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Lead substances selection using GHS approach for the classification of mixtures: Case study of painting in the work environment

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ABSTRACT

We developed a lead substances selection approach based on the concept of mixture classification of UN GHS for the purpose of efficient risk assessment of mixtures consisting of multiple components. Lead substances selection methods are being actively developed in Europe, but these methods are predicated on the regulations and information sources available within Europe and are therefore not readily applicable to countries outside Europe. In this study, the features of the GHS-based approach and the risk assessment results for outdoor painting work as a specific utilization example of the GHS-based approach were described. Comparison with the DPD + method and the CCA method proposed in Europe revealed that the GHS-based approach resulted in the selection of the safest lead substances. The GHS method, like the DPD + method, is a classification-based approach. We believe that a classification-based approach based on the GHS method can be an appropriate tool to efficiently implement risk assessment of mixtures for countries outside Europe. Some tools for business operators to conduct the management of chemicals using the GHS classification have been established in Japan. We plan to propose the GHS-based approach as a standardized assessment tool.

1. Introduction

At the 2002 World Summit on Sustainable Development held in Johannesburg, with the objective of proper management of chemicals, an international agreement was reached to “use and produce chemicals in ways that minimize significant adverse effects on human health and the environment.” In order to achieve this goal, in 2006, the International Council of Chemical Associations (ICCA) vowed to implement the Responsible Care Global Charter and the Global Product Strategy (GPS) (ICCA, 2016). In response to this announcement, in 2009, the Japan Chemical Industry Association (JCIA) commenced the Japan Initiative of Product Stewardship (JIPS), inaugurated the Evaluation Technology Working Group, and began to promote new voluntary chemicals management initiatives. One of the initiatives is the issuance of the JIPS Risk Assessment Guidance (JCIA, 2011). The Guidance, which consists of the Japanese translation of the ICCA Guidance on Chemical Assessment 2nd Edition and case studies conducted by JCIA, is serving as a guidebook for Japanese business operators engaged in GPS/JIPS activities to carry out risk assessment. However, the Guidance mainly describes risk assessment methods that are focused on chemicals consisting of a single substance, and many requests for risk assessment guidance for mixtures have arisen, mainly from business operators dealing with products consisting of

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mixtures. On a global basis, while various mixture risk assessment methods have been proposed for individual countries and regions or for specific sectors (e.g., agricultural chemicals), there currently is no harmonized, globally accepted risk assessment method (Feron et al., 1995; Feron and Groten, 2002; Groten, 2000; Meek et al., 2011; Money et al., 2011; Ökopol, 2012; Reffstrup et al., 2010; Teuschler, 2007; Wilkinson et al., 2000). Additionally, there have been ongoing debates on hazard interaction among components of chemical mixtures and the handling of mode of action (Feron et al., 1995; Feron and Groten, 2002; Groten, 2000; Wilkinson et al., 2000).

Lately, in Europe, so-called "lead substance is selected" methods have been actively developed and proposed, where subjects of risk assessment are narrowed down to substances with high hazard or content for the purpose of efficiently assessing mixtures consisting of multiple materials (CEFIC, 2009, 2010; ECHA, 2008). While the Dangerous Preparations Directive (DPD+) method or the Critical Component Approach (CCA) method proposed in Europe are particularly useful for business operators to efficiently carry out risk assessment or to determine risk management measures, they are predicated on regulations and information sources available within Europe (e.g., R phrase concentration limits, Derived No-Effect Level (DNEL)) and are not readily applicable to countries outside Europe. In light of this, we have developed a risk assessment method for mixtures by applying the mixture classification concept of the United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (United Nations, 2015) to the selection of lead substances. This report describes the features of the GHS-based approach, risk assessment results for outdoor painting work as a specific utilization example of the GHS-based approach, and results of comparisons with the DPD + method and the CCA method.

2. A brief review of selection of lead substance for mixture risk assessment

2.1. DPD + method

The DPD + method is used to select lead substances based on the former classification results in Europe and the content of components (CEFIC, 2009, 2010). The Lead Substance Index (LSI), an index for selecting lead substances, is calculated for each exposure route of inhalation, dermal, oral, local effect, and aquatic environment. The equation for calculating LSI is shown below, where Ci is the concentration of component i in the mixture, and CLi the R phrase concentration limit of component i in the mixture (EC, 1999). For inhalation exposure, the vapor pressure (VP) of each component is also taken into account.

$$\mathrm{LSI}_{\text{inhalation}} = \mathrm{Vp_i} \times \mathrm{C_i} / \mathrm{CL_i}$$

$$\mathrm{LSI}_{\text{dermal, oral, local effect, aquatic environment}} = \mathrm{C_i} / \mathrm{CL_i}$$

where Vp_i: vapor pressure of component i in the mixture (25 °C)

C_i: concentration of component i in the mixture.

CL_i: R phrase concentration limit of component i in the mixture.

The substance with the highest LSI is selected as the lead substance for each hazard endpoint. However, if the difference in LSI between the substance with the highest LSI and the substance with the second highest LSI is less than 10%, the substance with the second highest LSI is also selected as a lead substance, resulting in multiple substances selected as lead substances. Substances that fall under Category 1 or Category 2 in respiratory sensitization, carcinogenicity, mutagenicity or reproductive toxicity under the Dangerous Substances Directive (EEC, 1967), as well as PBT/vPvB substances, are always selected as lead substances.

2.2. CCA method

The CCA method was first introduced in the draft guidance documents prepared by the REACH Implementation Project 3.5, and was detailed in the Guidance for downstream users 2008 Edition by the European Chemicals Agency (ECHA, 2008). This is a method to select lead substances (called "Critical Component" in this method) from all components of mixture based on DNEL and Predicted No-Effect Concentration (PNEC). The Risk Determining Substance Score (RDSs), a score of substance requiring determination of risk, is calculated for each exposure route of inhalation, oral and dermal. For inhalation, the vapor pressure is included as a parameter as it greatly affects the exposure amount. The equation for calculating RDSs is:

$$\mathrm{RDSs}_{\text{inhalation}} = \mathrm{Vp_i} \times \mathrm{C_i} / \mathrm{DNEL}_{\text{inhalation}}$$

$$\mathrm{RDSs}_{\text{oral, dermal, aquatic environment}} = \mathrm{C_i} / \mathrm{DNEL_i}\ (\mathrm{PNEC_i}\ \text{for aquatic environment})$$

where Vp_i: vapor pressure of component i in the mixture (20/25 °C)

C_i: concentration of component i in the mixture.

