

Examples to illustrate Application of Bridging Principles for Skin and Eye Effects

1. Example n°1: Review of classification in case of change of composition of a mixture (CLP Article 15 and CLP Annex I, 1.1.3.6)

CLP Article 15.2: “Where the manufacturer, importer, or downstream user introduces a change to a mixture that has been classified as hazardous, that manufacturer, importer, or downstream user shall carry out a new evaluation in accordance with this Chapter where the change is either of the following:

- (a) a change in the composition of the initial concentration of one or more of the hazardous constituents in concentrations at or above the limits in Table 1.2 of Part 1 of Annex I;
 (b) a change in the composition involving the substitution or addition of one or more constituents in concentrations at or above the cut-off value referred to in Article 11 (3).”

CLP Article 15 (3) indicates that a new evaluation in accordance with Art. 15 (2) is not required if there is valid scientific justification that the changes in composition will not result in a change of classification.

CLP Annex I, Table 1.2 - Bridging Principle for changes in the composition of a mixture

Initial concentration range of the constituent	Permitted variation in initial concentration of the constituent
≤ 2.5 %	± 30%
2.5 < C ≤ 10 %	± 20%
10 < C ≤ 25 %	± 10%
25 < C ≤ 100 %	± 5%

As indicated in CLP Article 15 (2), this table may apply when a supplier introduces a change to a mixture of known composition that has been classified as hazardous.

If the concentration changes are outside the permitted ranges given above then a new classification assessment on the modified mixture must be undertaken.

Ingredient	Skin/Eye Classification	Mixture F Tested	Tolerance band for changes	Mixture M1 untested	Mixture M2 untested
Non-ionic surfactant P ¹	Eye Cat 1	6.0 %	4.8 – 7.2	7.0 %	10.0 %
Anionic surfactant K ²	Skin Cat 2 Eye Cat 1	14.0 %	12.6 – 15.4	15.0%	20.0 %
Citrate	Not classified	5.0 %	Not relevant constituent is not classified	5.5 %	6.0 %
Ethanol	Eye Cat 2	4.0 %	3.2 – 4.8	3.5 %	4.0 %
Polycarboxylate	Not classified	0.75 %	Not relevant constituent is not classified	0.8 %	0.9 %
Water		to 100		to 100	to 100
		Skin Cat 2 (by calculation) Eye Cat 2		Skin Cat 2 (by calculation) Eye Cat 2	Permitted variations not applicable

Note: All mixtures have comparable pH values which are in the following range: 2 < pH < 11.5.

¹ D-Glucopyranose, oligomeric, decyl octyl glycosides, CAS No. 68515-73-1

² Benzenesulphonic acid, C10-13-alkyl derivs., sodium salts, CAS No. 6411-30-3

Classification of tested Mixture F is based on:

Skin: Additivity approach

Eye: OECD TG 438 + histopathology and Low Volume Eye Test

Applying the 'permitted variations' bridging principle, the untested mixture M1 is classified for Eye Irritation Category 2. The additivity approach is applied for effects on skin, classifying for Skin Irritation Category 2.

Rationale:

