

# Guide for enforcement of mixture classification based on bridging principles

## Article 9(4) of the CLP Regulation Weight of evidence / Expert judgements

Adopted on 28 June 2024



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## Guide for enforcement of mixture classification based on bridging principles

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## Table of Contents

<b>MIXTURE CLASSIFICATION BASED ON BRIDGING PRINCIPLES.....</b>	<b>4</b>
1. Bridging method applied .....	6
2. Application of weight of evidence using expert judgement.....	6
3. Similarity of mixtures in the framework of 'substantially similar mixtures' .....	8
4. Classification method for tested reference mixtures.....	10
<b>ANNEX 1. PRACTICAL CASE NO.1 .....</b>	<b>12</b>
<b>ANNEX 2. PRACTICAL CASE NO.2.....</b>	<b>17</b>
<b>ANNEX 3. SUBSTANTIALLY SIMILAR MIXTURES UN GHS .....</b>	<b>20</b>
<b>ANNEX 4. TIERED APPROACH FOR MIXTURE CLASSIFICATIONS .....</b>	<b>21</b>

## Mixture classification based on bridging principles

The present guide is focused on four areas of interest concerning the enforcement of hazard classification of mixtures where the decision on classification, as performed by duty holders, was based on application of bridging principles<sup>1</sup> optionally supported by weight of evidence determination using expert judgement.

Two examples of enforcement of mixture classification are reported in Annex 1 and 2. The cases aim at clarifying the application of the principle of 'substantially similar mixture'.

The four areas of interest described in the guide are:

1. Bridging method applied
2. Application of weight of evidence using expert judgement
3. Similarity of mixtures in the framework of the bridging principle 'substantially similar mixtures'
4. Classification method for tested reference mixtures<sup>2</sup>

According to the tiered approach for mixture classification, as required in the CLP Regulation, bridging principles shall be applied for the cases where no information from test data on the mixture to be classified is available to duty holders. Bridging principles are based on information on individual substances / similar tested mixtures (reference mixtures) in accordance with Article 6(5) and Article 9(4) of the CLP Regulation.

The tiered approach for mixture classification is demonstrated in the flowchart reported in Annex 4 to this guide. The flowchart indicates to what extent weight of evidence using expert judgement can be applied in the evaluation of hazard information of mixtures.

National Enforcement Authorities (NEA) should generally consider the following key recommendations related to the four areas of interest indicated above when enforcing mixture classifications based on bridging principles in the following sequence:

- Only classified mixtures, i.e. classified based on adequate and reliable test data, can be used as reference mixtures for the application of bridging principles (related to Area 4).
- Only one single bridging principle can be applied in the evaluation of a hazard class of the untested mixture (related to Area 1)<sup>3</sup>.
- Weight of evidence of information on similar tested mixtures cannot be applied as a stand-alone classification method based on the evaluation of hazard information of an untested mixture according to Article 9(3) and 9(4) of the CLP Regulation. Only if more than one fitting reference mixture is available, duty holders can apply weight of evidence determination using expert judgement to select the most suitable tested reference mixtures in line with Article 6(5) of the CLP Regulation in their the evaluation of available information for the classification of the untested mixture. All reference mixtures must be classified in a consistent form based

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<sup>1</sup> Mainly the principle 'substantially similar mixtures' is applied by duty holders.

<sup>2</sup> The term '(tested) reference mixture' is used in this guide as in some cases it seems a more clear term. It is always used synonymic to the term 'similar tested mixture' used in Article 6(5) of the CLP Regulation.

<sup>3</sup> Only one bridging principle could be applied in the evaluation of a hazard class with the exception of Aerosols, where a mixture classified based on another bridging principle is used in an aerosol container. However, different bridging principles may be applied to different hazard classes.

on adequate and reliable test data. The general rule should always be 'no adequate and reliable test data - no conclusion on mixture classification outside the application of the calculation method/ingredient based approach'. (related to Area 2)

- The application of the bridging principle of 'substantially similar mixtures' shall be consistent with all relevant criteria defined in section 1.1.3.5 of Annex I of the CLP Regulation. NEA should identify and consider all the ingredient substances of the two similar mixtures that were used for bridging and check the similarity of the concerned mixtures, by identifying the ingredient groups A, B and C based on the criteria given in Section 1.1.3.5 of Annex I of the CLP Regulation. Consideration of synergism, differences in potency, difference in SCLs, buffering capacity, pH and acid/alkaline reserve can also be relevant<sup>4</sup>. (related to Area 3)

These key recommendations lead to the following questions that NEAs could clarify when controlling the application of bridging principles, and/or weight of evidence, for classification of an untested mixture by duty holders.

- Identification and examination of available information on mixtures:
  - Were only reliably classified mixtures (based on adequate and reliable test data) used as reference mixtures for the application of bridging principles?
- Weight of evidence determination using expert judgement:
  - Was weight of evidence of information on similar tested mixtures or on similar substances in the mixtures applied as a stand-alone classification method<sup>5</sup>?
  - If more than one reference mixture was available when applying bridging principles, did the duty holders apply a weight of evidence determination using expert judgement to select the most suitable tested reference mixtures in line with Article 6(5) of the CLP Regulation for the evaluation of the classification of the untested mixture?
- Bridging principles:
  - Was only one single bridging principle applied in the evaluation of a hazard class for the untested mixture?
  - Were all ingredients of the mixtures (relevant for bridging principles) identified and considered?
  - Can synergism, differences in potency, difference in SCLs, buffering capacity, pH and acid/alkaline reserve affect the classification?
  - Was the application of bridging principles based on the implementation of all relevant criteria defined in section 1.1.3 of Annex I of the CLP Regulation, e.g. criteria (a) to (d) in section 1.1.3.5 when applying the bridging principle 'substantially similar mixtures'?