$DNEL_i$, $PNEC_i$: DNEL, PNEC of component i in the mixture.

The substance with the highest RDSs is selected as the lead substance for each hazard endpoint. On selecting lead components, this method is predicated on calculation of the RDSs of all components in a mixture by obtaining their DNELs or PNECs.

3. GHS-based approach for selection of lead substance

3.1. GHS-based approach

The GHS-based approach is a method to select components that contribute to GHS classification of a mixture as lead substances. The GHS classification of a mixture is, as shown by the GHS classification criteria for mixtures in the UN GHS document, determined by the GHS classification and concentration of its components (United Nations, 2015). As an example, the GHS-based lead substance selection for mixtures with skin irritation or specific target organ toxicity is shown in Table 1. For skin corrosion/irritation, the concentrations of components in the same category are summed and the GHS classification of the mixture is determined by the total concentration. In Table 1, the total concentration of components falling under Category 1 exceeds the criteria (5%), and the mixture is classified under Category 1 for skin corrosion/irritation. Components A and B satisfy this criteria, and are selected as lead substances. These lead substances are responsible for local effects through the dermal route. For specific target organ toxicity (Category 1 or Category 2), the GHS classification of the mixture is determined based on the GHS classifications and concentrations of components whose concentrations are higher than the threshold concentration. In Table 1, components A and B are such components, and each enables the determination of the GHS classification of the mixture regardless of other components. Therefore, components A and B are selected as lead substances. These lead substances are responsible for systemic effects through the inhalation route.

3.2. Mixture risk assessment by lead substances

Selecting lead substances makes mixture risk assessment much more efficient. As shown in Fig. 1, similar to the process of risk assessment for single-substance chemicals, mixture risk assessment is carried out based on the following process: (1) Information gathering, (2) Hazard characterization, (3) Exposure assessment, (4) Risk characterization, and (5) Risk management measures. In

Table 1
GHS classification of the mixture and selection of the lead substances.

(1) Skin corrosion/irritation

Component	GHS classification	Content (%)	Corrected content (%)	Contribution to classifying mixture	Lead substance
A	Category 1	5	55	Yes	Yes
B	Category 1	50		Yes	Yes
C	Not classified	45	—	No	No

Criteria for classification: Σ (Category 1 Content) ≧5%

Type of exposure				
Systemic		Local		Others
Short term	Long term	Dermal	Eye	
		√		
		√		

(2) Specific target organ toxicity - Repeated exposure

Component	GHS classification	Content (%)	Contribution to classifying mixture	Lead substance
A	Category 1 (nervous system)	0.5	No	No
B	Category 1 (nervous system)	13.5	Yes	Yes
C	Not classified	86.0	No	No

Criteria for classification: Σ (Category 1 Content) ≧10%

Type of exposure				
Systemic		Local		Others
Short term	Long term	Dermal	Eye	
	√			

"(1) Information gathering," information is gathered on the exposure scenario, determination of exposure route, amount of use, etc., as well as on the physicochemical properties of components, the toxicity, and the existence of inter-component interaction. In "(2) Hazard characterization," lead substances are selected in accordance with a certain rule, and the hazard indices of lead substances for the identified route of exposure (e.g., Occupational Exposure Limit (OEL), DNEL) are determined. In "(3) Exposure assessment," exposure scenarios are established, and the estimated exposure concentration of the lead substance is calculated. In "(4) Risk characterization," risk assessment is carried out for each lead substance and the mixture using risk assessment indices, including Risk Characterization Ratio (RCR), and the risk is characterized. In "(5) Risk management measures," management measures for reducing the risk are implemented as necessary, based on the result of (4) above. The underlined sections in Fig. 1 are requirements specific to mixtures, namely, existence of inter-component interaction, selection of lead substance in accordance with a certain rule, and mixture risk characterization (RCR_{Total}).

4. Case study: mixture risk assessment by GHS-based approach

This section describes a case study of lead substance selected from a mixture using the GHS-based approach followed by exposure and risk assessment. The subjects of assessment were workers who handle urethane resin paints. The European Center for Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment (ECETOC TRA) version 3.1 worker exposure model was used for the exposure and risk assessment (ECETOC, 2009, 2012).

4.1. Chemicals

The paint used for this case study was a two-component

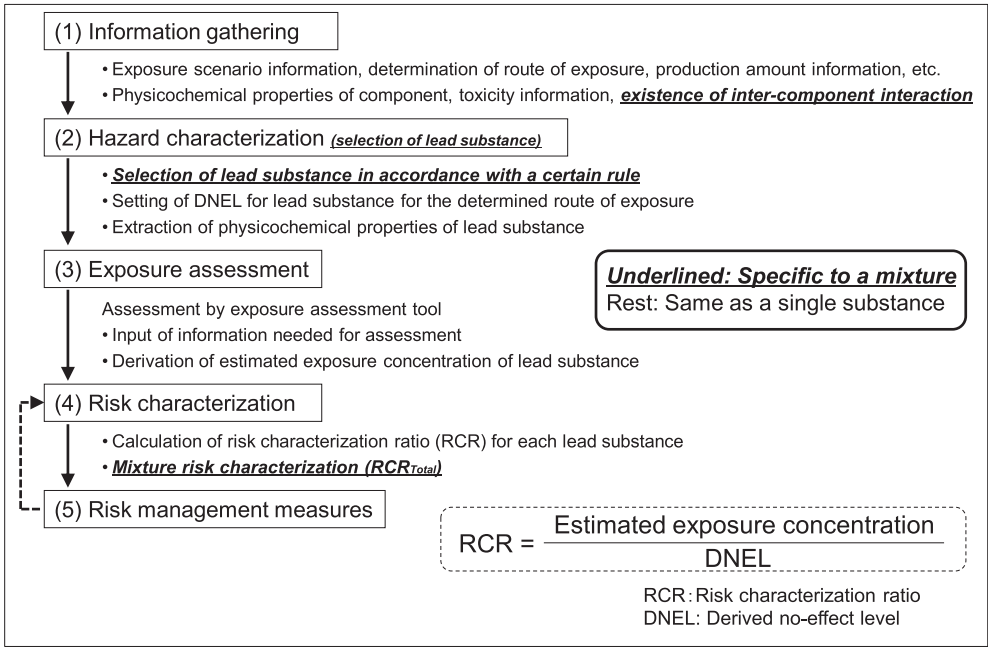

Fig. 1. Mixture risk assessment process.