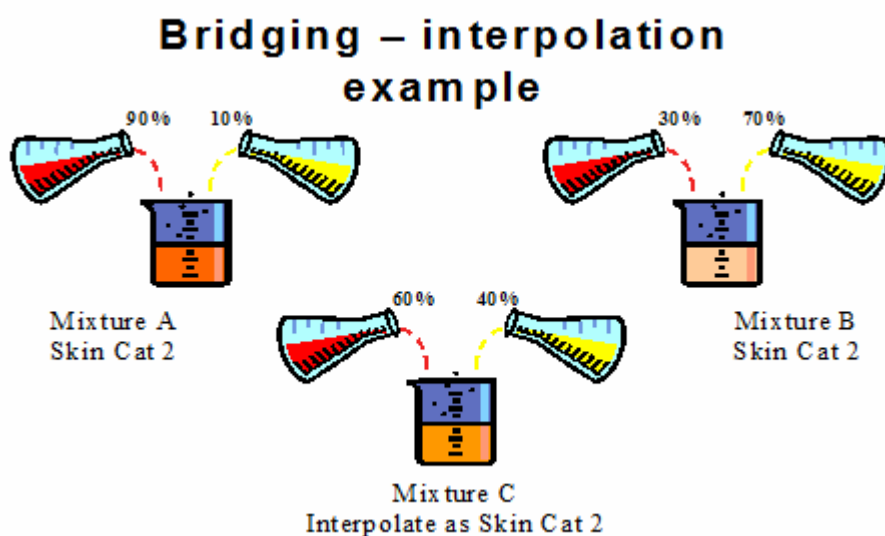
- (a) Classification of the mixture by using the criteria for classification of substances is not possible since skin corrosion/irritation or serious eye damage/eye irritation test data were not available for the untested mixture;
- (b) Classification via the application of bridging principles for effects on eyes can be considered since there are sufficient data on both the individual ingredients and a similar tested mixture;
- (c) Classification of the mixture based on additivity approach should be considered if the expert classifier chooses not to apply the bridging principle or sufficient data had not been available to apply the bridging principle (in this case for effects on skin);
- (d) The permitted variations bridging principle can be applied because:
 - Mixture F is classified as hazardous;
 - Mixtures F and M1 contain the same ingredients;
 - The concentrations of the hazardous ingredients in Mixture M1 are within permitted variations;

The permitted variations bridging principle based on Mixture F, cannot be applied to untested Mixture M2 because, although Mixtures F and M2 contain the same ingredients the concentrations of the surfactants in Mixture M2 are outside the permitted variations.

2.Example n°2: Interpolation within one toxicity category³ (CLP Annex I, 1.1.3.4)

CLP text: “In the case of the classification of mixtures covered by Sections 3.1 and 3.2 (...) for three mixtures (A, B and C) with identical components, where mixtures A and B have been tested and are in the same hazard category, and where untested mixture C has the same hazardous components as mixture A and B but has concentrations of those hazardous components intermediate to the concentrations in mixtures A and B, then mixture C is assumed to be in the same hazard category as A and B.”

For example: Untested Mixture C will have same skin hazard classification as tested Mixtures A and B if ingredient ‘red’ is between 30 and 90% and ingredient ‘yellow’ between 10 and 70%:



Scheme based on ECHA Guidance for the application of CLP criteria Fig. 1.6.3-b
See also UN GHS chapters 3.2.3.2.5 and 3.3.3.2.5⁴

Ingredient	Skin/Eye Classification	Mixture A tested	Mixture B tested	Mixture C untested
Anionic surfactant M ⁵	Skin Cat 2 Eye Cat 1	15.0%	20.0%	17.0%
Non-ionic surfactant P ⁶	Eye Cat 1	3.0%	1.0%	1.6%
Sodium hydroxide	Skin Cat 1A	<0.5%	0.9%	0.7%
Other ingredients not relevant to this endpoint	Not classified	<1.0%	<1.0%	<1.0%
Water		To 100	To 100	To 100
		Skin Not Class Eye Cat 2	Skin Not Class Eye Cat 2	Skin Not Class Eye Cat 2

Note: All mixtures have comparable pH values which are in the following range: 2 < pH < 11.5.

³ Has been amended the GHS 5th revised edition to use ‘hazard’ instead of toxicity i.e. interpolation within one hazard category – will be amended in CLP by the forthcoming 8th ATP

⁴ http://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev06/English/03e_part3.pdf

⁵ Sulfuric acid, mono-C16-18-alkyl esters, sodium salts; CAS No. 68955-20-4

⁶ D-Glucopyranose, oligomeric, decyl octyl glycosides, CAS No. 68515-73-1

Classification of Tested Mixtures A and B is based on:

Skin: OECD TG 439, test data are available for both mixtures

Eye: OECD TG 438 + histopathology and Low Volume Eye Test, test data are available for both mixtures

Applying the 'interpolation within one hazard category' bridging principle, the untested Mixture C is classified Eye Irritation Category 2 but is not classified for skin corrosion/irritation based on test data available for the similar tested mixtures A and B.

