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
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

I Background and Objectives
II Scope of Risk-based GHS Labelling
III Risk Assessment Process for GHS Labelling
   III-1 GHS Classifications for the Chronic Health Hazards
   III-2 Exposure Route
   III-3 Estimation of Consumer Exposure
      III-3-1 Estimation of Exposure based on an Extreme Conservative Assumption
      III-3-2 Estimation of Exposure considering the Practical Use Conditions
   III-4 Establishing Reference Values
   III-5 Risk Determination
      III-5-1 Risk Determination Methods for Reproductive Toxicity and Specific Target Organ Toxicity following Repeated Exposure
      III-5-2 Risk Determination Methods for Carcinogenicity
      III-5-3 Risk Determination Method where more than one ingredients shows Chronic Health Hazards exists

Reference Materials
   1. Definition of terminologies that can be used as the Reference value
   2. Uncertainty Factor (UF) used domestically and internationally

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

I. Purpose of this document
II Basic Exposure Scenario and Algorithm
III Specific Exposure Scenarios by the Application Category of the Products and Exposure Assessment Examples

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

Example of Risk Assessment No. 1 Xylene in the urethane varnish for wood
Example of Risk Assessment No. 2 p-dichlorobenzene used in toilet deodorant
Example of Risk Assessment No. 3 n-hexane in general-use rubber-based adhesive
Example of Risk Assessment No. 4 Ethanol in hand dishwashing detergent
Example of Risk Assessment No. 5 Linalool in fragrance (oil-based)

Accompanying Material

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

LABELLING OF CONSUMER PRODUCTS
# Table of Contents

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

I Background and Objectives ..................................................................................................................................................1

II Scope of Risk-based GHS Labelling ....................................................................................................................................4
   II-1 Consumer Products covered in Risk-based GHS Labelling .......................................................................................4
   II-2 Health Hazards covered in Risk-based GHS Labelling .................................................................................................4

III Risk Assessment Process for GHS Labelling ............................................................................................................................6
   III-1 GHS Classifications for Chronic Health Hazards ......................................................................................................8
   III-2 Exposure Route ...............................................................................................................................................................8
   III-3 Estimation of Consumer Exposure ...............................................................................................................................8
      III-3-1 Estimation of Exposure based on an Extreme Conservative Assumption ...............................................................9
      III-3-2 Estimation of Exposure considering the Practical Use Conditions ...............................................................9
   III-4 Establishing Reference Values .....................................................................................................................................10
      III-4-1 In case Reference Values have already been determined by an international or national authority ..................11
      III-4-2 In case Reference Values are to be determined by assessors ........................................................................12
   III-5 Determining the Risk .....................................................................................................................................................13
      III-5-1 Risk Determination Methods for Reproductive Toxicity and Specific Target Organ Toxicity following Repeated Exposure ...........................................................................................................13
      III-5-2 Risk Determination Methods for Carcinogenicity .................................................................................................14
      III-5-3 Risk Determination Method where more than one Ingredients shows Chronic Health Hazards ..........................16

Reference Material

1. Definition of terminologies that can be used as the Reference value
2. Uncertainty Factor (UF) used domestically and internationally
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 Annex 5 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 then chronic health hazards do not necessarily have to be included on GHS labels for consumer use (hereinafter risk-based labelling).


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.


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
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](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\textsuperscript{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.

\footnote{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.

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.

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.

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\(^5\) 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.

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(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.

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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 website of NITE.

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.


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.

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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. • • •

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

\[
EHE = \text{Product amount} \times \frac{\text{Concentration of the Chemical Substance}}{\text{Body Weight}}
\]

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.

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\(^8\) [http://ecb.jrc.it/tgd/](http://ecb.jrc.it/tgd/)

\(^9\) [http://www.heraproject.com/Library.cfm](http://www.heraproject.com/Library.cfm)

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\(^\text{11}\)
- Ministry of the Environment: Initial environmental risk assessment of chemicals (Vol. 1 - 5)\(^\text{12}\)
- Chemicals Evaluation and Research Institute, Japan (CERI): Chemical Substance Safety (Hazard) Data Collection\(^\text{13}\)
- OECD: SIDS Initial Assessment Report\(^\text{14}\)
- WHO/IPCS: Environmental Health Criteria (EHC)\(^\text{15}\)
- WHO/IPCS: Concise International Chemical Assessment Documents (CICAD)\(^\text{16}\)

\(^{11}\) http://www.safe.nite.go.jp/risk/risk_index.html
\(^{13}\) http://www.cerij.or.jp/db/sheet/sheet_index.html
\(^{14}\) http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html
EU: EU Risk Assessment Report
U.S Environmental Protection Agency: Integrated Risk Information System (IRIS)
International Programme on Chemical Safety (IPCS): INCHEM

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

NITE: Chemical Risk Information Platform (CHRIP)

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

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.

