Appendix 2

Examples of Risk Assessment of Consumer Products for GHS Labelling

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Appendix 2 aims to promote understanding of the content of “GUIDANCE ON A CONSUMER PRODUCT RISK ASSESSMENT FOR GHS LABELLING” (hereinafter referred to as Main Document). Please pay attention to the following to use it.

1. The “Risk Assessments” described in Appendix 2 are only “examples” to aid in understanding the flow of the risk assessment method, and must not be deemed as demonstrating the result of essential assessment, which is actually carried out.
2. The product information, hazard-based classifications, exposure scenarios, exposure factors, assessment reference values, and other information were only tentatively used to create “Risk Assessments”, but were not selected after substantial examination.
3. “Foreseeable misuse” may vary with consumer product. In addition, the appropriate method to deal with it (foreseeable misuse) may also vary in the risk assessment. And hence Appendix 2 does not specifically exemplify “foreseeable misuses”. However, in actual risk assessments, it is necessary to firstly consider what kind of misuse may occur for each product and then conduct risk assessments using the consideration result.
4. The Uncertainty Factors (UFs) used in Appendix 2 are based on the following guidance documented in reference material 2 in the Main Document. “The National Institute of Technology and Evaluation, Chemical Evaluation and Research Institute, Japan, “Guideline on Initial Risk Assessment” (Comprehensive Chemical Substance Assessment and Management Program, Project No. 1, New Energy and Industrial Technology Development Organization, 2007)”.
5. Some of the substances discussed in Appendix 2 have available values for assessment reference values such as TDI (Tolerable Daily Intake) and ADI (Acceptable Daily Intake), and these values can be used in assessments. In addition, this document indicates examples, in which the evaluators set their own Reference Values according to “III-4-2 Where Reference Values are to be Determined by Evaluators” in the Main Document

Example of Risk Assessment No. 1: Xylene in the urethane varnish for wood

This risk assessment concerns the Xylene contained in urethane varnish for wood.

Xylene

CAS Registration No.: 1330-20-7

Product/Usage Information

1) Product Information: Urethane varnish for wood (1 Liter, Weight of Product: 940 g), contains 1% Xylene.
2) Usage Information: Assume that 1 liter of urethane varnish for wood gets entirely used in one event to objects in rooms such as floors or tables, which corresponds to two application of 4.5 Tatami mats floor. When using the product, ensure adequate ventilation in the room and wear gloves or other such protection to protect the skin from the adhesion of the product.
   * Assume that 1 Liter of the product will be enough to paint a 4.5 Tatami mats floor twice and that it will require about half an hour per time.
   * Diluent is generally not used when applying the varnish.

1. Classification of Xylene based on the Hazard (Refer to III-1 in the Main Document)

The following classifications were conducted referring to the "GHS Classification Result Database"[1].

Carcinogenicity	Not classified
Reproductive Toxicity	Category 1B (possibly adversely affect sexual functionality or fertility)
Specific Target Organ/Systemic Toxicity (Repeated Exposure)	Category 1 (harmful to organs (respiratory or nerve system) with long-term or repeated exposure)

2. Evaluation of Exposure Route (Refer to III-2 in the Main Document)

The following possible exposure routes were determined according to its usage patterns and physiochemical properties.

1) Inhalation Exposure: Inhalation exposure may occur during application.
2) Dermal Exposure: As "foreseeable misuse", dermal exposure could occur if it is used with bare hands.
3) Oral Exposure: Although the possibility of oral exposure exists via accidental intake, it does not fall within the scope of this assessment because it is not included in the range of possible misuse.

3. Estimation of Human Exposure (Refer to III-3 in the Main Document)

The following algorithms in Appendix 1 were used to estimate the Amount of human exposure.

[1] http://www.safe.nite.go.jp/english/ghs_index.html

(1) Amount of Inhalation Exposure

<Exposure Scenario>

1 liter of urethane varnish for wood was applied (applied twice) to 4.5 Tatami mats flooring in a living room. The room volume was 1.62 m^2/Tatami x 4.5 Tatami mat x 2.1 m = 15.3 m^3. Each application was assumed to take the conservative time of 1 hour. In addition, the staying time between the first application end and the second application start was assumed to be zero. This is because the user would presumably exit the room after the first application until the object applied had dried. When applying, it is important to ensure sufficient ventilation. However, to take “foreseeable misuse” into consideration, the ventilation was assumed to be inadequate, and the work was carried out in a room with a ventilation rate of 0.2 times/h. Assume that the frequency of work is once a year.

<Estimation of Inhalation Exposure Amount>

The following are the values to be used to calculate the Amount of inhalation exposure (note that these are only assumptions).

Amount of Product Used (Applied Once): Ap	470 g
Weight Fraction of Xylene: Wr	1 %
Volume of Space: V	15.3 m^3
Ventilation Rate: N	0.2 times/h
Body Weight: BW	50 kg
Inhalation Rate: Q	0.833 m^3/h
Working Hours (Applied Once): t_a	1.0 h
Staying Time After Use: t_b	0.0 h
Description of Work	Applied Twice
Uptake fraction: a	100%
Mean Number of Events: n	Once/Year

Calculate the Inhalation Exposure amount by using the formula II-1-6 and the formula II-1-1, as described in Appendix 1, and assigning the Counts of application per event (applied twice) and Mean number of events per year.

Use the formula II-1-6 to calculate the Average Air Concentration (mg/m^3) during work (applied once).