reaction type acrylic urethane paint, where a main agent and a curing agent are mixed immediately before use and dried hard under normal temperatures. The main agent consists of an acrylic resin (solid), titanium dioxide, toluene, butyl acetate, ethyl acetate, methyl isobutyl ketone, ethylene glycol monoethyl ether acetate, additives, and others. The curing agent consists of hexamethylene diisocyanate trimer, hexamethylene diisocyanate, toluene, butyl acetate, ethyl acetate, and others. The main agent and the curing agent are mixed at a ratio of 9 to 1. The subject components of this assessment and the resulting contents after mixing the main agent and the curing agent are summarized in Table 2. Although the paint contains acrylic resin, titanium dioxide and other additives, they were excluded from the risk assessment because no direct exposure to these components is expected to occur considering the characteristics and the use of the product.

4.2. Exposure scenario

Based on interviews of relevant industry associations in Japan, as shown in Fig. 2, a typical situation for workers handling a urethane resin paint is to mix two solutions for about 10 min at an outdoor painting work site (not manual mixing), transfer the mixture to a smaller container for painting from a larger container for mixing, perform painting work all day, and finish the work by washing the equipment (e.g., brushes) and containers used. Therefore, exposure scenarios were set as Mix, Transfer, Paint and Wash.

4.3. Hazard assessment

4.3.1. Hazard information investigation

The result of GHS classification of components needed for selection of lead substances was sourced from the information obtained and disclosed by the Japanese government (NITE, 2016). Other necessary information, including physicochemical properties, was sourced from existing, publicly available information.

4.3.2. Selection of lead substance by GHS classification

The results of selection of lead substance by GHS classification for six components are shown in Table 3. Lead substances that contributed to mixture classification and required risk assessment were: butyl acetate and methyl isobutyl ketone for acute toxicity (inhalation: vapor); butyl acetate for acute toxicity (inhalation: dust, mist); butyl acetate and methyl isobutyl ketone for eye irritation; toluene and 2-ethoxyethyl acetate for reproductive toxicity; methyl isobutyl ketone for carcinogenicity; toluene, butyl acetate, ethyl acetate, methyl isobutyl ketone and 2-ethoxyethyl acetate for specific target organ toxicity (single exposure); and methyl isobutyl ketone for specific target organ toxicity (repeated exposure). The selection results are summarized in Table 4. Based on adverse health effects through the inhalation route, five components, namely, butyl acetate, methyl isobutyl ketone, toluene, ethyl acetate and 2-ethoxyethyl acetate, were selected as the lead substances. For the selected five components, hazard characterization, exposure assessment, risk characterization and risk management measures were carried out in accordance with Fig. 1. Regarding eye irritation, the risk management measure taken was a warning about local effects. Effects of inhalation route, carcinogenicity, and reproductive toxicity are described in the next section.

4.3.3. Occupational exposure limit

The short term and long term hazard assessment values needed for exposure and risk assessments of the five components above using ECETOC TRA were selected from the allowable inhalation concentrations available in Japan and overseas. The allowable inhalation concentrations stipulated by the Japan Society for Occupational Health, American Conference of Governmental Industrial Hygienists (ACGIH), European Agency for Safety and Health at Work (EU-OSHA), Germany, and the United Kingdom Health and Safety Executive (HSE) are shown in Table 5 (EU, 2000, 2006, 2009; DFG, 2012; JSOH, 2015; U.K. HSE, 2005; U.S. ACGIH, 2016). For this assessment, the lowest value was adopted among the gathered allowable inhalation concentrations. The short term hazard assessment values of butyl acetate, methyl isobutyl ketone, toluene, ethyl acetate and 2-ethoxyethyl acetate were 950, 166, 384, 1460 and 88 mg/m^3, respectively, while the long term hazard assessment values were 475, 82, 75, 720 and 11 mg/m^3, respectively. As shown in Table 4, toluene and 2-ethoxyethyl acetate were selected as lead substances as they respectively fall under Category 1A and Category 1B for reproductive toxicity, and methyl isobutyl ketone was selected because it falls under Category 2 for carcinogenicity. However, the reproductive toxicities of toluene and 2-ethoxyethyl acetate were taken into account for setting the allowable concentration (U.S. ACGIH, 2001; 2007), and they were therefore judged to not require individual assessment. The carcinogenicity of methyl isobutyl ketone was not included in this assessment because IARC classified it under Group 2B (IARC, 2012), while ACGIH judged that there was no clear evidence of carcinogenicity to humans (U.S. ACGIH, 2010).

4.4. Exposure assessment

Exposure assessment was conducted only by taking into account the inhalation exposure of workers. For the five lead substances selected by the GHS-based approach, ECETOC TRA input parameters were determined, and the maximum exposure concentrations and estimated exposure concentrations were calculated based on Section 4.2 Exposure Scenario. The ECETOC TRA input parameters are summarized in Table 6. The estimated exposure concentrations are shown in Table 7.

4.5. Risk characterization

The risk of the components was assessed by determining the RCR for each component, and it was judged that the “risk is managed” when the RCR was less than one. The RCR of each

Table 2
Components in this study.