Rationale:

- (e) Classification of the mixture by using the criteria for classification of substances is not possible since skin corrosion/irritation or serious eye damage/eye irritation test data were not available for the untested mixture;
- (f) Classification via the application of bridging principles can be considered since there are sufficient data on both the individual ingredients and similar tested mixtures;
- (g) Classification via the permitted variations bridging principle cannot be applied because the concentrations of the hazardous ingredients in Mixture C are outside the permitted variations on concentration for hazardous ingredients in tested Mixture A or in tested Mixture B;
- (h) Classification via the dilution bridging principle cannot be applied because at least one hazardous ingredient in Mixture C exceeds the concentration for this hazardous ingredient present in tested Mixture A or in tested Mixture B
- (i) Classification of the mixture based on additivity approach should be considered if the expert classifier chooses not to apply the bridging principle or sufficient data had not been available to apply the bridging principle;
- (j) The interpolation within one hazard category bridging principle can be applied because:
 - Mixtures A and B have both been tested and are in the same irritation/corrosion hazard category (i.e. Skin: Not classified and Eye Category 2); AND
 - Untested Mixture C has the same toxicologically active ingredients as tested mixtures A and B; AND
 - The concentrations of the anionic surfactant, non-ionic surfactant and sodium hydroxide in Mixture C are intermediate to the concentrations of the same ingredients in Mixtures A and B.

If the concentrations of the hazardous components in Mixture C are not intermediate to those in the tested mixtures then the use of another bridging principle ('substantially similar mixtures') should be investigated.

3. Example n°3: Substantially similar mixtures (CLP Annex I, 1.1.3.5)

CLP text: "Given the following:

(a) two mixtures each containing two ingredients

(i) A + B

(ii) C + B;

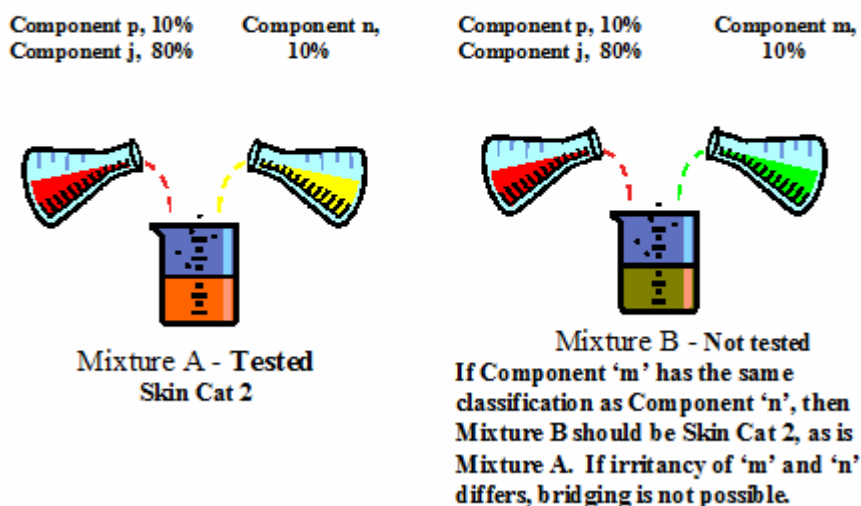
(b) the concentration of ingredient B is essentially the same in both mixtures;

(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."

Bridging – substantially similar mixtures, example



Scheme based on ECHA Guidance for the application of CLP criteria Fig. 1.6.3-c.
See also UN GHS chapters 3.2.3.2.6 and 3.3.3.2.6⁷

Ingredient	Skin/Eye Classification	Mixture A tested	Mixture D untested
Anionic surfactant K ⁸	Skin Cat 2 Eye Cat 1	15.0%	15.0%
Anionic surfactant T ⁹	Skin Cat 2 Eye Cat 1	3.0%	3.0%
Perfume A	Eye Cat. 1	5%	-
Perfume D	Eye Cat. 1	-	5%
Other ingredients not relevant to this endpoint	Not classified	<9.0%	<9.0%
Sodium Sulphate	Not classified	To 100	To 100
		Skin Not Class Eye Cat 2	Skin Not Class Eye Cat 2

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Note: Both mixtures have comparable pH values which are in the following range: 2 < pH < 11.5.