Average Air Concentration (mg/m^3) during work (applied once)

$$= \frac{\dfrac{470{,}000mg \times 0.01 \not{/} 1.0h}{0.2/h \times 15.3m^3} \times \left\{1.0h - \dfrac{1}{0.2/h} \times \left[1 - \exp\left(-0.2/h \times 1.0h\right)\right]\right\}}{1.0h}$$

$$= 143.8mg/m^3$$

Assign this answer to the formula II-1-1 to calculate the Amount of Inhalation Exposure.

$$\text{Amount of Inhalation Exposure} = \frac{143.8 mg/m^3 \times 0.833 m^3/h \times 1.0h \times 2 \times 1/365 day \times 1}{50kg}$$

$$= 0.013 mg/kg/day$$

* For more details on calculating the Amount of exposure refer to Appendix 1 - Chapter II, Chapter III-1-4 “Example: General-use adhesive (plastic model adhesive) Chemical substance: acetone”, and Chapter III-2-4 “Example 1) Household synthetic resin emulsion paint Chemical substance: Isopropyl Alcohol (IPA)” etc.

[Result of Inhalation Exposure Estimation]

Amount of Inhalation Exposure: 0.013 mg/kg/day

(2) Amount of Dermal Exposure

<Exposure Scenario>

One liter of urethane wood varnish is used to paint a 4.5 Tatami mats floor (applied twice). As “foreseeable misuse”, the user was considered to have worked without any skin adhesion prevention measure, such as wearing gloves, and therefore 0.5 % of the amount of the product used was assumed to have adhered to the skin. Assume that the frequency of work to be once a year.

<Estimation of Dermal Exposure Amount>

The following are the values to be used to calculate the Amount of Dermal Exposure (note that these are only assumptions).

Amount of Product Used (Applied Once)	470 g
Weight Fraction of Xylene: Wr	1 %
Body Weight: BW	50 kg
Description of Work	Applied Twice
Skin Adhesion Ratio: Md	0.5 %
Uptake fraction: a	100 %
Mean Number of Events:	Once/Year

Calculate the Dermal Exposure amount by using the formula II-2-3, as described in Appendix 1, and assigning the Counts of application per event (applied twice) and Mean Number of Events per year.

Use the formula II-2-3 to calculate the Amount of Dermal Exposure.

$$\text{Amount of Dermal Exposure} = \frac{470{,}000 mg \times 0.01 \times 0.005 \times 2 \times 1/365 day \times 1}{50kg}$$

$$= 0.003 mg/kg/day$$

* For more details on calculating the Amount of exposure refer to Appendix 1 - Chapter II, Chapter III-1-4 “Example: General-use adhesive (plastic model adhesive), Chemical substance: acetone”, and Chapter III-2-4 “Example 1) Household synthetic resin emulsion paint, Chemical substance: Isopropyl Alcohol (IPA)” etc.

[Result of Dermal Exposure Estimation]

Amount of Dermal Exposure: 0.003 mg/kg/day

(3) Estimated Human Exposure (EHE)

Since Estimated Human Exposure (EHE) = Amount of Inhalation Exposure + Amount of Dermal Exposure,

EHE = 0.013 mg/kg/day + 0.003mg/kg/day = 0.016 mg/kg/day

4. NOAELs and UFs used in Risk Assessments (Refer to III-4 in the Main Document)

1) Reproductive Toxicity

For the reproductive and developmental toxicity of Xylene, in the "Initial Risk Assessment Report of Chemical Substances Ver. 1.0, Xylene" (NITE, 2005)[2], no reproductive toxicity was observed in rats in inhalation exposure experiments using an isomeric mixture at the maximum dose of 500 ppm. For the developmental toxicity, a NOAEL 150 mg/m^3 (Ungvary et al., 1980b), which affect a rat fetuses at the gestational stage of 7 - 14 days in inhalation exposure experiments using *o*-xylene at a dose that can affect the dam, was adopted. This value can be converted to the Estimated Inhalation Intake Amount per day 110 mg/kg/day.

Uncertainty Factors (UFs) were taken to be 100 in consideration of intraspecies and interspecies differences.

NOAEL = 150 mg/m^3×0.26 m^3/day/0.35 kg= 110 mg/kg/day

(Inhalation Rate of Rat: 0.26 m^3/day, Weight of Rat: 0.35 kg)

UFs = 10 (intraspecies) × 10 (interspecies) = 100

2) Specific Target Organ/Systemic Toxicity (Repeated Exposure)

For the Specific Target Organ/Systemic Toxicity based on repeated exposure to Xylene the "Initial Risk Assessment Report of Chemical Substances Ver. 1.0, Xylene" (NITE, 2005) uses a NOAEL of 50 ppm (221 mg/m^3) (Korsak et al, 1994) with reference to the index of neurotoxicity (incoordination) for the rat in a 3 month inhalation experiment using *m*-xylene. As this value was obtained with a dose frequency of 6 h/day, 5 day/week, it can be converted to an Estimated Inhalation Intake Amount per day of 29 mg/kg/day. Uncertainty Factors (UFs) were taken to be 500 in consideration of intraspecies, interspecies, and duration of exposure.

NOAEL = 221 mg/m^3 × 0.26 m^3/day × 6 h/24 h × 5 day/7 day/0.35 kg

= 29 mg/kg/day

(Inhalation Rate of Rat: 0.26 m^3/day, Weight of Rat: 0.35 kg)

UFs = 10 (intraspecies) × 10(interspecies) × 5 (duration of exposure) = 500

5. Determination of Risk (Refer to III-5 in the Main Document)

In this example the risk was determined by comparing the MOE and UFs.

1) Reproductive Toxicity

[2] http://www.safe.nite.go.jp/risk/files/pdf_hyoukasyo/063riskdoc.pdf

NOAEL: 110 mg/kg/day, EHE: 0.016 mg/kg/day
MOE = NOAEL/EHE = 110/0.016 = 6,800
UFs: 100
MOE > UFs
From the above labelling is not required.

2) Specific Target Organ/Systemic Toxicity (Repeated Exposure)
NOAEL: 29 mg/kg/day, EHE: 0.016 mg/kg/day
MOE = NOAEL/EHE = 29/0.016 = 1,800
UFs: 500
MOE > UFs
From the above labelling is not required.

