norden

Nordic Council of Ministers

Ved Stranden 18
DK-1061 Copenhagen K

www.norden.org

NORDISKE ARBEJDSPAPIRER

N O R D I C W O R K I N G P A P E R S

Combining exposure scenario information for mixtures with combination effects

Piia Taxell, Petteri Talasniemi, Jouni Räisänen, Tiina Santonen

<http://dx.doi.org/10.6027/NA2015-909>
NA2015:909
ISSN 2311-0562

This working paper has been published with financial support from the Nordic Council of Ministers. However, the contents of this working paper do not necessarily reflect the views, policies or recommendations of the Nordic Council of Ministers.

norden

Nordic Council of Ministers

Ved Stranden 18
DK-1061 Copenhagen K

www.norden.org

NORDISKE ARBEJDSPAPIRER

N O R D I C W O R K I N G P A P E R S

Combining exposure scenario information for mixtures with combination effects

Piia Taxell, Petteri Talasniemi, Jouni Räisänen, Tiina Santonen

<http://dx.doi.org/10.6027/NA2015-909>
NA2015:909
ISSN 2311-0562

This working paper has been published with financial support from the Nordic Council of Ministers. However, the contents of this working paper do not necessarily reflect the views, policies or recommendations of the Nordic Council of Ministers.

Combining exposure scenario information for mixtures with combination effects

*Prepared by Piia Taxell¹, Petteri Talasniemi², Jouni Räisänen² and Tiina Santonen¹
for the Nordic Chemical Group (project no. 2098/2014)*

¹ Finnish Institute of Occupational Health, Helsinki, Finland

² Finnish Safety and Chemicals Agency, Helsinki, Finland

Content

Summary.....	2
Acknowledgements.....	3
Abbreviations.....	4
Introduction.....	5
Methods.....	7
Selection of example mixtures and collection of component data.....	7
Deriving component exposure scenarios.....	7
Combining exposure scenario information	8
Identification of combination effects	10
Assessment of adequacy of the safe use information.....	10
Results	14
Occurrence of mixtures with combination effects	14
Combination effects of the example mixtures	15
Adequacy of the safe use information.....	16
Discussion	20
Conclusions.....	23
References.....	24
Appendix 1: Mixture 1 (thinner).....	25
Appendix 2: Mixture 2 (coating)	29
Appendix 3: Mixture 3 (detergent)	34
Appendix 4: Mixture 4 (spray-paint).....	38
Appendix 5: Mixture 5 (detergent)	42
Appendix 6: Mixture 6 (paint)	48
Appendix 7: Mixture 7 (spray-paint).....	53
Appendix 8: Mixture 8 (adhesive).....	57
Appendix 9: List of hazard statements	60

Summary

The requirements of the REACH regulation ((EC) No. 1907/2006) are focused on individual substances. The majority of the chemical products used at workplaces are, however, mixtures of several substances. Formulators producing mixtures have an important role in combining the component-based information and communicating the safe use of the mixture to their customers.

The main aims of the present study were to examine how the existing methods for combining component-based exposure scenario information for mixtures cover combination effects of the components; to evaluate whether there is a need to develop further guidance to formulators for taking into consideration combination effects when combining exposure scenario information; and to evaluate the usability of the Mixie software on combination effects in the REACH context.

The project examined eight mixtures selected from the Finnish Register of Chemical Products. For these mixtures, components with potential additive (and/or synergistic) effects were identified applying the CLP hazard classification ((EC) No. 1272/2008) and the Mixie software. Safe use information for worker inhalation exposure was derived for 1–2 uses/work phases of each mixture, applying two methodologies for combining the component exposure scenarios: 1) the draft Lead Component Identification Methodology (LCID methodology) and 2) selection of the most stringent exposure control measures (MS methodology). The exposure levels for each of the components in the conditions of the safe use information were calculated by ECETOC TRA exposure modelling tool, and the adequacy of the safe use information was evaluated applying a dose-addition approach for the components with potential additive effects.

For the eight example mixtures, additive effects were not covered by the safe use information derived by the draft LCID methodology in at least one task/work phase of five mixtures, indicating that in its current form the draft methodology does not adequately protect from additive effects. By contrast, the safe use information derived by the MS methodology covered the additive effects for all mixtures, effects and work-tasks considered. Lowering the target risk characterisation ratio in the component exposure scenarios from 1 to 0.5 did not change the results significantly.

On the basis of the results, the MS methodology may be recommended as a simple and conservative approach for deriving safe use information for a mixture. A more detailed analysis would be necessary only in the cases where this approach seems to lead to overly stringent measures deviating significantly from those typically applied for the type of product and work-task. For the draft LCID methodology, there is a need to refine the methodology in respect to combination effects. The CLP hazard classification may be applied as a starting point for the identification of the components with potential additive effects, and the Mixie software may be additionally applied to refine the identification.

Acknowledgements

The authors would like to thank Matti Vartiainen, Anu Matilainen and Jouko Yrjönen from the Finnish Safety and Chemicals Agency for enabling and carrying out the searches in the Finnish Register of Chemical Products. The members of the Nordic Risk Assessment Group (NORAP) and the Nordic Exposure Group for Health (NEGh) are acknowledged for their valuable comments on the project plan and the final report.

The study was financially supported by the Nordic Council of Ministers.

Abbreviations

CEFIC	European Chemical Industry Council
CLP	Classification, labelling and packaging
CNS	Central nervous system
DNEL	Derived no-effect level
ECETOC	European Centre of Ecotoxicology and Toxicology of Chemicals
EC	European Commission
ECHA	European Chemicals Agency
ES	Exposure scenario
IRSST	Institut de recherche Robert-Sauvé en santé et en sécurité du travail
LCI	Lead component indicator
LCID	Lead Component Identification (methodology)
LEV	Local exhaust ventilation
MDI	Methylene diphenyl diisocyanate
MS	Selection of the most stringent exposure control measures
OC	Operational condition
PBT	Persistent, bioaccumulative and toxic
PROC	Process category
REACH	Registration, evaluation, authorisation and restriction of chemicals
RCR	Risk characterisation ratio
$\sum$ RCR	Combined risk characterisation ratio
RMM	Risk management measure
VCI	German Chemical Industry Association
vPvB	Very persistent and very bioaccumulative

Introduction

The requirements of the REACH regulation ((EC) No. 1907/2006) are focused on individual substances. The majority of the chemical products used at workplaces are, however, mixtures of several substances. It is, therefore, important that there is high-quality information available on the safe use of mixtures in the supply chain. Formulators producing mixtures have an important role in combining the component-based information and communicating the safe use of the mixture to their customers.

According to REACH (Art. 31.7), a formulator is obliged to “include relevant exposure scenarios, and use other relevant information, from the safety data sheet supplied to him when compiling his own safety data sheet”. A formulator has currently the possibility to fulfil this requirement by annexing the relevant exposure scenarios of the individual components of the mixture to its safety data sheet (ECHA 2014). However, this kind of unmodified component-based information is likely to be difficult to interpret and utilize by the downstream users further down in the supply chain. The formulator may also develop consolidated (combined) safe use information for the mixture by combining the information presented in the exposure scenarios of the individual components (ECHA 2014). The safe use information should include relevant operational conditions and risk management measures (OCs/RMMs), describing, e.g., the type, duration and frequency of the task, and the required exposure control measures. The safe use information may be attached to the safety data sheet of the mixture, or integrated into the relevant sections of the safety data sheet (ECHA 2014). These options are likely to result in more useful information for the downstream users of the mixture.

The methods for combining exposure scenarios of the individual components to derive safe use information for a mixture are still under development. A conservative approach, mentioned also in the downstream users’ guidance of the European Chemicals Agency (ECHA, 2014), is to select the most stringent OCs/RMMs of the individual components for the mixture. As an alternative, methods for identification of the risk determining components that also determine the exposure control measures needed for the mixture, have been introduced. The Lead Component Identification Methodology (LCID), under development in the European Chemical Industry Council (CEFIC) and the German Chemical Industry Association (VCI), is the most well-known of these. At the time of the present study, only the first commentary version of the methodology was available (CEFIC 2014).

In combining the exposure scenario information of the individual components the main principle should be that the exposure levels of each of the components stay below their derived no-effect level (DNEL) values in the conditions of the combined safe use information, i.e. that the risk characterisation ratio (RCR), expressing the ratio of the exposure level to the DNEL value, stays below one. In order to ensure that no adverse health effects are likely to occur, also the possible combination effects of the components need to be taken into consideration. For components having the same target organ and similar mode of action, the effects are considered to be

additive (EC 2011; Meek et al. 2011). Thus, for these components the combined risk characterisation ratio ($\sum RCR$) should stay below one in the conditions of the safe use information of the mixture. In some cases, the components may also have synergistic (greater-than-additive) effects, which may affect the adequacy of the individual-component- or additive-effects-based safe use information.

For the identification of the possible combination effects of chemical substances, the Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST) and the University of Montreal have developed a freely available web-based software, Mixie (IRSST 2010). Mixie includes a database of target organs/effects, and combination effects reported in the open literature, for approximately 700 chemical substances (Vyskocil et al. 2004; 2007). The software is primarily intended as decision-making aid for assessing combination effects of chemical substances present in the workplace air.

The main aims of the present study were 1) to examine how the existing methods for combining component-based exposure scenario information for mixtures cover combination effects of the components; 2) to evaluate whether there is a need to develop further guidance to formulators for taking into consideration combination effects when combining exposure scenario information; and 3) to evaluate the usability of the Mixie software in the REACH context.

Methods

Selection of example mixtures and collection of component data

Example mixtures (products) with components having potential combination effects were identified in the Finnish Register of Chemical Products¹. The search criteria included mixtures with ≥ 2 (or ≥ 3) components classified according to the CLP regulation ((EC) No. 1272/2008), or the earlier directive (67/548/EEC), for respiratory irritation (H335; R37), narcotic effects (H336; R67), reproductive toxicity (H360, H361; R60, R61, R62, R63) or target-organ toxicity (H370, H371, H372, H373; R39, R68, R48). Among the identified mixtures, eight mixtures were selected to be applied in the project (Table 1). The focus was on mixtures having an explicit use and containing registered components with DNEL values.

In order to further analyse the occurrence of mixtures containing components with possible combination effects in relevant quantities, the search was repeated allocating to mixtures containing ≥ 2 components having 1) the required hazard classification and 2) concentration above 5% (w/w).

The database of registered substances of the European Chemical Agency (ECHA) was applied as the primary source of information of the DNEL values of the mixture components. CLP hazard classification of the components was retrieved directly from the Finnish Register of Chemical Products. The ChemIDPlus database (U.S National Library of Medicine) was applied to collect molecular weight and vapour pressure data for the components.

Deriving component exposure scenarios

The operational conditions and risk management measures (OCs/RMMs) leading to inhalation exposure below the (systemic) long-term inhalation DNEL value for workers (i.e. risk characterisation ratio (RCR) < 1) were determined for each of the mixture components for 1–2 work tasks by ECETOC TRA exposure modelling tool (version 3.1). These OCs/RMMs correspond the exposure scenarios of the individual components for worker inhalation exposure.

In ECETOC TRA, the initial exposure prediction for worker inhalation exposure is a function of 1) the fugacity of the substance (volatility, dustiness) and 2) the circumstances of the use, described by the process category (PROC) (ECETOC 2004; 2012). The initial prediction may be modified by selecting additional OCs/RMMs as follows: decreased duration of the task (default: > 4 h), decreased concentration (default: 100%), work outdoors (default: indoors),

¹ Companies responsible for placing a chemical on the market or in use in Finland must submit a notification into the Finnish Register of Chemical Products. The information required in the notification corresponds to the information provided in the safety data sheet.

good/enhanced general ventilation (default: basic general ventilation), local exhaust ventilation (default: none), or respiratory protection (default: none).

In compiling the component exposure scenarios, the primary OCs/RMMs considered were the technical control measures included in ECETEC TRA, i.e. good general ventilation and local exhaust ventilation (LEV). If the target RCR was not achieved by these measures, limited duration of the task (1–4 h) and respiratory protection, respectively, were additionally considered. In the cases where the target RCR was not reached with limited duration of the task, but was reached with respiratory protection, respiratory protection could have been selected without limiting the duration of the task. It should be noted, however, that wearing respiratory protection for > 4 hours is not to be generally recommended. The exposure scenarios were derived for undiluted (100%) substances, i.e. the concentrations of the components in the mixture were not taken into consideration in this phase. In order to study the impact of the target RCR in the component exposure scenarios on the final outcome, the component exposure scenarios were also derived for exposure below 0.5 x DNEL value (i.e. RCR < 0.5).

In addition to the liquid components, four of the example mixtures contained gaseous, solid or polymeric compounds (indicated in Table 1). Since exposure scenarios for these compounds could not be derived by ECETOC TRA, these were excluded from further analysis.

Combining exposure scenario information

Two approaches were applied for combining the exposure scenarios of the components into safe use information for the mixtures: 1) the draft Lead Component Identification Methodology (LCID methodology), and 2) selecting the most stringent exposure control measures of the components (referred here to as MS methodology). The two approaches are explained further below.

Lead Component Identification (LCID) Methodology

The LCID methodology is based on identification of the risk determining “lead components” which determine OCs/RMMs for each exposure route to be included in the safe use information of the mixture. It should be noted that the project applied the first, unpublished commentary version of the methodology (CEFIC 2014), and that the methodology will be subject to changes before the final publication.

In the LCID methodology, components classified as carcinogenic or mutagenic are identified as “priority substances” for health hazards, and persistent and bioaccumulative components (PBT/vPvB) for the environmental hazards. If the mixture contains these type of components, their OCs/RMMs determine the safe use information of the mixture. If there are no priority substances present in the mixture, a “lead component indicator” (LCI), describing the relative importance of each of the components of the mixture in relation to each exposure route, is derived.