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<sup>4</sup> Especially assessment of synergism and differences in potency might be difficult for an NEA and assistance by experts from the competent authority might be necessary. Therefore, as a first check NEAs might identify the ingredient groups A, B and C based on the criteria given in Section 1.1.3.5 of Annex I of the CLP Regulation

<sup>5</sup> Such stand alone approach is excluded according to the rules for evaluation of hazard information for substances or mixtures as reported in Articles 9(3) and 9(4) of the CLP Regulation.

## 1. Bridging method applied

The general rule is that only one bridging principle can be applied per hazard class evaluated for the untested mixture.

The ECHA Guidance on the application of the CLP criteria<sup>6</sup> states that: “[..] only one bridging principle could be applied in the evaluation of a hazard class with the exception of aerosols, where a mixture classified based on another bridging principle is used in an aerosol container. However, different bridging principles may apply to different hazard classes [..]”.

Due to the similarity requirements of the bridging principle ‘substantially similar mixtures’ for the composition of the two concerned mixtures - i.e. identity of ingredients and concentrations - any approach that leads to apply more than one bridging principle per hazard class cannot be implemented by duty holders and such approach constitutes a breach with existing rules for the bridging principle ‘substantially similar mixtures. For example, applying the bridging principle ‘dilution’ for a defined sub-set of ingredients from the mixture composition together with the bridging principle ‘substantially similar mixtures’ is not possible.

## 2. Application of weight of evidence using expert judgement

The application of weight of evidence determination using expert judgement in the evaluation of available information shall be performed in line with Articles 5(1) and 6(1) of the CLP Regulation. The information used shall be adequate, reliable, and scientifically valid<sup>7</sup>. This also applies to any evaluation based on other information on individual substances and similar tested mixtures in line with Article 6(5) of the CLP Regulation.

In case available information is based on test data obtained by other test methods<sup>8</sup>, the evaluation of hazard information requires a comparative evaluation of the test methods applied and the test methods indicated in Article 8(3) of the CLP Regulation<sup>9</sup>.

When the criteria for classification for each hazard class or differentiation in part 2 to 5 of Annex I cannot be applied to the available information, weight of evidence determination using expert judgement can be applied in accordance with Article 9(3) of the CLP Regulation.

However, if only other available information on individual substances and similar tested mixtures can be identified<sup>10</sup>, this information shall be used in the evaluation by applying bridging principles in line with the first subparagraph of Article 9(4) of the CLP Regulation.

Weight of evidence using expert judgement as referred to in the second subparagraph of Article 9(4) of the CLP Regulation cannot be interpreted to define an individual additional tier available for mixture classification but it needs to be read as a reference to weight of evidence using expert judgement as outlined in Article 9(3) of the CLP Regulation. This means that weight of evidence using expert judgement always only can be part of the evaluation of hazard information and part of the decision on hazard classification in a tier 1 hazard classification assessment in case the criteria of Article 9(1) cannot be directly applied to the available information.

Weight of evidence used together with bridging principles applies only to that specific bridging

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<sup>6</sup> Reference: Section 1.6.3.2 of the ECHA Guidance.

<sup>7</sup> Reference: Article 5(2) and 6(2) of the CLP Regulation.

<sup>8</sup> Other than those referred to in Article 8(3) of the CLP Regulation.

<sup>9</sup> This is required as per Article 9(2) of the CLP Regulation.

<sup>10</sup> This is the other available information identified and examined according to Article 6(5) of the CLP Regulation.

principle in question<sup>11</sup> and should not violate its rules. For a clarification on the tiered approach see Figure 1.1 in the ECHA Guidance on the Application of the CLP Criteria. The flowchart reported in Annex 4 to this guide aims also at clarifying the tiered approach.

When applying bridging principles, weight of evidence using expert judgement can be applied for the evaluation of the available information for the similar tested mixture. When information on more than one similar tested mixture (i.e. reference mixture) is available, weight of evidence using expert judgement can be also applied to decide on the most appropriate reference mixture to be used.

When applying weight of evidence determination using expert judgement according to Article 9(3) and 9(4) of the CLP Regulation, all available information must be assessed for reliability and adequacy in the classification of the tested mixture or in the selection of the most appropriate tested mixture for bridging to untested mixtures. There must be sufficient data to adequately characterise the hazard of the tested mixture<sup>12</sup>. If there are insufficient data on tested mixtures, bridging is not permitted.

Duty holders might incorrectly apply weight of evidence using 'bridging' from multiple tested mixtures, each with insufficient information to adequately characterise the hazard of the tested mixtures. Such approach is not allowed since it does not meet the requirements of Article 6(5) of the CLP Regulation. It is important to highlight again that weight of evidence of information on similar mixtures is not a stand-alone method in the evaluation of hazard information for substances or mixtures in the context of Articles 9(3) and 9(4) of the CLP Regulation.

#### **Weight of evidence determination using expert judgement in the context of data on the mixture to be classified**

Based on Article 9(3) of the CLP Regulation, weight of evidence determination using expert judgement can be used where the standard criteria cannot be applied directly to the available identified information. Weight of evidence determination using expert judgement can be used for the evaluation of all available information according to Article 9(3) on the mixture to be classified. Only when the information available for the mixture to be classified are reliable and adequate, the mixture can be classified.

Weight of evidence shall be applied when there are several studies and information available on the mixture to be classified. Reliability of data, such as deficiencies, applicability domain, etc., should be considered in the weight of evidence application. When there is a doubt on the reliability of the information on the mixture to be classified, other methods/tiers may be more appropriate for the classification, for example bridging principles or ingredient-based approaches (i.e. summation and additivity methods).

#### **Weight of evidence determination using expert judgement in the context of data of similar tested mixtures**

Based on the first paragraph of Article 9(4) of the CLP Regulation, only when information referred to in Article 6(5) is available, bridging principles can be applied. Other methods should be applied when the available information does not allow the application of bridging principles and weight of evidence determination using expert judgement<sup>13</sup>.

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<sup>11</sup> When the bridging principle 'substantially similar mixtures' is used, application of weight of evidence determination using expert judgement is limited to the selection of tested reference mixture(s) to compare with from an available choice of suitable reference mixtures, see later in the text

<sup>12</sup> Reference: Section 1.1.3 of Annex I of the CLP Regulation.

