GUIDANCE ON A CONSUMER PRODUCT RISK ASSESSMENT FOR GHS LABELLING

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National Institute of Technology and Evaluation

Chemical Management Center

Introduction

This document provides guidance on the risk assessment of the chronic health hazards of consumer products within the scope of the “Globally Harmonized System of Classification and Labelling of Chemicals (GHS)” and its Annex 5 “Consumer Product Labelling Based on the Likelihood of Injury” (GHS Official text, Rev. 2 (2007)) as well as the document “Outlook on Risk Assessment for Consumer Products Based on Exposure for GHS Labelling” (GHS Inter-Ministerial Committee Document, January 11, 2007).

GHS is a system for classification and labelling based on hazards of chemicals. It is the system for classification and labelling based on the intrinsic “hazard” of all chemicals with regard to their physical hazards (inflammability and combustibility etc.), health hazards (acute toxicity, skin corrosion/irritation, specific target organ toxicity (repeated exposure) etc) and environmental hazards (hazardous to the aquatic environment).

On the other hand, as regard to the chronic health hazards (e.g., carcinogenicity, reproductive toxicity, or specific target organ toxicity following repeated exposure), if the exposure assessment and determination of the likelihood of injury (risk) reveal that the potential exposures are expected insignificant, chronic health hazards may not be included on the product label for consumer use.

Currently such risk assessment methodologies are not yet to be internationally harmonized and thus a competent authority in each country needs to provide the relevant risk assessment procedures to consumer product suppliers. The Ministry of Economy, Trade and Industry, a member of the GHS Inter-Ministerial Committee, therefore has requested the Chemical Management Center, National Institute of Technology and Evaluation (hereinafter referred to as “NITE”) to establish more specific guidance.

This guidance describes specific risk assessment approach for risk-based labeling of chronic health hazards.

The guidance includes the following documents.

(Main Document)
Basic Procedures of Risk Assessment for GHS Labelling of Consumer Product
(Annex 1)
Calculating the Estimated Human Exposure Used in the Risk Assessment of Consumer Products
(Annex 2)
Examples of Risk Assessment of Consumer Product for the GHS Labelling

General principles of this guidance are as follows.

- ✓ This guidance was created for the intended users (consumer product suppliers) who have necessary risk assessment knowledge.

  Exposures via environment or exposures arising from the use of the products outside of the

scope of GHS are not taken account of in this guidance,

- ✓ The guidance is neither complete nor compulsory and therefore if reliable information or reasonable scientific procedures become newly available in future, they can be used as alternatives.
- ✓ Consumer product suppliers can determine whether or not to carry out risk assessments. Once risk assessments are conducted by individual suppliers, they should be accountable for their risk assessments and their relevant results
- ✓ One of the purposes of GHS is global harmonization, and hence if new methods are released by any international authorities or foreign governments then the content of these methods should be carefully examined and this guidance should be revised accordingly as necessary.

This guidance was created in various stages: the NITE Chemical Management Center established an investigative commission in collaboration with related industrial associations, held a variety of discussions, and then had reviews by experts.

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Main Document BASIC PROCEDURES of RISK ASSESSMENT FOR GHS LABELLING OF CONSUMER PRODUCTS

Appendix 1: Basic Manual for Calculation of the Estimated Human Exposure Used in the Risk Assessment of Consumer Products

Appendix 2: Examples of Risk Assessment of Consumer Products for GHS Labelling

Accompanying Material

GHS Inter-Ministerial Committee Documents “Outlook on Risk Assessment for Consumer Products Based on Exposure for GHS Labelling” (January 11, 2007)

Main Document

BASIC PROCEDURES of RISK ASSESSMENT FOR GHS LABELLING OF CONSUMER PRODUCTS

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MAIN DOCUMENT: BASIC PROCEDURES OF RISK ASSESSMENT FOR GHS LABELLING OF CONSUMER PRODUCTS

I Background and Objectives

Based on the recognition for the need for an internationally-harmonized approach to classifying and labelling of chemicals, “Globally Harmonized System of Classification and Labelling of Chemicals (GHS)” resolution was adopted by the United Nations in July 2003. The first GHS version, which documented a classification and labelling method, was published in 2003 based on the abovementioned resolution. The document was subsequently revised in 2005 (first revised edition) and then in 2007 (hereinafter this document is referred to as the *“Second revised edition of GHS official text (2007)”*).

GHS requires the classifications and labelling focusing on the intrinsic hazards of individual chemical substances and their mixtures.

However, as consumer exposure is generally limited in terms of both quantity and duration, the likelihood of chronic health hazards through exposure arising from the use of the product is considered minimal. Therefore, in the Annex5 of GHS text, there is a description that if the risk (likelihood of injury) of adverse chronic health effects under the consumer product use condition is expected below a certain level[1] then chronic health hazards do not necessarily have to be included on GHS labels for consumer use (hereinafter risk-based labellinng).

> *The Second Revised Edition of GHS Official text (2007),* Annex 5 “Consumer Product Labelling Based on the Likelihood of Injury” A.5.1 Introduction
>
> A5.1.1 …However, it has been recognized that some systems provide information about chronic health hazards in consumer products only after considering additional data regarding potential exposures to consumers under normal conditions of use or foreseeable misuse. These systems thus provide information based on an assessment of risk, or the likelihood of injury occurring from exposure to these products. 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.

It is individual country government‘s decision whether to take the option of risk-based labeling for consumer products, and hence competent authorities need to outline risk assessment procedures, because risk assessment methodologies have not been harmonized internationally.

> *The Second Revised Edition of GHS Official text(2007), Chapter* 1.4 “Hazard Communication: Labelling”
>
> 1.4.10.5.5.2 “Consumer product labelling based on the likelihood of injury"
>
> ...however competent authorities may authorize consumer labelling systems providing information based on the likelihood of harm (risk-based labelling). In the latter case the competent authority would establish procedures for determining the potential exposure and risk for the use of the product.

[1] The statement of “below a certain level” is given as “insignificant” according to the original *Second revised edition of GHS Official text (2007)* Annex 5 A5.1 document

The Second Revised Edition of GHS Official text (2007), Annex 5 "Consumer Product Labelling Based on the Likelihood of Injury" A.5.1 Introduction

A5.1.2 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.