The LCI for **inhalation exposure of workers** is determined as follows:

$$LCI = (C_i \times C_{fug}) / DNEL_i \quad (1)$$

where C_i is the concentration of the component in the mixture, C_{fug} is the vapour pressure of the component (as hPa)², and $DNEL_i$ is the worker long-term systemic inhalation DNEL value of the component. Only the components driving the health hazard classification of the mixture for systemic effects are taken into consideration in the identification of the lead components. LCIs are not calculated for components causing local effects (e.g. respiratory irritation or sensitisation) or narcotic effects. However, the OCs/RMMs of these components are added to the lead-component-based safe use information of the mixture, where needed. Checking the appropriateness of the selected OCs/RMMs for the mixture as a whole is recommended, taking into consideration, e.g., substance-specificity of the measures and relevant exposure routes not related to the classification of the components.

The draft LCID methodology also provides an approach for managing components with additive effects. The approach includes summing of the LCIs of the additive components. If the summed value exceeds the LCIs of the other components in the mixture for the exposure route in question, selection of the OCs/RMMs of the component having the highest LCI among the additive components drives the safe use information for the mixture for the given exposure route. However, since the only effect considered as additive by the draft methodology was acute toxicity, and since narcotic effects and respiratory irritation were entirely excluded from the LCI considerations, we were not able to test this approach in the present project.

MS methodology – selection of the most stringent measures

In the MS methodology, the most efficient exposure control measures, i.e. the measures leading to the lowest exposure, presented in the component exposure scenarios, are chosen for the safe use information of the mixture. The approach is mentioned in the downstream users' guidance of the European Chemicals Agency (ECHA, 2014) but it is not described further. To be able to apply the approach one needs to have information available on the control efficiencies of the OCs/RMMs presented in the component exposure scenarios.

The methodology may be described by the following example of a two component mixture (components A and B): For both of the components, the component exposure scenarios have been derived by ECETOC TRA. For component A, the component exposure scenario requires application of local exhaust ventilation with efficiency of 80%, and for component B, decreased duration of the activity (1–4 h instead of > 4 h). In ECETOC TRA, the exposure modifying factor (corresponding to control efficiency) for decreased duration of 1–4 h is 60% (ECETOC, 2004). Thereby, the exposure scenario of component A is the most stringent (control efficiency 80% vs. 60%), and the control measures of this component (local exhaust ventilation with efficiency of 80%) will be selected for the safe use information of the mixture.

² There is also a possibility not to include vapour pressure (C_{fug}) in the equation if exposure to vapours is not considered relevant or if including the vapour pressure is considered to place too much weight on the physico-chemical properties. In the present study, however, the equation (1) was applied as presented.

Identification of combination effects

Identification of the components which potentially cause additive effects was primarily based on the CLP hazard classification of the components. Components having the same hazard classification, related to a similar effect in the same target organ, were assumed to cause additive effects. The effects considered included narcotic effects, respiratory irritation, adverse effects on fertility, developmental toxicity, and target organ toxicity in the cases where the classification was related to similar effect in the same target organ. In addition, components included in the same toxicological classes in the Mixie database (same target organ/effect) were also included in the analysis.

Assessment of adequacy of the safe use information

In order to assess the adequacy of the safe use information derived by the LCID methodology and by the MS methodology, RCR values for worker inhalation exposure were calculated by ECETOC TRA. The RCR values were calculated for each of the components identified to potentially cause additive effects, in the conditions of the safe use information for the mixture derived by the two methodologies.

The exposure levels applied for the RCR calculations were the mean exposure estimates of ECETOC TRA. The primary DNEL values applied as reference values were selected as follows: short-term local DNEL for respiratory irritation, short-term systemic DNEL for narcotic effects, and long-term systemic DNEL for reproductive effects (all related to worker inhalation exposure). The primary DNEL applied for target-organ toxicity was selected on the basis of the organ and the effect. In case the primary DNEL value was not available for a component, an alternative available value was chosen (e.g., a missing short-term DNEL was replaced by a long-term DNEL).

After calculating the RCR values for the components, the RCR values related to an additive effect were summed. A combined RCR ($\sum RCR$) below one indicated that the effect in question was not likely to occur in the conditions of the safe use information, i.e. that the safe use information for the mixture covered the additive effects. Correspondingly, a $\sum RCR$ above one indicated that the safe use information may not be adequately protective for the additive effects.

Table 1. Mixtures selected for the project and components classified as hazardous. The hazard statements are explained in Appendix 9.

Product	Inclusion criteria	CAS nr	Component name	Mean conc. (%)	Hazard statements (CLP)
Thinner (Mix no. 1)	Narcotic, ≥3 comp.	67-64-1	Acetone	15	H225, H304, H312, H332, H315, H336, H361d, H373
		123-86-4	Butyl acetate	10	H225, H319, H336, EUH066
		1330-20-7	Xylene (isomers) ^M	27	H226, H336, EUH066
		107-98-2	Methoxy-2-propanol	9.0	H226, H312, H315, H332
		108-88-3	Toluene ^L	39	H226, H336
					H225, H304, H315, H336, H361d, H373
Coating (Mix no. 2)	Reproductive toxicity, ≥2 comp.	111-40-0	Diethylenetriamine	30	H302, H312, H314, H317, H361fd, H411
		80-05-7	Bisphenol A	23	H302, H312, H314, H317
		25154-52-3	Nonylphenol ^L	8.5	H317, H318, H361f, H335
		140-31-8	1-(2-Ami-noethyl)piperazine ^M	8.5	H302, H314, H361fd, H400, H410
					H302, H311, H314, H317, H412
Deter-gent (Mix no. 3)	Target organ toxicity, ≥2 comp. (also narcotic, ≥3 comp.)	67-64-1	Acetone	10	H225, H301, H311, H331, H304, H315, H319, H336, H361d, H370, H411
		142-82-5	Heptane	20	H225, H319, H336, EUH066
		67-56-1	Methanol ^{L,M}	45	H225, H304, H315, H336, H400, H410
		108-88-3	Toluene ^M	20	H225, H301, H311, H331, H370
					H225, H304, H315, H336, H361d, H373
Spray-paint (Mix no. 4)	Narcotic, ≥3 comp.	67-64-1	Acetone	38	H222, H318, H336, H411
		106-97-8	Butane ^a	7.5	H225, H319, H336, EUH066
		71-36-3	1-Butanol ^L	3.8	H220
					H226, H302, H315, H318, H335, H336
		123-86-4	Butyl acetate	7.5	H226, H336, EUH066
		75-28-5	Isobutane ^a	7.5	H220
		108-65-6	Methoxy-1-methylethyl acetate ^M	7.5	H226
		78-93-3	Butanone	7.5	H225, H319, H336, EUH066
		74-98-6	Propane ^a	6.3	H220
		9004-70-0	Nitrocellulose ^a	1.8	H228
		7779-90-0	Zinc phosphate ^a	1.8	H400, H410

Continues on the next page.

Table 1 continues.

Product	Inclusion criteria	CAS nr	Component name	Mean conc. (%)	Hazard statements (CLP)
Detergent (Mix no. 5)	Respiratory irritation, ≥ 3 comp.	1330-20-7	Xylene ^{L,M}	1.3	H304, H335, H336, H411
		103-65-1	1-Propylbenzene	6.3	H226, H312, H315, H332
		64742-95-6	Solvent naphtha, light aromatic	38	H226, H304, H335, H411
		108-67-8	1,3,5-Trimethylbenzene	6.3	H304
		108-65-6	Methoxy-1-methylethyl acetate	38	H226, H335, H411
		98-82-8	Cumene ^M	6.3	H226
		95-63-6	1,2,4-Trimethylbenzene	1.3	H226, H304, H335, H411
Paint (Mix no. 6)	Narcotic, ≥ 3 comp.	64-17-5	Ethanol	13	H225, H304, H315, H317, H319, H336, H361d, H373
		100-41-4	Ethyl benzene ^M	2.0	H225
		68082-29-1	Fatty acids, C18-unsaturated, dimers, polymers ^a	7.5	H225, H332
		1330-20-7	Xylene ^M	7.5	H315, H317, H319
		107-98-2	Methoxy-2-propanol	7.5	H226, H312, H315, H332
		78-93-3	Butanone	13	H226, H336
		78-83-1	Isobutanol	3.0	H225, H319, H336, EUH066
		67-63-0	Isopropanol	7.5	H226, H315, H318, H335, H336
		108-88-3	Toluene ^L	43	H225, H319, H336
Spray-paint (Mix no. 7)	Reproductive toxicity, ≥ 2 comp.	67-64-1	Acetone	38	H225, H304, H315, H336, H361d, H373
		85-68-7	Benzyl butyl phthalate ^M	1.8	H222, H319, H360D, H336, H373, H411, EUH066
		106-97-8	Butane ^a	6.3	H225, H319, H336, EUH066
		108-10-1	4-Methylpentan-2-one ^L	6.3	H225, H319, H332, H335, EUH066
		78-93-3	Butanone	18	H225, H319, H336, EUH066
		74-98-6	Propane ^a	18	H220
		763-69-9	Ethyl 3-ethoxypropionate	6.3	H226, EUH066
		108-88-3	Toluene	6.3	H225, H304, H315, H336, H361d, H373

Continues on the next page.

Table 1 continues.

Product	Inclusion criteria	CAS nr	Component name	Mean conc. (%)	Hazard statements (CLP)
Adhesive (Mix no. 8)	Target organ toxicity, ≥ 3 comp. (also respiratory irritation, ≥ 3 comp.)	-	<i>Polymeric MDI^a</i>	63	H332, H315, H319, H334, H317, H351, H335i, H373i
		101-68-8	4,4'-MDI ^{L,M}	18	H332, H315, H319, H334, H317, H351, H335i, H373i
		5873-54-1	2,4'-MDI ^{L,M}	8.5	H332, H315, H319, H334, H317, H351, H335i, H373i
		2536-05-2	2,2'-MDI ^{L,M}	4.0	H332, H315, H319, H334, H317, H351, H335i, H373i

^a Component excluded from further analysis (gaseous, solid or polymeric substance for which a relevant component exposure scenario cannot be derived by ECETOC TRA).

^L Component identified as lead component for (worker) inhalation exposure by the Lead Component Identification methodology.

^M Component with the most stringent operational conditions and risk management measures in relation to worker inhalation exposure.

MDI: Methylene diphenyl diisocyanate.

Results

Occurrence of mixtures with combination effects

Table 2 presents the number of mixtures containing ≥ 2 or ≥ 3 components with a particular hazard classification identified in the Finnish Register of Chemical Products. For comparison, the number of products included in the Product Register was 31 874 in the early 2014. In Table 3, the search criteria are further specified to include only components present in concentrations of $\geq 5\%$ (w/w), in order to focus on additive components likely to impact the risk assessment.

In the light of the figures presented in Tables 2 and 3, consideration of additive effects in combining exposure scenario information would be particularly relevant for respiratory irritation and narcotic effects. However, even for these effects, the number of products containing, e.g., ≥ 3 components having the same hazard classification is only in the range of 2% of the total amount of products in the Product Register.

Table 2. Number of mixtures (products) in the Finnish Register of Chemical Products containing ≥ 2 or ≥ 3 components with a particular hazard classification.

Classification	Number of mixtures fulfilling the search criteria	
	≥ 2 components	≥ 3 components
Respiratory irritation	859	374
Narcotic effects	1786	261
Reproductive toxicity	77	3
Target-organ toxicity	251	20

Table 3. Number of mixtures (products) in the Finnish Register of Chemical Products containing ≥ 2 components with a particular hazard classification in a concentration of $\geq 5\%$ (w/w).

Classification	Number of mixtures fulfilling the search criteria						
	≥ 2 comp.	2 comp.	3 comp.	4 comp.	5 comp.	6 comp.	7 comp.
Respiratory irritation	297	90	138	52	17	-	-
Narcotic effects	258	22	86	102	37	10	1
Reproductive toxicity	2	1	1	-	-	-	-
Target-organ toxicity	22	2	15	5	-	-	-

Combination effects of the example mixtures

On the basis of the CLP hazard classification of the mixture components and the Mixie software, the following combination effects were identified for the example mixtures (for further information, see Appendices 1–8):

- Mixture no. 1 (thinner): Four components classified as narcotic and an additional component identified as central nervous system (CNS) depressant by Mixie => **Narcotic effects** identified as an additive effect of these components.
- Mixture no. 2 (coating): Two components classified as reprotoxic (adverse effects on fertility) and four components classified as corrosive or irritating to the respiratory tract => 1) **Adverse effects on fertility** and 2) **corrosive/irritating effects in the respiratory tract** identified as additive effects of these components.
- Mixture no. 3 (detergent): Three components classified as narcotic and an additional component identified as CNS depressant by Mixie => **Narcotic effects** identified as an additive effect of these components.
- Mixture no. 4 (spray-paint): Four components classified as narcotic => **Narcotic effects** identified as an additive effect of these components.
- Mixture no. 5 (detergent): Four components classified as irritating to the respiratory tract and two additional components identified as respiratory tract irritants by Mixie. In addition, Mixie identified these six components as CNS depressant => 1) **Respiratory irritation** and 2) **narcotic effects** identified as additive effects of these components.
- Mixture no. 6 (paint): Six components classified as narcotic and two additional components identified as CNS depressant by Mixie. Mixie suggests also synergistic (greater-than-additive) effects on the CNS for two pairs of the components => **Narcotic effects** identified as an additive/synergistic effect of these components.
- Mixture no. 7 (spray-paint): Two components classified as developmental toxicants. Three of the components classified as narcotic and an additional component identified as CNS depressant by Mixie => 1) **Developmental toxicity** and 2) **narcotic effects** identified as additive effects of these components.
- Mixture no. 8 (adhesive): Three components (isomers) classified as pulmonary toxicants and respiratory sensitizers => 1) **Pulmonary toxicity** and 2) **respiratory sensitization** identified as additive effects of these components.

Mixie software identified several components without the specific hazard classification as CNS depressant (narcotic) or respiratory irritant (Table 4). For example, several alkyl-substituted benzenes (e.g., xylene, ethyl benzene and cumene) were identified as CNS depressant by the Mixie software although these compounds do not have related hazard classification. One likely reason for the observed differences is that since standard toxicity tests related to narcotic effects

or respiratory irritation are not available, the effects may not be fully covered by the hazard classifications.