<sup>13</sup> Second subparagraph of Article 9(4) of the CLP Regulation

Given the reference to Article 6(5) in the first subparagraph of Article 9(4) only fully classified mixtures can be used as reference mixtures, i.e. mixtures classified based on adequate and reliable data. Any decision on the appropriateness of the test data and the classification of the tested mixtures should be taken into account when deciding on the classification of the tested mixtures. Weight of evidence may be applied as appropriate. However, once a decision on the classification of the tested mixtures is reached, no further weight of evidence on the appropriateness of the tested mixtures can be performed when using the tested mixture in an application of a bridging principle. Only if different tested and classified mixtures are available, weight of evidence determination using expert judgement may be further used to determine the most appropriate mixture(s) to be used as tested reference mixture(s). Alternatively the tested reference mixture(s) that results in the most stringent classification should be used.

When the criteria in section 1.1.3 of Annex I of the CLP Regulation are met for any of the bridging principles to compare the mixture to be classified with the reference mixture(s) and a choice of several reference mixtures is available to bridge from and all those reference mixtures have different hazard classifications, a weight of evidence determination using expert judgement shall be applied.

### **3. Similarity of mixtures in the framework of ‘substantially similar mixtures’**

Section 1.1.0 of Annex I of the CLP Regulation requires duty holders to “document fully the basis on which classification decisions are made and shall make available to the competent authorities and, on request, to the relevant enforcement authorities the documentation, together with the data and information on which classifications are based. However, where suppliers in an industry sector cooperate in this way, each supplier shall remain fully responsible for the classification, labelling and packaging of substances and mixtures he places on the market, and for meeting any other requirements of this Regulation.”

National enforcement authorities (NEA) can require the following information as part of the documentation referred in Article 9(4) of the CLP Regulation:

- Composition of the tested and untested mixtures, including the identifiers of each substance in the mixtures (and in each mixture contained in the concerned mixture). Percent concentrations and hazard classifications can be also required.
- Bridging method applied and the demonstration of its applicability for each affected hazard category.
- Potential effects on mixture classification imposed by ingredients that are not similar to both, the tested and the untested mixture or that do not have the same concentration (e.g. information on potency, synergistic/antagonistic effects, buffering capacity, acid alkaline reserve, SCLs, pH, etc.).
- If more than one tested mixture is included, the documentation for any weight of evidence applied for the selection of the most relevant reference mixture(s) for the classification of the untested mixture.

As outlined in the CARACAL document<sup>14</sup>, “The general view was that similarity only in classification does not suffice to allow application of this bridging principle “Substantially Similar Mixtures”. Rather, similarity would have to be demonstrated at the level of ingredient substance

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<sup>14</sup> Reference: 25<sup>th</sup> Meeting of Competent Authorities for REACH and CLP (CARACAL) Document CA/99/2017 - Open Session, Debrief of meeting of the CARACAL sub-group on ATPs to CLP – Bridging Principles, 10.11.2017.

identity." Additionally, NEA should consider the legal requirements for ingredients A, B and C as defined in section 1.1.3.5 of Annex I of the CLP Regulation.

It is mandatory to have a substantially similar mixture to perform a correct bridging when applying the bridging principle 'substantially similar mixtures'. Since complex mixtures can contain different hazardous ingredients with different chemical properties and functionalities, it could be a challenge for a duty holder to find suitable substantially similar mixtures. NEA should be aware of those challenges and verify if bridging principles were applied with reference to correct, consistent and adequate mixtures.

The key criteria prescribing the similarity of the tested and untested mixture are provided in section 1.1.3.5 of Annex I of the CLP Regulation, where the four requirements (a) to (d) for the ingredients A, B and C are defined for the two mixtures. An explanation of the application of these four requirements is also provided in Chapter 3.4 of the UNECE Guidance on the application of GHS criteria (see Annex 3 to this guide) with a reference to more relevant complex example mixtures. According to this UNECE Guidance ingredients A, B and C in complex real mixtures can be also considered to be groups of related substances, which is also in line with the considerations in the CARACAL document from 2017 on ingredients of mixtures that can be also groups of substances.

It is given practice of duty holders to select two or more tested reference mixtures for applying the bridging principle 'substantially similar mixtures'. This approach is taken when each tested mixture does not contain all the key ingredients with the same chemical properties and functionalities which are present in the untested mixture. In this way, when applying the bridging principle 'substantially similar mixtures', two or more reference mixtures are included in the comparison in order to eventually cover all key ingredients with the same chemical properties and functionalities present in the untested mixture. In this approach it also happens that the set of reference mixtures covers ingredients that may influence the hazard classification of a mixture but the additional ingredients are not present in the untested mixture. This approach for applying the bridging principle is not possible as tested and untested mixture are not substantially similar.

It can be concluded that once a tested mixture is missing a key ingredient, that is necessary for performing a correct comparison for the classification of the untested mixture - or contains additional ingredients that may influence the outcome of classification - those tested mixtures are not substantially similar to the untested mixture, and therefore cannot be used for the bridging.

In addition, for ingredients of the mixtures which are covered as "ingredient B" as defined in section 1.1.3.5. of Annex I of the CLP Regulation, bridging based on 'substantially similar mixtures' is not foreseen when such an ingredient considered in the reference mixture has a different hazard category for the same hazard class compared with the related ingredient in the mixture to be classified, even though the two related ingredients have the same chemical properties and fall in the same subcategory of chemicals.

### **Specific substance groups**

Section 1.1.3.5 of Annex I of the CLP Regulation requires that the ingredient B has the same substance identity in both mixtures. However, for ingredients A and C, section 1.1.3.5 does not require the same substance identity, but it requires the hazard category to be the same for both ingredients.

In addition to assessing conditions for ingredients A and C as defined in section 1.1.3.5. of Annex I of the CLP Regulation a more detailed assessment of substance identities for these ingredients might be important due to the specific chemical characteristics of the following substance

groups<sup>15</sup>.