In Japan, the GHS Inter-Ministerial Committee[2] released the relevant document "Outlook on Risk Assessment for Consumer Products Based on Exposure for GHS Labelling" [3](hereinafter referred to as the " GHS Inter-Ministerial Committee document 20070111") on January 11 of 2007. In this document, which is based on the GHS official text, the concept of risk-based labeling for consumer product and the framework of risk assessment procedure is shown.

GHS Inter-Ministerial Committee Document, 20070111 "Outlook on Risk Assessment for Consumer Products Based on Exposure for GHS Labelling":

…Consequently, the GHS-related Inter-ministerial Committee has confirmed that it is unnecessary to include information about the health hazard on the labels of products containing chemicals whose risks have been assessed in accordance with the concept of risk and assessment procedures outlined below and that, as a result of this assessment, it has been determined that the risk of effects on health are not at a level for concern.

Since the above document shows only the concept and the framework of risk assessment procedure, there was a requirement for a more specific and practical guidance on risk assessment for the convenience of the intended assessors (consumer product suppliers) And hence the NITE Chemical Management Center, by request of the Ministry of Economy, Trade and Industry, a member of the GHS Inter-Ministerial Committee, have developed this guidance in cooperation with industrial associations,

Currently consumer product GHS labelling is not required by any domestic regulations, and therefore it is left to the supplier's voluntary decision whether or not to apply GHS labelling. However, once a supplier decides to apply GHS for their products, the labelling needs to be indicated according to GHS classification. Even in this case, suppliers still have an option to conduct chronic health risk assessment and risk-based labelling

.

This guidance is not binding and does not intend to prevent anyone from using the latest information or reasonable scientific procedures as alternative. In case assessors conduct risk assessment by using their own method, it is important to assure transparency of the risk assessment.. Principle here is that while following this guidance, individual suppliers carry out risk assessments as their own responsibility. And they should be accountable for the labelling based

[2] The GHS Inter-Ministerial Committee was established in 2001 with the objective of sharing information regarding GHS as well as responding to the Japanese UN GHS sub-committee experts, and is made up of the departments in charge from the Ministry of Health, Labour and Welfare, the Ministry of Economy, Trade and Industry, the Ministry of the Environment, the Ministry of Internal Affairs and Communications, the Ministry of Agriculture, Forestry and Fisheries, the Ministry of Land, Infrastructure, Transport and Tourism, and the Ministry of Foreign Affairs of Japan.

[3] http://www.meti.go.jp/policy/chemical_management/GHS/Consumer_product_labelling.htm

on the assessment results.

Some published procedures are currently available for general risk assessment regarding consumer products such as the European Technical Guidance Documents[4]; however there is no published risk assessment method for consumer products specific to GHS. It is very important from the viewpoints of international trade and consumer benefits to ensure international harmonization of a method, and therefore when new methods are released by international authorities or foreign governments the content should be carefully investigated and this guidance might be revised accordingly as necessary.

This document discusses risk assessment by focusing on exposure from use of certain consumer products, but does not discuss exposures via environment or other consumer products outside the scope of GHS.

[4] http://ecb.jrc.it/tgd/

II Scope of Risk-based GHS Labelling

II-1 Consumer Products covered in Risk-based GHS Labelling

According to the GHS Official text, GHS applies to all pure chemical substances, and their dilute solutions and mixtures of chemical substances. Pharmaceuticals, food additives, cosmetics, and pesticide residues in food are not covered by GHS as they are of intentional intake. Furthermore, articles are outside the scope of the GHS.

> *The Second Revised Edition of GHS Official text (2007),* 1.1.2 "Scope"
>
> 1.1.2.4 Pharmaceuticals, food additives, cosmetics, and pesticide residues in food will not be covered by the GHS in terms of labelling at the point of intentional intake.
>
> 1.1.2.5 For example, at the point of intentional human intake or ingestion, or intentional application to animals, products such as human or veterinary pharmaceuticals are generally not subject to hazard labelling under existing systems. Such requirements would not normally be applied to these products as a result of the GHS.
>
> *The Second Revised Edition of GHS Official text (2007),* 1.3.2.1 "Scope of the system"
>
> 1.3.2.1.1 "Articles" as defined in the Hazard Communication Standard (29 CFR 1910.1200) of the Occupational Safety and Health Administration of the United States of America, or by similar definition, are outside the scope of the system.

The GHS allows risk-based labelling for chronic health effects given that the exposure from the use of consumer product is generally limited in terms of both quantity and duration.

This guidance shows risk assessment procedures of consumer products such as detergents, deodorizers, waxes, paints, adhesives, pesticides for nuisance insects. Neither exposures to chemicals included in articles and products subject to the Pharmaceutical Affairs Law (e.g., pharmaceuticals, quasi drugs, cosmetics) nor Agricultural Chemicals Regulation Law. Specifically are covered in this guidance.

II-2 Health Hazards covered in Risk-based GHS Labelling

According to the GHS Official text, one can apply risk-based GHS labeling only for chronic health hazard effects (e.g., carcinogenicity, reproductive toxicity, or target organ toxicity based on repeated exposure). Other hazards, such as acute toxicity or irritation, are not in the scope of the risk assessment for GHS labelling.

> *The Second Revised Edition of GHS Official text (2007),* Annex 5 "Consumer Product Labelling Based on the Likelihood of Injury" A.5.2 "General principles"
>
> A5.2.1 The labelling approach that involves a risk assessment should only be applied to chronic health hazards, e.g. carcinogenicity, reproductive toxicity, or target organ toxicity based on repeated exposure. The only chemicals it may be applied to are those in the consumer product setting where consumer exposures are generally limited in quantity and duration;

Hence this document defines carcinogenicity, reproductive toxicity[5] , and specific target organ toxicity (repeated exposure) as chronic health hazards[6].

Moreover, in this guidance, consumers are those who directly use consumer products. Secondary exposures (exposure to cohabiters) are not considered.

[5] As noted in the GHS Official Text Second Revision (2007), “reproductive toxicity” includes developmental toxicology.

[6] As noted above, the GHS Official text A5.2.1 describes these 3 types of hazards as chronic health hazards as “e.g.” And therefore the possibility exists that some other hazards, e.g., germ cell mutagenicity could be in the scope. However, it would not appear that a general risk assessment method has been established at the moment, and therefore they are not included in this guidance.