6. Conclusion (Labelling)

Carcinogenicity	Labelling is not required (from hazard assessment)
Reproduction Toxicity	Labeling is not required (from risk assessment)
Specific Target Organ/Systemic Toxicity (Repeated Exposure)	Labeling is not required (from risk assessment)

* In this assessment example, the necessity for labelling of any other hazard than stated above is not referred.

Example of Risk Assessment No. 2: *p*-dichlorobenzene used in lavatory deodorant

This risk assessment concerns the *p*-dichlorobenzene contained in lavatory deodorant.

_p_-dichlorobenzene (_p_-DCB)

CAS Registration No.: 106-46-7

Product/Usage Information

1) Product Information: Contains 100% *p*-DCB.
2) Usage Information: One product unit is placed in the lavatory. The product weight is 150 g and a period of use (product life) is 6 months.

1. Classification of *p*-DCB based on the Hazard (Refer to III-1 in the Main Document)

For reproduction toxicity and Specific Target Organ/Systemic Toxicity (repeated exposure) the "GHS Classification Result Database" [3] was used for classification. For carcinogenicity classification was conducted as follows using a report from the Ministry of Health and Welfare[4] .

Carcinogenicity	Not classified
Reproduction Toxicity	Category 1B (possibly adversely affect sexual functionality or fertility)
Specific Target Organ/Systemic Toxicity (Repeated Exposure)	Category 1 (respiratory, liver, nervous system), category 2 (kidney)

2. Evaluation of Exposure Route (Refer to III-2 in the Main Document)

The following possible exposure routes were determined according to its usage patterns and physiochemical properties.

1) Inhalation Exposure: Inhalation exposure may occur inside the lavatory.
2) Dermal Exposure: Exposure may occur through touching the product with bare hands when setting the product in place in the lavatory. However, as it is assumed that this would only be rarely and for a very short period, it was excluded from assessment.
3) Oral Exposure: Although the possibility of oral exposure via accidental intake of the product does exist, it can be excluded from the scope of assessment because it is not included in the range of misuse.

3. Estimation of Human Exposure (Refer to III-3 in the Main Document)

The following algorithms in Appendix 1 were used to estimate the Amount of human exposure.

(1) Amount of Inhalation Exposure

[3] http://www.safe.nite.go.jp/english/ghs_index.html
[4] Home Use Product Expert Conference (Toxicity Division) Report on p-dichlorobenzene", (Office for Environmental Chemical Safety, Planning Division, Environmental Health Bureau, Ministry of Health and Welfare, 1997)

<Exposure Scenario>

Assume that a user would inhale *p*-DCB from the deodorant in the lavatory and that the ventilation frequency is 0.5 time/hour through a window or a local ventilation system installed in the lavatory (2.0 m^3). One deodorant unit (150 g) is set in the lavatory. A conservative product life of the deodorant is assumed to be 4 months. The use count of the lavatory is 6 times a day, with a staying time of 5 minutes per stay[5]. The contribution of *p*-DCB being absorbed to dust (particulate substance) in the lavatory is not taken into consideration.

<Estimation of Inhalation Exposure Amount>

The following are the values to be used to calculate the Amount of inhalation exposure. Note that they are only assumptions.

Volume of Lavatory: V	20 m^3
Ventilation Rate: N	0.5 times/h
Body Weight: BW	50 kg
Inhalation Rate: Q	0.833 m^3/h
Staying Time in Lavatory: t	0.0833 hour/use
Emission Rate of *p*-DCB: G	52.1 mg/h/unit (150 g/4 months/unit)
Frequency of Using Lavatory: n	6 times/day
Uptake fraction: a	100 %

Use the formula II-1-10 and formula II-1-1 described in Appendix 1 and take the Frequency of Lavatory Use per day into consideration to calculate the Amount of Inhalation Exposure.

Use the formula II-1-10 to calculate the Average Air Concentration (mg/m^3) in the lavatory.

$$\text{Average Air Concentration in the lavatory} = \frac{52.1 mg/h}{0.5/h \times 2.0 m^3} = 52.1 mg/m^3$$

Assign this answer in the formula II-1-1 to calculate the Amount of Inhalation Exposure.

$$\text{Amount of Inhalation Exposure} = \frac{52.1 mg/m^3 \times 0.833 m^3/h \times 0.0833 h \times 6/day \times 1}{50 kg}$$

$$= 0.434 mg/kg/day$$

* For more details on calculating the Amount of exposure refer to Appendix 1 - Chapter II, Chapter III-5-4 “Example Air freshener for vehicle Chemical substance: d-limonene” and Chapter III-4-4 “Example 2) Electric vaporizer type repellent Chemical substance: Metofluthrin” etc.

[Result of Inhalation Exposure Estimation]

Amount of Inhalation Exposure: 0.434 mg/kg/day

(2) Estimated Human Exposure (EHE)

Since the Estimated Human Exposure (EHE) = Amount of Inhalation Exposure,

EHE = 0.434 mg/kg/day

[5] Abstracted from ”Everyone’s lavatory: How to build a public lavatory” on the Kochi Prefecture Civil Engineering Department Building Division Home page (http://www.pref.kochi.jp/~kenchiku/kenchiku/toile_onepoint.html)

4. NOAELs and UFs used in Risk Assessment (Refer to III-4 in the Main Document)

1) Reproductive Toxicity

For reproductive and developmental toxicity the "Initial Risk Assessment Report of Chemical Substances Ver. 1.0, *p*-dichlorobenzene" (NITE, 2005)[6] uses a NOAEL of 211 ppm (1,289 mg/m^3) (Neeper-Bradley, 1989 and Tyl, 1989) indicating increased significant perinatal mortality, reduced litter size, reduction in number of live fetuses per litter. As this value was obtained with a dose frequency of 6 h/day, 7 day/week, if it is converted to the Estimated Inhalation Intake Amount per day it results in a NOAEL of 240 mg/kg/day. Uncertainty Factors (UFs) were taken to be 100 in consideration of intraspecies and interspecies differences.