Components[a]	CAS No.	Molecular weight	Content (%)
Butyl acetate	123-86-4	116.2	19.2
Methyl isobutyl ketone	108-10-1	100.2	13.5
Toluene	108-88-3	92.1	8.2
Ethyl acetate	141-78-6	88.1	5.5
Hexamethylene diisocyanate trimer	3779-63-3	504.6	4.95
2-Ethoxyethyl acetate	111-15-9	132.2	1.8
Hexamethylene diisocyanate	822-06-0	168.2	0.05

[a] Alkali resin, titanium oxide and other additives were excluded, since it is assumed from their product characteristics and applications that there is no direct exposure to these substance.

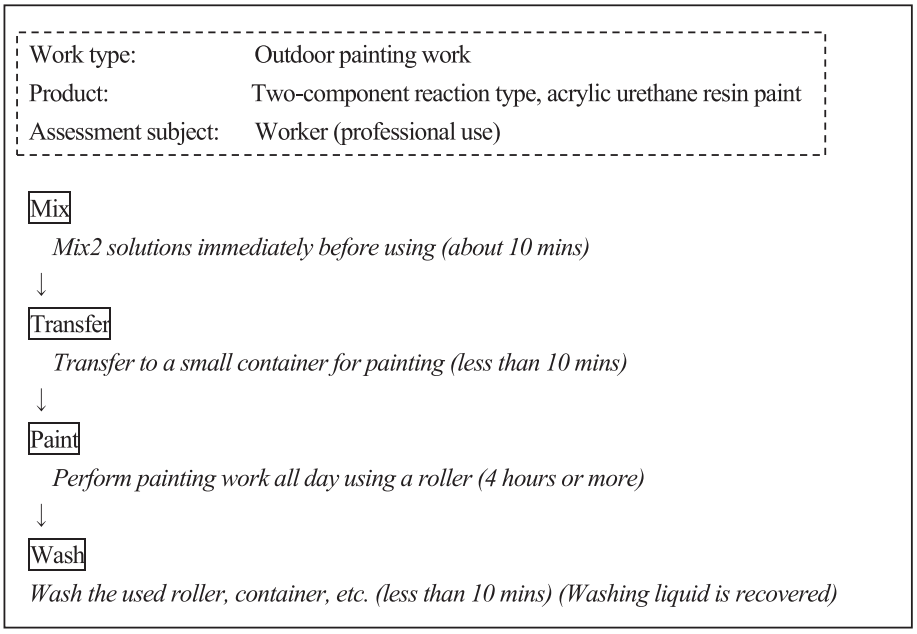

Fig. 2. Exposure scenario.

Table 3
Selection of lead substance by GHS classification.

Hazard class		Component	GHS classification	Content (%)	Contribution to classifying mixture	Lead substance	Type of exposure: Systemic – Short term	Systemic – Long term	Local – Dermal	Local – Eye	Others
Acute toxicity	Oral	Hexamethylene diisocyanate	4	0.05	—	—					
	Dermal	Hexamethylene diisocyanate	3	0.05	No	No					
	Inhalation: vapors	Hexamethylene diisocyanate	1	0.05	No	No					
		Butyl acetate	3	19.2	Yes	Yes	√				
		Methyl isobutyl ketone	3	13.5	Yes	Yes	√				
		Toluene	4	8.2	No	No					
		Ethyl acetate	4	5.5	No	No					
		2-Ethoxyethyl acetate	4	1.8	No	No					
	Inhalation: dusts and mists	Butyl acetate	3	19.2	Yes	Yes	√				
Skin corrosion/irritation		Toluene	2	8.2	Yes	Yes			√		
Serious eye damage/eye irritation		Butyl acetate	2 [1)]	19.2	Yes	Yes				√	
		Methyl isobutyl ketone	2 [1)]	13.5	Yes	Yes					
		Toluene	2 [1)]	8.2	No	No					
		Ethyl acetate	2 [1)]	5.5	No	No					
		2-Ethoxyethyl acetate	2 [1)]	1.8	No	No					
Respiratory sensitization		Hexamethylene diisocyanate	1	0.05	No	No					√
Skin sensitization		Hexamethylene diisocyanate	1	0.05	No	No					√
Reproductive toxicity		Toluene	1A	8.2	Yes	Yes					√
		2-Ethoxyethyl acetate	1B	1.8	Yes	Yes					
Carcinogenicity		Methyl isobutyl ketone	2	13.5	Yes	Yes					
Specific target organ toxicity - Single exposure		Toluene	1	8.2	No	No					
		Hexamethylene diisocyanate	1	0.05	No	No					
		Butyl acetate	2	19.2	Yes	Yes	√				
		Methyl isobutyl ketone	3	13.5	Yes	Yes	√				
		Toluene	3	8.2	Yes	Yes	√				
		Ethyl acetate	3	5.5	Yes	Yes	√				
		2-Ethoxyethyl acetate	3	1.8	Yes	Yes		√			
Specific target organ toxicity - Repeated exposure		Methyl isobutyl ketone	1	13.5	Yes	Yes					
		Toluene	1	8.2	No	No					
		Hexamethylene diisocyanate	1	0.05	No	No					
Aspiration hazard		Toluene	1	8.2	No	No					

1) Although it was described as "2B" in the source, it was handled as "2" in this study.

component obtained using ECETOC TRA is summarized in Table 8. For each exposure scenario of "Mix", "Transfer", "Paint" and "Wash", the RCRs of butyl acetate, methyl isobutyl ketone, toluene, ethyl acetate and 2-ethoxyethyl acetate were in the range of 0.018–0.21 for short term exposure, which is less than one, and it was judged that the "risk is managed". For long term exposure, the

Table 4
Selection of lead substance by GHS classification (summary).

Components	Content (%)	Route of exposure					Lead substance
		Systemic		Local		Others	
		Short term	Long term	Dermal	Eye		
Butyl acetate	19.2	✓			✓		Inhalation, Eye irritation
Methyl isobutyl ketone	13.5	✓	✓		✓	✓	Inhalation, Eye irritation, Carcinogenicity
Toluene	8.2	✓				✓	Inhalation, Reproductive toxicity
Ethyl acetate	5.5	✓					Inhalation
Hexamethylene diisocyanate trimer	4.95						
2-Ethoxyethyl acetate	1.8	✓				✓	Inhalation, Reproductive toxicity
Hexamethylene diisocyanate	0.05						

Table 5
Occupational exposure limits in this study.