III Risk Assessment Process for GHS Labelling

Generally, risk of a chemical substance means the probability of unfavorable effects on human health or organisms in the environment posed by the exposure to the substance. The level of risk is determined by the intrinsic “hazard” of chemical substances and “quantitative exposure” to humans or organisms in the environment.

The risk of consumer exposure is determined by comparing effect data (“estimated quantity at which no effect is expected even if human is exposed repeatedly for long-term”) and exposure data (“Estimated quantity of exposure” of the chemical substance contained in the consumer product.)

The GHS Official text states the following general rules for the risk assessment approach.

> *The Second Revised Edition of GHS Official text (2007),* Annex A5.2 “General principles”
>
> (c) Estimate of possible exposures and risks to consumers should be based on conservative, protective assumptions to minimize the possibility of underestimating exposure or risk.
>
> Exposure assessments or estimates should be based on data and/or conservative assumptions.
>
> Assessment of the risk and the approach to extrapolating animal data to humans should also involve a conservative margin of safety through establishment of uncertainty factors.

Figure III – 1 shows the flow chart of risk assessment process in this guidance.

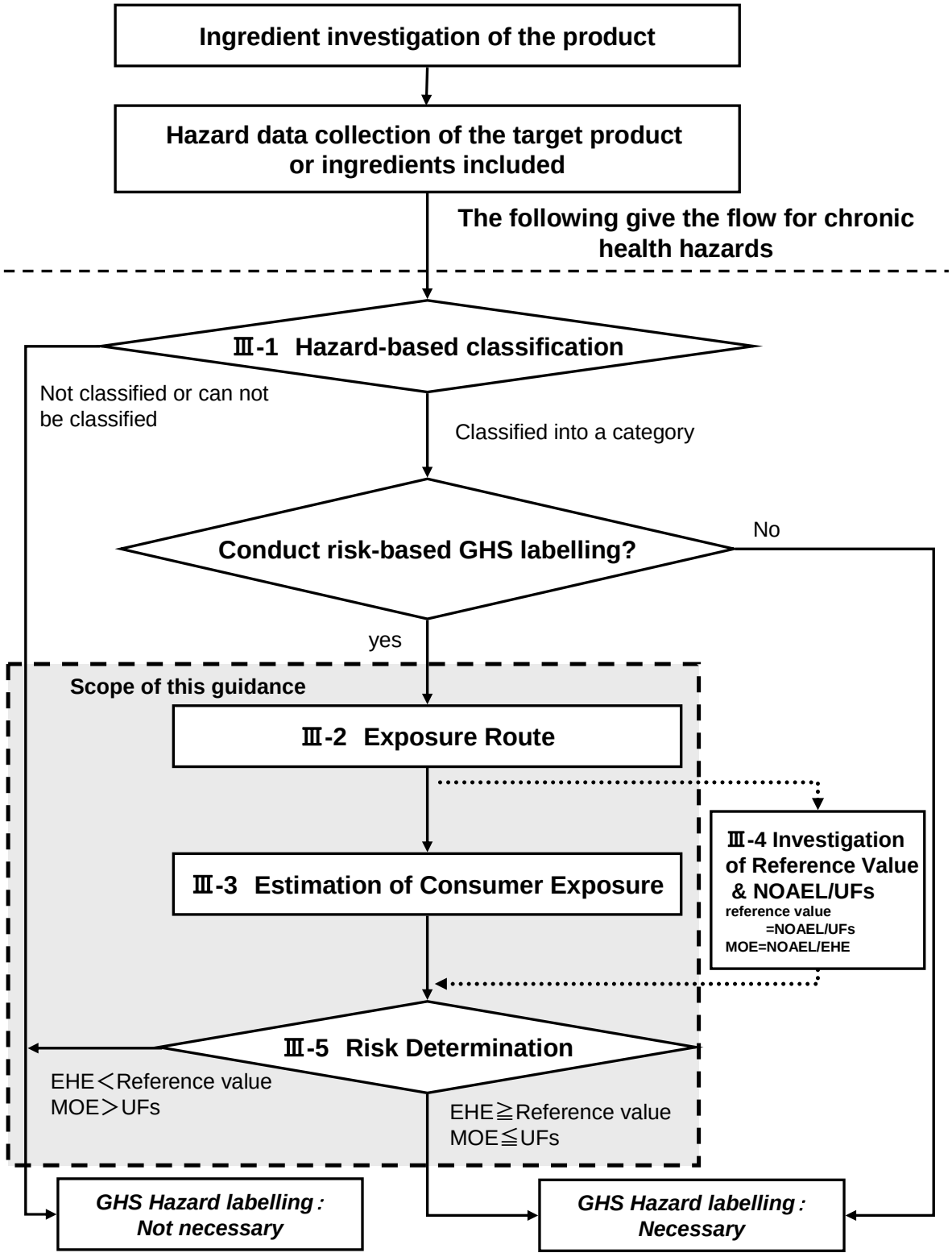

Figure Ⅲ – 1: Decision Process for the Necessity for GHS Hazard Labelling based on the Risk Assessment of Chronic Health Hazards

III-1 GHS Classifications for Chronic Health Hazards

Prior to risk assessment, hazard-based GHS classifications need to be carried out.

When a classification of consumer product or a chemical substance contained in the product results in any of the categories of chronic health hazard (carcinogenicity, reproductive toxicity, or specific target organ toxicity based on repeated exposure), risk assessment is to be conducted.

Note that even in this case, consumer product suppliers do not necessarily have to characterize the chronic health risks of their products and they may employ hazard-based GHS classification for the label of their products.

The hazard-based GHS classification process is not described in this guidance.

The assessors can obtain GHS classification results of some chemical substances from the web site of NITE[7].

III-2 Exposure Route

If risk assessment is to be conducted for consumer products, the exposure route needs to be identified as a first step.

The exposure route from the use of consumer products can be inhalation, dermal, oral or in combination. Possible exposure routes are examined with the following information in 1) and 2).

1) Product form and the physicochemical properties of its components
2) Intended use pattern of the product

If the possibility of exposure from a certain route is considered negligible, then such exposure route can be excluded from the scope of the assessment.

III-3 Estimation of Consumer Exposure

Consumer exposure estimation process consists of two steps; Estimation based on an extreme conservative assumption as first step and estimation considering the practical condition as a second step. The assessors not always need to conduct exposure estimations at both steps but they can select the appropriate process for their exposure estimation.