Surfactants have a wide range of chemical structures and properties. They can vary in their hydrophilic, lipophilic and ionic<sup>16</sup> characteristics. These characteristics result in different chemical behaviours, functionalities and compatibilities in mixtures. Applying bridging principles to surfactants should also be based on the specific criteria of section 1.1.3.5 of Annex I of the CLP Regulation, reflecting the full characteristics of the surfactants in the untested mixture as well as in reference mixture(s). In a mixture, the surfactants are chosen based on their desired functionalities, chemical characteristics, and compatibilities. The surfactant's structure also plays a role in meeting those criteria and therefore the exact substance identity of a surfactant can be very important

Surfactants are classified based on their hazardous properties. The CLP Regulation does not address the distinction and functional differences among surfactants. When applying bridging principles to surfactants, specific characteristics and compatibility may be relevant. Applying a bridging principle to surfactants relying solely on their CLP classification is not possible. Substance identities of surfactants need to match in the untested and in the tested mixture for the ingredients in groups A and C, ie. they can only be compared with each other based on criteria c) and d) of section 1.1.3.5 of Annex I of the CLP Regulation<sup>17</sup>.

Fragrances are complex mixtures containing many chemicals, they cannot be easily compared with each other for the purpose of applying bridging principles. The CLP calculation rules may need to be used instead of using bridging principle 'substantially similar mixtures' (when test data on mixture itself does not exist).

Preservatives have different chemical properties, and they can only be compared with each other based on the criteria of section 1.1.3.5 of Annex I of the CLP Regulation. For example, parabens can be compared with parabens. If parabens are compared with isothiazolinones, a justification of similarity based on requirements in section 1.1.3.5 of Annex I to the CLP should be included.

For the specific approach for mixtures that have an extreme pH see in section 4 of this Guide.

#### **4. Classification method for tested reference mixtures**

This area of interest poses challenges for NEA since the classification of tested reference mixture is often based on information from non-standard test methods. The specific knowledge required to assess such non-standard approaches for the classification of the tested reference mixture is in general not readily available in NEAs and contact with experts from the competent authorities might be required.

Therefore, as a general rule, NEAs are recommended to start the investigations about compliance of a mixture classification based on a bridging principles not with the area of interest number 4 but rather with areas of interest number 1 or 3 (Sections 1 or 3 of this document).

Any of in vitro test methods used to classify the reference mixture must be suitable to conclude on classification in accordance with Article 6 of the CLP Regulation and the concerned ECHA guidance, Chapter R.7a "Endpoint specific guidance". This is a prerequisite for applying a bridging principle according to Articles 6(5) and 9(4).

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<sup>15</sup> The group of substances listed gives some examples but is not comprehensive and not complete.

<sup>16</sup> As their anionic, cationic, and non-ionic forms.

<sup>17</sup> One argument for this approach can be the requirement of Section 1.1.3.5 of Annex I of the CLP Regulation that it can be established for ingredients A and C not to affect the hazard classification of ingredient B.

Regarding the eye corrosion/irritation endpoint, the ICE method is applicable for classification as Eye Dam. 1 or 'no classification'. Though it is limited and cannot predict classification in Eye Irrit. 2. The LVET test may be used for example for household detergents, cleaning products and surfactants in the classification of such as mixture as Eye Dam. 1 or Eye Irrit. 2 on a case-by-case basis.

Although not included in EU No 440/2008, it is considered that a careful review of an available LVET could be used as part of a weight of evidence with other data on the same tested mixture in deriving hazard classification for the Eye Corrosivity/Irritation endpoint. In the absence of any in vitro method for concluding Eye Irrit. 2 classification, non-standard data may need to be considered in the context of Article 9(3) of the CLP Regulation.

For mixtures to be classified that have an extreme pH value as referred in sections 3.2.3.1.2. or 3.3.3.1.2 of Annex I of the CLP Regulation the bridging principles can only be applied when a suitable test has been performed, confirming that the mixture to be classified has a low buffer capacity / a non-significant acid/alkaline reserve.

For the reference mixture used for the bridging method "substantially similar mixtures" it applies: if consideration of acid/alkaline reserve of the reference mixture suggests the mixture may not cause serious eye damage/ skin corrosion despite the low or high pH value, this needs to be confirmed by other data, preferably by data from an appropriate validated in vitro test.<sup>18</sup>

Please also note: CARACAL in a related document<sup>19</sup> indicated that "[..] according to the legal text a test, preferably an in vitro test, on the mixture itself would be needed to confirm non-corrosivity if suggested by data on the acid alkali reserve [..]".

Regarding bridging from non-hazardous tested mixtures, CARACAL agreed on the following: "[..] There was a general agreement that bridging from non-hazardous reference mixtures may be scientifically justified and valid on a case by case basis, when sufficient information is available that allows confidence in the non-classification which may depend on the hazard and the reliability and sensitivity of the test method to detect the specific hazard of concern. For example, a sensitisation hazard cannot be excluded if you have negative in vivo data on a mixture containing a sensitiser (above the GCL/SCL). It was agreed that bridging from a non-hazardous mixture introduced additional uncertainty due to the increased complexity related to the increased number of potential interactions between ingredients. An important element that was identified in this context was the 'sturdiness of the bridge', i.e. the quality and reliability of the data on the tested mixture, the identification of the composition of both the tested and untested mixture and additional uncertainty related to mixture effects being different in the untested mixture. It was acknowledged that the requirement for adequate and reliable data clearly applies for bridging in general but more confidence is needed for extrapolation from non-classified mixtures. A separate document on the legal analysis on bridging from non-hazardous reference mixtures is available [..]"