Further, Mixie seems to have less stringent criteria for defining substances as respiratory irritants, including also general descriptions of sensory irritation, which are excluded from the classification criteria (including only effects characterised by localised redness, oedema, pruritis and/or pain with symptoms such as cough, pain, choking, and breathing difficulties). For one of the mixtures (Mixture no. 6), Mixie also identified components with greater-than-additive effects (synergism) in relation to CNS effects, which may, at least qualitatively, be taken into consideration in the risk assessment and derivation of the safe use information for the mixture. Taken together, Mixie may complement the classification-based data in the identification of additive (and synergistic) effects, especially in the case of narcotic effects/CNS depression and (respiratory) irritation.

Table 4. Components of the example mixtures **without the specific hazard classification** but identified as central nervous system (CNS) depressant (narcotic) or respiratory irritant by Mixie.

Components identified as CNS depressant	Components identified as respiratory irritant
Xylene (dimethylbenzene)	Acetone
Trimethylbenzene	Butanone
Ethylbenzene	Butyl acetate
Propylbenzene	4-Methylpentan-2-one (methyl isobutyl ketone)
Methanol	Ethanol
4-Methylpentan-2-one (methyl isobutyl ketone)	Isopropanol
Solvent naphtha	Toluene (methylbenzene)
	Xylene (dimethylbenzene)
	Ethylbenzene
	Heptane
	Solvent naphtha

Adequacy of the safe use information

Adequacy for individual components

In order to assess if the safe use information for the example mixtures derived by the two methodologies was adequately protective for the **individual components** of the mixtures, the exposure levels of the components, calculated in the conditions (with the OCs/RMMs) of the safe use information, were compared with the DNEL values of the components (see Appendices 1–8). The estimated exposure levels exceeded the applied DNEL value, i.e. the RCR values of the individual components exceeded one, in one case only: For Mixture no. 2, the DNEL values of 1–2 components were exceeded in the conditions of the safe use information derived by the draft LCID methodology (see Appendix 2). The main reason was that corrosive effects included in our analysis were not considered in the draft LCID when choosing OCs/RMMs related to local effects in the respiratory tract. In the other cases, the estimated exposure levels for the components did

not exceed the applied DNEL values in the conditions of the safe use information (i.e., the RCR values of the individual components were below one).

The RCR values presented in Appendices 1–8 were calculated in relation to the DNEL values relevant for the additive effects considered, which may not be the lowest DNEL values of the components. Therefore, the RCR values of the individual components were separately calculated applying the lowest DNEL values of the components.

In addition to Mixture no. 2, the exposure estimate exceeded the lowest DNEL value of one individual component (xylene) in two cases in the conditions of safe use information derived by the draft LCID methodology: in mixing and spraying of Mixture no. 1 and in spraying of Mixture no. 6. For both of the mixtures, the safe use information was based on the OCs/RMMs of toluene. This indicates that the safe use information derived by the draft LCID methodology may not in all cases be adequately protective for all of the individual components of a mixture.

In the conditions of the safe use information derived by the MS methodology, the RCRs for the individual components were below one for all of the mixtures and work-tasks considered.

Adequacy for combination effects

In order to assess if the safe use information for the example mixtures derived by the two methodologies was adequately protective for the **additive effects of the components** of the mixtures, the combined RCR ($\sum RCR$) for the components with potential additive effects were calculated in the conditions (with the OCs/RMMs) of the safe use information (see Appendices 1–8).

Table 5 summarises the number of cases where the $\sum RCR$ for additive effects exceeded one at least for one effect and work-phase of the eight example mixtures. The $\sum RCR$ exceeded one **in the conditions of safe use information derived by the draft LCID methodology** in the following cases:

- For narcotic effects in spraying of Mixture no. 1 (thinner), when the target RCR in the component scenarios was < 1 .
- For corrosive/irritating effects in the respiratory tract in mixing or spreading of Mixture no. 2 (coating), when the target RCR in the component scenarios was < 1 or < 0.5 .
- For narcotic effects in dipping of articles to Mixture no. 3 (detergent), when the target RCR in the component scenarios was < 1 .
- For narcotic effects in spraying of Mixture no. 4 (spray-paint), when the target RCR in the component scenarios was < 1 .
- For narcotic effects in spreading and spraying of Mixture 6 (paint), when the target RCR in the component scenarios was < 1 , and for spreading also when the target RCR in the component scenarios was < 0.5 .

In the conditions of safe use information derived by the MS methodology the $\sum$ RCRs for the additive effects were below one for all of the mixtures, effects and work-tasks considered. For the mixture with possible synergistic effects (Mixture no. 6), the $\sum$ RCR for the effect in question ranged from 0.21 to 0.80. Taking into consideration the synergistic effect, the safe use information may not be adequately protecting when the $\sum$ RCR is approaching one.

Table 6 compares the safe use information derived by the draft LCID methodology ($\sum$ RCR > 1) and by the MS methodology ($\sum$ RCR < 1) in the cases described above. Except for Mixture no. 2, the differences between the safe use information were not dramatic: In comparison to LCID, MS methodology added respiratory protection or limited the duration of the task in spraying of Mixture nos. 1, 4 and 6 (thinner and paints), included good general ventilation in addition to local exhaust ventilation for spreading of Mixture no. 6 (paint), and added local exhaust ventilation for dipping of articles into Mixture no. 3 (detergent). For Mixture no. 2 (coating), the significant differences between the safe use information were largely due to the fact that the draft LCID methodology did not consider corrosive effects when choosing OCs/RMMs for inhalation exposure.

Although the components defining the safe use information differed between the two methodologies for most of the example mixtures (see Table 1), the concentration range of the components defining the safe use information did not differ significantly (range 1.3–45% for both of the methodologies; median 7.5% for MS and 8.5% for LCID).

A specific feature of the draft LCID methodology is that it principally takes into consideration only the components having a hazard classification in relation to the exposure route for which the OCs/RMMs are to be defined. For the example mixtures, the most stringent OCs/RMMs in relation to inhalation exposure were identified in two cases for components without a hazard classification in relation to inhalation exposure: For Mixture no. 2, the most stringent OCs/RMMs were identified for 1-(2-aminoethyl)piperazine, which is, however, classified as corrosive. For Mixture no. 4, the most stringent OCs/RMMs were identified for methoxy-1-methylethyl acetate, which does not have a hazard classification in relation to inhalation exposure. The DNEL value of the component is, however, based on respiratory irritation. In the draft LCID methodology, it would be up to the formulator to decide, if the OCs/RMMs of these components were relevant for inhalation exposure or not.

Table 5. Combined risk characterisation ratio for the additive effects exceeding one ($\sum$ RCR > 1) in the conditions of the safe use information for any effect/work-phase considered (eight mixtures in total). “Target RCR” refers to the target RCR in the exposure scenarios of the individual components (0.5 or 1).

	$\sum$ RCR > 1 for #/8 of the example mixtures	
	LCID methodology	MS methodology
Target RCR < 1 in component ESs	5/8	0/8
Target RCR < 0.5 in component ESs	2/8	0/8

ES: Exposure scenario. LCID: Lead Component Identification Methodology. MS: Selection of the most stringent exposure control measures. RCR: Risk characterisation ratio.

Table 6. Safe use information for the mixtures derived by the LCID methodology and by the MS methodology in the cases where combined risk characterisation ratio (Σ RCR) exceeded one for LCID but was below one for MS.

Work task	Safe use information derived by LCID methodology	Safe use information derived by MS methodology
Spraying of Mixture 1 (thinner) ^a	LEV (eff. 80%) + good general ventilation + duration 1–4 h	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)
Mixing of Mixture 2 (coating) ^a	None	LEV (eff. 80%) + good general ventilation + duration 1–4 h + respirator (eff. 90%)
Spreading of Mixture 2 (coating) ^a	LEV (eff. 80%)	LEV (eff. 80%) + good general ventilation + duration 1–4 h + respirator (eff. 90%)
Mixing or spreading of Mixture 2 (coating) ^b	LEV (eff. 80%)	LEV (eff. 80%) + good general ventilation + duration 1–4 h + respirator (eff. 90%)
Dipping of articles to Mixture 3 (detergent) ^a	Good general ventilation	LEV (eff. 80%)
Spraying of Mixture 4 (spray-paint) ^a	LEV (eff. 80%) + good general ventilation	LEV (eff. 80%) + good general ventilation + duration 1–4 h
Spreading of Mixture 6 (paint) ^a	LEV (eff. 80%)	LEV (eff. 80%) + good general ventilation
Spreading of Mixture 6 (paint) ^b	LEV (eff. 80%)	LEV (eff. 80%) + good general ventilation + duration 1–4 h
Spraying of Mixture 6 (paint) ^a	LEV (eff. 80%) + good general ventilation + duration 1–4 h	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)

^a Target RCR in the component exposure scenarios < 1. ^b Target RCR in the component exposure scenarios < 0.5. LEV: Local exhaust ventilation.

Discussion

The analysis of the mixtures in the Finnish Register of Chemical Products indicated that narcotic effects and respiratory irritation are among the most relevant additive health effects to consider when deriving safe use information for a chemical product. Although only a minor part of the available chemical products contains components having the same hazard classification, from the perspective of the users of these products, it is important to ensure that the safe use information of the products covers also the potential additive effects.

For the eight example mixtures, additive effects were not covered by the safe use information derived by the draft LCID methodology in at least one task/work phase of five mixtures, indicating that in its current form the draft methodology does not adequately protect from additive effects. The methodology is also in need of further testing to ensure that the safe use information is in all cases protective even for the individual components, and that relevant information included in the component exposure scenarios is not lost during the process. One possible problem is that the methodology principally takes into consideration only the components with a hazard classification related to a particular exposure route in the identification of the lead components for an exposure route, although the mixture may contain also other components with DNEL values and relevant OCs/RMMs for the exposure route in question. It should, however, be noted that the methodology will be subject to changes before final publication. Comments on the draft methodology were given separately in parallel to the present project.

By contrast, the safe use information derived by the MS methodology, i.e., by selection of the most stringent of the component OCs/RMMs, covered the additive effects for all mixtures, effects and work-tasks considered. The drawback of this methodology, and the probable reason why it has not been supported by the industry, is that it may lead to overly stringent safe use information if the mixture contains low concentration of a component with low DNEL value (i.e., stringent OCs/RMMs) for which the component exposure scenario has been derived for 100% substance (see Taxell et al. 2014). For the example mixtures, this did not seem to be the case. The differences in the safe use information derived by the LCID methodology and the MS methodology were generally not dramatic, and the more stringent OCs/RMMs required by the MS methodology were justified from the point of view of covering also the additive effects.

One option would be to recommend the MS methodology as a simple and conservative “first-tier” approach for deriving the safe use information for a mixture. Further considerations would be necessary only in the cases where the MS methodology seems to lead to overly stringent OCs/RMMs deviating significantly from those typically applied for the type of product and work-task. Preferably, these situations could be taken into consideration by the registrant, who may easily derive substance exposure scenarios for different concentration ranges (i.e. not only for 100% substance as is often the case). This is in particular recommended for substances having low DNEL values and therefore increased likelihood of communicating overly stringent OCs/RMMs if the concentration of the substance in the mixture is not taken into consideration.

Alternatively, the formulator may take the concentration of the component in the mixture into consideration and modify the OCs/RMMs accordingly (i.e., scaling). For example, for the work-tasks considered in the present project, addition of local exhaust ventilation decreased the predicted exposure level in ECETOC TRA by 80%. The same nominal reduction of exposure may also be achieved by decreasing the concentration from 100% to 5% (ECETOC 2009). Application of the MS methodology would require nominal control efficiencies of the OCs/RMMs to be included in the substance exposure scenarios, which is currently not always the case.

When considering the MS methodology, it is worth mentioning that forwarding the component exposure scenarios as such, which is also one option for the formulator, would most probably also lead to selection of the most stringent measures, since the downstream user is obliged to follow the safe use information given in (any of) the exposure scenarios.

For the example mixtures, lowering the target RCR in the component exposure scenarios from 1 to 0.5 did not change the results significantly. Additive effects were still not covered by the safe use information derived by the draft LCID methodology for two mixtures, and the MS methodology covered additive effects even if the target RCR in the component exposure scenarios was 1.

In identifying the additive effects to consider, CLP hazard classification of the components may be applied as a starting point. It should be noted, however, that a hazard class may include effects on different target organs (e.g., specific target organ toxicity) or occurring by a different modes of action (e.g., reproductive toxicity). If there is a need to refine the assessment, the Mixie software may be applied to identify if additive effects are expected. Mixie may also complement the classification-based data, especially in relation to narcotic and irritative effects. Since the harmonized hazard classifications given in the Annex VI of the CLP regulation for substances regulated by REACH are mainly focused on specific hazard classes (carcinogenicity, mutagenicity, reproductive toxicity, respiratory sensitisation), and since impurities present in a component may affect its hazard classification, it is recommended to refer to the hazard classification given by the supplier.

When considering the results, the uncertainties in our approach need to be taken into consideration. The applied DNEL values were categorically selected based on the type of the effect for additivity (see section “Assessment of adequacy of the safe use information”), irrespective of whether the value was based on this particular effect. For many of the components, background information on the DNEL value (e.g., the critical target organ/effect) was not available. This makes the assessment conservative in the cases where the considered additive effect was not the critical effect of the component. Also, the exposure modelling applied includes simplifications and uncertainties, and the related results can therefore be considered only as rough estimates of the likely exposure levels and RCR values. Due to the limits of the modelling tool (ECETOC TRA, version 3.1), gaseous, solid and polymeric compounds were excluded from the analysis. This is, however, not expected to have a major impact on the final outcome.

Availability of background information on the DNEL values, in particular information on the critical target organ and effect on which the value is based, is important for the consideration of combination effects. Currently, this information is usually not given in the component safety data sheets and may also be missing from the ECHA dissemination database on the registered

substances. In the cases where background information on the DNEL values is not available, selecting the lowest available DNEL value in respect to the exposure route and type of additive effect (local/systemic; long-term/short-term), as was done in the present project, could be recommended as a conservative default approach for deriving combined RCRs for mixtures.

