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Short guidance

on the use of in vitro test methods for the classification of products/mixtures for skin corrosion (H314)

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Short guidance on the use of in vitro test methods for the classification of products/mixtures for skin corrosion (H314)
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Skin corrosion

Products (mixtures) containing corrosive ingredients and/or having an extreme pH (≤ 2 or ≥ 11.5) can have potential corrosive hazard to the skin. The generic concentration limit for skin corrosion classification currently established for use within the additivity approach for products and mixtures (EU CLP[1]/UN GHS[2]), is lower compared to previous regulations (EU DPD[3]). This change affects in particular those products containing corrosive ingredients in the range of 5% to 10% and results in a higher number of products classified as skin corrosive Category 1 (H314) when the additivity approach is applied.

In Switzerland, a classification as skin corrosive Category 1 triggers downstream consequences such as the exclusion of retailing in self-service areas (Art. 63 ChemO). The skin corrosive Category 1 products/mixtures are assigned to Group 2 according to Annex 5 (1.2) ChemO, and anyone who commercially supplies a product assigned to Group 2 to private users must, at the time of supply, explicitly inform them of the precautions required and the correct method of disposal (Art. 65 ChemO).

This document provides guidance ***to manufacturers and formulators of products (mixtures)*** on a ***step-by-step practical procedure*** for the classification of the above referred mixtures having potential skin corrosive hazard. It is based on the revised Chapter 3.2 of the UN GHS[2] and the corresponding 8th Adaptation to Technical Progress to the CLP Regulation[4] as well as on current international recommendations on the use of an Integrated Approach for Testing and Assessment (IATA) of skin corrosion and irritation[5]. The recommended approach is composed of three main steps and aims to make best use of existing data, be resource efficient and take into account the use of currently available *in vitro* test methods. In particular, examples are given for mixtures having extreme pHs and for mixtures containing 5% to 10% corrosive ingredients but having no extreme pH.

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[1] EU CLP: European Union Regulation No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. Official Journal of the European Union L353, 1-1355, 2008.

[2] UN GHS: United Nations Globally Harmonized System of Classification and Labelling of Chemicals (2015). Sixth revised edition. Part 3: Health Hazards – Chapter 3.2 Skin corrosion/irritation. New York, USA, and Geneva, Switzerland: United Nations. p.125-136. Available at: http://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev06/English/ST-SG-AC10-30-Rev6e.pdf.

[3] EU DPD : European Union Directive 1999/45/EC relating to the classification, packaging and labelling of dangerous preparations. Official Journal of the European Communities L 200, 1-68, 1999.

[4] Regulation (EU) 2016/918. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1474460865370&uri=CELEX:32016R0918.

[5] OECD (2014). Guidance document No. 203: Integrated Approached to Testing and Assessment for Skin Irritation/Corrosion. Environment, Health and Safety Publications, Series on Testing and Assessment. Organisation for Economic Cooperation and Development, Paris. Available at: http://www.oecd.org/env/ehs/testing/seriesontestingandassessmenttestingforhumanhealth.htm.

Step 1: Gather existing, physico-chemical and non-testing data

- Collect existing and available information on human, animal and *in vitro* data on the skin effects of the product (mixture);
- Collect, measure or estimate physico-chemical properties of the product such as pH and acidic/alkaline reserve;
- Make use of non-testing methods such as the bridging principles based on existing and available information for similar mixtures from e.g. in house data sources or information from databases such as DetNet [6].

Bridging principle

The comparison of the product properties and composition with other products classified as non corrosive based on test results may lead to a conclusive result concerning the classification of the product under evaluation. This result must be reasonably justifiable in the context of verifications by the competent authorities.

If no conclusive decision can be made from the individual data sources available, consideration should be given to the totality of existing information using a WoE evaluation as described in Step 2.

Step 2: Evaluate the collected and relevant data using a weight of evidence (WoE) analysis

- If no decision can be made on classification and labelling based on Step 1, a WoE analysis should be conducted before additional testing is performed. The WoE analysis must be performed on a case-by-case basis and with expert judgment as generally recommended [2, 5, 7, 8]. This is especially true when there is conflict in information available on some parameters.
- The weighing of all available information should be transparent and needs to consider the quality, consistency, adequacy and relevance of each piece of information, as well as the coverage of the relevant parameters and observations and their consistency with other information.
- When consistency is seen among 'qualified' data elements and the relevant endpoint or information requirement has been sufficiently covered, the WoE evaluation may reach a conclusion on the classification and labelling in which case further testing is not necessary.
- When on the other hand, insufficient information remains after the 'non-qualified' data have been rejected/put aside and/or when the remaining information is inconsistent or contradictory, the WoE evaluation might lead to a conclusion that further testing is necessary.

[6] http://www.det-net.eu.

