Association Internationale de la Savonnerie, de la Détergence et des Produits d'Entretien
International Association for Soaps, Detergents and Maintenance Products

Explanatory notes on the assessment of new detergent mixtures on the basis of existing information from similar mixtures

Skin and eye irritation/corrosion endpoints under CLP

This document refers only to the derivation of classification based on existing information from similar mixtures. For other aspects of classification, please refer to the CLP text and the ECHA guideline on classification. It is not compulsory and is applied under the responsibility of the manufacturer. A.I.S.E. emphasizes that responsibility for correct classification, packaging and labelling in accordance with the laws and regulations of a Member State rests with the supplier of a mixture.

The following documents have been used in the preparation of these revised Explanatory Notes:

- *the EU Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures ('CLP Regulation' or 'CLP') as last amended by the 9th ATP - Commission Regulation (EU) No 2016/1179; and*
- *ECHA Guidance on the Application of CLP criteria version 4.1 from June 2015*

Document History

Version	Comment	Date
n.a.	First edition	31 October 2013
Version 2.0	Revision of the previous version to reflect stakeholder comments / suggestions. Changes include: **Main text** • Text added to front page to clarify which versions of the CLP Regulation + the ECHA guidance (on application of CLP criteria) have been used in preparation of the revised Notes. • Some editorial changes, e.g. to distinguish what is quoted from CLP legal text/the ECHA guidance and what is a recommendation from A.I.S.E. • Section 1 – Text added to introduce the use of bridging principles in the context of the tiered approach for classifying a mixture; Diagram added to illustrate differences in classification approach between DPD + CLP; Text added to introduce DetNet. • Section 2 – Note under Table 1 revised to separate text quoted from ECHA guidance and A.I.S.E. opinion on application of 'permitted variations' bridging principle to non-classified mixtures using expert judgement. • Section 4.2 – Skin corrosion/irritation table: 'Human experience' section revised to reflect GHS 5th rev edition text on use of absence of incidences data; 'Existing Human data' section revised noting GHS/CLP does not contain criteria for skin irritation classification based on human data. • Section 4.2 – Eye irritation table: heading amended; '*In vitro* data' section revised to introduce use of histopathology as additional endpoint for BCOP + ICE and A.I.S.E. work on ICE + histopathology; 'Human experience' section revised to reflect GHS 5th rev edition text on use of absence of incidences data. • Section 4.4.1 – 2nd paragraph has been reworked to remove text on the CESIO classification document (as it only refers to DSD classifications) and to introduce text covering sources of classification information on ingredients. **Appendix 1** Step 2 a. (i) – 1st sentence amended to also include reference to ECHA guidance section 3.2.3.2.1.1 on skin. **Appendix 2** Example no. 2 – Footnote added to highlight interpolation BP in GHS 5th revised edition now uses 'hazard category' instead of 'toxicity category'; Rationale revised to clarify why permitted variations and dilution bridging principles cannot be applied in this case. **Appendix 3** Four new practical examples inserted: Example 1 – APC – Dilution BP Example 2 – APC – Dilution BP with EJ (expert judgement) Example 3 – Laundry powder – interpolation within one toxicity category BP with EJ Example 4 – HDWL – Substantially similar mixtures BP with EJ These examples replace the previous versions which have been reworked to highlight better which BP is used in each case and further clarify use of EJ in the associated Classification Records. **Appendix 4** 1st sentence amended to include relevant ECHA guidance section number; Text added under the table to clarify that untested Mixture B doesn't contain any Skin Cat 1 ingredients and is not extreme pH thus mixture is not	January 2015

	classified as Skin Cat 1. **Appendix 5 added** – list of abbreviations used in the Explanatory Notes.	
Version 2.1.	Revision of the previous version to reflect stakeholder comments / suggestions as well as shanges in the terminology used throughout the documents to adapt latest DetNet developments- from "Reference Formulation" to "Tested Mixture", or from "Test Formulation" to "Untested Mixture". Changes include: **Main text** • Text added to front page to clarify which versions of the CLP Regulation + the ECHA guidance (on application of CLP criteria) have been used in preparation of the revised Notes. • Numbering of pages updated. • Some editorial changes, e.g. to adapt to what CLP Regulation or ECHA Guidance provides exactly • Section 2 – Title and content revised to reflect the wording of CLP Regulation on the Bridging Principle "for changes in the composition of a mixture. • Section 4.2. – Reference to the OECD Guidance Document on Integrated Approach to Testing and Assessment for skin irritation and corrosion (IATA) added in a new paragraph. • Section 4.2. – Update of the table on Serious eye damage/ Eye irritation in order to include latest developments on available validated *In vitro* test methods. • Section 4.2.– modification of note (c) on MAGAM below the table on Serious eye damage/ Eye irritation. This note now refers to a new Appendix to these Explanatory Notes (Appendix n°6) on MAGAM. • Section 4.4.1.- update of the table 3 (i.e. Non-exhaustive list of typical ingredient families and their anticipated contribution to the overall irritation/corrosion profile in detergent mixtures) and of the paragraph "Reading across from perborate to percarbonate" • Section 4.6.- clarification of paragraph 1) in page 22 to better reflect the data hierarchy according to OECD Guidance Document on Integrated Approach to Testing and Assessment for skin irritation and corrosion (IATA) **Appendix 1** Step 8- Last two sentences amended to include reference to Weight of Evidence and Expert Judgement and invert the generation of new data according to alternative test methods and the additivity approach as a last step. **Appendix 2** Review of the three examples in order to include: - The reference to UN GHS relevant chapters; - The addition of the chemical identity of the mixtures' ingredients as footnotes; - The reference to the testing methods used on reference Tested Mixtures. Example 3: pages 5 to 7- review of the whole example **Appendix 3** The four practical examples are now detailed in four separate documents. Revision of the layout according to new template for DetNet Classification Records. Example 1: Revision of the text for Supporting Data/ Justification for classification for both skin and eye effects.	October-December 2016