⁷ http://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev06/English/03e_part3.pdf

⁸ Benzenesulfonic acid, C10-13-alkyl derivs., sodium salts, CAS No. 6411-30-3

⁹ Sulfonic acids, C13-17-sec-alkane, sodium salts, CAS No.85711-69-9

Classification of tested Mixture A is based on:

Skin: OECD 439 + 4 hr Human Patch Test

Eye: OECD TG 438 + histopathology and Low Volume Eye Test

Composition Perfume A and Perfume D

Ingredient/Classification	Skin/Eye Classification	Perfume A % w/w	Perfume D % w/w
Geraniol	Eye Cat. 1	4.0	-
4-Methoxybenzyl alcohol	Eye Cat. 1	-	4.3
Isononyl alcohol	Skin Cat. 2, Eye Cat. 1	0.9	-
2-Phenylethanol	Eye Cat. 2	10.8	-
Linalool	Eye Cat. 2	-	9.6
Citronellol	Eye Cat. 2	-	5.1
Decanal	Eye Cat. 2	1.7	-
Menthyl acetate	Not classified	5.0	-
Methyl benzoate	Not classified	7.0	6.0
p-Cymene	Not classified	4.0	6.4
4-Methylanisole	Not classified	5.3	10.1
Phenylacetaldehyde	Not classified	3.0	4.7
		Additivity approach: Eye Cat. 1	Additivity approach: Eye Cat. 1

Test data are available for Mixture A, which demonstrates that Mixture A is not classified for effects on skin and is classified as Eye Category 2.

Applying the 'substantially similar mixtures' bridging principle, the untested Mixture D is classified Eye Category 2 but not classified for skin corrosion/irritation based on the test data available for the similar tested mixture (Mixture A) and Expert Judgement.

Rationale:

- Classification is not possible since skin corrosion/irritation or serious eye damage/eye irritation test data were not available for the Mixture D;
- Classification via the application of bridging principles can be considered since there are sufficient data on both the individual ingredients and the similar tested mixture;
- Classification of the mixture based on additivity approach should be considered if the expert classifier chooses not to apply the bridging principle or sufficient data had not been available to apply the bridging principle;
- The substantially similar mixtures bridging principle can be applied because:

Mixture D

- Tested Mixture A and untested Mixture D contain the same anionic surfactants, the amount of the surfactants is essentially the same in both mixtures;
- The concentration of Perfume D in untested mixture D equals Perfume A in tested mixture A;
- Both perfumes are complex mixtures consisting of several components. Hazard data for the single components are available showing that both perfume mixtures require a classification as Eye Category 1 based on the additivity approach.
- The amount of components triggering Eye Category 1 classification is in both perfume mixtures in the same range.

- At the concentration employed in Mixture A and Mixture D none of the perfume components is present above the generic cut-off values or specific concentration limits. The total quantity of Eye Category 1 perfume components amounts to only 0.245% in Mixture A and 0.215% in Mixture B, which is again below generic cut-off values, showing that the contribution of the perfumes to the overall eye irritation potential of both mixtures is, compared to the contained surfactants, negligible.
- Neither perfume mixture is expected to influence the irritancy of the other components in Mixture A and D.

A substantially similar mixture is therefore one for which a strong scientific case can be made to justify similarity of ingredients in terms of toxicity profiles (hazard classification), mechanism of action, concentration levels, any interactions between the ingredients and properties of the final mixture. The judgement of “substantially similar” must be well made and clearly documented for inspection. In all but the simplest cases it is best made by an expert with experience in toxicological assessments.