	Component	Occupational exposure limits (mg/m^3)[a]				
		Japan	ACGIH	Germany	United Kingdom	This study
Short term exposure	Butyl acetate	–	950	960	966	950
	Methyl isobutyl ketone	–	307	166	416	166
	Toluene	–	–	760	384	384
	Ethyl acetate	–	–	3000	1460	1460
	2-Ehoxyethyl acetate	–	–	88	–	88
Long term exposure	Butyl acetate	475	710	480	724	475
	Methyl isobutyl ketone	200	82	83	208	82
	Toluene	188	75	190	191	75
	Ethyl acetate	720	1400	1500	730	720
	2-Ehoxyethyl acetate	27	27	11	55	11

[a] U.S. ACGIH, 2016; EU, 2000; 2006; 2009; U.K. HSE, 2005; DFG, 2012; JSOH, 2015.

RCRs of butyl acetate, methyl isobutyl ketone, toluene, ethyl acetate and 2-ethoxyethyl acetate were in the range of 0.0011–0.11, which is less than one, and it was judged that the "risk is managed".

The risk of the mixture was assessed by summing the RCRs of each component, RCR_{Total} although ACGIH does not recommend dose additivity when the endpoints of mixture components are different. However an evaluation using an additive model was performed since the lead substances selected in this study are all volatile organic compounds and the endpoints would be similar. Similar to the risk assessment of individual components, it was judged that the "risk is managed" when the RCR_{Total} was less than one. The RCR_{Total} is summarized in Table 8. For each exposure scenario of "Mix", "Transfer", "Paint" and "Wash", the $RCRs_{Total}$ of butyl acetate, methyl isobutyl ketone, toluene, ethyl acetate and 2-ethoxyethyl acetate were in the range of 0.37–0.40 for short term exposure, which was less than one, and it was judged that the "risk is managed". For long term exposure, the $RCRs_{Total}$ of toluene, butyl acetate, ethyl acetate, methyl isobutyl ketone and 2-ethoxyethyl acetate were in the range of 0.028–0.33, which was less than one, and it was judged that the "risk is managed".

5. Discussion

We developed a lead substances selection approach based on the concept of mixture classification of UN GHS for the purpose of realizing efficient risk assessment of mixtures consisting of multiple components. Lead substances selection methods are being actively developed in Europe, but these methods are predicated on the regulations and information sources available within Europe and are therefore not readily applicable to countries outside Europe. In contrast, GHS is global and countries outside Europe are also familiar with it. In Japan, the national government has conducted the GHS classification of substances for more than 10 years, mainly for substances subject to legal regulations. The classification results are made available to the public as model GHS classification, and the number of classified substances exceeds 3000 (NITE, 2016). Therefore, by ignoring unclassified substances present in high concentration in the mixture, the possibility of influencing the selection of lead substances is low.

Additionally, the Ministry of Economy, Trade and Industry has made available to the public the GHS Mixture Classification System that enables the GHS classification of mixtures based on UN GHS Document (4th Revision as of 2016) for the purpose of assisting the GHS classification of mixtures by business operators (METI, 2013). As such, in Japan, tools for business operators to carry out the selection of lead substances using the GHS classification have been established. The representative lead substances selection methods developed in Europe are the DPD + method and the CCA method (CEFIC, 2009, 2010; ECHA, 2008). Lead substances selected by the GHS-based approach, DPD + method and CCA method are shown in

Table 6
Input items into ECETOC TRA.

Scenario	PROC	Work form	State	Vapor pressure at work temp	Work time	Ventilation condition	Content (%)	Respiratory protection (respirator)	Gloves
Mix	5: Mixing of preparations	Professional use	Liquid	270-9,999[a]	<15 min	Outdoor	1.8–19.2	95%[b]	APF5
Transfer	9: Transfer to small container	Professional use	Liquid	270-9,999[a]	<15 min	Outdoor	1.8–19.2	95%[b]	APF5
Paint	10: Roller painting	Professional use	Liquid	270-9,999[a]	>4 h	Outdoor	1.8–19.2	95%[b]	APF5
Wash	13: Processing by dipping or pouring in	Professional use	Liquid	270-9,999[a]	<15 min	Outdoor	1.8–19.2	95%[b]	APF5

[a] Vapor pressure of each component (see the table of physicochemical properties above).
[b] Determined by referencing a report by Hobara and Ogata (1978).

Table 7
Estimated exposure concentration.

Scenario		Estimated exposure concentration (mg/m^3)				
		Butyl acetate	Methyl isobutyl ketone	Toluene	Ethyl acetate	2-Ethoxyethyl acetate
Short term exposure	Mix	40.7	35.1	32.3	30.8	1.54
	Transfer	40.7	35.1	32.3	30.8	1.54
	Paint	40.7	35.1	32.3	30.8	3.85
	Wash	40.7	35.1	32.3	30.8	1.54
Long term exposure	Mix	1.02	0.877	0.806	0.771	0.0385
	Transfer	1.02	0.877	0.806	0.771	0.0385
	Paint	10.2	8.77	8.06	7.77	0.964
	Wash	1.02	0.877	0.806	0.771	0.0385

Estimated exposure concentrations are all expressed as 8 h-time weighted average (8 h-TWA).

Table 8
Risk assessment result of each component and mixture.

Scenario		RCR of each component					
		Butyl acetate	Methyl isobutyl ketone	Toluene	Ethyl acetate	2-Ethoxyethyl acetate	RCR_{Total}
Short term exposure	Mix	0.043	0.21	0.084	0.021	0.018	0.38
	Transfer	0.043	0.21	0.084	0.021	0.018	0.38
	Paint	0.043	0.21	0.084	0.021	0.044	0.40
	Wash	0.043	0.21	0.084	0.021	0.018	0.37
Long term exposure	Mix	0.0021	0.011	0.011	0.0011	0.0035	0.028
	Transfer	0.0021	0.011	0.011	0.0011	0.0035	0.028
	Paint	0.021	0.11	0.11	0.011	0.088	0.33
	Wash	0.0021	0.011	0.011	0.0011	0.0035	0.028

RCR: Estimated exposure concentration (Table 7)/Occupational exposure limits (Table 5).