	Example 2: Revision of the text for Supporting Data/ Justification for classification for both skin and eye effects. Changes in the ingredients' list in the mixture comparison charts for skin and eye. Addition of a table at the end (according to IATA matrix) in order to further illustrate the different pieces of information used to support the Weight of Evidence approach and the Expert Judgement. Example 3: Revision of the text for Supporting Data/ Justification for classification for both skin and eye effects. Changes in the ingredients' list in the mixture comparison charts for skin and eye. Example 4: Revision of the text for Supporting Data/ Justification for classification for both skin and eye effects. Changes in the ingredients' list in the mixture comparison charts for skin and eye. Addition of a table at the end (according to IATA matrix) in order to further illustrate the different pieces of information used to support the Weight of Evidence approach and the Expert Judgement. **Appendix 4** Page 1- Addition of asterisk at the end of the page with the chemical identity of non-ionic and anionic surfactants as illustrative examples Page 2- Insertion of a footnote to explain the rationale as a basis for the Expert Judgement **Appendix 6 added**- MAGAM II study	

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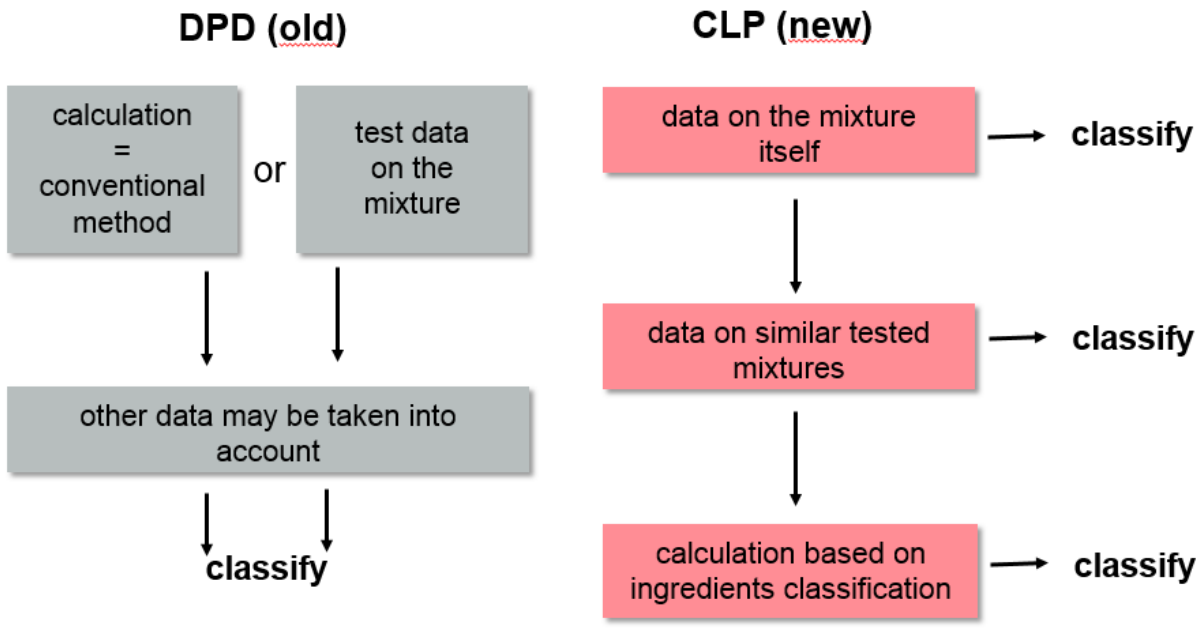
Appendix 6 MAGAM study 201610.25 (new)

1. Introduction

In comparison with the Dangerous Preparations Directive (Directive 1999/45/EC, DPD), the EU Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures ('CLP Regulation') introduces important changes on the hierarchy of data that can be used for classification of mixtures. These changes are summarised in the diagram below:



In practice, if a company doesn't have test data on the mixture itself or similar tested mixtures, it can either generate skin/eye *in vitro* data on the untested mixture or use the CLP additivity approach (with applicable generic or specific concentration limits) to derive the classification of the untested mixture.

It is important to note that CLP does not allow testing on humans for classification purposes and new tests on animals can only be undertaken in certain circumstances. Existing *in vivo* data (animal, human) and *in vitro* data can be used together with any new data generated using *in vitro* test methods.

Before running new tests, it is advisable to check whether the classification of the mixture to be tested can be derived from the classification already established for other mixtures.

To this end, existing data within A.I.S.E. member companies on skin or eye irritation/corrosion of relevant mixtures have been gathered into a database. This database

is the key element of DetNet, the Detergent Industry Network for the Classification under CLP.

Through DetNet, all manufacturers/suppliers of detergents and cleaning products can have access to shared test data and expertise to help them when classifying detergent mixtures for skin and eye effects according to CLP criteria. Tested Mixture compositions are made available to classification experts from companies using a fixed format that contains sufficient detail to enable evaluation of classification and application of bridging principles (i.e. classify an untested mixture by comparing it with similar tested mixtures and applying one of the bridging principles in CLP Annex I, 1.1.3).