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<sup>18</sup> Section 3.2.3.1.2. and 3.3.3.1.2 of Annex I of the CLP Regulation require all mixtures having an extreme pH value combined with a significant acid/alkaline reserve to be classified for the related hazard based on this test data if not already classified based on higher tier test data available. Given this requirement for mixtures any classification of mixtures having an extreme pH value based on bridging principles can only apply to those mixtures (mixture to be classified as well as reference mixtures) which have a non-significant acid/alkaline reserve. This systematic approach in the CLP Regulation for combining data available on the extreme pH value and any application of bridging principles is also emphasised in Chapters 3.2 and 3.3 (Figures 3.2.2 and 3.3.2) of the GHS revision 10, see: <https://unece.org/transport/documents/2023/07/standards/ghs-rev10>

From an enforcement perspective it is important to ask for transparency of the classification approach and to require the non-significant acid/alkaline reserve of the mixtures involved to be confirmed by other data. in line with the requirements of the CLP Regulation.

<sup>19</sup> Reference: 25th Meeting of Competent Authorities for REACH and CLP (CARACAL) Document CA/99/2017 - Open Session, Debrief of meeting of the CARACAL sub-group on ATPs to CLP – Bridging Principles, 10.11.2017.

## Annex 1. Practical case no.1

### Practical example no.1 of mixture classification based on the application of bridging principles

This example is based on information provided by a duty holder related to the classification of a mixture.

Product Category: Liquid laundry detergent

Method used for classification by duty holder: Weight of evidence with expert judgement

Result: Classification according to CLP criteria, Eye Irritation Cat. 2

Comparison with: Classification with calculation method, serious Eye Damage Cat. 1

	Eye Classification	Untested Mixture	Reference mixture 1	Reference mixture 2	Reference mixture 3	Reference mixture 4
Test			LVET	ICE	LVET	LVET
Classification of the mixture		?	Eye Irritation Cat. 2	No prediction can be made	Eye Irritation Cat. 2	Eye Irritation Cat. 2
Soap 1	Not classified as hazardous to eye	3%				
Soap 2	Not classified as hazardous to eye		9%			13%
Soap 3	Not classified as hazardous to eye			5%		
Soap 4	Eye Irrit. 2				12%	
Anionic surfactant 1	Eye Dam. 1				32%	
Anionic surfactant 2	Eye Dam. 1	8%				
Anionic surfactant 3	Eye Dam. 1		4%			
Anionic surfactant 4	Eye Dam. 1		17%			35%
Anionic surfactant 5	Eye Dam. 1			11%		
Anionic surfactant 6	Eye Dam. 1	15%		9%		
Nonionic surfactant 1	Eye Dam. 1	14%				
Nonionic surfactant 2	Eye Dam. 1				25%	
Nonionic surfactant 3	Eye Dam. 1		13%			8%
Nonionic surfactant 4	Eye Dam. 1			15%		
Builder 1	Not classified as hazardous to eye				2%	
Builder 2	Eye Irrit. 2		7%			5%
Builder 3	Eye Irrit. 2		8%			
Builder 4	Not classified as hazardous to eye			2%		
Alcohol 1	Eye Irrit. 2	5%	2%			
Alcohol 2	Not classified as hazardous to eye	3%	8%		20%	14%
Water		52%	32%	58%	9%	25%

## 1.1 Identification and examination of available information of reference mixtures provided by the duty holder

### Test data of the reference mixtures provided by the duty holder:

- Reference mixture 1, 3 and 4: test data based on LVET
- Reference mixture 2: test data based on ICE with result as 'no prediction can be made'

### Evaluation of the test methods of the reference mixtures 1, 3 and 4

- Application of LVET test (Guidance on the Application of the CLP Criteria; Version 6.0 – January 2024, S.307):
  - Eye Dam. 1: positive data from the LVET test could be a trigger for considering classification in Category 1 on its own
  - For 'no classification' or 'eye irritation category 2' (H319): data from Low Volume Eye Test (LVET) not accepted as a conclusive singular data basis
  - Consideration should be given on a case-by-case basis to the limited use of LVET data as supplementary in vivo data in a weight of evidence determination in order to assess if the criteria for classification are met. A weight of evidence could include, for example, the results of appropriate validated in vitro tests, relevant and conclusive human and animal data, extreme pH
  - However, for Reference mixture 1, 3, and 4, only LVET data are available. Therefore, these three mixtures could not be classified with 'eye irritation category 2' only via LVET.
- Evaluation of the test methods of the reference mixture 2. Application of ICE test (Guidance on the Application of the CLP Criteria; Version 6.0 – January 2024, p. 311):
  - ICE with the result 'No prediction can be made' is not an appropriate validated in vitro test for eye irritation category 2.
  - A mixture can be considered as causing serious eye damage (Category 1) based on positive results in the ICE test. Negative results from the ICE test methods can be used for classification purposes i.e. 'bottom-up approach', but for other test methods the negative in vitro corrosivity responses in these tests must be followed by further testing.
  - However, for Reference mixture 2 only ICE data are available. Therefore, the mixture could not be not classified with "eye irritation category 2" only via ICE.

Only reliably classified mixtures based on adequate and reliable test data could be used as a reference mixture. No reference mixture fulfilled these conditions related to eye irritation cat. 2 and therefore the application of bridging principles is not possible for this hazard category.

The duty holder could not use this insufficient information to adequately characterise the hazard category of the reference mixtures. Such approach is not allowed since it does not meet the requirements of Article 6(5) of the CLP Regulation.

## 1.2 Bridging principles: Could bridging principles be applied?

As in section 1.1, it is already explained the reference mixtures are not classified based on adequate and reliable test data and this step is not relevant anymore. Please consider that the following explanations are only provided to explain the conditions that needs to be fulfilled for bridging principles.

In the following description, the untested mixture is compared with each of the four specific reference mixtures, i.e. compared with reference mixture 1, reference mixture 2, reference mixture 3 and reference mixture 4.