[7] ECHA (2015). Guidance on the Application of the CLP criteria. Guidance to regulation EC N. 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. Version 4.1. Chapter 3.2. Skin corrosion/irritation. Available at: https://echa.europa.eu/documents/10162/13562/clp_en.pdf.

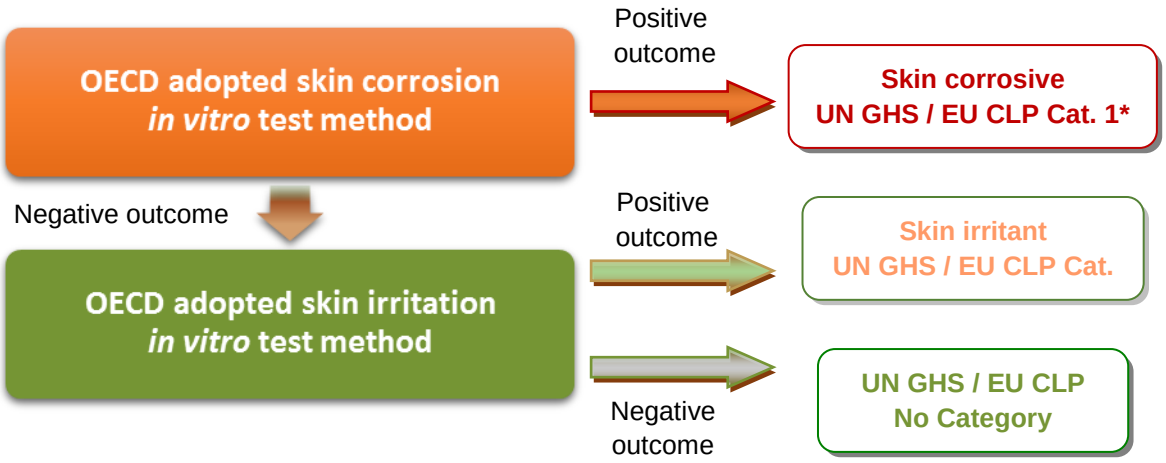
[8] Guidance "Swiss CLP, Chapter 4.4.3. Available at: https://www.anmeldestelle.admin.ch/chem/de/home/themen/recht-wegleitungen/wegleitungen-interpretationshilfen.html

Products (mixtures) having extreme pH (≤ 2 or ≥ 11.5)

Without any other information these products are considered to be skin corrosive Category 1. However, mixtures having extreme pH but a low buffering capacity may be not corrosive[9]. The relation is quantitatively expressed by: if pH + 1/12 alkaline reserve ≥ 14.5 or pH -1/12 acid reserve ≤ -0.5, the mixture should be considered corrosive. Where consideration of alkali/acid reserve suggests the substance not to be corrosive, the result is considered inconclusive, and further testing should be considered on an OECD-adopted *in vitro* test method as described in Step 3.

Step 3: Perform additional testing based on *in vitro* methods

- In case the weight of evidence analysis is inconclusive regarding the skin corrosive properties of the product (mixture), further testing shall be conducted as described below. A table in appendix shows the different OECD adopted *in vitro* test method and their applicability and limitations.



* According to the 8th ATP to the CLP Regulation[4] substances and mixtures can be classified as skin corrosive Category 1 if data are not sufficient for sub-categorisation. For the assignment of chemicals to Group 2 according to Annex 5 (1.2) ChemO[10], no skin corrosive sub-category is needed..

[9] Young J.R., How M.J., Walker A.P., Worth W.M.H. (1988), Classification as corrosive or irritant to skin of preparations containing acidic or alkaline substances, without testing on animals. Toxicology In Vitro 2S, 19-26.

[10] SR. 813.11. Available at: http://www.admin.ch/opc/de/classified-compilation/20141117/index.html.

Mixtures having an extreme pH (≤ 2 or ≥ 11.5) and an acid/alkaline reserve indicating the mixture not to be corrosive

Based on current knowledge and experiences gained so far in the enforcement context, it is recommended for products having an extreme pH to perform *in vitro* test methods according to the OECD TG 431 or the OECD TG 435. The final choice will, however, depend on the type of product (e.g. bleaching agents, laundry detergents) and the compatibility of the product with the applicability domain and limitations of each *in vitro* test method (as described in the table in appendix).

- **Mixtures having an extreme pH will not fall within Group 2 of Annex 5 (1.2) ChemO, if:**
  - they have an acid/alkaline reserve indicating the mixture not to be corrosive, and
  - the outcome of an OECD-adopted *in vitro* test method for skin corrosion is negative.