The CLP Regulation incorporates the concept of using existing data by suggesting the following steps in the process:

- Evaluation of the degree of mixture modification: Bridging principle for changes in the composition of a mixture (‘permitted variations’).
- Assessment of new mixtures on the basis of existing information on similar mixtures;
- Use of Expert Judgement and Weight of Evidence.

This document presents the aspects to be considered within each step and provides definitions as well as guidance on how to implement the approach at a practical level (see Appendix 1 on classification process). While in principle the concept is also applicable to other toxicological endpoints, this guidance will focus on skin and eye irritation/corrosion.

2. Evaluation of the degree of mixture modification: Bridging Principle for changes in the composition of a mixture (see practical example n°1 in Appendix 2)

The CLP Regulation implies in Article 15(2) that the assessment of a newly developed mixture does not need to be carried out if the modification, in comparison to a classified tested mixture for which skin or eye irritation/corrosion data are available, lies within the permitted variations, as shown in Table 1:

Table 1: Principles for permitted variations in the composition of a mixture[1]

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%

Note: In the Guidance on the Application of CLP Criteria (page 69), ECHA relates the principles for permitted variations to a change in the composition of mixtures already classified as hazardous. The ECHA guidance also indicates that '*A change in the composition of non-hazardous mixtures may result in concentration thresholds being reached and a need to classify the changed mixture as hazardous. Where the manufacturer, importer or downstream user introduces a change to a mixture* ***not*** *classified for a specific hazard, that manufacturer, importer or downstream user must therefore always carry out a new evaluation for that hazard in accordance with Chapter 2 of Title II to CLP (see Article 15(1) of CLP)*'.

A.I.S.E. experts are of the opinion that, in some cases, using expert judgment the 'permitted variations' bridging principle could be applied for non-classified mixtures, (see example in Appendix 4).

Moreover, a revised assessment of a newly developed mixture is also not required if the modification in the composition relative to the tested mixture involves the substitution or addition of one or more constituents in concentrations below the generic cut-off values for skin irritation/corrosion and eye irritation/serious damage to eyes, as extracted from the CLP Regulation and presented in Table 2 below.

[1] Annex I, Table 1.2 of Part 1, section 1.1.3.6. of EU Regulation (EC) No. 1272/2008

Table 2: Generic cut-off values[2]

Hazard class	Generic cut-off values to be taken into account
Skin corrosion/Irritation	1%
Serious damage to eyes/eye irritation	1%

Note: The generic cut-off values generally apply to substances unless lower concentrations are given in Annex VI of the CLP Regulation or there is a presumption (e.g. in the case of corrosive ingredients) that an ingredient present at a concentration of less than 1% can still be relevant for classifying the mixture for skin and eye effects. Generic cut-off values are in weight percentages except for gaseous mixtures where they are in volume percentage.

Minor substances below the generic cut-off value such as colorants, perfumes and preservatives contained in household and cleaning products do generally not change the irritancy profile of a surfactant mixture. The generic cut-off values in Table 2 above reveal that the legislation has also taken this fact into account. Hence, in case the concentrations of such minor substances in the newly developed mixture fall below the cut-off limits for the endpoint of consideration, they do not have to be considered for calculation of classification according to the additivity approach. It is also of further note that Article 15(3) of the CLP Regulation clarifies that in accordance with the above mentioned criteria, a new assessment is not required if there is a valid scientific justification by experts that the newly introduced modification will not result in a change of classification.

If the changes introduced in the newly developed mixture exceed those that are considered ‘minor’, then the CLP Regulation requires the assessment of the new mixture on the basis of the existing toxicological information by applying the bridging principles and/or Weight of Evidence determinations involving Expert Judgement. The framework of the bridging principles as well as potential chemical factors that might impact the outcome of the assessment is described in the following chapter.

[2] Annex I, Table 1.1 of Part 1, EU Regulation (EC) No. 1272/2008

3. Assessment of new mixtures on the basis of existing toxicological information on similar mixtures

The CLP Regulation requires in Article 6(5) companies to use other available information on similar tested mixtures if no or inadequate test data on the mixture itself are available. The underlying concept encompasses the comparison ('bridging') of the scientific information and data pertinent to the assessment of the toxicological endpoint of interest (i.e., the skin or eye irritation/corrosion profile) of well defined tested mixtures to newly developed detergent mixtures that are considered similar.

At a practical level, a tested mixture is defined as a mixture of known composition which
(1) has been tested for the toxicological endpoint in question (i.e.: skin or eye irritation/corrosion) and
(2) for which reliable data are available allowing the determination of its classification and labelling in compliance with the CLP Regulation. The latter should include data on final mixture pH and reserve alkalinity/acidity in case of pH extreme mixtures. Information on toxicological properties and classification of individual substances present in final mixture (namely after any reaction that may have occurred during production process) should also be provided.

The following 'bridging principles' are defined in the CLP Regulation[3]:

- **Dilution**

"If a tested mixture is diluted with a substance (diluent) which has an equivalent or lower hazard category classification than the least hazardous original ingredient substance and which is not expected to affect the hazard classification of other ingredient substances, then one of the following shall be applied:

— the new mixture shall be classified as equivalent to the original mixture;
— the method explained in each section of Part 3 and in Part 4 for classification of mixtures when data are available for all components or only some components of the mixture;
(— ….)."

- **Batching**

"The hazard category of a tested production batch of a mixture can be assumed to be substantially equivalent to that of another untested production batch of the same commercial product, when produced by or under the control of the same supplier, unless there is reason to believe there is significant variation such that the hazard classification of the untested batch has changed. If the latter occurs, a new evaluation is necessary."