Not only potential exposure under normal conditions of use but also foreseeable misuse such as excessive use of products should be taken into consideration from a safety point of view.

> *The Second Revised Edition of GHS Official text (2007),* Annex 5 “Consumer Product Labelling Based on the Likelihood of Injury” A.5.1 Introduction
>
> A5.1.1 …However, it has been recognized that some systems provide information on chronic health hazards in consumer products only after considering additional data regarding potential exposures to consumers under normal conditions of use or foreseeable misuse.

[7] GHS classification result database (http://www.safe.nite.go.jp/english/index.html)

In this guidance, “foreseeable misuse” is limited to usage with long-term/repeated exposure and does not include misuse, such as an accidental ingestion, which should be assessed from the acute toxicity point of view.

III-3-1 Estimation of Exposure based on an Extreme Conservative Assumption

A very simple method of exposure estimation is to use an extreme conservative assumption. In this case, it is assumed that a consumer use up the entire product in a day. The exposure route will not be considered. GHS Official text refers to the example of the United States Consumer Products Safety Commission: CPSC as below.

> *The Second Revised Edition of GHS Official text (2007),* Annex 5 “Consumer Product Labelling Based on the Likelihood of Injury” A.5.2.2 “An Example of risk-based labelling used in the United States Consumer Product Safety Commission”
> A5.2.2.7 …For a conservative estimate of exposure, one can assume that the consumer will use the entire consumer product in a day and /or assume that all of the hazardous substance/mixture that the consumer is exposed to will be absorbed. If the resulting exposure is lower than the “acceptable daily intake” not hazard communication would be required. If the exposure level is higher than the ADI, then a more refined quantitative assessment could be performed before making a final labelling decision.・・・

Following formula is used to calculate the Estimated Human Exposure (EHE).

EHE = Product amount × Concentration of the Chemical Substance / Body Weight

If this assumption is apparently not realistic and a more precise estimation is possible, this step may be skipped.

III-3-2 Estimation of Exposure considering the Practical Use Conditions

In this section, the estimation procedure considering practical use conditions of a consumer product is shown.

The methodology is based on “Technical Guidance Document on Risk Assessment” (EU)[8], “Guidance Document Methodology (Feb. 2005)”[9] (Human and Environmental Risk Assessment on Ingredient of Household Cleaning Products (HERA)), and “Exposure and Risk Screening Methods for Consumer Product Ingredients (Apr. 2005)” [10](The Soap and Detergent Association (SDA)).

Principally following formulas are used to calculate the EHE for each exposure route.

[8] http://ecb.jrc.it/tgd/
[9] http://www.heraproject.com/Library.cfm
[10] http://cleaning101.com/files/Exposure_and_Risk_Screening_Methods_for_Consumer_Product_Ingredients.pdf

EHE (inhalation) =Air concentration of the substance ×Air Inhalation rate / Body weight

EHE (dermal) = Amount of the substance left on the skin × Adhesion ratio / Body weight

EHE (oral) = Concentration of the substance in oral intake × Amount of oral intake / Body weight

As these are the estimates based on appropriate exposure scenarios, algorithms (estimation formula), and exposure factors (parameters that relate to the exposure), they are thought to be more realistic estimation than the abovementioned “Estimation of Exposure based on an Extreme Conservative Assumption”. Though there are still some gaps between EHEs calculated here and the actual consumer exposure.

Following are procedures for estimation of EHE.

1) Determine the “basic exposure scenario” for each exposure route (inhalation, dermal, or oral).
2) Determine “algorithms” for each of the basic exposure scenarios determined in 1).
3) Apply appropriate exposure factors to the algorithm determined in 2) to calculate EHE for each exposure route.
4) If multiple routes are possible for a product, EHE for each route are to be summed up for the total Estimated Human Exposure (EHE).

If reliable exposure factors are not available, then the conservative default values should be used. The detail is described in Appendix 1 of this guidance.

III-4 Establishing Reference Values

The “estimated quantity at which no adverse effect is expected even if repeatedly exposed for long-term”, which is to be compared to the quantity of exposure, needs to be determined. In this guidance that value will be called as “Reference value‘. The following documents can be referred as data sources when assessors collect necessary hazard information.

・NITE: Initial Risk Assessment Reports for Chemical Substances[11]

・Ministry of the Environment: Initial environmental risk assessment of chemicals (Vol. 1 - 5)[12]

・Chemicals Evaluation and Research Institute, Japan (CERI): Chemical Substance Safety (Hazard) Data Collection[13]

・OECD：SIDS Initial Assessment Report[14]

・WHO/IPCS： Environmental Health Criteria (EHC)[15]

・WHO/IPCS: Concise International Chemical Assessment Documents (CICAD)[16]

[11] http://www.safe.nite.go.jp/risk/risk_index.html
[12] http://www.env.go.jp/chemi/report/h18-12/index.html
[13] http://www.cerij.or.jp/db/sheet/sheet_indx.html
[14] http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html
[15] http://www.who.int/ipcs/publications/ehc/ehc_numerical/en/index.html

・EU：EU Risk Assessment Report[17]

・WHO International Agency for Research on Cancer (IARC): IARC Monographs Programme on the Evaluation of Carcinogenic Risk to Humans[18]

・U.S Environmental Protection Agency: Integrated Risk Information System (IRIS)[19]

・International Programme on Chemical Safety (IPCS): INCHEM[20]

If any other reliable information sources are available, they should also be utilized[21]. One can use the following web-site which has links to a variety of hazard assessment documents.

NITE: Chemical Risk Information Platform (CHRIP)[22]

III-4-1 In case Reference Values have already been determined by an international or national authority

For certain chemical substances the “estimated quantity at which no adverse effect is expected even if repeatedly exposed for long-term”, such as TDI (Tolerable Daily Intake) and ADI (Acceptable Daily Intake), is published by international or national authorities as well as academic organizations. Where available they can be used as reference values. In addition to TDI and ADI there are other values, as indicated below, which can be used as reference values. The terminology and the relevant authorities are shown in the attached Reference Materials at the end of this document.