In general:

- Untested mixture: three substances contained in the untested mixture with eye dam. 1
- Comparison with the four specific reference mixtures:
  - these three substances are either not part of the reference mixtures (reference mixture 1, reference mixture 3 and reference mixture 4), or
  - for reference mixture 2, one of the three substances (anionic surfactant 6) is present in a significantly lower concentration

### Bridging principles analysis

i. Dilution: two substances in the untested mixture are not part of the reference mixtures (no dilution of a reference mixture)

ii. Batching: batching is not appropriate because untested mixture and each of the four specific reference mixtures have significantly different compositions

iii. Concentration of highly hazardous mixtures: not appropriate because untested mixture and each of the four specific reference mixtures have significantly different compositions

iv. Interpolation within one hazard category: not appropriate because untested mixture and each of the four specific reference mixtures have significantly different compositions

v. Substantially similar mixtures: Comparison of the untested mixture with the four specific reference mixtures separately (NOT comparison of the untested mixture with four reference mixtures in one step). Bridging under substantially similar mixtures can include only one tested mixture used for bridging. Therefore, the untested mixture is compared with reference mixture 1, reference mixture 2, reference mixture 3 and reference mixture 4. When in the end several tested mixtures, which have different classifications, would fulfill the rules for substantially similar mixture, weight of evidence assessment can be used to select the most relevant mixture to bridge with.

#### Section 1.1.3.5 of Annex I to CLP Regulation:

##### 1.1.3.5. *Substantially similar mixtures*

Given the following:

(a) two mixtures each containing two ingredients:

(i) A + B

(ii) C + B;

(b) the concentration of ingredient B is essentially the same in both mixtures;

(c) the concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);

(d) hazard data for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the hazard classification of B.

Ingredient B determines the hazard class to be used for bridging. Each of the two mixtures contains an additional ingredient which is not identical with each other (A or C); however they are present in equivalent concentrations and neither of them is expected to affect the hazard classification of the other ingredient (B).

#### Definition of ingredient B<sup>20</sup>:

<sup>20</sup> The condition indicated in the last sentence of (d) in Section 1.1.3.5 of Annex I to CLP only considers the effect of either A or C on the hazard classification of B, but it does not consider the effect of B on the hazard classification of either A or C. This condition is only meaningful once it is assured that the hazard classification of B is always the driver of the hazard potential of the substantially similar mixtures (untested mixture and tested mixture) for the hazard category in question. For NEAs strong evidence for the significance of a substance for the classification of the mixture is a substance classification in the most severe classification present in the mixture and a relevant concentration. Therefore, all substances with a

**Can the surfactants in the untested mixture and the surfactants in one of the four reference mixtures classified with eye dam. 1 be grouped under B?**

**No, because:** in this example the surfactants classified as Eye dam. 1 cannot be defined as B, because the surfactants are different in the untested mixture and in each of the four specific reference mixtures.

**Could other substances in the untested mixture and in one of the four reference mixtures be grouped under B?**

**No, because:** these ingredients do not significantly determine the classification of the complete mixture in the hazard category in question and therefore cannot be grouped under B. In addition, the remaining ingredients (not surfactants) like soaps and alcohols in the untested mixture and the reference mixtures differ substantially.

**Definition of ingredient A and ingredient C:**

**Could the surfactants classified with Eye dam. 1 be grouped under A and C?**

As B could not be defined, the conditions to apply the bridging principle 'substantially similar mixtures' are already not fulfilled. The following explanations are only provided to explain the conditions to be fulfilled for a definition of A and C:

*Sub-condition (c) the concentration of ingredient A in the untested mixture equals that of ingredient C in the reference mixture.*

Comparison of concentrations of surfactants classified eye dam. 1:

- Untested mixture: 37 %,
- Reference mixture 1: 34 %
- Reference mixture 2: 35 %
- Reference mixture 3: 57 %
- Reference mixture 4: 43 %

The concentration of surfactants classified with Eye dam. 1 in the untested mixture is in the same range as in Reference mixture 1 and Reference mixture 2 but not as in Reference mixture 3 and 4.

*Sub-condition (d) hazard data for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the hazard classification of B.*

As all surfactants of the example are classified with Eye Dam. 1, they are in the same hazard category, but could only be defined as B. Please see also the considerations of sub-condition under "1. definition of ingredient B".

**Conclusion** for Substantially similar mixtures: As it is not possible to define ingredients A, B and C, the untested mixture could not be classified with the principle 'substantially similar mixtures'.

vi. Review of classification where the composition of a mixture has changed: not appropriate, as the reference mixtures are not variations of initial concentrations

vii. Aerosols: not appropriate because as the untested mixture is not an aerosol

### 1.3 Conclusion

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classification in the most severe classification need to be grouped in B while observing also the other condition for the definition of B (essentially same concentrations in both mixtures).

Weight of evidence and bridging principles are not applicable.

Weight of evidence with expert judgement of data on similar tested substances or mixtures is not a stand-alone classification method in the evaluation of hazard information for substances or mixtures in the context of CLP Articles 9(3) and 9(4).

The reference mixtures are not reliably and fully classified mixtures based on adequate and reliable data, so that the four classified mixtures cannot be used as reference mixtures in the application of Bridging Principles.

For applying the bridging principle the key criteria prescribing the similarity of the tested and untested mixtures are not fulfilled.

## Annex 2. Practical case no.2

### Practical example no.2 of mixture classification based on the application of bridging principles

This example is based on information provided by a duty holder related to the classification of a mixture.

Product Category: Liquid cleaner

Method used for classification by duty holder: Substantially similar mixtures

Comparison with: Classification according to CLP criteria, Eye Irritation Cat. 2

pH  $\leq$  2; the duty holder provided only the information that acidic/alkaline reserve indicates that the mixture is not corrosive despite the low pH value (test results are not available for the NEA)

Test data are available for the reference mixture (OECD 405).

	Eye Classification	Untested Mixture (i)	Reference mixture 1 (ii)
<b>Classification of the mixture</b>		?	Eye Irritation Cat. 2
<b>water</b>			
<b>acid 1</b>	Eye Irrit. 2	3%	6%
<b>acid 2</b>	Eye Irrit. 2	1,5%	2,7%
<b>acid 3</b>	Eye Dam. 1	0	1,2%
<b>non-ionic surfactant 1</b>	Eye Dam. 1	1,7%	0
<b>non-ionic surfactant 2</b>	Eye Dam. 1	0,5%	1,9%

### 2.1 Identification and examination of available information of reference mixture provided by the duty holder

#### Test data of the reference mixtures provided by the duty holder:

Test data are available for the reference mixture. The OECD 405 in vivo test is included in EU No 440/2008.

