6h/d (equivalent to 0.001 mg/l/6h/d). This value meets the GHS classification criteria for Category 1 (0.02-0.2mg/l/6h/d). Thus the product is classified. To determine if the product needs to be labeled for specific target organ toxicity one then does a risk assessment to determine the likelihood of injury. If the likelihood of injury (risk) is negligible under exposure then the product is not labeled. Assessment of the likelihood of injury indicates that there is no significant risk via inhalation exposure under conditions of consumer use.

Specifically, a study conducted by Hedricks [80] indicates an average consumer exposure of 0.27 ug detergent dust per cup of product used for machine washing. The median consumer use of detergent per week is 7.8 cups or approximately 1 cup per day. If one assumes that the product contains 34.2% sodium aluminosilicate in the product, then the consumer exposure to sodium aluminosilicate is 0.09ug/day. If one assumes that all the aluminosilicate is in a head space of $2m^3$ then the consumer exposure is 0.045ug/m^3. On the other hand, TDI is calculated as 1 ug/m^3/6h/d by dividing the LOAEL 1 mg/m^3/6h/d with uncertainty factor 1,000 [conversion of LOAEL to NOAEL (10), animal to human variation(10), human to human variation (10)]. Thus exposure is well below the TDI. This is a highly conservative assessment for several reasons : 1) the duration of exposure for the consumer is only minutes per day, while the exposure time in animal study, which is used for the TDI, was 6 hours per day, and 2) it is assumed that all the aluminosilicate in the detergent is in the head space and inhaled.

Therefore, although the product is classified for Specific Target Organ Toxicity -- Repeated Exposure, it would not be labeled because the likelihood of injury (risk) is negligible under consumer use.

Classification: Category 1 Specific Target Organ Toxicity -- Repeated Exposure inhalation.
Label: No label based on consideration of likelihood of injury (risk).

9) Aspiration Hazard:

Human experience indicates that granular detergents do not represent an aspiration hazard. Additionally this product is a solid and does not meet the physical characteristics described for classification in the GHS i.e. the granular detergent is not a hydrocarbon associated with an aspiration hazard and does not meet the viscosity criteria i.e. kinematic viscosity of 20.5 mm^2 /s or less at 40^o C, indicating that it would not represent an aspiration hazard[81]. Therefore, the model formula is not classified into any hazard category as regards aspiration hazard.

Classification: None.
Label: No label.

*** Supplemental Information**

[80] Hedricks M.H. June,(1970), Measurement of Enzyme Laundry Product Dust Levels and Characteristics in Consumer Use. *Journal of the American Chemists' Society* **47:** 207-211.

[81] Craan , Andre (1996). Aspiration hazard and consumer products: a review.. *International Journal for Consumer Safety* ***3.****(3),* 153-164.

Human experience information on marketed products can also be used as data for classification if information is available on marketed products having similar formula. A classification example on serious eye damage/eye irritation based on human experience information is shown below.

Model formula (2) to be classified and composition range of marketed laundry granule detergents of which human experience information was used for determining classification of the model formula (2) are shown below. According to the procedure stipulated in A2.2 of Annex 2, model formula(2)and marketed laundry granule were compared on following points, i) physicochemical properties and pattern of use; ii) composition; and iii) level of differences of composition that affects the classification. Consequently, the bridging principles may be applied to the classification (see A2.2 of Annex 2 “bridging principles”).

Model formula (2)

Anionic surfactant:	20%
Nonionic surfactant:	5%
Zeolite:	25%
Silicate:	5%
Carbonate:	25%
Sulfate:	10%
Polymeric organic builders:	5%
Others:	Balance

Composition of marketed products similar to model formula (2)

Anionic surfactant:	5-25%
Nonionic surfactant:	0-15%
Zeolite:	10-30%
Silicate:	0-5%
Carbonate:	10-40%
Sulfate:	5-25%
Polymeric organic builders:	0-10%

Some manufactures have collected human experience information[22] that products get into eyes resulting pain and hyperemia. Of the cases the time course of which can be followed up, every one of them were recovered within about 7 days. This shows that the cases were reversible mild eye irritation. There was no case with serious effects reported.

Therefore, the marketed laundry granule detergent is considered to fall into category 2B.

As mentioned above, the similarity between model formula (2) and the marketed product is confirmed. Based on bridging principles, model formula (2) is classified into category 2B of serious eye damage/eye irritation.

Classification: Category 2B
Label: following label is needed

Symbol	None
Signal word	Warning
Hazard statement	Causes eye irritation
Precautionary statement	Refer to Labeling Guidance[48]

TableA3-3 Example of Classification and Labeling Evaluation for a Laundry Granule Detergent

Hazard Class		Information used for Classification	Other information	Classification	Consideration of Likelihood of Injury	label -ing	Sym- bol	Signal word/ Hazard statement	Precautionary statement
Acute toxicity	Oral exposure	LD50 of the subject formula does not meet the GHS criteria.		None		No label			
	Skin exposure	Human experience with similar formula does not suggest dermal toxicity. Dremal LD_{50} of the subject formula does not meet the GHS criteria by estimation from oral LD_{50}		None		No label			
	Inhalation exposure	Data not available	Exposure level is negligible. No lethality or serious effects in human experience.	None		No label			
Skin corrosion/irritation		Human patch test result of similar formula does not meet GHS criteria.		None		No label			
Severe eye damage/eye irritation		LVET result of the subject formula does not meet GHS criteria.		None		No label			
Respiratory or skin sensitization		Respiratory: Adequate data not available. Skin: Negative in human repeat patch test of the subject formula.		None		No label			
Germ cell mutagenicity		Germ cell mutagenicity not identified on ingredients.		None		No label			
Carcinogenicity		Under consideration							
Reproductive toxicity		Reproductive toxicity not identified on ingredients.		None	N/A	No label			
STOT (repeated exposures)		Oral: LOAELs on ingredients do not meet GHS criteria. Inhalation: LOAEL of aluminosilicate meets GHS criteria Category 1.		Oral: None Inhalation: Category 1	Consideration shows no likelihood of injury under use condition.	No label			
Aspiration hazard		Human experience and physicochemical properties do not meet GHS criteria.		None		No label			

Note: This table summarizes an evaluation example for determining classification and labeling example of a laundry granule detergent model formula described in A3.3.