NOAEL = 1289 mg/m^3 × 0.26 m^3/day × 6 h/24 h/0.35 kg = 240 mg/kg/day

(Inhalation Rate of Rat: 0.26 m^3/day, Weight of Rat: 0.35 kg)

UFs = 10 (intraspecies) × 10 (interspecies) = 100

2) Specific Target Organ/Systemic Toxicity (Repeated Exposure)

For Specific Target Organ/Systemic Toxicity based on repeated exposure the "Initial Risk Assessment Report of Chemical Substances Ver. 1.0, *p*-dichlorobenzene" (NITE, 2005) uses a NOAEL of 75 ppm (458 mg/m^3) (JBRC, 1995) indicating hepatotoxicity from a 104 week inhalation exposure experiment on the rat. As this value was obtained with a dose frequency of 6 h/day, 5 day/week, if it is converted to the Estimated Inhalation Intake Amount per day it results in a NOAEL of 61 mg/kg/day. Uncertainty Factors (UFs) were taken to be 100 in consideration of intraspecies and interspecies differences.

NOAEL = 458 mg/m^3 × 0.26 m^3/day × 6 h/24 h × 5 day/7 day/0.35 kg

= 61 mg/kg/day

(Inhalation Rate of Rat: 0.26 m^3/day, Weight of Rat: 0.35 kg)

UFs = 10 (intraspecies) × 10 (interspecies) = 100

5. Determination of Risk (Refer to III-5 in the Main Document)

In this example the risk was determined comparing the MOE and UFs.

1) Reproductive Toxicity

NOAEL: 240 mg/kg/day, EHE: 0.434 mg/kg/day

MOE = NOAEL/EHE = 240/0.434 = 550

UFs: 100

MOE > UFs

From the above labelling is not required.

2) Specific Target Organ/Systemic Toxicity (Repeated Exposure)

NOAEL: 61 mg/kg/day, EHE: 0.434 mg/kg/day

MOE = NOAEL/EHE = 61/0.434 = 140

UFs: 100

[6] http://www.safe.nite.go.jp/risk/files/pdf_hyoukasyo/140riskdoc.pdf

MOE > UFs

From the above labelling is not required.

6. Conclusion (Labelling)

Carcinogenicity	Labelling is not required (from hazard assessment)
Reproduction Toxicity	Labelling is not required (from risk assessment)
Specific Target Organ/Systemic Toxicity (Repeated Exposure)	Labelling is not required (from risk assessment)

* In this assessment example, the necessity for labelling of any other hazard than stated above is not referred.

Example of Risk Assessment No. 3: *n*-hexane in general-use rubber-based adhesive

This risk assessment concerns the *n*-hexane in general-use rubber-based adhesive.

_n_-hexane

CAS Registration No.: 110-54-3

Product/Usage Information

1) Product Information: Contains 10% *n*-hexane.
2) Usage Information: Application Frequency is 1–6 times/year, and usage amount 5 g/use (weight of adhesive). The application was conducted in a living room with the good ventilation of open windows, with the working time (use time of the product) being 15 minutes.

1. Classification of *n*-hexane based on Hazard (Refer to III-1 in the Main Document)

The following classifications were conducted using examples from the "GHS Classification Result Database"[7].

Carcinogenicity	Classification not possible
Reproductive Toxicity	Category 2 (substances possibly adversely affecting sexual functionality or fertility)
Specific Target Organ/Systemic Toxicity (Repeated Exposure)	Category 1 (central nervous system, peripheral nervous system)

2. Evaluation of Exposure Route (Refer to III-2 in the Main Document)

The following possible exposure routes determined according to its usage patterns and physiochemical properties.

1) Inhalation Exposure: Inhalation exposure may occur during application.
2) Dermal Exposure: Within the scope of accidental misuse with normal product, there is a possibility of adhering to the hand during use.
3) Oral Exposure: Although the possibility of oral exposure via accidental intake of the product or unintended intake of the substance from adhering to the hands during use exists, it was excluded from the scope of assessment because they are not included in the range of misuse with normal product use.

3. Estimation of Human Exposure (Refer to III-3 in the Main Document)

The following algorithms in Appendix 1 were used to estimate the Amount of human exposure.

(1) Amount of Inhalation Exposure

<Exposure Scenario>

[7] http://www.safe.nite.go.jp/english/ghs_index.html

General-use rubber-based adhesive contains 10 % *n*-hexane. 5 g of this adhesive is used when repairing shoes. For a conservative assessment it was assumed that the work took place in a living room without any extra intentional ventilation (20 m^3, ventilation rate 0.2 times/h) for a period of 15 minutes, and the user stayed in the room repairing the shoes for an additional 60 minutes after that. Assume the frequency of application to be once a month.

<Estimation of Inhalation Exposure Amount>

The following are the values to be used to calculate the Amount of inhalation exposure. Note that they are only assumptions.

Amount of Product Used: Ap	5 g
Weight Fraction: Wr	10 %
Volume of Space: V	20 m^3
Ventilation Rate: N	0.2 times/h
Body Weight: BW	50 kg
Inhalation Rate: Q	0.833 m^3/h
Working Hours: t_a	0.25 h
Staying Time in Room: t_b	1.0 h
Uptake fraction: a	100 %
Mean Number of Event: n	Once/month

Calculate the Amount of Inhalation Exposure by using the formula II-1-6, formula II-1-9, and formula II-1-1 described in Appendix 1 and considering the Frequency of Work per a Year.

Use the formula II-1-6 to calculate the Average Air Concentration (mg/m^3) during work.