Conclusions

Selection of the most stringent OCs/RMMs presented in the component exposure scenarios may be recommended as a simple and conservative approach for deriving safe use information for a mixture. This approach is expected in most cases to cover also the possible additive effects of the components. A more detailed analysis would be necessary only in the cases where this approach seems to lead to overly stringent measures deviating significantly from those typically applied for the type of product and work-task.

On the basis of our analysis, there is a need to refine the draft LCID methodology in respect to combination effects. The CLP hazard classification could be applied as a starting point for identification of the components with additive effects, and the Mixie software may be additionally applied to refine the identification. Because of the incompleteness of the suggested approach for managing additive effects presented in the draft, we were not able to test the approach in its current form. In a later stage, however, the approach should be tested, for example applying a similar approach as in the present project, to ensure that the additive effects of the components are covered by the resulting safe use information.

A way for the formulator to ensure that the safe use information, derived either by selection of the most stringent measures, by the LCID methodology or by any other approach, covers all of the components and also the additive effects, would be to calculate the RCRs and $\sum$ RCRs in the conditions of the safe use information similarly as was done in the present project. Although this would be highly recommended, a majority of the formulators, in particular the smaller companies, are not likely to have the expertise and resources needed for this type of detailed analysis. Therefore, it would be very important to have straightforward approaches for deriving safe use information for mixtures, which have been carefully designed and adequately tested to ensure that the resulting safe use information really is safe.

References

EC. (2011) Toxicity and Assessment of Chemical Mixtures. Brussels: European commission, Directorate-General for Health & Consumers.

ECETOC. (2004) Targeted Risk Assessment. Technical Report No. 93. Brussels: European Centre for Ecotoxicology and Toxicology of Chemicals.

ECETOC. (2009) Addendum to ECETOC Targeted Risk Assessment Report No. 93. Brussels: European Centre for Ecotoxicology and Toxicology of Chemicals.

ECETOC. (2012) ECETOC TRA version 3: Background and rationale for the improvements. Technical Report No.114. Brussels: European Centre for Ecotoxicology and Toxicology of Chemicals.

ECHA. (2014) Guidance for downstream users. Version 2.1. October 2014. Helsinki: European Chemicals Agency.

CEFIC. (2014) DRAFT REACH Practical Guide on Exposure Assessment and Communication in the Supply Chains. Safe Use Information for Mixtures under REACH. Draft Version 3–9 December 2014. Brussels: European Chemical Industry Council / German Chemical Industry Association.

IRSST. (2010) Mixie: Mixtures of substances in the workplace: computer-based tool for evaluating the chemical risk. Available at: http://www.irsst.qc.ca/media/outils/intertox/jsndx_en.htm. Montreal: Institut de recherche Robert-Sauvé en santé et en sécurité du travail.

Meek ME, Boobis AR, Crofton KM et al. (2011) Risk assessment of combined exposure to multiple chemicals: a WHO/IPCS framework. *Regul Toxicol Pharmacol*; 60: S1–14.

Taxell P, Koponen M, Kallio N, Santonen T. (2014) Consolidating Exposure Scenario Information for Mixtures—Experiences and Challenges. *Ann Occup Hyg*; 58: 793–805.

Vyskocil A, Drolet D, Viau C et al. (2004). Database for the toxicological evaluation of mixtures in occupational atmospheres. *Environ Toxicol Pharmacol*; 18: 235–242.

Vyskocil A, Drolet D, Viau C et al. (2007). A web tool for the identification of potential interactive effects of chemical mixtures. *J Occup Environ Hyg*; 4: 281–287.

Appendix 1: Mixture 1 (thinner)

Example mixture no. 1 was a thinner. Relevant data on the components of the mixture are given in Table 1_1.

Table 1_1. Components of the example product with DNEL values for long-term and short-term inhalation exposure of workers and the lead component indicators (LCI).

Component	Classification (CLP)	Mean conc. (%)	Vapour press. 25 °C (hPa)	DNEL, long systemic (mg/m ³)	DNEL, long local (mg/m ³)	DNEL, short systemic (mg/m ³)	DNEL, short local (mg/m ³)	LCI
Acetone	H225, H319, H336	15	310	1210	-	-	2410	narc.
Butyl acetate	H226, H336	10	15	480	480	960	960	narc.
Xylene (iso-mers)	H226, H312, H315, H332	27	11	77	-	289	289	3.7
Methoxy-2-propanol	H226, H336	9	17	369	-	-	554	narc.
Toluene	H225, H304, H315, H336, H361d, H373	39	38	192	192	384	384	7.7

LCI: (mean concentration) x (vapour pressure) / DNEL long-term systemic ($C_i \times V_{p_i} / DNEL_i$)

narc.: LCI not calculated for narcotic effects.

Exposure scenarios for the components

The required operational conditions and risk management measures (OCs/RMMs) to achieve $RCR < 1$ and $RCR < 0.5$ were derived for each of the components for two work tasks: mixing (PROC5) and spraying (PROC11) in professional settings (Table 1_2).

Table 1_2. Operational conditions and risk management measures (OCs/RMMs) leading to inhalation exposure below the DNEL or below 0.5 x DNEL (i.e. risk characterization ratio (RCR) < 1 or RCR < 0.5), calculated by ECETOC TRA v3.1. RCRs calculated for undiluted (100%) substance, applying worker long-term (systemic) DNEL values as reference.

Component	OCs/RMMs (RCR < 1)	RCR	OCs/RMMs (RCR < 0.5)	RCR
Mixing, professional (PROC5)			Mixing, professional (PROC5)	
Acetone	good general ventilation	0.70	LEV (eff. 80%)	0.20
Butyl acetate	good general ventilation	0.70	LEV (eff. 80%)	0.20
Xylene (iso- mers)	LEV (eff. 80%) + good general ventilation	0.80	LEV (eff. 80%) + good general ventilation + duration 1–4 h	0.42
Methoxy-2- propanol	good general ventilation	0.70	LEV (eff. 80%)	0.20
Toluene	LEV (eff. 80%)	0.40	LEV (eff. 80%)	0.40
Spraying, professional (PROC11)			Spraying, professional (PROC11)	
Acetone	LEV (eff. 80%)	0.40	LEV (eff. 80%)	0.40
Butyl acetate	LEV (eff. 80%) + good general ventilation	0.70	LEV (eff. 80%) + good general ventilation + duration 1–4 h	0.42
Xylene (iso- mers)	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)	0.40	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)	0.40
Methoxy-2- propanol	LEV (eff. 80%) + good general ventilation	0.70	LEV (eff. 80%) + good general ventilation + duration 1–4 h	0.42
Toluene	LEV (eff. 80%) + good general ventilation + duration 1–4 h	0.84	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)	0.14

Combining exposure scenario information

Toluene was identified as the lead component by the LCID methodology. In addition, OCs/RMMs of **acetone**, **butyl acetate** and **methoxy-2-propanol** were to be taken into consideration (narcotic effects). However, the OCs/RMMs of toluene covered the OCs/RMMs of these substances, and they did therefore not contribute to the safe use information of the mixture.

OCs/RMMs of **xylene** were identified as the most stringent of the component OCs/RMMs, and these were selected for the mixture by the MS methodology.

Safe use information for the mixture, derived by the two methods, is presented in Table 1_3.

Table 1_3. Safe use information for the example product (worker inhalation exposure only) based on Lead Component Identification Methodology (LCID) and selection of the most stringent measures (MS). Safe use information were based on the OCs/RMMs of the single components corresponding to $RCR < 1$ and $RCR < 0.5$, according to Table 1_2.

Work task	Safe use descript. by LCID	Safe use descript. by MS
Mixing, prof. ($RCR < 1$)	LEV (eff. 80%)	LEV (eff. 80%) + good general ventilation
Mixing, prof. ($RCR < 0.5$)	LEV (eff. 80%)	LEV (eff. 80%) + good general ventilation + duration 1–4 h
Spraying, prof. ($RCR < 1$)	LEV (eff. 80%) + good general ventilation + duration 1–4 h	LEV (eff. 80%) + good general ventilation + respiratory protection (eff. 90%)
Spraying, prof. ($RCR < 0.5$)	LEV (eff. 80%) + good general ventilation + respiratory protection (eff. 90%)	LEV (eff. 80%) + good general ventilation + respiratory protection (eff. 90%)

Identification of the combination effects

Based on their CLP classification, four of the components cause narcotic effects (Table 1_4). According to Mixie, also the fifth component, xylene, may affect the central nervous system (CNS). Mixie also identified four of the components as upper respiratory tract and eye irritants.

Table 1_4. Common toxicological effects/target organs of the components based on their CLP hazard classification and the Mixie database.

Component	Classification (CLP)		Mixie		
	Narcotic (H366)	Skin irrit. (H315)	Eye irrit.	Upper resp. tract irrit.	Narcotic/ other CNS disorder
Acetone	x	-	x	x	x
Butyl acetate	x	-	x	x	-
Xylene (isomers)	-	x	x	x	x
Methoxy-2-propanol	x	-	nd	nd	nd
Toluene	x	x	x	x	x

nd: component not included in the Mixie database.

Assessment of adequacy of the safe use information

Narcotic effects were identified as a common effect of all of the five components of the mixture. Tables 1_5a and 1_5b present the RCR values of the components calculated in the conditions of the safe use information for the mixture derived by the two methodologies (given in Table 1_3). Although the RCR values of the components were all below one (i.e., exposure levels of the single components stay below their DNEL values), the combined RCR exceeded one in spraying in the conditions of safe use information derived by the draft LCID methodology (Table 1_5a).

If the target RCR in the component exposure scenarios was < 0.5 instead of < 1 , combined RCR below one was achieved by both of the methodologies (Table 1_5b).

Table 1_5a. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 1_3 (**short-term systemic** DNEL as the primary reference value). **RCR < 1** targeted in the component scenarios.

Component	Safe use descript. by LCID		Safe use descript. by MS	
	RCR in mixing	RCR in spraying	RCR in mixing	RCR in spraying
Acetone ^a	0.12	0.10	0.08	0.02
Butyl acetate	0.06	0.13	0.04	0.02
Xylene (isomers)	0.30	0.64	0.21	0.06
Methoxy-2-propanol ^a	0.12	0.25	0.09	0.04
Toluene	0.20	0.42	0.14	0.10
ΣRCR	0.80	1.5	0.56	0.24

^a Long-term systemic DNEL applied since a short-term systemic DNEL was not available.

Table 1_5b. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 1_3 (**short-term systemic** DNEL as the primary reference value). **RCR < 0.5** targeted in the component scenarios.

Component	Safe use descript. by LCID		Safe use descript. by MS	
	RCR in mixing	RCR in spraying	RCR in mixing	RCR in spraying
Acetone ^a	0.12	0.02	0.05	0.02
Butyl acetate	0.06	0.02	0.03	0.02
Xylene (isomers)	0.30	0.06	0.13	0.06
Methoxy-2-propanol ^a	0.12	0.04	0.05	0.04
Toluene	0.20	0.10	0.08	0.10
ΣRCR	0.80	0.24	0.34	0.24

^a Long-term systemic DNEL applied since a short-term systemic DNEL was not available.

Appendix 2: Mixture 2 (coating)

Example mixture no. 2 was a coating. Relevant data on the components of the mixture are given in Table 2_1.

Table 2_1. Components of the example product with DNEL values for long-term and short-term inhalation exposure of workers and the lead component indicators (LCI).

Component	Classification (CLP)	Mean conc. (%)	Vapour press. 25 °C (Pa)	DNEL, long systemic (mg/m ³)	DNEL, long local (mg/m ³)	DNEL, short systemic (mg/m ³)	DNEL, short local (mg/m ³)	LCI
Diethylenetriamine	H302, H312, H314, H317	30	31	15.4	0.9	92.1	2.6	no class.
Bisphenol A	H318, H317, H361f, H335	23	0.00005	10	-	10	10	1.2E-6
Nonylphenol	H302, H314, H361fd, H400, H410	9	0.003	0.5	-	1.0	-	5.3E-4
1-(2- Ami-noethyl)piperazine	H302, H311, H314, H317, H412	9	5	3.6	-	21.4	-	no class.

LCI: (mean concentration) x (vapour pressure) / DNEL long-term systemic ($C_i \times V_{pi} / DNEL_i$)

no class.: LCI not calculated since the component does not have a classification in relation to inhalation exposure.

Exposure scenarios for the components

The required operational conditions and risk management measures (OCs/RMMs) to achieve $RCR < 1$ and $RCR < 0.5$ were derived for each of the components for two work tasks: mixing (PROC5) and low-energy spreading (PROC10) in professional settings (Table 2_2).

Table 2_2. Operational conditions and risk management measures (OCs/RMMs) leading to inhalation exposure below the DNEL or below 0.5 x DNEL (i.e. risk characterization ratio (RCR) < 1 or RCR < 0.5), calculated by ECETOC TRA v3.1. RCRs calculated for undiluted (100%) substance, applying the lowest of the worker long-term DNEL values as reference.

Component	OCs/RMMs (RCR < 1)	RCR	OCs/RMMs (RCR < 0.5)	RCR
Mixing, prof. (PROC5)			Mixing, prof. (PROC5)	
Diethylenetriamine	LEV (eff. 80%)	0.56	LEV (eff. 80%) + good general ventilation	0.39
Bisphenol A	none	0.10	none	0.10
Nonylphenol	none	0.78	LEV (eff. 80%)	0.16
1-(2- Ami- noethyl)piperazine	LEV (eff. 80%) + good general ventilation + duration 1–4 h + respirator (eff. 90%)	0.27	LEV (eff. 80%) + good general ventilation + duration 1–4 h + respirator (eff. 90%)	0.27
Spreading, prof. (PROC10)			Spreading, prof. (PROC10)	
Diethylenetriamine	LEV (eff. 80%) + good general ventilation	0.97	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)	0.10
Bisphenol A	LEV (eff. 80%)	0.02	LEV (eff. 80%)	0.02
Nonylphenol	LEV (eff. 80%)	0.16	LEV (eff. 80%)	0.16
1-(2- Aminoethyl)piperazine	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)	0.52	LEV (eff. 80%) + good general ventilation + duration 1–4 h + respirator (eff. 90%)	0.31

Combining exposure scenario information

Nonylphenol was identified as the lead component by the LCID methodology (Table 2_1). In addition, OCs/RMMs of **bisphenol A** were to be taken into consideration (respiratory irritation). However, the OCs/RMMs of nonylphenol covered the OCs/RMMs of bisphenol A, and they did therefore not contribute to the safe use information of the mixture.