Only classified mixtures based on adequate and reliable test data could be used as a reference mixture. The reference mixture fulfilled these conditions.

### 2.2 Bridging principles: Could bridging principles be applied?

Untested mixture: due to the extreme pH, the mixture would have to be classified with eye damage 1 (CLP Annex I, section 3.3.2.2.4), unless other data prove that the classification with eye dam. 1 is not necessary.

Bridging principles: Comparison of the untested mixture with one specific reference mixture:

- reference mixture is classified with eye irritant 2
- Two acids are contained in the untested mixture, compared to the reference mixture the acids are contained in lower concentrations or not at all

#### Further questions for the application of bridging principles:

- Are substances in the untested mixtures considered, which are in concentrations below the generic cut-off values?
- Does the non-ionic surfactant 2 at a concentration of 0.5% in the untested mixture

have to be considered for a comparison and classification via bridging principles?

Conclusion for further steps by the application of bridging principles:

Since an untested mixture is compared with a reference mixture and the test was performed on the reference mixture with all ingredients, substances below the generic or specific limits are also considered. It cannot be ruled out that the ingredients below the generic or specific limits also had an influence on the test result.

Interpretation is used that concentrations below the generic cut-off values are considered.

#### Bridging principles analysis:

- i. Dilution: relevant substance (non-ionic surfactant 1) is not part of the reference mixture. Therefore, the reference mixture is not diluted with a substance (diluent).
- ii. Batching: batching is not appropriate because the untested mixture and reference mixture have significantly different compositions
- iii. Concentration of highly hazardous mixtures: not appropriate because untested mixture and reference mixture have significantly different compositions
- iv. Interpolation within one hazard category: not appropriate because untested mixture and reference mixture have significantly different compositions. To use this bridging principle, two tested reference mixtures would be required.
- v. Substantially similar mixtures: not fulfilled, in more detail:

#### Section 1.1.3.5 of Annex I to CLP Regulation:

##### 1.1.3.5. *Substantially similar mixtures*

Given the following:

(a) two mixtures each containing two ingredients:

(i) A + B

(ii) C + B;

(b) the concentration of ingredient B is essentially the same in both mixtures;

(c) the concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);

(d) hazard data for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the hazard classification of B.

If mixture (i) or (ii) is already classified based on test data, then the other mixture shall be assigned the same hazard category.

	Eye Classification	Untested Mixture (i)	Reference mixture 1 (ii)
<b>Classification of the mixture</b>		?	Eye Irritation Cat. 2
<b>water</b>			
<b>acid 1</b>	Eye Irrit. 2	3%	6%
<b>acid 2</b>	Eye Irrit. 2	1,5%	2,7%
<b>acid 3</b>	Eye Dam. 1	0	1,2%
<b>non-ionic surfactant 1</b>	Eye Dam. 1	1,7%	0
<b>non-ionic surfactant 2</b>	Eye Dam. 1	0,5%	1,9%

Untested mixture (i): A + B

A (acid1, acid 2, non-ionic surfactant 1) + B (i) (non-ionic surfactant 2)

Reference mixture (ii): C + B

C (acid1, acid 2, acid 3) + B (ii) (non-ionic surfactant 2)

**Definition of ingredient B<sup>21</sup>:**

*Sub-condition d) "hazard data for A and C (...) are not expected to affect the hazard classification of B"*

Considering an interpretation for the background of this sub-condition the ingredients grouped in B must be "the driver of the hazard potential" of the mixture for this hazard-category in question. Ingredients grouped in B must significantly determine the classification of the complete mixture.

*Sub-condition b) concentration of ingredient B is essentially the same in both mixtures*

Conditions for B not fulfilled, because:

Non-ionic surfactant 2 classified with Eye Dam. 1 might potentially be grouped as B, because non-ionic surfactant 2 is part of the untested mixture and the reference mixture and determines significantly the classification of the complete mixture. However, the concentration of ingredient B is not the same in both mixtures (0,5% in untested mixture versus 1,9% in reference mixture),

**Definition of ingredient A and ingredient C:**

As B could not be defined, the conditions to apply the bridging principle 'substantially similar mixtures' are already not fulfilled. The following explanations are only provided to explain the conditions to be fulfilled for a definition of A and C:

*Sub-condition c) not fulfilled: concentration of ingredient A (6,2 %) in mixture (i) not equal that of ingredient C (9,9%) in mixture (ii);*

*Sub-condition d) not fulfilled: hazard data for A and C are available and not substantially equivalent, i.e. the different substances are not in the same hazard category. Please see also the considerations of sub-condition d) under "1. definition of ingredient B".*

**Conclusion:** bridging principle 'substantially similar mixtures' is not applicable

vi. Review of classification where the composition of a mixture has changed: not appropriate, as not all substances are part of the mixture.

vii. Aerosols: not appropriate because the untested mixture is not an aerosol.

**2.3 Conclusion**

Bridging principles are not applicable.

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<sup>21</sup> The condition indicated in the last sentence of (d) in Section 1.1.3.5 of Annex I to CLP only considers the effect of either A or C on the hazard classification of B, but it does not consider the effect of B on the hazard classification of either A or C. This condition is only meaningful once it is assured that the hazard classification of B is always the driver of the hazard potential of the substantially similar mixtures (untested mixture and tested mixture) for the hazard category in question. For NEAs a strong evidence for the significance of a substance for the classification of the mixture is a substance classification in the most severe classification present in the mixture and a relevant concentration. Therefore, all substances with a classification in the most severe classification need to be grouped in B while observing also the other condition for the definition of B (essentially same concentrations in both mixtures).