Table 9. Basic information on lead substances selection by the DPD + method and the CCA method is listed in Appendix 1 and Appendix 2, respectively. The number of substances selected by the GHS-based approach was the largest with five, and the substance selected by the CCA method was the smallest with one. Substances selected by the GHS-based approach cover all substances selected by the DPD + method and the CCA method, indicative of the selection having been made as safely as possible. The RCRs of components for the "Paint" scenario, as listed in Table 8, are shown in Table 9. The RCR of short term exposure was the highest for methyl isobutyl ketone with 0.21, followed by toluene at 0.084, 2-ethoxyethyl acetate at 0.044, butyl acetate at 0.043 and ethyl acetate at 0.021, with the RCRs of methyl isobutyl ketone and toluene higher than the rest by a great degree. Meanwhile, the RCR of long term exposure was again the highest for methyl isobutyl ketone at 0.11, followed by toluene at 0.11, 2-ethoxyethyl acetate at 0.088, butyl acetate at 0.021 and ethyl acetate at 0.011, with the RCR of methyl isobutyl ketone higher than the rest by a great degree. These results indicate methyl isobutyl ketone and toluene contributed to the risk of the mixture for short term exposure and methyl isobutyl ketone for long term exposure. It is therefore important that these substances are selected as lead substances as targets of assessment. The GHS-based approach selected all of these substances for short term exposure through the inhalation route, indicative of its capability to enable appropriate lead substances selection. As a side note, though hexamethylene diisocyanate trimer and hexamethylene diisocyanate were not selected as lead substances, risk assessment were conducted since these substances are obviously sensitizing substances and especially hexamethylene diisocyanate has a very low OEL (0.034 mg/m^3) (U.S. ACGIH, 2016). We confirmed that the estimated exposure concentration using the Advanced Reach Tool (ART) for the scenario of this study was lower than the OEL hexamethylene diisocyanate. Additionally, it was reported that hexamethylene diisocyanate trimer (1 mg/m^3) would have an orders of magnitude higher OEL compared with hexamethylene diisocyanate (Lee et al., 2003; Pauluhn and Mohr, 2001). Therefore, we also concluded that there is no risk for these substances.

The GHS method, like the DPD + method, is a classification-based approach. We recognize that the GHS method is not based on NOAELs from specialized and/or repeated exposure studies to arrive at meaningful occupational exposure levels relative to exposure potential like CCA method. However it is not easy to use CCA method for countries outside the EU for which the hazard assessment values, like DNEL, of many substances have not yet been proposed. Therefore, we believe that the classification-based approach based on the GHS method can be an appropriate tool to efficiently implement risk assessment of mixtures.

We realize that this case study does not fully explain the benefits of choosing more adequate lead materials with lower toxicity, and that there might be an advantage in choosing an exposure profile as different as possible for components with higher toxicity. Currently, we are conducting various case studies to further explore this.

In Europe, for the purpose of consolidating exposure scenarios for components of mixtures, methods other than the DPD + method and the CCA method have been proposed (ENES, 2012, 2013; Finking and Bögi, 2013; Taxell et al., 2014). For example, the Lead Component Identification methodology (LICD) is a method combining the DPD + method and the CCA method where lead substances are selected using DNEL or PNEC, or LD50, EC50, if DNEL or PNEC is unavailable. The Lead Component Index (LCI), an index for selecting lead substances, is derived for inhalation, oral, dermal, local effect, and aquatic environment, and the component with the highest LCI is selected as a lead substance. We plan to validate the proposed GHS-based lead substances selection through risk assessment of various mixtures, while monitoring the trend of new lead substances selection approaches, especially those proposed by industry groups in Europe.

6. Conclusion

In this study, we developed a lead substances selection approach based on the concept of mixture classification of UN GHS

Table 9
Selection of lead substances by GHS-based approach, DPD+ method and CCA method (except for local effect).

Substance name	GHS-based approach	DPD+ method	CCA method	RCR of each component Scenario: Paint	
				Short term	Long term
Methyl isobutyl ketone	○	○[c]	○	0.21	0.11
Toluene	○[b]	○		0.084	0.11
2-Ehoxyethyl acetate	○[b]	○[d]		0.044	0.088
Butyl acetate	○[b]			0.043	0.021
Ethyl acetate	○[b]			0.021	0.011
Hexamethylene diisocyanate trimer				<1[a]	<1[a]
Hexamethylene diisocyanate				<1[a]	<1[a]

[a] By using the Advanced Reach Tool (ART).
[b] Selected based only on acute effect.
[c] Selected based on its carcinogenicity.
[d] Selected based on its reproductive toxicity.

for the purpose of efficient risk assessment of mixtures consisting of multiple components. The features of the GHS-based approach and the risk assessment results for outdoor painting work as a specific utilization example of the GHS-based approach were described. Comparison with the DPD + method and the CCA method proposed in Europe revealed that the GHS-based approach enabled the selection of more substances as lead substances, the selection of all the substances with major contribution to the risk of the mixture as lead substances, and therefore the selection of the safest lead substances. The GHS method, like the DPD + method, is a classification-based approach. We believe that the classification-based approach based on the GHS method can be an appropriate tool to efficiently implement risk assessment of mixtures for countries outside Europe. Tools for business operators to carry out the management of chemicals using the GHS classification have been established in Japan, and we plan to propose the GHS-based approach as a standardized assessment tool.

Conflict of interest statement

We declare that there are no competing interests related to our manuscript.

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Transparency document

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Appendix 1

Selection of lead substance by DPD + method.