Average Air Concentration during work:

$$= \frac{\frac{5{,}000mg \times 0.1 \diagup 0.25h}{0.2/h \times 20m^3} \times \left\{0.25h - \frac{1}{0.2/h} \times \left[1 - \exp\left(-0.2/h \times 0.25h\right)\right]\right\}}{0.25h}$$

$$= 12.29mg/m^3$$

Assign this to the formula II-1-1 to calculate the Amount of Inhalation Exposure while working.

$$\text{Amount of Inhalation Exposure} = \frac{12.29mg/m^3 \times 0.833m^3/h \times 0.25h \times 12 \diagup 365\text{day} \times 1}{50kg}$$

$$= 0.002mg/kg/day$$

Then use the formula II-1-5 to calculate the Air Concentration (mg/m^3) immediately after application has completed.

Air Concentration immediately after application has completed

$$= \frac{5{,}000mg \times 0.1 \diagup 0.25h}{0.2/h \times 20m^3} \times \left[1 - \exp\left(-0.2/h \times 0.25h\right)\right] = 24.39mg/m^3$$

Use this answer in the formula II-1-9 to calculate the Average Air Concentration (mg/m^3) during the stay in the room after work has completed.

Average Air Concentration (mg/m^3) during stay in room after work has completed

$$= \frac{\frac{24.39 mg/m^3}{0.2/h} \times [1 - \exp(-0.2/h \times 1.0h)]}{1.0h} = 22.11 mg/m^3$$

Assign this to the formula II-1-1 to calculate the Amount of Inhalation Exposure during the stay in the room after work has completed.

$$\text{Amount of Inhalation Exposure during stay in room after the work was completed} = \frac{22.11 mg/m^3 \times 0.833 m^3/h \times 1.0h \times 12/365 \text{day} \times 1}{50 kg}$$

$$= 0.012 mg/kg/day$$

Amount of Inhalation Exposure = 0.002 mg/kg/day + 0.012 mg/kg/day = 0.014 mg/kg/day

* For more details on calculating the Amount of exposure refer to Appendix 1 - Chapter II, Chapter III-1-4 “Example General-use adhesive (plastic model adhesive) Chemical substance: acetone”, Chapter III-2-4 “Example 2) Indoor Floor Wax Chemical Substance: Diethylene glocol monoethyl ether” etc.

[Result of Inhalation Exposure Estimation]

Amount of Inhalation Exposure: 0.014 mg/kg/day

(2) Amount of Dermal Exposure

<Exposure Scenario>

General-use rubber-based adhesive contains 10 % *n*-hexane. 5 g of this adhesive is used to repair shoes. Assume that 0.5 % of the volume of product used adheres to the skin. Assume that the Frequency of the Work is once a month.

<Estimation of Dermal Exposure Amount>

The following are the values to be used to calculate the Amount of Dermal Exposure. Note that they are only assumptions.

Amount of Product Used: Ap	5 g
Weight Fraction: Wr	10 %
Body Weight: BW	50 kg
Skin Adhesion Ratio: Md	0.5 %
Uptake fraction: a	100 %
Mean Number of Events: n	Once/month

Use the formula II-2-3 described in Appendix 1, and take the Frequency of the Work per Year into consideration when calculating the Amount of Dermal Exposure.

Use the formula II-2-3 to calculate the Amount of Dermal Exposure.

$$\text{Amount of Dermal Exposure} = \frac{5{,}000mg \times 0.1 \times 0.005 \times {}^{12}\!/_{365}day \times 1}{50kg}$$

$$= 0.002mg/kg/day$$

* For more details on calculating the Amount of exposure refer to Appendix 1 - Chapter II, Chapter III-1-4 “Example General-use adhesive (plastic model adhesive) Chemical substance: acetone”, Chapter III-2-4 “Example 2) Indoor Floor Wax Chemical Substance: Diethylene glocol monoethyl ether” etc.

[Result of Dermal Exposure Estimation]

Amount of Dermal Exposure: 0.002 mg/kg/day

(3) Estimated Human Exposure (EHE)

Since the Estimated Human Exposure (EHE) = Amount of Inhalation Exposure + Amount of Dermal Exposure,

EHE = 0.014 mg/kg/day + 0.002 mg/kg/day = 0.016 mg/kg/day

4. Reference Value used in Risk Assessment (Refer to III-4 in the Main Document)

1) Reproductive Toxicity

For the reproduction and developmental toxicity of *n*-hexane, the “Integrated Risk Information System (IRIS)“[8] used a NOAEL of 200 ppm according to the experiments conducted by Mast et al (1987). Although, Mast used the concentration ranges of 0, 200, 1,000, and 5,000 ppm *n*-hexane, and a statistically reduction in fetal body weights gain in males at 1000 and 5000 ppm n-hexane exposure was observed, the experiments were considered to be inadequate for use in assessment because the next highest dose of NOAEL was 1,000 ppm (EPA, 2005). However the “Environmental Risk Assessment of Chemical Substances”[9]of the Ministry of the Environment (Ministry of the Environment, 2002) used above mentioned NOAEL. The aforementioned 200 ppm (705 mg/m^3) was used as an interim NOAEL for this document. And as this value results in an inhalation dose for 20 hours/day on gestational days (GDs) 6-19, it can be converted to an Estimated Inhalation Intake Amount per day into the interim NOAEL of 436 mg/kg/day. Uncertainty

[8] http://www.epa.gov/iris/subst/0486.htm
[9] http://www.env.go.jp/chemi/report/h14-05/chap01/03/33.pdf

Factors (UFs) were taken to be 100 in consideration to intraspecies and interspecies differences.[10]

Interim NOAEL = 705 mg/m^3 x 0.26 m^3/day x 20 h/24 h/0.35 kg = 436 mg/kg/day

(Inhalation Rate of Rat: 0.26 m^3/day, Weight of Rat: 0.35 kg)