- **Concentration of highly hazardous mixtures**

"In the case of the classification of mixtures for skin corrosion/irritation and serious eye damage/eye irritation (sections 3.1 and 3.2 of Annex I of CLP), if a tested mixture is classified in the highest hazard category or sub-category, and the concentration of the components of the tested mixture that are in that category or sub-category is increased, the resulting untested mixture shall be classified in that category or sub-category without additional testing."

[3] Annex I, section 1.1.3 of Regulation (EC) No 1272/2008 as last amended by Commission Regulation (EU) No 2016/1179

- **Interpolation within one toxicity category (see practical example n°2 in Appendix 2)**

"In the case of the classification of mixtures for skin corrosion/irritation and serious eye damage/eye irritation (sections 3.1 and 3.2 of Annex I of CLP), 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."

- **Substantially similar mixtures (see practical example n°3 in Appendix 2)**

"Given the following:

(a) two mixtures each containing two ingredients[4]:
(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."

The principles 'Interpolation within one toxicity category' and 'substantially similar mixtures' are considered to be the most relevant bridging principles for comparison of a reference mixture with a new mixture in the A.I.S.E. product range. The detailed rules for the use of the bridging principles are given in the CLP Regulation and further illustrated in the ECHA Guidance on the application of CLP criteria[5].

The applicability of the bridging principles is subject to a number of conditions and chemical considerations which the expert assessor has to take into account when drawing conclusions on the suitability of using data or information on the skin or eye irritation/corrosion potential of reference mixtures for the assessment of a newly developed mixture. Any specific physico-chemical or chemical considerations going into the final assessment of the applicability of the bridging principles should be fully recorded by the expert assessor along with any decisions using expert judgement. Potential conditions and considerations are described and discussed in the following section. Some additional practical examples have been prepared by experts and can be found in Appendix 3.

[4] An ingredient can be comprised by one or more than one substance each.
[5] https://echa.europa.eu/documents/10162/13562/clp_en.pdf/

4. **Elements to consider when classifying similar mixtures**

4.1. Availability of information on composition

A prerequisite for bridging data from a tested mixture to a new mixture under assessment is the availability of sufficient compositional and physico-chemical information on the new mixture as well as the tested mixture. This includes the identification of the relevant individual ingredients contained in the mixture ideally with their respective CAS numbers, their levels in the mixture, their toxicological profile as well as their classification according to CLP. Moreover, the expert assessor should have information on the pH of the new mixture as well as its reserve alkalinity or acidity in case of mixtures with extreme pH (i.e.: pH ≤ 2 or ≥ 11.5). The bridging of data from a tested mixture to a new mixture is not feasible if the pH and the reserve alkalinity/acidity of the tested mixture and the mixture under assessment (for mixtures whose pH is ≤ 2 or ≥ 11.5) are not in agreement, namely the new mixture's irritation/corrosion related hazard classification based on its pH and reserve alkalinity/acidity according to the Young *et al*.[6] method should be the same or lower than that of the tested mixture.

A.I.S.E. has developed an approach for sharing of data on tested mixtures in DetNet which protects commercially sensitive information but discloses sufficient detail to allow detailed and toxicologically relevant comparisons.

4.2. Information of relevance for classification of detergent mixtures for skin and eye irritation/corrosion

The following provides an overview of the type of data/information that may be available on the new mixture under review, on similar mixtures or on ingredients contained in the mixture.

In 2014 OECD has published a Guidance Document on Integrated Approach to Testing and Assessment for Skin Irritation and Corrosion (IATA)[7]. The IATA describes several modules which group information sources and analysis tools, and provides guidance on (i) how to integrate and use existing testing and non-testing data for the assessment of the skin irritation and skin corrosion potentials of chemicals and (ii) proposes an approach when further testing is needed. Furthermore, an OECD IATA for serious eye damage and eye irritation is currently under development.

[6] J.R. Young, M.J. How, A.P. Walker and W.M.H. Worth (1988), 'Classification as corrosive or irritant to skin of preparations containing acidic or alkaline substances, without testing on animals', Toxic. *In Vitro* 2(1): pp. 19-26.

[7] Guidance Document on Integrated Approach to Testing and Assessment for Skin Irritation and Corrosion (IATA), Series on Testing and Assessment No. 203, 2014

http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)19&doclanguage=en

Skin corrosion/irritation

The following table presents an overview of the type of information/data that can be used for the skin corrosion/irritation evaluation of detergent mixtures:

Type	Detail	Comments
Physico-chemical information (Non-testing method)	Determination of pH and reserve alkalinity/acidity (Young et al. 1988)	CLP indicates that a mixture should be considered as corrosive to skin in case **pH ≤ 2 or ≥ 11.5** Likewise, considering the reserve acidity/ alkalinity, a mixture is classified as corrosive if **pH + 1/12 alkali reserve ≥ 14.5** **pH – 1/12 acid reserve ≤ - 0.5** In case of extreme pH that consideration of reserve alkalinity/acidity suggests the mixture not to be corrosive, then further testing (preferably *in vitro*) shall be conducted for confirmation
***In vitro* data** (Testing method)	**Validated Test Methods for skin corrosion:** • Transcutaneous Electrical Resistance Test (TER) (EU test method B40, OECD TG 430) • Human Skin Model (HSM) Test (EU test method B40 bis, OECD TG 431) • Membrane Barrier Test (Corrositex) (OECD TG 435) **Validated Test Methods for skin irritation:** • Reconstructed Human Epidermis Test (EU test method B46, OECD TG 439)	New methods may become available in the future according to ECVAM/ICCVAM validations programs. For outcome of A.I.S.E. *in vitro* project, refer to A.I.S.E. document on 'Findings of *in vitro* project on skin and eye irritation and corrosion'
Existing animal data (Testing method)	• Acute dermal irritation/ corrosion (EU test method B4, OECD TG 404)	Further information on irritation potential can also be gained from acute dermal toxicity studies on rabbits or rats (OECD TG 402) or guinea pig skin sensitisation studies (OECD TG 406). Due to different protocols and the interspecies differences in sensitivity, the use of such data for classification purposes requires a case by case evaluation.
Human experience (Non-testing method)	• Occupational data • Data from accident databases • Market surveillance data • Epidemiological studies • Well documented case reports/observations	An assessment of the human experience data regarding its robustness, quality and statistical power has to be taken into account, along with other evidence, to define the classification and labelling of a specific detergent mixture; GHS 5th revised edition indicates that although human data from accident or poison centre databases can provide evidence for classification, absence of incidents is not itself evidence for no classification as exposures are generally unknown or uncertain.
Existing human data (Testing method)	• Epidemiological studies • Existing Human Patch Test (4-hour occluded or semi-occluded)	Existing studies usually performed on detergent mixtures and not for hazard identification purposes; serve as a confirmatory test for the assumption of safety made previously on the basis of other existing information. It should be noted that GHS/CLP does not contain criteria for classification for skin irritation based on human data [a].

In section R.7.2.4.2 of ECHA REACH Guidance it is specified that available good quality Human Patch Test data should be considered as appropriate and used for Classification and Labelling decision making, which is in accordance with OECD IATA. In contrast to the OECD IATA, ECHA REACH Guidance only foresees the use of positive human data (irritant or corrosive) for classification purposes (see decision logic Figure R.7.2–2). Negative Human Patch Test data can be used in combination with other data in a Weight of Evidence assessment.

Serious eye damage/Eye irritation

The following table presents an overview of the type of information/data that can be used for the eye irritation evaluation of detergent mixtures:

Type	Detail	Comments
Physico-chemical information (Non-testing method)	Determination of pH and reserve alkalinity/acidity (Young et al. 1988)	CLP indicates that a mixture should be considered as corrosive to skin in case **pH ≤ 2 or ≥ 11.5** Likewise, considering the reserve acidity/ alkalinity, a mixture is classified as corrosive if **pH + 1/12 alkali reserve ≥ 14.5** **pH – 1/12 acid reserve ≤ - 0.5** In case of extreme pH but that consideration of reserve alkalinity/acidity suggests the mixture not to be corrosive, then further testing (preferably *in vitro*) shall be conducted for confirmation.
***In vitro* data** (Testing method)	**Validated Test Methods to identify Eye Cat 1:** • Bovine Corneal Opacity and Permeability Assay (BCOP) (EU test method B47, OECD TG 437) • Isolated Chicken Eye Test (ICE) (EU test method B48, OECD TG 438) • Fluorescein Leakage test (OECD TG 460) • Short Time Exposure (STE) (OECD TG 491) **Validated Test Methods to identify Eye not-classified:** • Bovine Corneal Opacity and Permeability Assay (BCOP) (EU test method B47, OECD TG 437) • Isolated Chicken Eye Test (ICE) (EU test method B48, OECD TG 438) • Short Time Exposure (STE) (OECD TG 491) • EpiOcular Eye Irritation Test (EIT) (OECD TG 492) Other Test methods: • Cytosensor Microphysiometer test	New methods may become available in the future according to ECVAM/ICCVAM validations programs. OECD TG 437 and 438 and OECD GD160 encourage the use of histopathology as an additional endpoint to the standard BCOP and ICE prediction model, since it is potentially useful to get a more complete characterization of corneal damage. Use of histopathology in the ICE has been shown to improve identification of non-pH extreme detergent and cleaning products classified as Category 1 based on persistent effects *in vivo*, thus increasing the overall sensitivity of the standard ICE prediction model (Cazelle et al., 2014[a]). For outcome of A.I.S.E. *in vitro* project, refer to A.I.S.E. document on 'Findings of *in vitro* project on skin and eye irritation and corrosion'
Existing animal data (Testing method)	• Acute eye irritation/corrosion, EU test method B5 (equivalent to OECD TG 405) • Existing Low Volume Eye test (LVET)	ECHA REACH Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance R.7.2.9.1[b] indicates: 'within the applicability domain of household detergents, cleaning products and their main ingredients, positive LVET data (be it Category 2 or Category 1) can be used for the appropriate classification for either serious eye damage or eye irritation, but negative data from LVET as a *standalone method* (in the absence of any other information) are not conclusive for *no classification*." Existing LVET data on household detergent and cleaning products refer to data generated prior June 2009.
Human experience (Non-testing method)	• Occupational data • Data from accident databases (e.g. MAGAM study[c]) • Market surveillance data • Epidemiological studies • Well documented case reports and observations	An assessment of the human experience data regarding its robustness, quality and statistical power has to be taken into account, along with other evidence, to define the classification and labelling of a specific detergent mixture; GHS 5th revised edition indicates that although human data from accident or poison centre databases can provide evidence for classification, absence of incidents is not itself evidence for no classification as exposures are generally unknown or uncertain.

***Notes*:**

(a) Cazelle E., Eskes C., Hermann M., Jones P., McNamee P., Prinsen M., Taylor H., Wijnands M. (2014): Suitability of histopathology as an additional endpoint to the Isolated Chicken Eye Test for classification of non-extreme pH detergent and cleaning products; Toxicol. *in Vitro* 28, 657-666

(b) http://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf

(c) For more information on MAGAM study, please refer to Appendix 6.