Explanation

Explanation

This explanation is to explain items that are prescribed/described in the main body and Annexes, specifically views and rationale on the choice of classes and categories.

1 Physical hazards

Among the physical hazard classes listed in the GHS Official Text, as to the items for which hazard communication to consumers are being took place under the Fire Defense Law and the High-Pressure Gas Safety Law, e.g., flammable gases, flammable aerosols, gas under pressure and flammable liquid, the rules and regulations under the laws are continue to be observed.

The incorporation of those items into the present Guidance is to be examined depending on the progress of the movement of these laws to accord with GHS. Examinations on the items not covered by current laws, such as corrosive to metals, are to be continued, and the classes which are evaluated as necessary based on the properties and uses of products are to be incorporated in the Guidance.

2 Rationale of the choices of Heath related classes and categories

2.1 Acute toxicity

Currently, within the scientific community, acute toxicity beyond the limits of Category 4 for any route of exposure is considered to be very low. For example, the OECD acute oral toxicity test guideline does not demand any dose higher than 2,000 mg/kg. On the other hand, if Category 5 is applied, many of the household consumer products as to which fatal cases are not found at 2,000 mg/kg in a limit test and judged to have LD50 higher than 2,000 mg/kg may need to label hazard information shown below.

Label elements (oral)

	Symbol	Signal word	Hazard statement
Category 5	No symbol	Warning	Harmful if swallowed

For household consumer products, adequate consumer use has been promoted by examining the effects from acute exposure for the ranges corresponding to GHS classification categories 1 to 4. Furthermore, it was reported that labeling for generally insignificant hazard levels as found in Category 5 (with LD 50 values or acute toxicity range estimated of 2,000 to 5,000 mg/kg) might result in decrease in the effectiveness of warnings for more significant hazard levels (i.e., Categories 1 to 4))[82] Considering the above, Categories 1 to 4 are to be applied because classification and labeling based on hazard level ranges of Categories 1 to 4 is considered to provide appropriate information to consumers.

[82] IOMC/ILO/HC6/00.13 "An Option for Consumer Product Labeling Based on the Likelihood of Injury" September 21, 2000
http://www.cleaninginstitute.org/assets/1/AssetManager/hc60013%20IOE%20risk%20based%20labeling%20Rome%20Oct-Nov%202000.pdf

2.2 Skin corrosion/irritation

The GHS Official Text states that Subcategories 1A, 1B, and 1C and Category 3 apply to only some authorities (para. 3.2.2.4.2, 3.2.2.5.4, and Table 3.3.3). Subcategories 1A, 1B, and 1C of Category 1 may be necessary for some particular purposes, such as securing the optimized cleaning of accidental spill (when transporting, etc.), but it is not relevant for hazard classification and labeling of consumer products. As for Category 3, which is introduced in the GHS particularly for the purpose of hazard classification of pesticides by the US EPA, the GHS Official Text mentions pesticides as an example in this category (para. 3.2.2.5.4.). Application of Category 3 to consumer products may prevent consumers' attention from focusing on reasonably significant alarms[82]. Consequently, Categories 1 (with no Subcategories) and 2 shall be applied.

2.3 Serious eye damage/irritation

Category 2 (reversible effects on the eye) has Subcategories 2A (irritating to eyes) and 2B (mildly irritating to eyes) depending on the duration to reverse, as the option (para. 3.3.2.9). In the present Guidance, it is preferable to apply subcategories (2A and 2B) when possible for the purpose of clear and adequate hazard communication to consumers.

The Subcategories 2A and 2B of Category 2 are differentiated from each other by symbol and hazard statement. Subcategory 2A involves a symbol and is associated with "serious eye damage" while Subcategory 2B involves no symbol and is associated with "eye irritation". These labeling differences would encourage the consumers to notice the difference in severity of ocular irritancy.

Comparison of Label elements

	Symbol	Signal word	Hazard statement
Subcategory 2A		Warning	Causes serious eye irritation
Subcategory 2B	No symbol	Warning	Causes eye irritation

Some consumer products tend to cause such mild eye irritation that should fall under Subcategory 2B. It is expected that the subcategories improve hazard communication for consumers, by identifying the effects of the accidental ocular exposure to the product and facilitating prompt action on exposure to highly irritant chemicals.

2.4 Reproductive toxicity

No standard assessment method has been established for "the effects on or via lactation". Therefore, categories 1A, B and 2 are to be applied at present, and assessment method development is to be monitored. After experiences in other countries are reviewed, utilization of this class may be reconsidered.

2.5 Specific target organ toxicity (single exposure)

Under discussion whether and how to apply this class.

2.6 Aspiration hazard

Category 1 is based on adequate human experience data, and may be reasonably used in aspiration hazard assessment. As for Category 2, based on animal data, no adequate methodology has so far been established so far for assessment of human aspiration hazard. The GHS Official Text says "positive experimental evidence with animals can only serve as a guide to possible aspiration toxicity in humans. Particular care must be taken in evaluating animal data for aspiration hazards" (para. 3.10.1.6.2).

3. Environmental hazard

Under discussion whether and how to apply this class.