UFs = 10 (intraspecies) × 10 (interspecies) = 100

Reference Value = 436 mg/kg/day／100 = 4.36 mg/kg/day

2) Specific Target Organ/Systemic Toxicity (Repeated Exposure)

For the Specific Target Organ/Systemic Toxicity based on repeated dose of *n*-hexane no reliable oral exposure data could be obtained from the "Environmental Risk Assessment of Chemical Materials" (Ministry of the Environment). For inhalation exposure, the LOAEL of 204 mg/m^3 (headaches, paraesthesia of the extremities, muscle weakness, etc) obtained from human epidemiologic studies was adopted because this value was the minimum reliable value. The Ministry of the Environment set 1 mg/m^3 for NOAEL-like value (2002). This value was obtained by adjusting the above LOAEL to 49 mg/m^3 because of consideration given to the exposure conditions, then divided by 10 because the value is a LOAEL, and then divided by 5 because the number of people was small and the exposure history was uncertain. This value can be converted to an Estimated Inhalation Intake Amount per day of 0.4 mg/kg/day. As the Uncertainty Factors (UFs), when converting from the LOAEL to the NOAEL, were already included[11], the Reference Value will be 0.040 mg/kg/day by considering only the intraspecies differences,.

NOAEL = 1 mg/m^3 x 20 m^3/day/50 kg = 0.4 mg/kg/day

Reference Value = 0.4 mg/kg/day/10 (intraspecies) = 0.040 mg/kg/day

5. Determination of Risk (Refer to III-5 in the Main Document)

In this example the risk was determined by comparing the EHE and Reference Value.

1) Reproduction Toxicity

EHE: 0.016 mg/kg/day, Reference Value: 4.36 mg/kg/day

EHE < Reference Value

From the above labelling is not required.

2) Specific Target Organ/Systemic Toxicity (Repeated Exposure)

EHE: 0.016 mg/kg/day, Reference Value: 0.040 mg/kg/day

EHE < Reference Value

From the above labelling is not required.

[10] Although the "Environmental Risk Assessment of Chemical Materials"(Ministry of the Environment, 2002) documented the above content as part of the hazard assessments a NOAEL value from Repeated Toxicity (LOAEL) is used in the risk assessment and therefore a UF has not been set. Hence the UF here used the one from the report made by Mast et al. (1987) based on the "GUIDANCE ON A CONSUMER PRODUCT RISK ASSESSMENT METHOD FOR GHS LABELLING".

[11] The "Environmental Risk Assessment of Chemical Materials" (Ministry of the Environment, 2002) documented the above content as part of the hazard assessment, and the risk assessment was conducted using the UFs given in the guideline stated by the Ministry of the Environment. This document uses the UFs stated by the Ministry of the Environment without any modification.

6. Conclusion (Labelling)

Carcinogenicity	Labelling is not required (not enough information available for classification)
Reproductive Toxicity	Labelling is not required (from risk assessment)
Specific Target Organ/Systemic Toxicity (Repeated Exposure)	Labelling is not required (from risk assessment)

* In this assessment example, the necessity for labelling of any other hazard than stated above is not referred.

Example of Risk Assessment No. 4: Ethanol in hand dishwashing detergent

This risk assessment concerns the ethanol in hand dishwashing detergent.

Ethanol

CAS Registration No.: 64-17-5

Product/Usage Information

1) Product Composition: hand dishwashing detergent containing 5% ethanol.
2) Usage Information: Used after every meal. The possibility of the product being used with bare hands is assumed.

1. Classification of Reproduction Toxicity in Ethanol based on the Hazard (Refer to III-1 in the Main Document)

The following classifications were conducted using examples from the "GHS Classification Result Database"[12].

Reproductive Toxicity	Category 1A (possibly adversely affects sexual functionality or fertility)

2. Evaluation of Exposure Route (Refer to III-2 in the Main Document)

The following possible exposure routes were determined according to its usage patterns and physiochemical properties.

1) Inhalation Exposure: Not Assumed
2) Dermal Exposure: Dermal exposure could occur when handwashing the dishes using hand dishwashing detergent.
3) Oral Exposure: Oral exposure could occur from the contact between food and the hand dishwashing detergent remaining on dishes, or indirect exposure could occur if vegetables and/or fruit are washed with hand dishwashing detergent and some of the liquid remains on the vegetables or fruit.

3. Estimation of Human Exposure (Refer to III-3 in the Main Document)

(1) Amount of Dermal Exposure

<Exposure Scenario>

Assume dermal exposure from handwashing dishes using hand dishwashing detergent. Assume the frequency of dishwashing to be 3 times a day (45 minutes/wash).

<Estimation of Dermal Exposure Amount>

The following are the values to be used to calculate the Amount of Dermal Exposure. Note that they are only assumptions.

[12] http://www.safe.nite.go.jp/english/ghs_index.html

Weight Fraction: Wr	5 %
Exposed Body Area: Sp	1,980 cm^2
Concentration of Product	100 mg/cm^3
Dermal Absorption Rate: MI	0.8 x 0^{-3} cm/h
Exposure Time: t	0.75 hour/wash
Frequency of Use: n	3 times/day
Body Weight: BW	50 kg
Uptake fraction: a	100 %

Use the formula II-2-2 described in Appendix 1 to calculate the Amount of Dermal Exposure.

The unit of MI in the above-mentioned column is different from that in the formula II-2-2, and it is necessary to convert into the same unit. Using the concentration of ethanol (Concentration of Product and Weight Fraction of Ethanol), MI results in 4.0 x 10^{-3} $mg/cm^{2/}h$.

$$\text{Amount of Dermal Exposure} = \frac{1980cm^2 \times 4.0 \times 10^{-3} mg/cm^2/h \times 0.75h \times 3/day}{50kg}$$

$$= 0.356mg/kg/day$$

* For more details on calculating the Amount of exposure refer to Chapter II and Chapter III-3-4 “Hand Dishwashing Detergent Chemical Substance: Ethanol” etc described in Appendix 1.