4.3. Prerequisite for evaluation of information: data quality

Skin or eye irritation data derived from *in vitro*, animal or clinical studies is generally viewed as acceptable if they received following review a reliability score of 1 or 2 according to the Klimisch[8] criteria.

In short, Klimisch 1 rated studies or data ('reliable without restrictions') were generated according to generally valid and/or internationally accepted testing guidelines, typically under conditions of Good Laboratory or Clinical Practice (GLP; GCP). Klimisch 2 rated studies/data ('reliable with restrictions') may not totally comply with specific testing guideline, but are well documented and assessed to be scientifically acceptable.

4.4. Factors impacting mixtures' skin or eye irritation/corrosion profile

A range of chemical and toxicological factors should be taken into account when assessing the irritation/corrosion profile of a new mixture on the basis of data on tested mixtures. These are:

- Irritation/corrosion profile of individual substances or substance family;
- Potential synergistic or antagonistic effects in mixtures;
- pH and reserve alkalinity/acidity;
- Proximity of irritation/corrosion data on tested mixtures to classification cut-off levels.

4.4.1 Irritation/corrosion profile of the individual substances or substance families

In most detergent mixtures only a few substances/substance groups are the major contributors to the irritation/corrosion potential of the mixture. They can be ranked with respect to their potential to contribute to skin or eye irritation/corrosion potential of mixtures. Such ranking distinguishes between 'high', 'medium' or 'low' contributors. It is not only the inherent irritation/corrosion potential of a substance, but also its concentration in the mixture that will determine its contribution to the irritation/corrosion potential of the mixture. For example, a substance that is considered to be a 'medium'

[8] Klimisch *et al.*, 1997. A systematic approach to evaluating the quality of experimental toxicological and ecotoxicological data. Regulatory Toxicology and Pharmacology, **25,** 1–5.

contributor may be critical to the irritation/corrosion potential of the mixture if it is present at high concentrations.

Substances that have a related chemical structure and a similar toxicological profile may be grouped together. The latter is typically related to the same toxicological endpoint and chemicals having the same mode of action and similar potency. Chemicals of the same group or sub-group of substances may exert the same or similar irritation/corrosion potential. Information needed to compare irritation/corrosion potential of individual ingredients can be obtained from various sources. The supplier's Safety Data Sheet (SDS) is the primary source of information regarding the hazard classification (and any specific concentration limits for skin/eye effects if applicable) of an ingredient. Additional information on an ingredient may also be found in the ECHA REACH Registered Substances database and the Classification & Labelling Inventory[9].

The following points should be kept in mind when using hazard information sources other than the applicable supplier's SDS:
- ensure the exact same ingredient is being looked at when searching the ECHA databases;
- ECHA cannot guarantee the correctness of the information and the content is subject to change without prior notice, especially the information in the Classification & Labelling Inventory need a thoroughly check for plausibility;
- a harmonised classification for a substance listed in CLP Annex VI may not cover all endpoints thus self-classification for a particular endpoint such as skin and/or eye may be required.

Table 3 below provides a non-exhaustive list of chemical families, groups and substance subgroups which are typically used in detergent mixtures, separated with regard to their anticipated contribution to the irritation/corrosion profile of the mixture. As can be seen, surfactants, bleaches as well as alkalis and acids in alkaline or acidic mixtures are considered to be the most important contributors to the overall irritation/corrosion profile of detergent mixtures.

[9] Access via the 'Search for Chemicals' function on the ECHA Homepage at http://echa.europe.eu

Table 3: Non-exhaustive list of typical ingredient families and their anticipated contribution to the overall irritation/corrosion profile in detergent mixtures

Relevance to irritation/ corrosion profile of mixture	Substance type	Group	Examples of specific substances
High	Surfactants	Cationic surfactant	Alkyltrimethylammonium salts Dialkyldimethylammonium salts Alkyldimethylbenzylammonium salts Amine oxides (at acid pH) Ester quats – NB: lower hazard profile than other cationic surfactants
		Anionic surfactant	Alkyl sulphates, Alkyl ether sulphates; Linear alkyl benzene sulphonates; Secondary alkane sulphonates; Alpha-olefin sulphonates Sulphosuccinates
		Non-ionic surfactant	Alcohol ethoxylates; Alcohol alkoxylates; Alkyl polyglycosides; Glucose amides; Block copolymers; Fatty acid amides; Amine oxides (at neutral/ alkaline pH)
		Amphoteric surfactants	Betaines; Imidazolinone derivatives
	Bleach		Sodium perborate; Sodium percarbonate; Sodium hypochlorite; Hydrogen peroxide; Sodium Dichloroisocyanurate
	Alkali in alkaline mixtures		Sodium carbonate; Sodium hydroxide; Sodium silicate (waterglass); Potassium hydroxide
	Acids in acidic mixtures		Citric acid; Acetic acid; Formic acid; Hydrochloric acid; Phosphoric acid; Sulphamic acid; Sulphuric acid;
Medium	Soaps		Sodium Cocoate; Potassium Palmkernellate;
	Solvents		Ethanol; Isopropanol; 2-Butoxy ethanol; Butoxy diglycol; Propylene glycol; Dipropylene glycol
	Bleach activator		Tetraacetyl ethylene diamine (TAED)

Low	Hydrotropes		Sodium cumene sulphonate; Sodium xylene sulphonate; Sodium toluene sulphonate
	Builders		Phosphates Zeolites
	Alkali/acids for pH adjustment (i.e., low levels)		Low concentrations of e.g. sodium hydroxide or citric acid
	Colorants		Minor substances if present below the cut-off limit for classification & labelling
	Enzymes		Minor substances if present below the cut-off limit for classification & labelling
	Perfume		
	Preservatives		

In general, substances present at very low levels (i.e. ≤ 1%) can be assumed to have a negligible influence on the irritation/corrosion potential of a mixture.