TDI (Tolerable Daily Intake)
ADI (Acceptable Daily Intake)
RfD (Reference Dose)
RfC (Reference Concentration)
MRL (Minimum Risk Level)
PDE (Permitted Daily Exposure)
RSD (Risk Specific Dose)
VSD (Virtually Safe Dose)

When assessors use one of these Reference values, it is important to check the background of

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16 http://www.who.int/ipcs/assessment/en/

17 http://ecb.jrc.it/esis/esis/php?PGM=ora

18 http://monographs.iarc.fr/

19 http://www.epa.gov/iris/

20 http://www.inchem.org/
INCHEM on the IPCS site is a comprehensive searchable database that includes SIDS, EHE, CICAD, IARC Monograph and others.

21 For sources of information on human health hazards refer to the “GHS Classification Manual」(by GHS Inter-Ministerial Committee: http://www.safe.nite.go.jp/english/pdf/ghs_manual_e.pdf) or the “Risk Assessment of Chemical Substances Guidebook” (Ministry of Economy, Trade and Industry: http://www.meti.go.jp/policy/chemical_management/law/prtr/pdf/guidebook_nyumon.pdf) and other documentation can be used to reference access to information.

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

Reference value setting, and to examine that value is appropriate for their risk assessment or not.

III-4-2 In case Reference Values are to be determined by assessors

Even when Reference values are not set by international authorities, the assessors may determine reference value by themselves if a NOAEL (No Observed Adverse Effect Level) of a substance is available from reliable studies.

1. For each available toxic test data, adverse effects posed by the substance and their dose-response relationships need to be determined. Based on the dose-response relationship, set the maximum quantity, at which any biological and statistical significant toxic effects are not found, as NOAEL. If a NOAEL can not be determined, then select a LOAEL (Lowest Observed Adverse Effect Level). The NOAEL (or LOAEL) should be represented as the dose per 1 kg of body weight per day.
2. If more than one NOAEL can be obtained from several toxic test data, then select the lowest NOAEL considering the sensitivity of the animals used in the test, the exposure duration, exposure route etc. However, when several test results show the same effect in the same target organ, selection of the lowest NOAEL is not always the best. depending on the setting of dosage. In this case, one can choose an appropriate NOAEL with careful examination of each of the test results[23] [24] [25].
3. It is very rare that NOAEL is identified in epidemiological studies. LOAEL, identified based on the results of several epidemiological studies, may be used.
4. NOAEL (or LOAEL) obtained from animal toxic test data or epidemiological studies includes some inevitable uncertainties or variability relating to the difference in sensitivity among individuals, the differences in sensitivity between animals and humans or the duration of exposure. These uncertainties (variability) should be represented as Uncertainty Factors (UFs) and the NOAEL (or LOAEL) should be divided by them to derive a Reference value.

Reference value = NOAEL/UFs

In this guidance, following values are recommended for Uncertainty Factors.[26] A list of Uncertainty Factors used in domestic and international chemical risk assessments are provided in Reference Material 2. Appropriate factors can be determined by assessors based on the

[23]For detailed Risk Assessment Series 3/toluene", Advanced Industrial Science and Technology (AIST), Research Center for Chemical Risk Management (MARUZEN, 2005)

[24]Refer to p.36 and p.49-51 "Issues with the highest or lowest regarding a NOAEL" from "How to Handle Uncertainty (Risk Assessment Pearls of Wisdom Series 2)", Advanced Industrial Science and Technology (AIST), Research Center for Chemical Risk Management (MARUZEN, 2007) for the results of detailed document research.

[25] http://www.mhlw.go.jp/shingi/2004/12/s1210-13.html

[26] Refer to "Initial Risk Evaluation for Chemical Substances" (NITE) http://www.safe.nite.go.jp/risk/files/guidance_ver2_20070115.pdf.

abovementioned list[27] ,

Intraspecies variability: 10

Interspecies variability: 10

Extrapolation from LOAEL to NOAEL: 10

Duration of Exposure (Extrapolation Subchronic to Chronic effects):

1 month – shorter than 3 months: 10

3 months - shorter than 6 months: 5

6 months – shorter than 12 months: 2

12 months or longer: 1

Type of effect (Carcinogenicity): 10

For the body weight and inhalation rate of humans and animals, following values are applied.

Human: Inhalation rate 20 m^3/day (0.833 m^3/hour), Body weight 50kg

Rat: Inhalation rate 0.26 m^3/day (0.011 m^3/hour), Body weight 0.35kg

Mouse: Inhalation rate 0.05 m^3/day (0.0021 m^3/hour), Body weight 0.03kg

The U.S. EPA (1988)[28] provides values for other animals, which can also be used.

III-5 Determining the Risk

III-5-1 Risk Determination Methods for Reproductive Toxicity and Specific Target Organ Toxicity following Repeated Exposure

Risk determination of reproductive toxicity and specific target organ toxicity following repeated exposure is carried out by comparing Estimated Human Exposure (see III-3) and Reference value (see III-4).

In case more than one exposure routes are assumed for a consumer product (for example inhalation and dermal routes), then the total EHE as the sum of EHE of each route is to be used. And in this case, if Reference values are available for each exposure route, the most conservative Reference value (i.e. the minimum value) should be used.

However, when the appearance of toxicity is limited to a certain route, and the possibility of exposure is limited to that certain route, the reference value and the EHE of the relevant route should be compared to determine the risk.

Moreover, if the reference value for a corresponding route is not available, the reference value of another route may be used in the assessment[29] only after the assessors provide careful examination of the adequacy of the route to route extrapolation.

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[27] These values are used when the Uncertainty Factors and weight or volume of breathed by humans and animals are required in the practical examples of Annex 2.

[28] U.S. EPA (1988) Recommendation for and Documentation of Biological Values for use in Risk Assessment EPA 600/6-87/008, NTIS PB88-179874/AS, February 1988.

[29] For the conditions for route to route extrapolation to be established, refer to the “How to Handle Uncertainty (Risk Assessment Pearls of Wisdom Series 2)”, p.22-23 Advanced Industrial Science and Technology (AIST), Research Center for Chemical Risk Management (MARUZEN, 2007) and the description and cited reference in “The First Step: Risk Assessment of Chemical Substances” (Sousuke Hanai, MARUZEN, 2003) p.14 Chapter 7.

The risk is determined as follows.

EHE < Reference value ----- the risk is not at a level of concern (labelling is not required)

EHE >= Reference value ----- the risk is at a level of concern (labelling based on GHS hazard classification is required)

When the EHE is slightly larger than the Reference value it is recommended not to jump to conclusion that “the risk is at a level of concern” but to perform a careful review by re-checking the assessment process before reaching conclusion.