Mixtures containing corrosive ingredients in the range of 5% to 10% but with no extreme pH (2 < pH < 11.5)

For mixtures containing skin corrosive ingredients in the range of 5% to 10 % but with no extreme pH, the application of the additivity approach[1,2] will lead to a rather conservative classification as skin corrosive Category 1 (H314) . In the absence of a conclusive weight of evidence analysis, in particular based on the bridging principle with similar mixtures (see Steps 1 and 2), it is therefore recommended to perform, for this type of mixtures, additional testing based on OECD-adopted *in vitro* test methods. The choice of the *in vitro* test method will depend on the type (e.g. bleaching agents, laundry detergents) and the compatibility of the product with the applicability domain and limitations of each *in vitro* test method (as described in the table in appendix).

- **Mixtures with no extreme pH having corrosive ingredients in the range of 5% to 10% will not fall within Group 2 of Annex 5 (1.2) ChemO, if:**

  - the outcome of an OECD-adopted *in vitro* test method for skin corrosion is negative.

Appendix: OECD *in vitro* test methods and their applications

	***In vitro* skin corrosion**		
	TER test method (OECD TG 430)	**Reconstructed human Epidermis (RhE) test method (OECD TG 431)**	**Membrane barrier test (OECD TG 435)**
Regulatory classification	**UN GHS / EU CLP Cat. 1** vs. non-corrosives	**UN GHS / EU CLP Cat. 1** vs. non-corrosives **UN GHS / EU CLP Subcat. 1A** and a combination of **Subcat. 1B-and-1C**	**UN GHS / EU CLP Cat. 1** vs. non-corrosives **UN GHS / EU CLP Subcat. 1A, Subcat. 1B and Subcat. 1C**
Commercially available methods accepted	Not applicable	- EPISKIN™ Standard Model (SM) - EpiDerm™ Skin Corrosion Test (SCT) - SkinEthic™ RHE - epiCS® (previously named EST-1000)	- Corrositex®
Regulatory use	Substances and mixtures (as an extension to the applicability to substances)	Substances and mixtures (as an extension to the applicability to substances)	Substances and mixtures
Limitations	- Not able to distinguish the three GHS subcategories (1A, 1B and 1C) - Not designed to provide information on skin irritation - Not applicable to gases and aerosols. - May be considered an animal test in some countries	- Does not allow discrimination between skin corrosive Sub.cat. 1B and 1C - Not designed provide information on skin irritation - Not applicable to gases and aerosols - Results obtained with test chemicals having non-specific interactions with MTT ≥ 50% should be taken with caution when OD is used as measurement for cell viability. This may be circumvented in case HPLC/UPLC is used. - Fatty amine derivatives risk under-prediction[11]	- Not designed to give information on skin irritation - Not applicable to gases and aerosols - Test chemicals not causing detectable changes in the chemical detection system cannot be tested (e.g. aqueous test chemicals with a pH in the range 4.5-8.5 often do not qualify[12]) - In EU, considered valid only for acids, bases and their derivatives
Role in the OECD IATA	If non-corrosive outcome, an *in vitro* skin irritation test should be conducted. Furthermore if need for corrosive sub-categorization, other *in vitro* test methods should be used.	If non-corrosive outcome, an *in vitro* skin irritation test should be conducted. Furthermore if need for discrimination between Subcat. 1B from Subcat. 1C, OECD TG 435 should be considered, or the EpiSkin™ non-adopted prediction model for that purpose may be considered in a weight of evidence approach.	If non-corrosive outcome, an *in vitro* skin irritation test should be conducted.

[11] Houthoff E, Rugen P, Hart D (2015) Predictability of in vitro dermal assays when evaluating fatty amine derivatives. Toxicology *in Vitro* 29, 1263-1267.

[12] NIH (1999). *Corrositex®: an in vitro test method for assessing dermal corrosivity potential of chemicals*. NIH Publication No. 99-4495. Research Triangle Park, NC, USA: NIEHS.

Appendix: OECD *in vitro* test methods and their applications

	***In vitro* skin irritation**
	Reconstructed human *Epidermis* test method (OECD TG 439)
Regulatory classification	**UN GHS / EU CLP Cat. 2** when supported by corrosive negative results, and **UN GHS / EU CLP No-Category**
Commercially available methods accepted	- EPISKIN™ Skin Irritation Test (SIT) - EpiDerm™ SIT - SkinEthic™ SIT[42bis] - LabCyte EPI-MODEL24 SIT
Regulatory use	Substances and mixtures (as an extension to the applicability to substances)
Limitations	- Not designed to distinguish the optional GHS Cat. 3 for mild irritants, corrosive chemicals, gases and aerosols - Results obtained with test chemicals presenting non-specific interactions with MTT ≥ 50% should be taken with caution when OD is used as measurement for cell viability. This may be circumvented in case HPLC/UPLC is used.
Role in the OECD IATA	If positive outcome, an *vitro* skin corrosion test should be conducted.