[Result of Dermal Exposure Estimation]

Amount of Dermal Exposure: 0.356 mg/kg/day

(2) Amount of Oral Exposure

<Exposure Scenario>

Consider the Amount of Oral Exposure through dishes. Oral exposure through dishes is caused by the transfer of washing liquid remaining on the dishes to food and that food then being eaten. In addition, it can also occur through washing vegetables or fruit using hand dishwashing detergent and the liquid remaining on the vegetables or fruit.

<Estimation of Oral Exposure Amount>

The following are the values to be used to calculate the Amount of oral exposure. Note that they are only assumptions.

Weight Fraction of Ethanol: Wr	5 %
Concentration of Product in Remained Liquid on Dishes	0.8 mg/cm^3
Residual Fluid Amount on the Dish Surface	5.5 x 10^{-5} cm^3/cm^2
Contact Area of Food and Dish: Sf	5,400 cm^2/day
Transition Rate from Dish to Food: Mfd	100 %
Body Weight: BW	50 kg
Residual Amount of Detergent in Vegetable: Cf_1	0.0014 mg/g
Intake Amount of Vegetable: Wf_1	263 g/day
Residual Amount of Detergent in Fruit: Cf_2	0.00024 mg/g
Intake Amount of Fruit: Wf_2	256 g/day
Uptake fraction: a	100 %

Use the formula II-3-2 and formula II-3-3 described in Appendix 1 to calculate the Amount of Oral Exposure.

Use the formula II-3-3 to calculate the Amount of Oral Exposure from ethanol in the detergent solution remaining on the dishes. The Residual Amount of Detergent on the Dish Surface per day Cd (mg/day) will be 1.188 x 10^2 mg/day when calculating using the Concentration of Product in Remained Liquid on Dishes, Weight Fraction of Ethanol, Residual Fluid Amount on the Dish Surface and Contact Area of Food and Dish.

$$\text{Amount of Oral Exposure from ethanol in cleaning substance remained on the dishes} = \frac{1.188\times10^{-2}\,mg/day\times1\times1}{50kg}$$

$$= 2.38\times10^{-4}\,mg/kg/day$$

Use the formula II-3-2 to calculate the Amount of Oral Exposure of ethanol in the cleaning substance remaining on vegetables.

$$\text{Amount of Oral Exposure of ethanol in the cleaning substance remained on vegetable} = \frac{0.0014mg/g\times263g/day\times1}{50kg}$$

$$= 7.36\times10^{-3}\,mg/kg/day$$

Use the formula II-3-2 to calculate the Amount of Oral Exposure of ethanol in the cleaning substance remaining on fruit.

$$\text{Amount of Oral Exposure of Ethanol in the cleaning substance remained on fruit} = \frac{0.00024 mg/g \times 256 g/day \times 1}{50 kg}$$

$$= 1.23 \times 10^{-3} mg/kg/day$$

* For more details on calculating the Amount of exposure refer to Appendix 1 - Chapter II and Chapter III-3-4 "Hand Dishwashing Detergent Chemical Substance: Ethanol" etc.

[Result of Oral Exposure Estimation]

Amount of Exposure through dishes: 2.38×10^{-4} mg/kg/day

Amount of Exposure through vegetables: 7.36×10^{-3} mg/kg/day

Amount of Exposure through fruit: 1.23×10^{-3} mg/kg/day

Amount of Oral Exposure: 2.38×10^{-4} mg/kg/day + 7.36×10^{-3} mg/kg/day + 1.23×10^{-3} mg/kg/day

= 0.009 mg/kg/day

(3) Estimated Human Exposure (EHE)

Since the Estimated Human Exposure (EHE) = Amount of Dermal Exposure + Amount of Oral Exposure,

EHE = 0.356 mg/kg/day + 0.009 mg/kg/day = 0.365 mg/kg/day

4. Reference Value used in Risk Assessment (Refer to III-4 in the Main Document)

As ethanol has no official ADI (Acceptable Daily Intake) or TDI (Tolerable Daily Intake) stated by public organizations such as JECFA (FAO/WHO Joint Expert Committee on Food Additives), the Assessment Reference Values are caluculated here using the data extracted from reliable review documents such as OECD-SIDS, and IARC[13].

1) Reference Value of Reproductive Toxicity from Animal Experiments[14]

The lowest value confirmed as a NOAEL (No Observed Adverse Effect Level) for ethanol with the fertility of the rat is 2,000 mg/kg/day. In consideration of intraspecies and interspecies differences, Assessment Reference Value will be 20 mg/kg/day.

NOAEL = 2,000 mg/kg/day

UFs = 10 (intraspecies) × 10 (interspecies) = 100

Reference Value = 2g/kg/day/100 = 20 mg/kg/day

2) Reference Value of Reproductive Toxicity from Human Data[15]

A value of 28.5 ml/day (if that weight is converted using the specific gravity of 0.789 it is equivalent to 22.49 g/day) was reported as the threshold value for alcohol intake during pregnancy that can affect fetuses or new born babies. This value is equivalent to the LOAEL, and the Reference Value will be 4.05 mg/kg/day in consideration of intraspecies differences.

[13] The 4.05mg/kg/day used in this document was also extracted as the recommended value for the maximum limit of alcohol intake for pregnant woman recommended in the "Human Developmental Toxicants", The US Department of Health, Education and Welfare (currently the U.S. HHS).

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

[15] Affects of alcohol in pregnancy, Med J Aust. (1980). Vol.2 No.1.