As discussed before, the CLP defines generic cut-off levels for different hazards including skin corrosion/irritation and serious damage to eyes or eye irritation. The cut-off levels for skin corrosion/ irritation effects and serious eye damage/ eye irritation effects have been set at 1% unless specific concentration limits indicate that a substance is corrosive/irritant below 1% (see Table 2).

Reading across from perborate to percarbonate

Oxygen containing bleaches are widely used in laundry and home care applications and are also considered to be contributors to the overall irritation profile of detergent mixtures. The two most prominent oxygen-based bleaches are sodium perborate and sodium percarbonate. Historical detergent reference tested mixtures contain mostly sodium perborate while sodium percarbonate is contained in more recent and new detergent mixtures.
In powder and tablet mixtures both bleaches are precursors of hydrogen peroxide, the active component, and release it upon contact with water. This allows the comparison of the irritation profile of detergent mixtures containing different oxygen bleach agents by comparing the amount of formed hydrogen peroxide (H_2O_2) at molar level:

Perborate monohydrate hydrolysis:

$$Na_2B_2H_4O_8 + 2\ H_2O \rightarrow 2\ NaH_2BO_3 + 2\ H_2O_2 \quad (1)$$

Percarbonate decomposition:

$$2\ Na_2CO_3 \bullet 3H_2O_2 \rightarrow\ 2Na_2CO_3\ +\ 3H_2O_2 \quad (2)$$

	Theoretical H_2O_2 release
Sodium perborate monohydrate	34.1 % (w/w)
Sodium percarbonate	32.5 % (w/w)

Many tested mixtures for powder laundry detergents include sodium perborate monohydrate as oxygen bleach. The table above shows that sodium perborate monohydrate and sodium percarbonate release comparable levels of hydrogen peroxide.

Furthermore, both oxygen based bleaching agents have the same classification and comparable specific concentration limits of 22 % for sodium perborate monohydrate respectively 25 % for sodium percarbonate for eye damage category 1, being driven by the release of Hydrogen Peroxide:

From the classification and labelling depicted above, it can be concluded that persalts in typical laundry detergents will mainly impact the eye irritation potential of the mixture.

Conclusion:

Since i) sodium perborate monohydrate and sodium percarbonate have the same classification and specific concentration limits by far exceeding the default concentration limits of 1 % for eye category 2 and 3 % for eye category 1, and ii) both substances release comparable levels of hydrogen peroxide (that induces eyes effects classified as eye damage category 1), it can be concluded that a formulation containing percarbonate can be compared to tested mixtures containing perborate monohydrate with regard to the endpoint eye damage category 1 (and vice versa).

4.4.2 Potential synergistic or antagonistic effects in mixtures

When assessing the possible contribution of a specific surfactant system to the overall irritation/corrosion profile of a detergent mixture, it is not only important to distinguish between anionic, non-ionic, cationic or amphoteric surfactants, but also to look at the combinations of surfactant groups that are used in the detergent mixture. The CLP Regulation indicates in Article 12 that existing adequate and reliable information demonstrating the potential synergistic or antagonistic effects should be taken into account for mixture classification purposes.

Experience and test data on detergent mixtures have shown that the mixtures exhibit lower acute irritation potential than predicted by simple summation of the irritation potential of the individual substances. It has been shown that interactions of surfactants in simple mixtures could decrease irritation potential compared to that predicted by the aggregated irritancy potential of each individual surfactant substance[10]. Though this has been demonstrated in simple mixtures, and accepting the limitations of such methodology, there is no reason to suppose that this will not also be applicable for more complex detergent mixtures. However, when dealing with highly complex detergent mixtures, an appropriate, fully documented scientific justification will be required by the

[10] Paye, M. et al. (2006). Antagonism of surfactants: the case of laundry detergents. Tenside Surf. Det. 43, 6, 290-292.

expert classifier when taking antagonistic or synergistic effects in the final classification decision into account.

4.4.3 pH and reserve alkalinity/acidity

When assessing the irritation potential of detergent mixtures, the presence of alkaline substances in alkaline mixtures and acidic substances in acidic mixtures has to be taken into account. Therefore, information on the pH as well as the mixture's reserve alkalinity or acidity must be available. The latter is, however, only required in the case of extreme pH mixtures (i.e. pH ≤ 2 or ≥ 11.5). The pH of mixtures should be provided for the neat (low viscous) liquids and in case of high solid viscous liquids/ solids/powders mixtures for their 10% aqueous solutions as described in Young *et al*[11].

In this context it is important to consider that the pH value alone cannot be used in an assessment as the pH value is not the only driver for irritation. For example, formic acid having a pH of 1.1 is corrosive whereas hydrochloric acid with a pH of 1.0 is only irritating. The ability to penetrate tissue and its titratable acid and alkaline reserve are critical to the mixtures irritation/corrosion assessment. The latter reflects the amount of acid or alkali that needs to be added in order to reach a pH of 4 for acidic mixtures and a pH of 10 for alkaline mixtures. Higher titratable acid and alkaline reserve generally translates into greater tissue damage. Moreover, since the potencies of different acids and bases are different, they cannot be grouped together and considered equivalent but need to be compared in terms of concentration limits or other indications of potency. Existing concentration limits for acids and bases can be found in Annex VI Tables 3.1 and 3.2 of the CLP Regulation[12].