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.

\[
\text{Reference value} = \frac{\text{NOAEL}}{\text{UFs}}
\]

In this guidance, following values are recommended for Uncertainty Factors. 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

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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.
abovementioned list\textsuperscript{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\textsuperscript{3}/day (0.833 m\textsuperscript{3}/hour), Body weight 50kg
- Rat: Inhalation rate 0.26 m\textsuperscript{3}/day (0.011 m\textsuperscript{3}/hour), Body weight 0.35kg
- Mouse: Inhalation rate 0.05 m\textsuperscript{3}/day (0.0021 m\textsuperscript{3}/hour), Body weight 0.03kg

The U.S. EPA (1988)\textsuperscript{28} provides values for other animals, which can also be used.

\section*{III-5 Determining the Risk}

\subsection*{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\textsuperscript{29} only after the assessors provide careful examination of the adequacy of the route to route extrapolation.

\textsuperscript{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.


\textsuperscript{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"
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).

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

\[
\text{VSD (mg/kg/day) of inhalation exposure} = \frac{10^{-6}}{\text{UR} \left( \text{mg/m}^3 \right)^{-1}} \times 20 \text{ m}^3/\text{day} / 50 \text{ kg}
\]

\[
\text{VSD (mg/kg/day) of oral exposure} = \frac{10^{-6}}{\text{CSF} \left( \text{mg/kg/day} \right)^{-1}}
\]

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.

---


\(^{32}\) American Conference of Governmental Industrial Hygienists (ACGIH), TLVs and BEIs (2007) p.79. APPENDIX E: “Threshold Limit Values for Mixtures”.
Index = \frac{EHE_a}{Reference\ value\ a} + \frac{EHE_b}{Reference\ value\ b} + \cdots + \frac{EHE_n}{Reference\ value\ n}

EHE_a, b, \cdots, n: EHE value of ingredient a, ingredient b, \cdots, ingredient n

Reference\ value\ a, b, \cdots, n: Reference value of ingredient a, ingredient b, \cdots, 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

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Abbreviation</th>
<th>Definition</th>
<th>Administering</th>
<th>The effect of the hazard</th>
<th>Source of information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolerable Daily Intake</td>
<td>TDI</td>
<td>Estimate of the amount of a chemical substance per kg 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); <a href="http://unit.aist.go.jp/prisa/crm/mainmenu3-1.html#p">http://unit.aist.go.jp/prisa/crm/mainmenu3-1.html#p</a>)</td>
<td>WHOCI/FAO, Codex Committee on Pesticide Residues</td>
<td>Assumed as effects with a toxic threshold.</td>
<td></td>
</tr>
<tr>
<td>Reference Dose</td>
<td>RID</td>
<td>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 (Dose) 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); <a href="http://unit.aist.go.jp/prisa/crm/mainmenu3-1.html#p">http://unit.aist.go.jp/prisa/crm/mainmenu3-1.html#p</a>)</td>
<td>U.S. EPA (included in IRIS)</td>
<td>Basically assumed as effects with a toxic threshold.</td>
<td></td>
</tr>
<tr>
<td>Reference Concentration</td>
<td>RfC</td>
<td>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 (RD) and Reference Concentration (RfC) is adopted to derive substance specific health guidance levels for noncancerous effects. (ATSDR Home Page; <a href="http://www.atsdr.cdc.gov/mrls/ftbookmark02">http://www.atsdr.cdc.gov/mrls/ftbookmark02</a>)</td>
<td>U. S. ATSDR (U.S. Agency for Toxic Substances and Disease Registry)</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Minimum Risk Level</td>
<td>MRL</td>
<td>Estimate of the daily human exposure that is likely to have no appreciable risk of adverse noncancerous 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; <a href="http://www.env.go.jp/council/05hokenry051-42a.html">http://www.env.go.jp/council/05hokenry051-42a.html</a>)</td>
<td>International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH); <a href="http://www.pmda.go.jp/ich/ich05/h08a.htm">http://www.pmda.go.jp/ich/ich05/h08a.htm</a></td>
<td>Assumed as threshold effects.</td>
<td></td>
</tr>
<tr>
<td>Permitted Daily Exposure</td>
<td>POE</td>
<td>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; <a href="http://www.pmda.go.jp/ich/03c_06_3_30.pdf">http://www.pmda.go.jp/ich/03c_06_3_30.pdf</a>)</td>
<td>U.S. EPA</td>
<td>Assumed as non-threshold effects. RD or WC may be calculated for some chemical substances which are considered to have threshold effects.</td>
<td></td>
</tr>
<tr>
<td>Risk Specific Dose</td>
<td>RSD</td>
<td>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 threshold, is 10^-6 of the NOAEL or LOAEL). Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000)</td>
<td>U.S. EPA</td>
<td>Considered as non-threshold effects.</td>
<td></td>
</tr>
</tbody>
</table>