Component	Content (%)	Vapor pressure (hPa)	DSD classification (67/548/EEC)[a]		R-phrases Concentration limits (%)	Route	DPD+		
							LSI[b] (Inhalation)	LSI[c] (Dermal)	Lead substance
Butyl acetate	19.2	12	R10; R66; R67	R66	20.0	Dermal		1.0	Dermal
				R67	25.0	Inhalation	7.7		
Methyl isobutyl ketone	13.5	21	F; R11; Xn; R20; Xi; R36/37; R66	R20	25.0	Inhalation	6.7		
				R36/37	20.0	Eye/Inhalation	8.4		
Toluene	8.2	38	F; R11; Repr. Cat. 3; R63; Xn; R48/20-65; Xi; R38; R67	R38	20.0	Dermal		0.41	
				R48-20	10.0	Inhalation	31.2		
				R63	5.0	Inhalation	62.3		Inhalation
				R65	25.0	Stomach		0.33	
				R67	25.0	Inhalation	12.5		
Ethyl acetate	5.5	99.992	F; R11; Xi; R36; R66; R67	R36	20.0	Eye		0.28	
				R66	20.0	Dermal		0.28	
				R67	25.0	Inhalation	41.6		
Hexamethylene diisocyanate trimer	4.95	–	–	–	–	–	–	–	–
2-Ethoxyethyl acetate	1.8	2.7	R10; Repr. Cat. 2; R60-61; Xn; R20/21/22	R60	0.5	Inhalation	22		
				R61	0.5	Inhalation	22		
				R20/21/22	25.0	Inhalation/Dermal/Oral	0.4	0.1	
Hexamethylene diisocyanate	0.05	0.07	T; R23; Xi; R36/37/38; R42/43	R23	3.0	Inhalation	0.0012		
				R36/37/38	20.0	Stomach/Inhalation/Dermal	0.0025	0.0025	
				R42/43	1.0	Inhalation/Dermal	0.050	0.050	

[a] EEC, 1967.
[b] LSI: Lead Substance Index.
[c] $LSI_{dermal,\ oral,\ local\ effect,\ aquatic\ environment} = C_i/CL_i$, $LSI_{inhalation} = Vp \times C_i/CL_i$, C_i: Concentration of componet i in mixture, CL_i: R-phrases concentration limits of componet i in mixture, Vp_i: Vapor of componet i in mixture (25 °C).

Appendix 2

Selection of lead substance by CCA method.

Component	Content (%)	Vapor pressure (hPa)	DNEL inhalation[a] (mg/m^3)	DNEL dermal[a] (mg/kg)	CCA		
					RDS[b] (inhalation)	RDS[b] (dermal)	Lead substance
Butyl acetate	19.2	12	480	–	0.48	–	
Methyl isobutyl ketone	13.5	21	83	11.8	3.4	1.1	Inhalation
Toluene	8.2	38	192	6.25	1.6	1.3	
Ethyl acetate	5.5	99.992	734	63	0.75	0.087	
Hexamethylene diisocyanate trimer	4.95	–	–	–	–	–	
2-Ethoxyethyl acetate	1.8	2.7	27	0.44	0.18	4.1	Dermal
Hexamethylene diisocyanate	0.05	0.07	0.035	–	0.10	–	

[a] ECHA, 2016.

[b] RDSs: Risk Determining Substance, $RDSs_{inhalation}=Vp_i \times C_i/DNEL_{inhalation}$, $RDSs_{oral,\ dermal,\ aquatic\ environment}=C_i/DNEL_i$ ($PNEC_i$ for aquatic environment), Vp_i: Vapor of componet i in mixture (20/25 °C), C_i: Concentration of componet i in mixture, $DNEL_i$, $PNEC_i$; DNEL, PNEC of componet i.

References

CEFIC, 2009. REACH: Exposure Scenarios for Preparations. Methodology for the Identification of Substances that Present the Dominant Risks to Human Health and/or the Environment and the Drivers for Risk Management Measures. European Chemical Industry Council, Brussels, Belgium.

CEFIC, 2010. REACH Practical Guide on Exposure Assessment and Communication in the Supply Chains. Part III: Mixtures under REACH. European Chemical Industry Council, Brussels, Belgium.

DFG, 2012. Deutsche Forschungsgemeinschaft, List of MAK and BAT Values 2012. Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. Report No. 48. Wiley-VCH.

EC, 1999. Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations. Off J L 200, 1–68. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31999L0045&from=EN (last accessed October 2016).

ECETOC, 2009. Addendum to ECETOC Targeted Risk Assessment Report No. 93. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium. http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-107-Addendum-to-ECETOC-TRA-report-93.pdf (last accessed October 2016).

ECETOC, 2012. ECETOC TRA Version 3: Background and Rationale for the Improvements. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium. http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-114-ECETOC-TRA-v3-Background-rationale-for-the-improvements.pdf (last accessed October 2016).

ECHA, 2016. European chemical agency (2015a) Search for chemicals. http://echa.europa.eu/ (last accessed October 2016).

ECHA, 2008. Guidance Document on Downstream Users Requirement. Section 14: Information on Preparation to Be Delivered by Formulators. Appendix 2.

EEC, 1967. Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. Off. J. 196, 1–98. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31967L0548&from=en (last accessed October 2016).

ENES, 2012. Third meeting of the ECHA-Stakeholder Exchange Network on Exposure Scenarios (ENES 3), 20–21 November 2012, Brussels.

ENES, 2013. Fourth meeting of the ECHA-Stakeholder Exchange Network on Exposure Scenarios (ENES 4), 16–17 May 2013, Helsinki.

EU, 2000. Commission directive 2000/39/EC of 8 June 2000 establishing a first list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32000L0039&from=EN (last accessed October 2016).

EU, 2006. Commission directive 2006/15/EC of 7 February 2006 establishing a second list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC and amending Directives 91/322/EEC and 2000/39/EC. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006L0015&from=EN (last accessed October 2016).

EU, 2009. Commission directive 2009/161/EU of 17 December 2009 establishing a third list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC and amending Commission Directive 2000/39/EC. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009L0161&from=EN (last accessed October 2016).

Feron, V.J., Groten, J.P., 2002. Toxicological evaluation of chemical mixtures. Food Chem. Toxicol. 40, 825–839.