Note) Other methods of representing of the risk are as follows. Any of these can be used instead of above-mentioned method because results will be the same.

(1) HQ Method (Hazard Quotient approach)

HQ = EHE / Reference value

If HQ < 1, the risk is not at a level of concern; if HQ >= 1 the risk is at a level of concern

(2) MOE (Margin of Exposure) Method

This is an approach where the risk is determined by comparing MOE (Margin of Exposure) and Uncertainty Factors (UFs) of hazard data. The advantage of this method is that the reliability of the hazard data is clearly understood by UFs.

Formula below show that “EHE < Reference value” is equal to “MOE > UFs”.

Note that the MOE here does not include the term of Uncertainty Factors (UFs). However, in some other assessment methods, “MOE” might include the term of Uncertainty Factors (UFs).

MOE = NOAEL/EHE

*Reference value = NOAEL/UFs

MOE > UFs -----the risk not at a level of concern (labelling is not required)

MOE <= UFs -----the risk at a level of concern (labelling based on hazard classification is required)

III-5-2 Risk Determination Methods for Carcinogenicity

Internationally there is still no agreed method for risk assessment of carcinogenicity, and therefore risk assessment must be performed deliberately in consideration of the process of carcinogenicity as well as the presumed mode of action, genotoxic or non-genotoxic.

This guidance follows the description as to carcinogenic risk assessment in "GHS Inter-Ministerial Committee document 20070111”

GHS Inter-Ministerial Committee document 20070111

With regard to carcinogenicity, it is possible to perform risk assessment as outlined above for chemicals for which NOAEL (LOAEL) can be obtained, but in many cases of carcinogenicity, risk evaluation is difficult because these values cannot be established. In the case, however, that standard values and/or permissible exposure amounts (concentrations) have been established through evaluations of carcinogenicity performed by national or international organizations, those values may be used in risk evaluation. In such cases, it is necessary to thoroughly consider the differences between the scope of application for established standard values and permissible exposure amounts (concentrations) (work environment, general environment, etc.) and consumer exposure conditions (exposure pathway, exposure period, exposure frequency).

Depending on how genotoxicity and carcinogenicity are related, there are different approaches.; one approach is that carcinogenic substances are assumed to have intrinsically genetic toxicity and there assumed to be no toxic threshold as in the U.S., and another is that existence of toxic threshold of a substance is assessed by genotoxic testing data as in WHO and EU.

In this guidance, carcinogenicity assessment is described in two cases; for a substance with a toxic threshold and for without a toxic threshold.

(1) Carcinogenic substance with a toxic threshold

For a carcinogenic substance assumed to have a toxic threshold, risk assessment is carried out according to abovementioned “Risk Determination Methods for Reproductive Toxicity and Specific Target Organ Toxicity following Repeated Exposure” (III-5-1)

(2) Carcinogenic substance without a toxic threshold

For a carcinogenic substance assumed to have no toxic threshold, Unit Risk (UR) or Cancer Slope Factor (CSF) will be used to determine the risk.

The GHS Official text provides the following description in the examples of the risk-based labelling used by the United States Consumer Product Safety Commission (CPSC).

The Second Revised Edition of GHS Official text (2007), Annex 5 “Consumer Product Labelling Based on the Likelihood of Injury” A.5.2.2 “An Example of risk-based labelling used in the United States Consumer Product Safety Commission”

A5.2.2.8 For carcinogens, a unit risk from exposure to the carcinogen would be calculated based on liner extrapolation with the multistage model as a default model.・・・

The Second Revised Edition of GHS Official text (2007), Annex 5 “Consumer Product Labelling Based on the Likelihood of Injury” A.5.2.2 “An Example of risk-based labelling used in the United States Consumer Product Safety Commission”

A5.2.2.9 The competent authority will need to establish what level of risk is acceptable to implement such an approach to consumer product labelling for chronic effects. For example, CPSC recommends labelling for a cancer

hazard if the lifetime excess risk exceeds one-in-a-million from exposure during “reasonably foreseeable handling and use.”

Likewise, in this guidance 10^{-6} will be used as the acceptable risk level.

If UR or CSF of a substance are provided in IRIS, normally the Permissible Exposure Limits (known as the Virtually Safe Dose) of 10^{-4} - 10^{-6} are listed; a VSD of 10^{-6} can be recalculated using the following formula.

VSD (mg/kg/day) of inhalation exposure＝ 10^{-6} / UR ($(mg/m^3)^{-1}$) × 20 m^3/day / 50 kg

VSD (mg/kg/day) of oral exposure＝ 10^{-6} / CSF ($(mg/kg/day)^{-1}$)

This VSD (Virtually Safe Dose) are to then be compared with the EHE to determine the risk, similar to the method in III-5-1.

III-5-3 Risk Determination Method where more than one Ingredients shows Chronic Health Hazards

Certain consumer products have more than one ingredients which pose chronic health hazards In this section, risk determination method for such products is described.

1) When hazard data of the product itself is available, risk determination is to be conducted with that data and the method described in III-5-1.

2) When hazard data of the product itself is not available, the data of a similar product with similar use patterns may be used as appropriate.

3) When no hazard data of the product nor of similar products are available, currently no concrete method has been determined internationally. On the other hand, there are some proposals in which hazard information of the individual ingredients are used for the risk assessment.

An approach for multiple exposures assessment using the following formula has been suggested for a case where, each ingredient has the same specific target organ effect and those reference values are already known [30] [31] [32]. This concept may be considered applicable in risk assessment for consumer products that contain several ingredients with chronic health hazards. However, before an assessor use this method, he/she should examine its reasonableness considering various factors such as the toxicity mechanism of each ingredient or cross-interaction among the ingredients.

[30] EPA/630/R-00/002 August 2000, Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures: http://www.epa.gov/ncea/raf/pdfs/chem_mix/chem_mix_08_2001.pdf

[31] ”Recommendation of Occupational Exposure Limits (2007)” Japan Society for Occupational Health (Journal of Occupational Health Vol. 49, 149 (2007))

[32] American Conference of Governmental Industrial Hygienists (ACGIH), TLVs and BEIs (2007) p.79. APPENDIX E: “Threshold Limit Values for Mixtures”.