**Source:** Adapted from **Glossary of Risk Assessment Terminology (Japanese Version Only);** [http://unit.aist.go.jp/prisa/crm/mainmenu3-1.html#p](http://unit.aist.go.jp/prisa/crm/mainmenu3-1.html#p)
### Reference Material 2: Examples of Uncertainty Factor used domestically and internationally

|----------|----------------------------------------------------------|-------------------------------------------------------------|-----------------------------|--------------------------------|----------|--------|----------------------------------------------------------|-----------------------------|----------------------------------|

#### Interspecies

<table>
<thead>
<tr>
<th>Coverage</th>
<th>10</th>
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<th>10</th>
</tr>
</thead>
</table>

- When data available, use TK and MOE:
  - Rat: 7
  - Mouse: 5
  - Guinea pig: 3
  - Rabbit: 2

- TD: toxicodynamics, TK: toxicokinetics

#### Intraspaces

<table>
<thead>
<tr>
<th>Coverage</th>
<th>10</th>
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</thead>
</table>

- When data available, use TK and MOE:
  - Rat: 5
  - Mouse: 2
  - Dog: 2
  - Rabbit: 2
  - Monkey: 2
  - Other animals: 10

#### Exposure duration

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Up to 10</th>
<th>10</th>
<th>10</th>
<th>10</th>
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</thead>
</table>

- Subacute to Chronic: 10
- Subacute to Subchronic: 5
- Short term: 5
- Mid long term: 5
- Mid term: 3
- Mid-long term: 2
- Short term: 1

#### LOAEL to NOAEL

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Up to 10</th>
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</table>

- 1 for lethal toxicity associated with maternal toxicity
- 5 for lethal toxicity with no maternal toxicity
- 10 for a teratogenic effect with maternal toxicity
- 10 for a teratogenic effect without maternal toxicity

#### Characteristics of toxicity (such as carcinogenicity with threshold value)

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Up to 10</th>
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</table>

- Up to 10
- Normally 10
- (1 - 10)**

**Can be added depending on the type and quality of test and evaluation of judgment of the UFs. If the UFs exceed 10,000, the data will not be used.

#### Remarks

- Definition of test duration: 1 month = 1 - less than 3 months, 3 months = 3 - less than 6 months, 6 months = 6 - less than 12 months, 12 months = 12 months and more

#### Comparison of Uncertainty Factors of NEDO 1 PRO and ICH

Carcinogenicity with threshold value:

- Species difference (10), Individual specificity (10), Test period (2)

Uncertainty Factor in the ICH described above: Species difference (3), Individual specificity (10), Test period (10)

#### INCOMPETENCE OF DB

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Up to 10</th>
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#### Incompleteness of DB

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- 10 for a teratogenic effect without maternal toxicity

#### Explanation of the quantity and quality of scientific data

### References

10. [http://ecb.jrc.it/euses/](http://ecb.jrc.it/euses/)

### Notes

1) *Guideline on Initial Risk Assessment Ver.2.0*, 2007.1
4) [http://www.mhlw.go.jp/shingi/200304/o428-4b.htm](http://www.mhlw.go.jp/shingi/200304/o428-4b.htm)
8) [http://www.ich.org/LOB/media/MEDA623.pdf](http://www.ich.org/LOB/media/MEDA623.pdf)
9) [http://ecb.jrc.it/euses/](http://ecb.jrc.it/euses/)
10) [http://ecb.jrc.it/euses/](http://ecb.jrc.it/euses/)