OCs/RMMs of **1-(2-aminoethyl)piperazine** were identified as the most stringent of the component OCs/RMMs (Table 2_2), and these were selected for the mixture by the MS methodology.

Safe use information for the mixture, derived by the two methods, is presented in Table 2_3.

Table 2_3. Safe use information for the example product (worker inhalation exposure only) based on Lead Component Identification Methodology (LCID) and selection of the most stringent measures (MS). Safe use information were based on the OCs/RMMs of the single components corresponding to RCR < 1 and RCR < 0.5, according to Table 2_2.

Work task	Safe use descript. by LCID	Safe use descript. by MS
Mixing, prof. (RCR < 1)	none	LEV (eff. 80%) + good general ventilation + duration 1–4 h + respirator (eff. 90%)
Mixing, prof. (RCR < 0.5)	LEV (eff. 80%)	LEV (eff. 80%) + good general ventilation + duration 1–4 h + respirator (eff. 90%)
Spreading, prof. (RCR < 1)	LEV (eff. 80%)	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)
Spreading, prof. (RCR < 0.5)	LEV (eff. 80%)	LEV (eff. 80%) + good general ventilation + duration 1–4 h + respirator (eff. 90%)

Identification of the combination effects

Based on their CLP classification, bisphenol A and nonylphenol have adverse effects on the fertility (Table 2_4). All of the components are classified as corrosive or irritative to eyes and the respiratory tract. Except for skin sensitisation, no other common classifications were identified. Only one of the components, diethylenetriamine, was included in the Mixie database.

Table 2_4. Common toxicological effects/target organs of the components based on their CLP hazard classification and the Mixie database.

Component	Classification (CLP)				Mixie			
	Eye irrit./corr. (H318/H314)	Resp. irrit./corr. (H355/H314)	Skin sensit. (H317)	Reprod. toxicity (H361f)	Eye irrit./corr.	Upper resp. tract irrit.	Resp. sensit.	Skin irrit./corr.
Diethylenetriamine	x	x	x	-	x	x	x	x
Bisphenol A	x	x	x	x	nd	nd	nd	nd
Nonylphenol	x	x	-	x	nd	nd	nd	nd
1-(2-Aminoethyl)piperazine	x	x	x	-	nd	nd	nd	nd

nd: component not included in the Mixie database.

Assessment of adequacy of the safe use information

Adverse effects on fertility were identified as a common effect for bisphenol A and nonylphenol. Tables 2_5a and 2_5b present the RCR values of these components calculated in the conditions of the safe use information for the mixture defined by the two methodologies (given in Table 2_3). Combined RCR below one was achieved by both of the methodologies.

In addition, irritative (incl. corrosive) effects in the respiratory tract were identified as a common effect for all of the four components. Tables 2_6a and 2_6b present the corresponding RCR values of the components calculated in the conditions of the safe use information for the mixture. In this case, both RCRs of the single components and the combined RCRs exceed one in the conditions of safe use information derived by the draft LCID methodology, both if the target RCR in the component exposure scenarios was 1 or 0.5. The main reason for this is that the draft LCID methodology does not consider corrosive effects when choosing the OCs/RMMs related to local effects in the respiratory tract.

Table 2_5a. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 2_3 (**long-term systemic** DNEL as the primary reference value). **RCR < 1** targeted in the component scenarios.

Component	Safe use descript. by LCID		Safe use descript. by MS	
	RCR in mixing	RCR in spreading	RCR in mixing	RCR in spreading
Bisphenol A	0.06	0.01	0.0005	0.0008
Nonylphenol	0.47	0.09	0.004	0.007
ΣRCR	0.53	0.10	0.005	0.008

Table 2_5b. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 2_3 (**long-term systemic** DNEL as the primary reference value). **RCR < 0.5** targeted in the component scenarios.

Component	Safe use descript. by LCID		Safe use descript. by MS	
	RCR in mixing	RCR in spreading	RCR in mixing	RCR in spreading
Bisphenol A	0.01	0.01	0.0005	0.0005
Nonylphenol	0.09	0.09	0.004	0.004
ΣRCR	0.10	0.10	0.005	0.005

Table 2_6a. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 2_3 (**short-term local** DNEL as the primary reference value). **RCR < 1** targeted in the component scenarios.

Component	Safe use descript. by LCID		Safe use descript. by MS	
	RCR in mixing	RCR in spreading	RCR in mixing	RCR in spreading
Diethylenetriamine	17	8.3	0.14	0.57
Bisphenol A	0.06	0.01	0.0005	0.0008
Nonylphenol ^a	0.24	0.05	0.002	0.003
1-(2- Ami- noethyl)piperazine ^a	1.5	0.75	0.01	0.05
ΣRCR	19	9.1	0.15	0.62

^a Short-term systemic DNEL value applied since local DNELs were not available.

Table 2_6b. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 2_3 (**short-term local** DNEL as the primary reference value). **RCR < 0.5** targeted in the component scenarios.

Component	Safe use descript. by LCID		Safe use descript. by MS	
	RCR in mixing	RCR in spreading	RCR in mixing	RCR in spreading
Diethylenetriamine	3.3	8.3	0.14	0.35
Bisphenol A	0.01	0.01	0.0005	0.005
Nonylphenol ^a	0.05	0.05	0.002	0.002
1-(2- Ami- noethyl)piperazine ^a	0.30	0.75	0.01	0.03
ΣRCR	4.1	9.1	0.15	0.39

^a Short-term systemic DNEL value applied since local DNELs were not available.

Appendix 3: Mixture 3 (detergent)

Example mixture no. 3 was a detergent. Relevant data on the components of the mixture are given in Table 3_1.

Table 3_1. Components of the example product with DNEL values for long-term and short-term inhalation exposure of workers and the lead component indicators (LCI).

Component	Classification (CLP)	Mean conc. (%)	Vapour press. 25 °C (hPa)	DNEL, long systemic (mg/m ³)	DNEL, long local (mg/m ³)	DNEL, short systemic (mg/m ³)	DNEL, short local (mg/m ³)	L CI
Acetone	H225, H319, H336	10	310	1210	-	-	554	narc.
Heptane	H225, H304, H315, H336, H400, H410	20	61	2085	-	-	-	narc.
Methanol	H225, H301, H311, H331, H370	45	170	260	260	260	260	29
Toluene	H225, H304, H315, H336, H361d, H373	20	38	192	192	384	384	3.9

LCI: mean concentration x vapour pressure / DNEL long-term systemic ($C_i \times V_{pi} / DNEL_i$)

narc.: LCI not calculated since narcotic effects is the only classification in relation to inhalation exposure.

Exposure scenarios for the components

The required operational conditions and risk management measures (OCs/RMMs) to achieve $RCR < 1$ and $RCR < 0.5$ were derived for each of the components for two work tasks: transfers, loading and filling (PROC8a) and treatment of articles by dipping or pouring (PROC13) in professional settings (Table 3_2).

Table 3_2. Operational conditions and risk management measures (OCs/RMMs) leading to inhalation exposure below the DNEL or below 0.5 x DNEL (i.e. risk characterization ratio (RCR) < 1 or RCR < 0.5), calculated by ECETOC TRA v3.1. RCRs calculated for undiluted (100%) substance, applying worker long-term systemic DNEL values as reference.

Component	OCs/RMMs (RCR < 1)	RCR	OCs/RMMs (RCR < 0.5)	RCR
Transfers, prof. (PROC8a)			Transfers, prof. (PROC8a)	
Acetone	good general ventilation	0.70	LEV (eff. 80%)	0.20
Heptane	none	0.20	none	0.20
Methanol	LEV (eff. 80%)	0.51	LEV (eff. 80%) + good general ventilation	0.36
Toluene	LEV (eff. 80%)	0.40	LEV (eff. 80%)	0.40
Dipping, prof. (PROC13)			Dipping, prof. (PROC13)	
Acetone	none	0.49	none	0.49
Heptane	none	0.20	none	0.20
Methanol	good general ventilation	0.90	LEV (eff. 80%)	0.26
Toluene	LEV (eff. 80%)	0.40	LEV (eff. 80%)	0.40

Combining exposure scenario information

Methanol was identified as the lead component by the LCID methodology (Table 3_1). In addition, OCs/RMMs of **acetone**, **heptane** and **toluene** were to be taken into consideration (narcotic effects). However, the OCs/RMMs of methanol covered the OCs/RMMs of these substances, and they did therefore not contribute to the safe use information of the mixture.

OCs/RMMs of **methanol** or **toluene**, depending on the task and target RCR, were identified as the most stringent of the component OCs/RMMs (Table 3_2), and these were selected for the mixture by the MS methodology.

Safe use information for the mixture, derived by the two methods, is presented in Table 3_3.

Table 3_3. Safe use information for the example product (worker inhalation exposure only) based on Lead Component Identification Methodology (LCID) and selection of the most stringent measures (MS). Safe use information was based on the OCs/RMMs of the single components corresponding to RCR < 1 and RCR < 0.5, according to Table 3_2.

Work task	Safe use descript. by LCID	Safe use descript. by MS
Transfers, prof. (RCR < 1)	LEV (eff. 80%)	LEV (eff. 80%)
Transfers, prof. (RCR < 0.5)	LEV (eff. 80%) + good general ventilation	LEV (eff. 80%) + good general ventilation
Dipping, prof. (RCR < 1)	good general ventilation	LEV (eff. 80%)
Dipping, prof. (RCR < 0.5)	LEV (eff. 80%)	LEV (eff. 80%)

Identification of the combination effects

Based on their CLP classification, three of the components cause narcotic effects (Table 3_4). According to Mixie, also the fourth component, methanol, may affect the central nervous system (CNS). Mixie also identifies three of the components as upper respiratory tract and eye irritants.

Table 3_4. Common toxicological effects/target organs of the components based on their CLP hazard classification and the Mixie database.

Component	Classification (CLP)		Mixie		
	Narcotic (H366)	Skin irrit. (H315)	Narcotic/other CNS disorder	Eye irrit.	Upper resp. tract irrit.
Acetone	x	-	x	x	x
Heptane	x	x	x	x	x
Methanol	-	-	x	-	-
Toluene	x	x	x	x	x

Assessment of adequacy of the safe use information

Narcotic effects were identified as a common effect of all of the four components of the mixture. Tables 3_5a and 3_5b present the RCR values of the components calculated in the conditions of the safe use information for the mixture defined by the two methodologies (given in Table 3_3). Although the RCR values of the components were all below one (i.e. exposure levels of the single components stay below their DNEL values), the combined RCR exceeded one in dipping in the conditions of safe use information derived by the draft LCID methodology (Table 3_5a).

If the target RCR in the component exposure scenarios was < 0.5 instead of < 1, combined RCR below one was achieved by both of the methodologies (Table 3_5b).

Table 3_5a. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 3_3 (**short-term systemic** DNEL as the primary reference value). **RCR < 1** targeted in the component scenarios.

Component	Safe use descript. by LCID		Safe use descript. by MS	
	RCR in transfers	RCR in dipping	RCR in transfers	RCR in dipping
Acetone ^a	0.12	0.21	0.12	0.06
Heptane ^a	0.02	0.08	0.02	0.02
Methanol	0.51	0.90	0.51	0.26
Toluene	0.12	0.42	0.12	0.12
ΣRCR	0.77	1.6	0.77	0.46

^a Long-term systemic DNEL applied since a short-term systemic DNEL was not available.

Table 3_5b. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 3_3 (**short-term systemic** DNEL as reference value). RCR < 0.5 targeted in the component scenarios.

Component	Safe use descript. by LCID		Safe use descript. by MS	
	RCR in transfers	RCR in dipping	RCR in transfers	RCR in dipping
Acetone ^a	0.08	0.06	0.08	0.06
Heptane ^a	0.02	0.02	0.02	0.02
Methanol	0.35	0.26	0.35	0.26
Toluene	0.08	0.12	0.08	0.12
ΣRCR	0.53	0.46	0.53	0.46

^a Long-term systemic DNEL applied since a short-term systemic DNEL was not available.

Appendix 4: Mixture 4 (spray-paint)

Example mixture no. 4 was a spray-paint. Relevant data on the components of the mixture are given in Table 4_1.

Table 4_1. Components of the example product with DNEL values for long-term and short-term inhalation exposure of workers and the lead component indicators (LCI).

Component	Classification (CLP)	Mean conc. (%)	Vapour press. 25 °C (hPa)	DNEL, long systemic (mg/m ³)	DNEL, long local (mg/m ³)	DNEL, short systemic (mg/m ³)	DNEL, short local (mg/m ³)	LCI
Acetone	H225, H319, H336	38	310	1210	-	-	2420	narc.
1-Butanol	H226, H302, H315, H318, H335, H336	3.8	8.9	310	-	-	-	0.11
Butyl acetate	H226, H336	7.5	15	480	480	960	960	narc.
Methoxy-1-methylethyl acetate	H226	7.5	5.2	-	275	-	-	no class.
Butanone	H225, H319, H336	7.5	121	600	-	-	-	narc.

LCI: (mean concentration) x (vapour pressure) / DNEL long-term systemic ($C_i \times V_{pi} / DNEL_i$)

narc.: LCI not calculated for narcotic effects.

no class.: LCI not calculated since the component does not have a classification in relation to inhalation exposure.

Exposure scenarios for the components

The required operational conditions and risk management measures (OCs/RMMs) to achieve $RCR < 1$ and $RCR < 0.5$ were derived for each of the components for spraying in professional settings (PROC11) (Table 4_2).