Index = EHE_a / Reference value $_a$ + EHE_b / Reference value $_b$ + ･･･+ EHE_n / Reference value $_n$

$EHE_{a, b,\cdots, n}$: EHE value of ingredient a, ingredient b, ･･･, ingredient n

Reference value $_{a, b,\cdots, n}$: Reference value of ingredient a, ingredient b, ･･･, ingredient n

If the calculated result of Index is less than 1 (one) then it is concluded that the GHS labelling is "not required" for the chronic health hazards.

Reference Material 1: Definitions of terminology that can be used as Reference values

Terminology	Abbreviatio	Definition	Administering	The effect of the hazard	Source of information
Tolerable Daily Intake	TDI	Estimate of the amount of a chemical substance per 1kg body weight per day which can be ingested daily over a lifetime without it posing a significant risk to human health. In many cases "Tolerable" is used for chemical substances that are not directly beneficial to humans such as by-products. Refer to the "Acceptable Daily Intake" section. (Advanced Industrial Science and Technology (AIST), Research Center for Chemical Risk Management (CRM) Glossary of Risk Assessment Terminology (Japanese Version Only) : http://unit.aist.go.jp/riss/crm/mainmenu/3-1.html#タ)		Basically assumed as effects with a toxic threshhold. TDI can also be calculated as VSD (Virtually Safe Dose) for non-threshold effects.	
Acceptable Daily Intake	ADI	Estimate of the amount of a chemical substance per 1kg body weight per day which can be ingested daily over a lifetime without it posing a significant risk to human health. In many cases "Acceptable" is used for chemical substances that are beneficial to humans such as food additives and pesticides. Refer to the "Tolerable Daily Intake" (Advanced Industrial Science and Technology (AIST), Research Center for Chemical Risk Management (CRM) Glossary of Risk Assessment Terminology (Japanese Version Only): http://unit.aist.go.jp/riss/crm/mainmenu/3-1.html#カ)	WHO/FAO, CCPR (Codex Committee on Pesticide Residues)	Assumed as effects with a toxic threshhold.	
Reference Dose	RfD	Estimated value of a daily exposure concentration (dose) over a lifetime for humans that is likely to pose no appreciable risk of deleterious effects. Based on the noncarcinogenic effect the Reference Concentration (Dosage) is normally calculated using the NOAEL (or LOAEL) divided by the Uncertainty Factors (UFs). (Advanced Industrial Science and Technology (AIST), Research Center for Chemical Risk Management (CRM) Glossary of Risk Assessment Terminology (Japanese Version Only): http://unit.aist.go.jp/riss/crm/mainmenu/3-1.html#サ)	U.S. EPA (included in IRIS)	Basically assumed as effects with a toxic threshold.Unit Risk or Slope Factor are calculated for some chemical substances which are considered to have non-thresholds effects).	http://cfpub.epa.gov/ncea/iris/compare.cfm
Reference Concentration	RfC				
Minimum Risk Level	MRL	Minimum Risk Levels (MRLs) were developed as an initial response to the mandate and are estimates of the daily human exposure to hazardous substances that are likely to have no appreciable risk of adverse noncancerous health effects over a specific duration of exposure. A practice similar to that of the EPA's Reference Dose (RfD) and Reference Concentration (RfC) is adopted to derive substance specific health guidance levels for non neoplastic endpoints. (ATSDR Home Page: http://www.atsdr.cdc.gov/mrls/#bookmark02)	U. S. ATSDR (U.S. Agency for Toxic Substances and Disease Registry)	Basically assumed as effects with a toxic threshold.Unit Risk or Slope Factor are calculated for some chemical substances which are considered to have non-thresholds effects).	http://www.atsdr.cdc.gov/mrls/#bookmark02
		Estimate of the daily human exposure that is likely to have no appreciable risk of adverse health effects except carcinogenicity over a specific duration of exposure. (Memorandum of The 42nd Central Environmental Council, Environment and Health Division meeting, Chemical Substance Screening Subcommittee: http://www.env.go.jp/council/05hoken/y051-42a.html)			
Permitted Daily Exposure	PDE	The maximum pharmaceutically acceptable intake of residual solvents per day value. (Guideline for pharmaceutical residual solvents - Notification of Pharmaceutical Safety Bureau of Ministry of Health and Welfare: http://www.pmda.go.jp/ich/q/q3c_98_3_30.pdf)	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) http://www.pmda.go.jp/ich/ichtoha.htm	Assumed as threshold effects.	
Risk Specific Dose	RSD	The dose specific to the risk level of carcinogenicity based on the Linear Low Concentration extrapolation. (Target Risk Level, for example, the dose associated with the 10-6) (EPA-822-B-00-005, Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000)	U.S. EPA	Assumed as non-threshold effects. RfD or RfC may be calculated for some chemical substances which considered to have threshold effects).	
Virtually Safe Dose	VSD	The dose (concentration) where the risk of a chemical substance causing carcinogenicity and so on is sufficiently low and acceptable. (Ministry of Economy, Trade and Industry, "Guidebook for Risk Assessment of Chemical Substances, Appendix" : http://www.meti.go.jp/policy/chemical_management/law/prtr/pdf/guidebook_fuzokusho.pdf)	U.S. EPA	Considered as non-threshold effects.	
		VSD has been explained as the idea if the carcinogenicity risk is extremely low (for example at the 10-6 level) no special measures are considered necessary with risk management as their exposure level are probably negligible. The dose that can be calculated backward from certain negligible carcinogenicity risk levels using the inverse function of the dose-response function.("Handbook for Environmental Risk Management" edited by Jyunko Nakanishi, Masashi Gamo, Atsuo Kishimoto, Kenichi Miyamoto (Asakura Publishing Co., Ltd., 2003))			

Reference Material 2: Examples of Uncertainty Factor used domestically and internationally