4.4.4 Proximity of irritation/corrosion data on tested mixtures to classification cut-off levels

The acceptable degree of variation between two mixtures is also influenced by the test results of the tested mixture: the closer the test data of the tested mixture is to the cut-off levels for classification as skin or eye irritant or corrosive, the less variation in composition can be accepted between the tested and the new mixture. Likewise, if the tested mixture has been shown to result in no or mild irritation (or clear irritation or corrosion), then expert judgement may allow a larger degree of variation for data bridging.

4.5. Use of Expert Judgement (see example in Appendix 4)

Generally, CLP criteria for using bridging principles for classification of mixtures on the basis of tested mixtures are narrow and therefore of limited use. The CLP Regulation allows using Weight of Evidence and Expert Judgement to support a classification or

[11] J.R. Young, M.J. How (1993), 'Product Classification as Corrosive or Irritant by Measuring pH and Acid/Alkali Reserve', Toxic. *In Vitro* Skin Toxicology Vol. 10, B. *In Vitro* Approaches, I. Physicochemical Methods, B I-1: pp. 23-27.

[12] http://ec.europa.eu/enterprise/sectors/chemicals/documents/classification/index_en.htm#h2-1

non-classification of new mixtures. However, the CLP Regulation falls short in providing guidance on how Expert Judgement can be applied to complex mixture system such as a detergent mixture.

Bridging test data requires knowledge of the chemistry and toxicological profile of the product categories in question, chemical factors impacting/driving the irritation/corrosion profile of detergent mixtures as well as the appropriate expertise to weigh the relevance of the evidence of different types of test systems and information. The latter is particularly important when the classification of the tested mixture is based on heterogeneous datasets including data from scientifically valid but not fully validated methodologies or in cases of conflicting information.

4.5.1. Expert qualification

While the CLP Regulation does not specifically provide an expert qualification profile, it will be important for companies to be able to demonstrate that appointed experts have acquired a broad knowledge of the following:

- Spectrum of mixtures of the product category in question;
- General toxicological profile of detergent mixtures;
- Function and toxicological profile of individual mixture ingredients;
- Chemical and physico-chemical factors of a detergent mixture that may alter the toxicological profile and hence classification & labelling requirements;
- Test systems including protocols and scoring schemes;
- Detailed regulatory provisions by the CLP for the classification & labelling of substances or mixtures for hazardous properties.

Furthermore, the ECHA Practical Guide "How to report weight of evidence"[13] states that *"Expert Judgement is vital in the construction and appraisal of the weight of evidence package. For example, the use of sound scientific judgement is important when considering reliability, relevance and adequacy, integrating and comparing different pieces of information and assigning a weight to each piece of data. The person who provides this scientific judgement must have expertise concerning the relevant endpoint(s) and study methods. The expert will need to assess the reliability, relevance, adequacy of the available data and to judge whether the combined evidence is enough to draw a conclusion about the properties or the potential effects of the substance".* Additional elements on weighing of information are provided in the following section.

4.6. Weighing of information

The CLP Regulation specifies in Annex I, 1.1.1.3 that a determination of the classification of a substance or mixture requires the consideration of all available

[13] http://echa.europa.eu/documents/10162/13655/pg_report_weight_of_evidence_en.pdf

information bearing on the determination of hazard. A Weight of Evidence assessment should be carried out before any additional *in vitro* or *in vivo* testing is performed. This includes results of *in vitro* tests, relevant animal data, chemical category information, QSAR results, human experience such as occupational data and data from accident databases, epidemiological and clinical studies and well documented case reports. The quality and consistency of the information has to be given the appropriate weight. Positive and negative results should be assembled together in a single Weight of Evidence determination by the expert. The OECD IATA for skin Irritation and corrosion provides an example of a matrix for Weight of Evidence analyses.

The priority given to different pieces of information is generally determined on a case by case basis using Expert Judgement. The CLP Regulation gives some general guidance in case that there is a conflict of findings[14]. From that, some basic qualitative rules can be established for the classification and labelling of detergent mixtures for skin or eye irritation/corrosion:

1. In case several studies with conflicting results are available for one tested mixture, the quality and reliability of the studies as well as their relevance for classification and labelling have to be taken into account.

   When the reliability of available studies is comparable, then those studies assessed to be most relevant for the irritation/corrosion hazard in humans are given most weight in the determination. The CLP Regulation stipulates a general relevance hierarchy of human data > *in vitro* and *in vivo* studies > other studies. This is also further highlighted in the OECD Guidance Document on an integrated approach on testing and assessment (IATA) for skin corrosion and irritation, as well as in the draft OECD Guidance Document on an integrated approach on testing and assessment (IATA) for serious eye damage and eye irritation. However, it needs to be considered that, for example, due to some study design limitations certain human or animal studies may not necessarily overrule data derived from *in vitro* methodologies and vice versa. Hence, the final assessment of which studies are most relevant to the assessment of the human hazard is subject to Expert Judgement.

2. In case the study results of two or more tested mixtures are in conflict, the degree of similarity of the tested mixture to the new mixtures in addition to the factors mentioned under ‘1’ will need to find considerations. The data from the tested mixture that is judged to be the closest to the new mixture under assessment should be given most weight.

3. In case no real differences in reliability, ranking of study relevance or similarity in mixtures can be established, the study giving rise to the highest concern should be taken as the key study for the classification of the new product mixture.

[14] Annex I, 1.1.1.4 of Regulation (EC) No 1272/2008