Table 4_2. Operational conditions and risk management measures (OCs/RMMs) leading to inhalation exposure below the DNEL or below 0.5 x DNEL (i.e. risk characterization ratio (RCR) < 1 or RCR < 0.5), calculated by ECETOC TRA v3.1. RCRs calculated for undiluted (100%) substance, applying worker long-term (systemic) DNEL values as reference.

Component	OCs/RMMs (RCR < 1)	RCR	OCs/RMMs (RCR < 0.5)	RCR
Spraying, prof. (PROC11)			Spraying, prof. (PROC11)	
Acetone	LEV (eff. 80%)	0.40	LEV (eff. 80%)	0.40
1-Butanol	LEV (eff. 80%)	0.99	LEV (eff. 80%) + good general ventilation + duration 1–4 h	0.42
Butyl acetate	LEV (eff. 80%) + good general ventilation	0.70	LEV (eff. 80%) + good general ventilation + duration 1–4 h	0.42
Methoxy-1-methylethyl acetate	LEV (eff. 80%) + good general ventilation + duration 1–4 h	0.84	LEV (eff. 80%) + good general ventilation + duration 1–4 h + respirator (eff. 90%)	0.08
Butanone	LEV (eff. 80%) + good general ventilation	0.70	LEV (eff. 80%) + good general ventilation + duration 1–4 h	0.42

Combining exposure scenario information

1-Butanol was identified as the lead component by the LCID methodology (Table 4_1). In addition, OCs/RMMs of **acetone**, **butyl acetate** and **butanone** were to be taken into consideration (narcotic effects). Of these, butyl acetate and butanone had more stringent OCs/RMMs than the lead component, and these were therefore added to the safe use information of the mixture.

OCs/RMMs of **methoxy-1-methylethyl acetate** were identified as the most stringent of the component OCs/RMMs (Table 4_2), and these were selected for the mixture by the MS methodology.

Safe use information for the mixture, derived by the two methods, is presented in Table 4_3.

Table 4_3. Safe use information for the example product (worker inhalation exposure only) based on Lead Component Identification Methodology (LCID) and selection of the most stringent measures (MS). Safe use information was based on the OCs/RMMs of the single components corresponding to RCR < 1 and RCR < 0.5, according to Table 4_2.

Work task	Safe use descript. by LCID	Safe use descript. by MS
Spraying, prof. (RCR < 1)	LEV (eff. 80%) + good general ventilation	LEV (eff. 80%) + good general ventilation + duration 1–4 h
Spraying, prof. (RCR < 0.5)	LEV (eff. 80%) + good general ventilation + duration 1–4 h	LEV (eff. 80%) + good general ventilation + duration 1–4 h + respirator (eff. 90%)

Identification of the combination effects

Based on the CLP classification, four of the six components cause narcotic effects (Table 4_4). According to Mixie, the same components cause also eye irritation, and three of them also upper respiratory tract irritation, although only two of them are classified as eye irritants and none as respiratory irritant.

Table 4_4. Common toxicological effects/target organs of the components based on their CLP hazard classification and the Mixie database.

Component	Classification (CLP)		Mixie		
	Narcotic (H366)	Eye irrit. (H319)	Narcotic/other CNS disorder	Eye irrit.	Upper resp. tract irrit.
Acetone	x	x	x	x	x
1-Butanol	x	-	x	x	-
Butyl acetate	x	-	-	x	x
Methoxy-1-methylethyl acetate	-	-	nd	nd	nd
Butanone	x	x	-	x	x

Assessment of adequacy of the safe use information

Narcotic effects were identified as a common effect of four of the components of the mixture. Tables 4_5a and 4_5b present the RCR values of the components calculated in the conditions of the safe use information for the mixture defined by the two methodologies (given in Table 4_3). Although the RCR values of the components were all below one (i.e. exposure levels of the single components stay below their DNEL values), the combined RCR exceeded one in the conditions of safe use information derived by the draft LCID methodology (Table 4_5a).

If the target RCR in the component exposure scenarios was < 0.5 instead of < 1, combined RCR below one was achieved by both of the methodologies (Table 4_5b).

Table 4_5a. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 4_3 (**short-term systemic** DNEL as the primary reference value). **RCR < 1** targeted in the component scenarios.

Component	Safe use descript. by LCID RCR in spraying	Safe use descript. by MS RCR in spraying
Acetone ^a	0.30	0.17
1-Butanol ^a	0.14	0.08
Butyl acetate	0.21	0.13
Butanone ^a	0.42	0.25
ΣRCR	1.1	0.63

^a Long-term systemic DNEL applied since a short-term systemic DNEL was not available.

Table 4_5b. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 4_3 (**short-term systemic** DNEL as the primary reference value). **RCR < 0.5** targeted in the component scenarios.

Component	Safe use descript. by LCID	Safe use descript. by MS
	RCR in spraying	RCR in spraying
Acetone ^a	0.17	0.02
1-Butanol ^a	0.08	0.01
Butyl acetate	0.13	0.01
Butanone ^a	0.25	0.03
ΣRCR	0.63	0.07

^a Long-term systemic DNEL applied since a short-term systemic DNEL was not available.

Appendix 5: Mixture 5 (detergent)

Example mixture no. 5 was a detergent. Relevant data on the components of the mixture are given in Table 5_1.

Table 5_1. Components of the example product with DNEL values for long-term and short-term inhalation exposure of workers and the lead component indicators (LCI).

Component	Classification (CLP)	Mean conc. (%)	Vapour press. 25 °C (hPa)	DNEL, long systemic (mg/m ³)	DNEL, long local (mg/m ³)	DNEL, short systemic (mg/m ³)	DNEL, short local (mg/m ³)	LCI
Xylene	H226, H312, H315, H332	1.3	11	77	-	289	289	0.17
1-Propylbenzene ^a	H226, H304, H335, H411	6.3	4.6	100	-	250	-	local
Solvent naphtha ^b	H304	38	33	100	-	-	-	no class.
1,3,5-Trimethylbenzene	H226, H335, H411	6.3	33	100	100	100	100	local
Methoxy-1-methylethyl acetate	H226	38	52	-	275	-	-	no class.
Cumene	H226, H304, H335, H411	6.3	60	100	-	250	-	local
1,2,4-Trimethylbenzene	H226, H315, H319, H332, H335, H411	1.3	28	100	-	100	100	0.04

^a Not registered. DNEL values of cumene (isopropylbenzene) applied as surrogate.

^b Solvent naphtha (petroleum), light aromatic (<0.1 % w/w benzene); consists predominantly of C8–C10 aromatic hydrocarbons. Physico-chemical data of trimethylbenzene (C9) applied as surrogate.

LCI: (mean concentration) x (vapour pressure) / DNEL long-term systemic ($C_i \times Vp_i / DNEL_i$)

local: LCI not calculated for local effects in the respiratory tract.

no class.: LCI not calculated since the component does not have a classification in relation to inhalation exposure.

Exposure scenarios for the components

The required operational conditions and risk management measures (OCs/RMMs) to achieve $RCR < 1$ and $RCR < 0.5$ were derived for each of the components for two work tasks: transfers, loading and filling (PROC8a) and low-energy spreading (PROC10) in professional settings (Table 5_2).

Table 5_2. Operational conditions and risk management measures (OCs/RMMs) leading to inhalation exposure below the DNEL or below $0.5 \times$ DNEL (i.e. risk characterization ratio (RCR) < 1 or $RCR < 0.5$), calculated by ECETOC TRA v3.1. RCRs calculated for undiluted (100%) substance, applying worker long-term systemic DNEL values as reference.

Component	OCs/RMMs ($RCR < 1$)	RCR	OCs/RMMs ($RCR < 0.5$)	RCR
Transfers, prof. (PROC8a)			Transfers, prof. (PROC8a)	
Xylene	LEV (eff. 80 %) + good general ventilation	0.81	LEV (eff. 80 %) + good general ventilation + duration 1–4 h	0.49
1-Propylbenzene	good general ventilation	0.88	LEV (eff. 80%)	0.25
Solvent naphtha	good general ventilation	0.88	LEV (eff. 80%)	0.25
1,3,5-Trimethylbenzene	good general ventilation	0.88	LEV (eff. 80%)	0.25
Methoxy-1-methylethyl acetate	LEV (eff. 80%)	0.40	LEV (eff. 80%)	0.40
Cumene	LEV (eff. 80 %) + good general ventilation	0.70	LEV (eff. 80 %) + good general ventilation + duration 1–4 h	0.42
1,2,4-Trimethylbenzene	good general ventilation	0.88	LEV (eff. 80%)	0.25
Spreading, prof (PROC10)			Spreading, prof (PROC10)	
Xylene	LEV (eff. 80 %) + good general ventilation	0.81	LEV (eff. 80 %) + good general ventilation + duration 1–4 h	0.49
1-Propylbenzene	good general ventilation	0.88	LEV (eff. 80%)	0.25
Solvent naphtha	good general ventilation	0.88	LEV (eff. 80%)	0.25
1,3,5-Trimethylbenzene	good general ventilation	0.88	LEV (eff. 80%)	0.25
Methoxy-1-methylethyl acetate	LEV (eff. 80%)	0.40	LEV (eff. 80%)	0.40
Cumene	LEV (eff. 80 %) + good general ventilation	0.70	LEV (eff. 80 %) + good general ventilation + duration 1–4 h	0.42
1,2,4-Trimethylbenzene	good general ventilation	0.88	LEV (eff. 80%)	0.25

Combining exposure scenario information

Xylene was identified as the lead component by the LCID methodology (Table 5_1). In addition, OCs/RMMs of **1-propylbenzene**, **1,3,5-trimethylbenzene**, **1,2,4-trimethylbenzene** and **cumene** were to be taken into consideration (respiratory irritation). However, the OCs/RMMs of xylene covered the OCs/RMMs of these substances, and they did therefore not contribute to the safe use information of the mixture.

OCs/RMMs of **xylene** or **cumene** were identified as the most stringent of the component OCs/RMMs (Table 5_2), and these were selected for the mixture by the MS methodology.

Safe use information for the mixture, derived by the two methods, was identical (Table 5_3).

Table 5_3. Safe use information for the example product (worker inhalation exposure only) based on Lead Component Identification Methodology (LCID) and selection of the most stringent measures (MS). Safe use information was based on the OCs/RMMs of the single components corresponding to $RCR < 1$ and $RCR < 0.5$, according to Table 5_2.

Work task	Safe use descript. by LCID	Safe use descript. by MS
Transfers, prof. ($RCR < 1$)	LEV (eff. 80 %) + good general ventilation	LEV (eff. 80 %) + good general ventilation
Transfers, prof. ($RCR < 0.5$)	LEV (eff. 80 %) + good general ventilation + duration 1–4 h	LEV (eff. 80 %) + good general ventilation + duration 1–4 h
Spreading, prof. ($RCR < 1$)	LEV (eff. 80 %) + good general ventilation	LEV (eff. 80 %) + good general ventilation
Spreading, prof. ($RCR < 0.5$)	LEV (eff. 80 %) + good general ventilation + duration 1–4 h	LEV (eff. 80 %) + good general ventilation + duration 1–4 h

Identification of the combination effects

Based on their CLP classification, four of the seven components cause respiratory irritation (Table 5_4). According to Mixie, six of the components cause upper respiratory tract and eye irritation, and also narcotic effects/CNS depression.

Table 5_4. Common toxicological effects/target organs of the components based on their CLP hazard classification and the Mixie database.

Component	Classification (CLP)		Mixie		
	Respiratory irrit. (H335)	Skin irrit. (H315)	Upper resp. tract irrit.	Eye irrit.	Narcotic/other CNS disorder
Xylene	-	x	x	x	x
n-Propylbenzene	x	-	x	x	x
Solvent naphtha	-	-	x	x	x
1,3,5-Trimethylbenzene	x	-	x	x	x
Methoxy-1-methylethyl acetate	-	-	nd	nd	nd
Cumene	x	-	x	x	x
1,2,4-Trimethylbenzene	x	x	x	x	x

Assessment of adequacy of the safe use information

Upper respiratory tract irritation and narcotic effects were identified as common effects of six of the components. Tables 5_5a and 5_5b present the RCR values of these components related to respiratory irritation, and Tables 5_6a and 5_6b related to narcotic effects, calculated in the conditions of the safe use information for the mixture defined by the two methodologies (given in Table 5_3). Combined RCRs below one were achieved by both of the methodologies.

Table 5_5a. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 5_3 (**short-term local DNEL** as the primary reference value). **RCR < 1** targeted in the component scenarios.

Component	Safe use descript. by LCId		Safe use descript. by MS	
	RCR in transfers	RCR in spreading	RCR in transfers	RCR in spreading
Xylene	0.04	0.04	0.04	0.04
n-Propylbenzene ^a	0.04	0.04	0.04	0.04
Solvent naphtha ^b	0.18	0.18	0.18	0.18
1,3,5-Trimethylbenzene	0.11	0.11	0.11	0.11
Cumene ^a	0.17	0.17	0.17	0.17
1,2,4-Trimethylbenzene	0.04	0.04	0.04	0.04
ΣRCR	0.58	0.58	0.58	0.58

^a Short-term systemic DNEL value applied since local DNELs were not available.

^b Long-term systemic DNEL applied since local or short-term systemic DNELs were not available.

Table 5_5b. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 5_3 (**short-term local** DNEL as the primary reference value). **RCR < 0.5** targeted in the component scenarios.

Component	Safe use descript. by LCId		Safe use descript. by MS	
	RCR in transfers	RCR in spreading	RCR in transfers	RCR in spreading
Xylene	0.03	0.03	0.03	0.03
n-Propylbenzene ^a	0.03	0.03	0.03	0.03
Solvent naphtha ^b	0.11	0.11	0.11	0.11
1,3,5-Trimethylbenzene	0.06	0.06	0.06	0.06
Cumene ^a	0.10	0.10	0.10	0.10
1,2,4-Trimethylbenzene	0.02	0.02	0.02	0.02
ΣRCR	0.35	0.35	0.35	0.35

^a Short-term systemic DNEL value applied since local DNELs were not available.