NOAEL = 22,490 mg/day/10 (applying the LOAEL)/55.5 kg = 40.5 mg/kg/day

(Weight of Japanese pregnant woman: 55.5 kg)

Reference Value = 40.5 mg/kg/day/10 (intraspecies) = 4.05 mg/kg/day

The “Reference Value of Reproduction Toxicity from Human Data” is used in this assessment example.

5. Determination of Risk (Refer to III-5 in the Main Document)

In this example the risk was determined by comparing the EHE and Assessment Reference Value.

EHE = 0.365 mg/kg/day

Reference Value for Reproductive Toxicity: 4.05 mg/kg/day

Reproductive Toxicity: EHE < Assessment Reference Value

From the above labelling is not required.

6. Conclusion (Labelling)

Reproductive Toxicity	Labeling is not required (from risk assessment)

* In this assessment example, the necessity for labelling of any other hazard than stated above is not referred.

Example of Risk Assessment No. 5: Linalool in air freshener (oil-based)

This risk assessment concerns linalool in air freshener (oil type).

Linalool

CAS Registration No.: 78-70-6

Product/Usage Information

1) Product Information: Oil based indoor air freshener. Product amount used is 100 g with the product containing 5.4% Linalool.
2) Usage Information: Set in rooms with a usage period of 2 months.

1. Classification of Linalool based on the Hazard (Refer to III-1 in the Main Document)

The classification from the Air Fresheners & Deodorizers Conference[16] was used as reference.

Carcinogenicity	Not classified
Reproductive Toxicity	Category 2 (possibly adversely affects sexual functionality or fertility)
Specific Target Organ/Systemic Toxicity (Repeated Exposure)	Not classified

2. Evaluation of Exposure Route (Refer to III-2 in the Main Document)

The following possible exposure routes were considered according to its usage patterns and physiochemical properties.

1) Inhalation Exposure: Inhalation exposure may occur in living rooms.
2) Dermal Exposure: Exposure could occur by touching the product with the bare hands when setting the product in place.
3) Oral Exposure: Although the possibility of oral exposure exists via accidental intake, it does not fall within the scope of this assessment because it is not included in the range of possible misuse.

3. Estimation of Human Exposure (Refer the III-3 in the Main Document)

The following algorithms in Appendix 1 were used to estimate the Amount of Human Exposure.

(1) Amount of Inhalation Exposure

<Exposure Scenario>

Assume that a 100g unit of indoor air freshener containing 5.4% linalool is used in a living room. Assume that the user stays in the living room (20 m^3, ventilation rate of 0.2 times/h) for 20 hours a day. Product-life of Indoor air freshener is usually 2 months, however, assume that it will be one month in conducting a conservative assessment.

[16] The Air Fresheners & Deodorizers Conference conducted the classification based on the "OECD SIDS Initial Assessment Report" (OECD, 2002) (http://www.chem.unep.ch/irptc/sids/OECDSIDS/78706.pdf).

<Estimation of Inhalation Exposure Amount>

The following are the values to be used to calculate the Amount of Inhalation Exposure. Note that they are only assumptions.

Volume of Space: V	20 m^3
Ventilation Rate: N	0.2 times/h
Body Weight: BW	50 kg
Inhalation Rate: Q	0.833 m^3/h
Staying Time: t	20.0 h
Emission Rate: G	7.5 mg/h/unit (00 g×5.4 %/1 month/unit)
Uptake fraction: a	100 %

Use the formula II-1-10 and formula II-1-1 described in Appendix 1 to calculate the Amount of Inhalation Exposure.

Use the formula II-1-10 to calculate the Average Air Concentration (mg/m^3) in the room.

$$\text{Average Air Concentration in the room} = \frac{7.5mg/h}{0.2/h \times 20m^3} = 1.88mg/m^3$$

Use the answer in the formula II-1-1 to calculate the Amount of Inhalation Exposure.

$$\text{Amount of Inhalation Exposure} = \frac{1.88mg/m^3 \times 0.833m^3/h \times 20.0h/day \times 1}{50kg}$$

$$= 0.626mg/kg/day$$

* For more details on calculating the Amount of exposure refer to Appendix 1 - Chapter II, Chapter III-5-4 “Example Air freshener for vehicle Chemical substance: d-limonene”, Chapter III-4-4 “Example 2) Electric vaporizer type repellent Chemical substance: Metofluthrin” etc.

[Result of Inhalation Exposure Estimation]

Amount of Inhalation Exposure: 0.626 mg/kg/day

(2) Estimated Human Exposure (EHE)

Since the Total Amount of Exposure (EHE) = Amount of Inhalation Exposure,

EHE = 0.626 mg/kg/day

4. NOAEL and UFs used in Risk Assessment (Refer to III-4 in the Main Document)

1) Reproductive Toxicity

For the reproductive and developmental toxicity of linalool, the “OECD SIDS Initial Assessment Report” (OECD, 2002) stated a NOAEL for oral doses of 365 mg/kg/day based on the decrease litter size at birth and pup morbidity/mortality. As a NOAEL value for the inhalation route was not

obtained, use the oral dose NOAEL.

UFs = 10 (intraspecies) × 10 (interspecies) = 100

5. Determination of Risk (Refer to III-5 in the Main Document)

In this example the risk was determined by comparing the MOE and UFs.

1) Reproductive Toxicity

NOAEL: 365 mg/kg/day, EHE: 0.626 mg/kg/day

MOE = NOAEL/EHE = 365/0.626 = 580

UFs: 100

MOE > UFs

From the above labelling is not required.

6. Conclusion (Labelling)

Carcinogenicity	Labelling is not required (from hazard assessment)
Reproduction Toxicity	Labelling is not required (from risk assessment)
Specific Target Organ/Systemic Toxicity (Repeated Exposure)	Labelling is not required (from hazard assessment)

* In this assessment example, the necessity for labelling of any other hazard than stated above is not referred.