### **Annex 3. Substantially similar mixtures in UN GHS**

The example of bridging principle 'substantially similar mixtures' as reported in the UN GHS implementation and guidance section of the UNECE website (guidance on application of GHS criteria, chapter 3.4) demonstrates the application of bridging principle on two complex mixtures.

The complex mixtures consist of five ingredients. The example also demonstrates the importance of the ingredient A, B, and C, as referred in section 1.1.3.5 of Annex I to the CLP. A, B and C can be also seen as groups of ingredients. In this way each ingredient group in the mixtures includes more than one, out of the five, ingredient substances. The specific rules for grouping into ingredient groups A, B and C should be observed, as stipulated in the requirements (a) to (d) in section 1.1.3.5 of Annex I to the CLP.

References:

<https://unece.org/transport/documents/2021/01/ghs-guidance-substantially-similar-mixtures-bridging-principle-example>

[https://unece.org/sites/default/files/2021-01/3-4a\\_2010-15e.pdf](https://unece.org/sites/default/files/2021-01/3-4a_2010-15e.pdf)

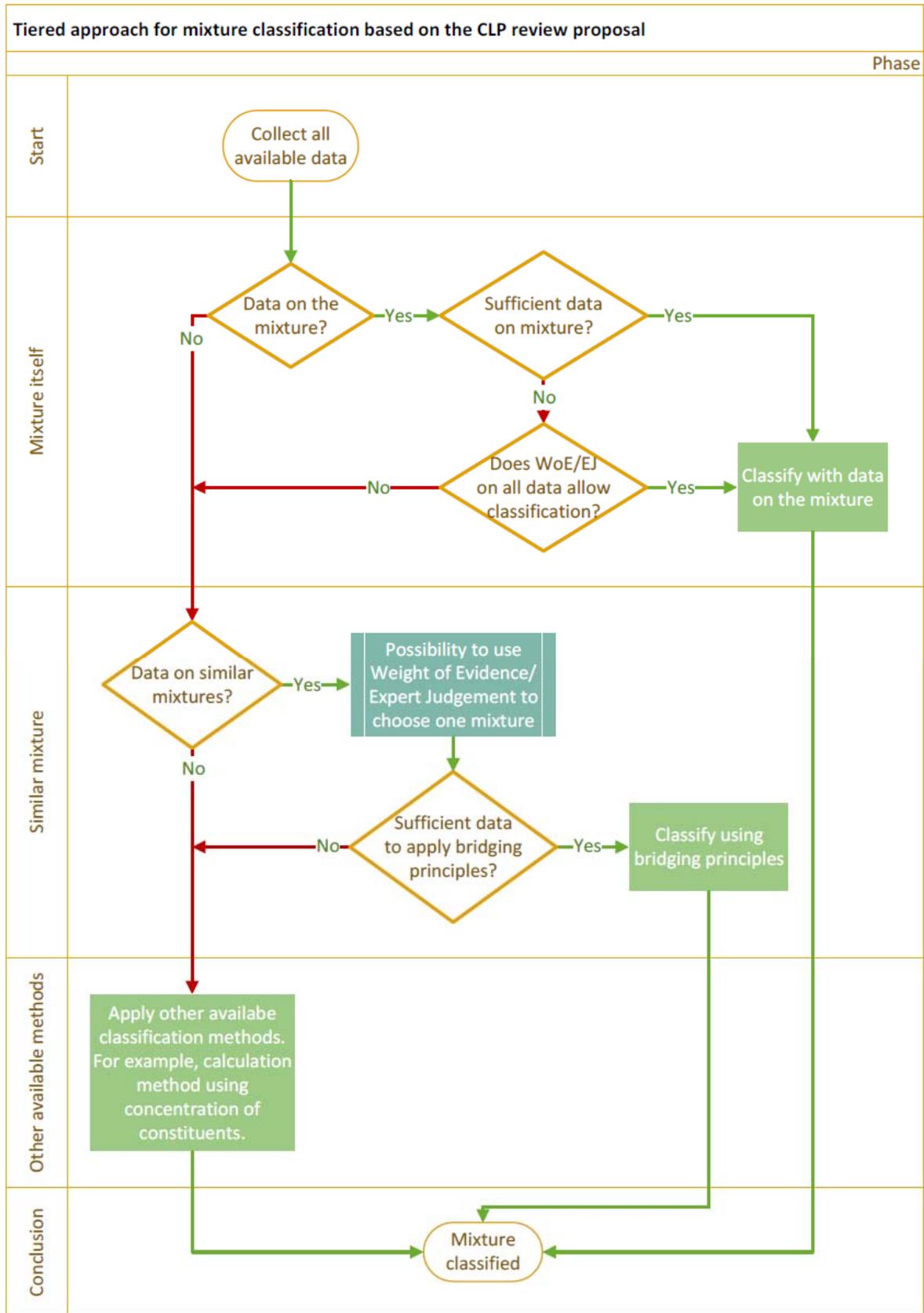
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## Annex 4. Tiered approach for mixture classifications

The flow chart reported below can be used by inspectors when checking the classification of a mixture based on the application of bridging principles and weight of evidence using expert judgement. The flow chart reports three steps:

1. Is there data on the mixture itself? Is there sufficient data for classifying the mixture according to Article 9(1) or 9(2) of CLP or have weight of evidence using expert judgement been used to classify the mixture (Article 9(3) of CLP)? If not:
2. Are there test data on similar mixtures available? Is the similar mixture chosen relevant according to Article 9 (4) of the CLP Regulation, section 1.1.3 of the CLP Regulation and the ECHA Guidance on the Application of the CLP Criteria? If not:
3. The mixture should be classified according to the calculation method (Article 9(4), last sentence, of CLP)

Remark: given the arguments provided in this guide the flow chart applies also to the version of the CLP Regulation before the CLP Revision from 2024, as the CLP Revision mainly provides further clarification with respect to the existing rules for application of a weight of evidence determination using expert judgement (see Section 2 'The approach to be taken when applying weight of evidence determination using expert judgement').



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