^b Long-term systemic DNEL applied since local or short-term systemic DNELs were not available.

Table 5_6a. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 5_3 (**short-term systemic** DNEL as the primary reference value). **RCR < 1** targeted in the component scenarios.

Component	Safe use descript. by LCId		Safe use descript. by MS	
	RCR in transfers	RCR in spreading	RCR in transfers	RCR in spreading
Xylene	0.04	0.04	0.04	0.04
n-Propylbenzene	0.04	0.04	0.04	0.04
Solvent naphtha ^a	0.18	0.18	0.18	0.18
1,3,5-Trimethylbenzene	0.11	0.11	0.11	0.11
Cumene	0.17	0.17	0.17	0.17
1,2,4-Trimethylbenzene	0.04	0.04	0.04	0.04
ΣRCR	0.58	0.58	0.58	0.58

^a Long-term systemic DNEL applied since a short-term systemic DNEL was not available.

Table 5_6b. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 5_3 (**short-term systemic** DNEL as the primary reference value). **RCR < 0.5** targeted in the component scenarios.

Component	Safe use descript. by LCId		Safe use descript. by MS	
	RCR in transfers	RCR in spreading	RCR in transfers	RCR in spreading
Xylene	0.03	0.03	0.03	0.03
n-Propylbenzene	0.03	0.03	0.03	0.03
Solvent naphtha ^a	0.11	0.11	0.11	0.11
1,3,5-Trimethylbenzene	0.06	0.06	0.06	0.06
Cumene	0.10	0.10	0.10	0.10
1,2,4-Trimethylbenzene	0.02	0.02	0.02	0.02
ΣRCR	0.35	0.35	0.35	0.35

^a Long-term systemic DNEL applied since a short-term systemic DNEL was not available.

Appendix 6: Mixture 6 (paint)

Example mixture no. 6 was a paint. Relevant data on the components of the mixture are given in Table 6_1.

Table 6_1. Components of the example product with DNEL values for long-term and short-term inhalation exposure of workers and the lead component indicators (LCI).

Component	Classification (CLP)	Mean conc. (%)	Vapour press. 25 °C (hPa)	DNEL, long systemic (mg/m ³)	DNEL, long local (mg/m ³)	DNEL, short systemic (mg/m ³)	DNEL, short local (mg/m ³)	LCI
Ethanol	H225	13	79	950	-	-	1900	no class.
Ethyl benzene	H225, H332	2.0	13	77	-		293	0.33
Xylene	H226, H312, H315, H332	7.5	11	77	-	289	289	1.0
Methoxy-2-propanol	H226, H336	7.5	17	369	-	-	554	narc.
Butanone	H225, H319, H336	13	121	600	-	-	-	narc.
Isobutanol	H226, H315, H318, H335, H336	3.0	14	310	-	-	-	narc.
Isopropanol	H225, H319, H336	7.5	61	500	-	-	-	narc.
Toluene	H225, H304, H315, H336, H361d, H373	43	38	192	192	384	384	8.4

LCI: mean concentration x vapour pressure / DNEL long-term systemic ($C_i \times V_{pi} / DNEL_i$)

narc.: LCI not calculated for narcotic effects.

no class.: LCI not calculated since the component does not have a classification in relation to inhalation exposure.

Exposure scenarios for the components

The required operational conditions and risk management measures (OCs/RMMs) to achieve $RCR < 1$ and $RCR < 0.5$ were derived for each of the components for two work tasks: low-energy spreading (PROC10) and spraying (PROC11) in professional settings (Table 6_2).

Table 6_2. Operational conditions and risk management measures (OCs/RMMs) leading to inhalation exposure below the DNEL or below $0.5 \times DNEL$ (i.e. risk characterization ratio (RCR) < 1 or $RCR < 0.5$), calculated by ECETOC TRA v3.1. RCRs calculated for undiluted (100%) substance, applying worker long-term systemic DNEL values as reference.

Component	OCs/RMMs ($RCR < 1$)	RCR	OCs/RMMs ($RCR < 0.5$)	RCR
Spreading, prof (PROC10)			Spreading, prof (PROC10)	
Ethanol	none	0.20	none	0.20
Ethyl benzene	LEV (eff. 80%) + good general ventilation	0.80	LEV (eff. 80%) + good general ventilation + duration 1–4 h	0.48
Xylene	LEV (eff. 80%) + good general ventilation	0.80	LEV (eff. 80%) + good general ventilation + duration 1–4 h	0.48
Methoxy-2-propanol	good general ventilation	0.71	LEV (eff. 80%)	0.20
Butanone	LEV (eff. 80%)	0.50	LEV (eff. 80%)	0.50
Isobutanol	none	0.99	LEV (eff. 80%)	0.20
Isopropanol	none	0.50	none	0.50
Toluene	LEV (eff. 80%)	0.40	LEV (eff. 80%)	0.40
Spraying, prof (PROC11)			Spraying, prof (PROC11)	
Ethanol	good general ventilation	0.71	LEV (eff. 80%)	0.20
Ethyl benzene	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)	0.57	LEV (eff. 80%) + good general ventilation + duration 1–4 h + respirator (eff. 90%)	0.24
Xylene	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)	0.40	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)	0.40
Methoxy-2-propanol	LEV (eff. 80%) + good general ventilation	0.71	LEV (eff. 80%) + good general ventilation + duration 1–4 h	0.43
Butanone	LEV (eff. 80%) + good general ventilation	0.70	LEV (eff. 80%) + good general ventilation + duration 1–4 h	0.42
Isobutanol	LEV (eff. 80%)	0.99	LEV (eff. 80%) + good general ventilation + duration 1–4 h	0.41
Isopropanol	LEV (eff. 80%)	0.50	LEV (eff. 80%)	0.50
Toluene	LEV (eff. 80%) + good general ventilation + duration 1–4 h	0.84	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)	0.14

Combining exposure scenario information

Toluene was identified as the lead component by the LCID methodology (Table 6_1). In addition, OCs/RMMs of **methoxy-2-propanol**, **butanone**, **isobutanol** and **isopropanol** were to be taken into consideration (narcotic effects). However, the OCs/RMMs of toluene covered the OCs/RMMs of these substances, and they did therefore not contribute to the safe use information of the mixture.

OCs/RMMs of **ethyl benzene** or **xylene** were identified as the most stringent of the component OCs/RMMs (Table 6_2), and these were selected for the mixture by the MS methodology.

Safe use information for the mixture, derived by the two methods, is presented in Table 6_3.

Table 6_3. Safe use information for the example product (worker inhalation exposure only) based on Lead Component Identification Methodology (LCID) and selection of the most stringent measures (MS). Safe use information was based on the OCs/RMMs of the single components corresponding to $RCR < 1$ and $RCR < 0.5$, according to Table 6_2.

Work task	Safe use descript. by LCID	Safe use descript. by MS
Spreading, prof. ($RCR < 1$)	LEV (eff. 80%)	LEV (eff. 80%) + good general ventilation
Spreading, prof. ($RCR < 0.5$)	LEV (eff. 80%)	LEV (eff. 80%) + good general ventilation + duration 1–4 h
Spraying, prof. ($RCR < 1$)	LEV (eff. 80%) + good general ventilation + duration 1–4 h	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)
Spraying, prof. ($RCR < 0.5$)	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)	LEV (eff. 80%) + good general ventilation + duration 1–4 h + respirator (eff. 90%)

Identification of the combination effects

According to CLP classification, five of the components have narcotic properties. In addition to these components, Mixie identified also xylene and ethyl benzene as narcotic/CNS depressant. According to Mixie, all of the components (except methoxy-2-propanol which is not included in the Mixie database) are irritative to eyes, and six of the components also irritative to the respiratory tract.

Mixie suggests also synergistic (greater-than-additive) effects due to 1) inhibition of xylene metabolism in the presence of butanone and 2) inhibition of xylene and toluene metabolism when present simultaneously, which may lead to potentiation of the neurotoxic effects.

Table 6_4. Common toxicological effects/target organs of the components based on their CLP hazard classification and the Mixie database.

Component	Classification (CLP)			Mixie			
	Narcotic (H336)	Eye irrit. (H318/ H319)	Skin irrit. (H315)	Narcotic/ other CNS disorder	Eye irrit.	Upper resp. tract irrit.	Skin irrit.
Ethanol	-	-	-	-	x	x	-
Ethyl benzene	-	-	-	x	x	x	-
Xylene	-	-	x	x	x	x	-
Methoxy-2- propanol	x	-	-	nd	nd	nd	nd
Butanone	x	x	-	-	x	x	x
Isobutanol	x	x	x	-	x	-	x
Isopropanol	x	x	-	x	x	x	-
Toluene	x	-	x	x	x	x	-

Assessment of adequacy of the safe use information

Narcotic effects were identified as a common effect of seven components of the mixture. Tables 6_5a and 6_5b present the RCR values of the components calculated in the conditions of the safe use information for the mixture defined by the two methodologies (given in Table 6_3). Although the RCR values of the components were all below one (i.e. exposure levels of the single components stay below their DNEL values), the combined RCR exceeded one in both in low-energy spreading and in spraying in the conditions of safe use information derived by the draft LCID methodology (Table 6_5a). Even if the target RCR in the component exposure scenarios was < 0.5 instead of < 1, combined RCR still exceeded one in low-energy spreading (Table 1_5b). The synergistic effects of xylene with butanone and toluene are expected to further increase the risk of narcotic effects.

Table 6_5a. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 6_3 (**short-term systemic** DNEL as the primary reference value). **RCR < 1** targeted in the component scenarios.

Component	Safe use descript. by LCID		Safe use descript. by MS	
	RCR in spreading	RCR in spraying	RCR in spreading	RCR in spraying
Ethyl benzene ^a	0.23	0.48	0.16	0.08
Xylene	0.18	0.39	0.13	0.06
Methoxy-2- propanol ^a	0.12	0.26	0.09	0.04
Butanone ^a	0.30	0.25	0.21	0.04
Isobutanol ^a	0.04	0.08	0.03	0.01
Isopropanol ^a	0.06	0.12	0.04	0.02
Toluene	0.20	0.41	0.14	0.07
ΣRCR	1.1	2.0	0.80	0.32

^a Long-term systemic DNEL applied since a short-term systemic DNEL was not available.

Table 6_5b. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 6_3 (**short-term systemic** DNEL as the primary reference value). **RCR < 0.5** targeted in the component scenarios.

Component	Safe use descript. by LCID		Safe use descript. by MS	
	RCR in spreading	RCR in spraying	RCR in spreading	RCR in spraying
Ethyl benzene ^a	0.23	0.08	0.10	0.05
Xylene	0.18	0.06	0.08	0.04
Methoxy-2-propanol ^a	0.12	0.04	0.05	0.03
Butanone ^a	0.30	0.04	0.13	0.03
Isobutanol ^a	0.04	0.01	0.02	0.01
Isopropanol ^a	0.06	0.02	0.03	0.01
Toluene	0.20	0.07	0.08	0.04
ΣRCR	1.1	0.32	0.49	0.21

^a Long-term systemic DNEL applied since a short-term systemic DNEL was not available.

Appendix 7: Mixture 7 (spray-paint)

Example mixture no. 7 was a spray-paint. Relevant data on the components of the mixture are given in Table 7_1.

Table 7_1. Components of the example product with DNEL values for long-term and short-term inhalation exposure of workers and the lead component indicators (LCI).

Component	Classification (CLP)	Mean conc. (%)	Vapour press. 25 °C (hPa)	DNEL, long systemic (mg/m ³)	DNEL, long local (mg/m ³)	DNEL, short systemic (mg/m ³)	DNEL, short local (mg/m ³)	LCI
Acetone	H225, H319, H336	38	310	1210	-	-	2420	narc.
Benzyl butyl phthalate	H360Df, H400, H410	1.8	0.000011	4.36	-	-	-	<0.01
4-Methylpentan-2-one	H225, H319, H332, H335	6.3	27	83	83	208	208	2.0
Butanone	H225, H319, H336	18	121	600	-	-	-	narc.
Ethyl 3-ethoxypropionate	H226	6.3	2.3	610	610	-	-	no class.
Toluene	H225, H304, H315, H336, H361d, H373	6.3	38	192	192	384	384	1.2

LCI: mean concentration x vapour pressure / DNEL long-term systemic ($C_i \times V_{p_i} / DNEL_i$)

narc.: LCI not calculated for narcotic effects.

no class.: LCI not calculated since the component does not have a classification in relation to inhalation exposure.

Exposure scenarios for the components

The required operational conditions and risk management measures (OCs/RMMs) to achieve $RCR < 1$ and $RCR < 0.5$ were derived for each of the components for spraying in professional settings (PROC11) (Table 7_2).

Table 7_2. Operational conditions and risk management measures (OCs/RMMs) leading to inhalation exposure below the DNEL or below $0.5 \times DNEL$ (i.e. risk characterization ratio (RCR) < 1 or $RCR < 0.5$), calculated by ECETOC TRA v3.1. RCRs calculated for undiluted (100%) substance, applying worker long-term systemic DNEL values as reference.

Component	OCs/RMMs ($RCR < 1$)	RCR	OCs/RMMs ($RCR < 0.5$)	RCR
Spraying, prof. (PROC11)			Spraying, prof. (PROC11)	
Acetone	LEV (eff. 80%)	0.40	LEV (eff. 80%)	0.40
Benzyl butyl phthalate ^a	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)	0.83	LEV (eff. 80%) + good general ventilation + duration 1–4 h + respirator (eff. 90%)	0.50
4-Methylpentan-2-one	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)	0.35	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)	0.35
Butanone	LEV (eff. 80%) + good general ventilation	0.70	LEV (eff. 80%) + good general ventilation + duration 1–4 h	0.42
Ethyl 3-ethoxypropionate	good general ventilation	0.70	LEV (eff. 80%)	0.20
Toluene	LEV (eff. 80%) + good general ventilation + duration 1–4 h	0.84	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)	0.14

^a Exposure assessment carried out for the real concentration in the mixture (1–5%) since $RCR < 1$ was not reached with any OC/RMM combination for the undiluted (100%) substance.