Feron, V.J., Woutersen, R.A., Arts, J.H., Cassee, F.R., de Vrijer, F., van Bladeren, P.J., 1995. Safety evaluation of the mixture of chemicals at a specific workplace: theoretical considerations and a suggested two-step procedure. Toxicol. Lett. 76, 47–55.

Finking, R., Bögi, C., 2013. Lead substance identification: "CLPplus" by BASF. Fourth meeting of the ECHAStakeholder Exchange Network on Exposure Scenarios (ENES 4), 16–17 May 2013. https://echa.europa.eu/documents/10162/12738969/enes4_pres_33130516_clpplus-basf_en.pdf (last accessed October 2016).

Groten, J.P., 2000. Mixtures and interactions. Food Chem. Toxicol. 38, S65–S71.

Hobara, T., Ogata, M., 1978. Health control of workers using organic solvents Part IV. Relation between concentration of organic solvents in the air and urinary glycine conjugates after short time exposure. J. Okayama Medical Assoc. 90, 1473–1477.

IARC, 2012. International Agency for Research on Cancer, Monographs, vol. 101. Methyl isobutyl ketone. https://monographs.iarc.fr/ENG/Monographs/vol101/mono101-008.pdf (last accessed October 2016).

ICCA, 2016. The International council of chemical associations. Homepage Chemicals management. https://www.icca-chem.org/chemicals-management/ (last accessed October 2016).

JCIA, 2011. Japan chemical industry association, JIPS risk assessment guidance. http://www.nikkakyo.org/documentDownload.php?id=4700 (last accessed October 2016).

JSOH, 2015. The Japan society for occupational health, recommendation of occupational exposure limits (2015–2016). J. Occup. Health 57, 394–417. https://www.sanei.or.jp/images/contents/310/OEL-e_2015-2016.pdf (last accessed October 2016).

Lee, C.-L., Friedman, M., Poovey, H.G., Ie, S.R., Rando, R.J., Hoyle, G.W., 2003. Pulmonary toxicity of polymeric hexamethylene diisocyanate aerosols in mice. Toxicol. Appl. Phram 188, 154–164.

Meek, M.E., Boobis, A.R., Crofton, K.M., Heinemeyer, G., Raaij, M.R., Vickers, C., 2011. Risk assessment of combined exposure to multiple chemicals: a WHO/IPCS framework. Regul. Toxicol. Pharmacol. 60, S1–S14. http://ac.els-cdn.com/S0273230011000638/1-s2.0-S0273230011000638-main.pdf?_tid=0b9d04a6-94da-11e6-b3b6-00000aab0f01&acdnat=1476757670_de7869db78b5689-f5a17d4da1c22f565 (last accessed October 2016).

METI, 2013. The GHS mixture classification System. http://www.meti.go.jp/policy/chemical_management/int/ghs_auto_classification_tool_ver4_EG.html (last accessed October 2016).

Money, C., Margary, A., Noij, D., 2011. Generic exposure scenarios: their development, application, and interpretation under REACH. Ann. Occup. Hyg. 55, 451–464. http://annhyg.oxfordjournals.org/content/55/5/451.full.pdf (last accessed October 2016).

NITE, 2016. National institute of Technology and evaluation, chemical risk information platform. http://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop (last accessed October 2016).

Ökopol, 2012. Consolidation of Information for Mixtures under REACH. Analysis of the DPD+-approach Final Report –Part I Analysis Report. http://www.reach-hamburg.de/fileadmin/user_upload/dokumentationen/Materialien/4_5_3_Kommunikation_in_der_Lieferkette/120508_Mixtures_under_REACH_v3.pdf (last accessed October 2016).

Pauluhn, J., Mohr, U., 2001. Inhalation toxicity of 1,6-hexamethylene diisocyanate homopolymers (HDI-IC and HDI-BT): results of subacute and subchronic repeated inhalation exposure studies. Inhal. Toxicol. 13, 513–532.

Reffstrup, T.K., Larsen, J.V., Meyer, O., 2010. Risk assessment of mixtures of pesticides. Current approaches and future strategies. Regul. Toxicol. Pharmacol. 56, 174–192.

Taxell, P., Koponen, M., Kallio, N., Santonen, T., 2014. Consolidating exposure scenario information for mixtures–experiences and challenges. Ann. Occup. Hyg. 58, 793–805. http://annhyg.oxfordjournals.org/content/early/2014/05/21/annhyg.meu031.full.pdf (last accessed October 2016).

Teuschler, L.K., 2007. Deciding which chemical mixtures risk assessment methods work best for what mixtures. Toxicol. Appl. Pharmacol. 223, 139–147.

U.K. HSE, 2005. United Kingdom Health and Safety Executive, EH40/2005 Workplace exposure limits containing the list of workplace exposure limits for use with the Control of Substances Hazardous to Health Regulations (as amended). http://www.hse.gov.uk/pubns/priced/eh40.pdf (last accessed October 2016).

U.S. ACGIH, 2001. American Conference of Governmental Industrial Hygienists

Documentation of the threshold limit values and biological exposure indices, 7th ed., Supplement 2007, Cincinnati, OH.
U.S. ACGIH, 2007. American Conference of Governmental Industrial Hygienists Documentation of the threshold limit values and biological exposure indices, 7th ed. (2001), Supplement 2007, Cincinnati, OH.
U.S. ACGIH, 2010. American Conference of Governmental Industrial Hygienists Documentation of the threshold limit values and biological exposure indices, 7th ed. (2001), Supplement 2010, Cincinnati, OH.
U.S. ACGIH, 2016. American Conference of Governmental Industrial Hygienists TLVs and BEIs.
United Nations, 2015. Globally Harmonized System of Classification and Labelling of Chemicals (GHS) Sixth Revised Edition. http://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev06/English/ST-SG-AC10-30-Rev6e.pdf (last accessed October 2016).
Wilkinson, C.F., Christoph, G.R., Julien, E., Kelley, J.M., Kronenberg, J., McCarthy, J., Reiss, R., 2000. Assessing the risks of exposures to multiple chemicals with a common mechanism of toxicity: how to cumulate? Regul. Toxicol. Pharmacol. 31, 30–43.