	NITE CERI "Guideline on Initial Risk Assessment Ver.2.0", 2007.[1]	Cabinet Office, Government of Japan Food Safety Commission "Glossary regarding Food Safety (Revised version, addenda)" 2006.[2]	Ministry of Health, Labour and Welfare Health Sciences Council Section Meeting on Living Environment, and Drinking Water "Reviews regarding Water Quality Standards" 2003.[3]	Ministry of the Environment "Initial Environmental Risk Assesment of Chemicals Vol 5" Guideline for Initial Risk Assessment of Chemicals 2006.[4]	GHS Inter-Ministerial Committee Outlook on Risk Assessment for Consumer Products Based on Exposure for GHS Labelling, 2007.[5]	U.S. EPA A REVIEW OF REFERENCE DOSES AND REFERENCE CONCENTRATION PROCESSES. EPA/630/P-02/002F, 2002.[6]	WHO/IPCS Environmental Health Criteria 210: Principles for assessing the risk to human health from exposure to chemicals, 1999.[7]	ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) ICH Harmonised Tripartite Guideline Impurities: Guideline for Residual Solvents Q3C(R3),1997.[8]	ECB (European Chemical Bureau) EUSES2.0 Background Report III, Model Calculations page III-191, Table III-108, 2004.[9]	ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) Technical Report No. 86, 2003.[10]	Australia Department of Health and Ageing Environmental Health Risk Assessment, Guidelines for assessing human health risks from environmental hazards, 2004.[11]
Interspecies	10	10	10	10	10	when data available, TK Mouse; 7 Rat; 4 Guinea pig; 3 Rabbit; 2 } TD ×3	10 → TD $10^{0.4}$(2.5) 10 → TK $10^{0.6}$(4.0)	Rat: 5 Mouse: 12 Dog: 2 Rabbit: 2.5 Monkey: 3 Other animals: 10	Rat: 4 Mouse: 7 Guinea pig: 3 Rabbit: 2.4 Monkey: 2 Dog: 1.4 } ×2.5	Mouse: 7 Rat: 4 Monkey: 2 Dog: 2 Inhalation area: 1	10
Intraspecies	10	10	10		10	10	10 → TD $10^{0.5}$(3.2) 10 → TK $10^{0.5}$(3.2)	10	Workers: 5 General population: 10	(systemic effects, local effects) General population: 5 Workers: 3	10
Exposure duration	1 month: 10 3 months: 5 6 months: 2 12 months: 1		Up to 10	10	1 ~ 10	Subchronic to Chronic: 10 Not applicable to a shorter period than Subchronic	(10)	Half-life *) or more:1 Mid-long term**) ; 2 Mid term***) ; 5 Short term ; 10	Subacute to Subchronic: 3 Subchronic to Chronic: 2 Subacute to Chronic: 6	Subacute to Chronic: 6 Subchronic to Chronic: 2 Local Effects by Inhalation: 1	
LOAEL to NOAEL	10		Up to 10	10	1 ~ 10	10	3 or 10	10		3	10
Incompleteness of DB	*)		Up to 10			Depends on condition 3 or 10	Take into account (value larger than 1)				1 ~ 10*)
Characteristics of toxicity (such as carcinogenicity with threshold value)	Carcinogenicity with threshold: 10		Up to 10 *) 10 **)	Up to 10 *) Normally 10 (1 ~ 10) **)			Up to 10	1 for fetal toxicity associated with maternal toxicity 5 for fetal toxicity without maternal toxicity 5 for a teratogenic effect with maternal toxicity 10 for a teratogenic effect without maternal toxicity	Take into account *) No specific value		1 ~ 10
Remarks [Uncertainty Factors (UFs) and others]	*) Can be added depending on the type and quality of text at evaluator's judgment. If the UFs exceed 10,000 the data will not be used. Definition of test duration: 1 month = 1 - less than 3 month, 3 months = 3 - less than 6 months, 6 months = 6 - less than 12 months, 12 months = 12 months and more	Generally the setting of ADI use 100 which is the mix of interspecies and intraspecies, and depending on the quality of data, adopt larger factors (such as 500, 1000, 1500).	*) if the characteristics of toxicity is severe, **) if carcinogenicity exists.	Should be set as the factor to use in calculating the MOE. *) if N(L)OAEL is set using non-carcinogenic effects but possibly carcinogenic to human. **) if N(L)OAEL is set using carcinogenic effects.		The Technical Panel recommends limiting the total UF applied for any particular chemical to no more than 3000 and avoiding the derivation of a reference value that involves application of the full 10-fold UF in four or more areas of extrapolation. *)in the absence of any other specific toxicokinetic or toxicodynamic data, a default factor of 3 (in conjunction with HEC derivation) or 10 is applied.	TD: toxicodynamics, TK: toxicokinetics No description during the test, however, it is taken into consideration with drinking water quality setting.	*) 1 year for rodents or rabbits. 7 years for cats, dogs, and monkeys. **) 6-month study in rodents, or a 3.5-year study in non-rodents. ***) 3-month study in rodents, 2-year study in non-rodents.	In addition extrapolation from route to route is considered. *) It is considered as the uncertainty in the extrapolation of the dose-reaction, including the uncertainty associated with the characteristic of the effect and quality of the database.	Extrapolation between routes (Oral to Inhalation, Inhalation to Dermal) are stated as "not set".	*) Representation of the "quantity and quality of scientific data".

1) http://www.safe.nite.go.jp/risk/files/guidance_ver2_20070115.pdf
2) http://www.fsc.go.jp/yougoshu_fsc.pdf
3) http://www.mhlw.go.jp/shingi/2003/04/s0428-4b.html
4) http://www.env.go.jp/chemi/report/h18-12/pdf/chpt1/1-2-1.pdf
5) http://www.meti.go.jp/policy/chemical_management/kokusai/GHS/consumer_product_labelling.htm
6) http://www.epa.gov/IRIS/RFD_FINAL[1].pdf
7) http://www.inchem.org/documents/ehc/ehc/ehc210.htm
8) http://www.ich.org/LOB/media/MEDIA423.pdf
9) http://ecb.jrc.it/euses/
10) ECETOC, Derivation of Assessment Factors for Human Health Assessment, Technical Report No.86 (2003)
11) http://www.health.gov.au/internet/wcms/publishing.nsf/Content/ohp-ehra-2004.htm~ohp-ehra-2004-objectives.htm

Comparison of Uncertainty Factors of NEDO 1 PRO and ICH

Ex) NEDO 1 Pro initial risk assessment for formaldehyde
Adopt the NOAEL from the 26 weeks inhalation exposure test on the monkey
Uncertainty Factor: Species difference (10), Individual specificity (10), test period (2)
Uncertainty Factors: 10×10×2= **200**
Uncertainty Factor in the ICH described above: Species difference (3), Individual specificity (10), Test period (10)
Uncertainty Factors: 3×10×10= **300**