Combining exposure scenario information

4-Methylpentan-2-one was identified as the lead component in the LCID methodology (Table 7_1). In addition, OCs/RMMs of **acetone**, **butanone** and **toluene** were to be taken into consideration (narcotic effects). However, the OCs/RMMs of 4-methylpentan-2-one xylene covered the OCs/RMMs of these substances, and they did therefore not contribute to the safe use information of the mixture.

OCs/RMMs of **benzyl butyl phthalate** were identified as the most stringent of the component OCs/RMMs (Table 7_2), and these were selected for the mixture by the MS methodology.

Safe use information for the mixture, derived by the two methods, is presented in Table 7_3.

Table 7_3. Safe use information for the example product (worker inhalation exposure only) based on Lead Component Identification Methodology (LCId) and selection of the most stringent measures (MS). Safe use information was based on the OCs/RMMs of the single components corresponding to $RCR < 1$ and $RCR < 0.5$, according to Table 7_1.

Work task	Safe use descript. by LCId	Safe use descript. by MS
Spraying, prof. ($RCR < 1$)	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)
Spraying, prof. ($RCR < 0.5$)	LEV (eff. 80%) + good general ventilation + respirator (eff. 90%)	LEV (eff. 80%) + good general ventilation + duration 1–4 h + respirator (eff. 90%)

Identification of the combination effects

Based on their CLP classification, benzyl butyl phthalate and toluene are developmental toxicants (Table 7_4). In addition, three of the components are classified for eye irritation and three for narcotic effects. According to Mixie, four of the components cause upper respiratory tract and eye irritation, and three of them also narcotic effects.

Table 7_4. Common toxicological effects/target organs of the components based on their CLP hazard classification and the Mixie database.

Component	Classification (CLP)			Mixie		
	Narcotic (H366)	Eye irrit. (H319)	Develop. toxicity (H360D/H361d)	Upper resp. tract irrit.	Eye irrit.	Narcotic/ other CNS disorder
Acetone	x	x	-	x	x	x
Benzyl butyl phthalate ^a	-	-	x	nd	nd	nd
4-Methylpentan-2-one	-	x	-	x	x	x
Butanone	x	x	-	x	x	-
Toluene	x	-	x	x	x	x

nd: component not included in the Mixie database.

Assessment of adequacy of the safe use information

Developmental toxicity was identified as a common effect for benzyl butyl phthalate and toluene. Tables 7_5a and 7_5b present the RCR values of these components calculated in the conditions of the safe use information for the mixture defined by the two methodologies (given in Table 7_3). Combined RCR below one was achieved by both of the methodologies, although it approached one for the LCID methodology when the target RCR in the component exposure scenarios was one.

In addition, narcotic effects were identified as a common effect of four of the components. Tables 7_6a and 7_6b present the corresponding RCR values of the components calculated in the conditions of the safe use information for the mixture. Combined RCR below one was achieved by both of the methodologies.

Table 7_5a. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 7_3 (**long-term systemic** DNEL as the primary reference value). **RCR < 1** targeted in the component scenarios.

Component	Safe use descript. by LCID	Safe use descript. by MS
	RCR in spraying	RCR in spraying
Benzyl butyl phthalate	0.83	0.50
Toluene	0.08	0.05
ΣRCR	0.91	0.55

Table 7_5b. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 7_3 (**long-term systemic** DNEL as the primary reference value). **RCR < 0.5** targeted in the component scenarios.

Component	Safe use descript. by LCID	Safe use descript. by MS
	RCR in spraying	RCR in spraying
Benzyl butyl phthalate	0.50	0.50
Toluene	0.05	0.05
ΣRCR	0.55	0.55

Table 7_5a. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 7_3 (**short-term systemic** DNEL as the primary reference value). **RCR < 1** targeted in the component scenarios.

Component	Safe use descript. by LCID	Safe use descript. by MS
	RCR in spraying	RCR in spraying
Acetone ^a	0.03	0.02
4-Methylpentan-2-one	0.08	0.05
Butanone ^a	0.04	0.03
Toluene	0.04	0.03
ΣRCR	0.19	0.13

^a Long-term systemic DNEL applied since a short-term systemic DNEL was not available.

Table 7_5b. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 7_3 (**short-term systemic** DNEL as the primary reference value). **RCR < 0.5** targeted in the component scenarios.

Component	Safe use descript. by LCID	Safe use descript. by MS
	RCR in spraying	RCR in spraying
Acetone ^a	0.02	0.02
4-Methylpentan-2-one	0.05	0.05
Butanone ^a	0.03	0.03
Toluene	0.03	0.03
ΣRCR	0.13	0.13

^a Long-term systemic DNEL applied since a short-term systemic DNEL was not available.

Appendix 8: Mixture 8 (adhesive)

Example mixture no. 8 was an adhesive. Relevant data on the mixture components are given in Table 8_1.

Table 8_1. Components of the example product with DNEL values for long-term and short-term inhalation exposure of workers and the lead component indicators (LCI).

Component	Classification (CLP)	Mean conc. (%)	Vapour press. 20 °C (Pa)	DNEL, long systemic (mg/m ³)	DNEL, long local (mg/m ³)	DNEL, short systemic (mg/m ³)	DNEL, short local (mg/m ³)	LCI
4,4'-MDI	H332, H315, H319, H334, H317, H351, H335i, H373i	18	0.001	-	0.05	-	0.10	prior.
2,4'-MDI	H332, H315, H319, H334, H317, H351, H335i, H373i	9	0.001	-	0.05	-	0.10	prior.
2,2'-MDI	H332, H315, H319, H334, H317, H351, H335i, H373i	4	0.001	-	0.05	-	0.10	prior.

MID: Methylenediphenyl diisocyanate.

prior.: LCI not calculated since the component is classified as carcinogenic (priority substance).

Exposure scenarios for the components

The required operational conditions and risk management measures (OCs/RMMs) to achieve RCR < 1 and RCR < 0.5 were derived for each of the components for two work tasks: mixing (PROC5) and low-energy spreading (PROC10) in professional settings (Table 8_2). Identical OCs/RMMs were required for both of the work tasks.

Table 8_2. Operational conditions and risk management measures (OCs/RMMs) leading to inhalation exposure below the DNEL or below 0.5 x DNEL (i.e. risk characterization ratio (RCR) < 1 or RCR < 0.5), calculated by ECETOC TRA v3.1. RCRs calculated for undiluted (100%) substance, applying worker long-term DNEL values as reference.

Component	OCs/RMMs (RCR < 1)	RCR	OCs/RMMs (RCR < 0.5)	RCR
Mixing/spreading, prof. (PROC 5/10)			Mixing/spreading, prof. (PROC 5/10)	
4,4'-MDI	LEV (eff. 80%) + good general ventilation + duration 1-4 h + respirator (eff. 90 %)	0.18	LEV (eff. 80%) + good general ventilation + duration 1-4 h + respirator (eff. 90 %)	0.18
2,4'-MDI	LEV (eff. 80%) + good general ventilation + duration 1-4 h + respirator (eff. 90 %)	0.18	LEV (eff. 80%) + good general ventilation + duration 1-4 h + respirator (eff. 90 %)	0.18
2,2'-MDI	LEV (eff. 80%) + good general ventilation + duration 1-4 h + respirator (eff. 90 %)	0.18	LEV (eff. 80%) + good general ventilation + duration 1-4 h + respirator (eff. 90 %)	0.18

Combining exposure scenario information

All of the components are classified as carcinogenic (H351) and were therefore identified as priority substances in the LCID methodology (Table 8_1). Since OCs/RMMs for all of the components were the same, the safe use information of the mixture was based on the OCs/RMMs of **any/all of the components**.

Since the OCs/RMMs for all of the components were the same (Table 8_2), the safe use information of the mixture was based on the OCs/RMMs of **any/all of the components** in the MS methodology.

Safe use information for the mixture, derived by the two methods, was identical (Table 8_3).

Table 8_3. Safe use information for the example product (worker inhalation exposure only) based on Lead Component Identification Methodology (LCID) and selection of the most stringent measures (MS). Safe use information was based on the OCs/RMMs of the single components corresponding to RCR < 1 and RCR < 0.5, according to Table 8_2.

Work task	Safe use descript. by LCID	Safe use descript. by MS
Mixing & spreading, prof. (RCR < 0.5 or 1)	LEV (eff. 80%) + good general ventilation + duration 1-4 h + respirator (eff. 90 %)	LEV (eff. 80%) + good general ventilation + duration 1-4 h + respirator (eff. 90 %)

Identification of the combination effects

Both the CLP classification and the Mixie database recognise MDIs as respiratory irritants, respiratory sensitizers, eye irritants and skin sensitizers. CLP classification is additionally given for pulmonary toxicity in repeated exposure and for skin irritation.

Table 8_4. Common toxicological effects/target organs of the components based on their CLP hazard classification and the Mixie database.

Component	Classification (CLP)						Mixie			
	Resp. tract irrit. (H335)	Resp. tract toxic (H373)	Resp. tract sens. (H334)	Eye irrit. (H319)	Skin irrit. (H315)	Skin sens. (H317)	Upper resp. tract irrit.	Resp. tract sens.	Eye irrit.	Skin sens.
4,4'-MDI	x	x	x	x	x	x	x	x	x	x
2,4'-MDI	x	x	x	x	x	x	x	x	x	x
2,2'-MDI	x	x	x	x	x	x	x	x	x	x

Assessment of adequacy of the safe use information

Pulmonary toxicity and respiratory sensitisation were identified as the common effects for all of the three components. Table 8_5 presents the RCR values of these components calculated in the conditions of the safe use information for the mixture defined by the two methodologies (given in Table 8_3). Combined RCR below one was achieved by both of the methodologies.

Table 8_5. Risk characterisation ratios (RCR) of the components in the conditions corresponding the safe use information defined in Table 8_3 (**long-term local** DNEL as the primary reference value). **RCR < 0.5 or 1** targeted in the component scenarios.

Component	Safe use descript. by LCId	Safe use descript. by MS
	RCR in mixing/spreading	RCR in mixing/spreading
4,4'-MDI	0.11	0.11
2,4'-MDI	0.11	0.11
2,2'-MDI	0.04	0.04
ΣRCR	0.26	0.26

Appendix 9: List of hazard statements

Physical hazards

H200: Unstable explosive
H201: Explosive; mass explosion hazard
H202: Explosive; severe projection hazard
H203: Explosive; fire, blast or projection hazard
H204: Fire or projection hazard
H205: May mass explode in fire
H220: Extremely flammable gas
H221: Flammable gas
H222: Extremely flammable aerosol
H223: Flammable aerosol
H224: Extremely flammable liquid and vapour
H225: Highly flammable liquid and vapour
H226: Flammable liquid and vapour
H227: Combustible liquid
H228: Flammable solid
H229: Pressurized container: may burst if heated
H230: May react explosively even in the absence of air
H231: May react explosively even in the absence of air at elevated pressure and/or temperature
H240: Heating may cause an explosion
H241: Heating may cause a fire or explosion
H242: Heating may cause a fire
H250: Catches fire spontaneously if exposed to air
H251: Self-heating; may catch fire
H252: Self-heating in large quantities; may catch fire
H260: In contact with water releases flammable gases which may ignite spontaneously
H261: In contact with water releases flammable gas
H270: May cause or intensify fire; oxidizer
H271: May cause fire or explosion; strong oxidizer
H272: May intensify fire; oxidizer
H280: Contains gas under pressure; may explode if heated
H281: Contains refrigerated gas; may cause cryogenic burns or injury
H290: May be corrosive to metals

EUH001: Explosive when dry
EUH006: Explosive with or without contact with air
EUH014: Reacts violently with water
EUH018: In use may form flammable/explosive vapour-air mixture
EUH019: May form explosive peroxides

EUH044: Risk of explosion if heated under confinement

Health hazards

H300: Fatal if swallowed
H301: Toxic if swallowed
H302: Harmful if swallowed
H303: May be harmful if swallowed
H304: May be fatal if swallowed and enters airways
H305: May be harmful if swallowed and enters airways
H310: Fatal in contact with skin
H311: Toxic in contact with skin
H312: Harmful in contact with skin
H313: May be harmful in contact with skin
H314: Causes severe skin burns and eye damage
H315: Causes skin irritation
H316: Causes mild skin irritation
H317: May cause an allergic skin reaction
H318: Causes serious eye damage
H319: Causes serious eye irritation
H320: Causes eye irritation
H330: Fatal if inhaled
H331: Toxic if inhaled
H332: Harmful if inhaled
H333: May be harmful if inhaled
H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled
H335: May cause respiratory irritation
H336: May cause drowsiness or dizziness
H340: May cause genetic defects
H341: Suspected of causing genetic defects
H350: May cause cancer
H350i: May cause cancer by inhalation
H351: Suspected of causing cancer
H360: May damage fertility or the unborn child
H361: Suspected of damaging fertility or the unborn child
H360F: May damage fertility
H360D: May damage the unborn child
H361f: Suspected of damaging fertility
H361d: Suspected of damaging the unborn child
H362: May cause harm to breast-fed children
H370: Causes damage to organs
H371: May cause damage to organs
H372: Causes damage to organs through prolonged or repeated exposure
H373: May cause damage to organs through prolonged or repeated exposure
H373i: May cause damage to organs through prolonged or repeated exposure if inhaled

EUH029: Contact with water liberates toxic gas

EUH031: Contact with acids liberates toxic gas
EUH032: Contact with acids liberates very toxic gas
EUH066: Repeated exposure may cause skin dryness or cracking
EUH070: Toxic by eye contact
EUH071: Corrosive to the respiratory tract

Environmental hazards

H400: Very toxic to aquatic life
H401: Toxic to aquatic life
H402: Harmful to aquatic life
H410: Very toxic to aquatic life with long lasting effects
H411: Toxic to aquatic life with long lasting effects
H412: Harmful to aquatic life with long lasting effects
H413: May cause long lasting harmful effects to aquatic life
H420: Harms public health and the environment by destroying ozone in the upper atmosphere