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Classification criteria and related hazard communication: use of non-animal testing methods for classification of health hazards

Consequential amendments to Chapter 3.2 due to the revision of GHS Chapter 3.3 to fully incorporate non-animal test methods

Transmitted by the experts from the United Kingdom and the Netherlands on behalf of the Informal Working Group on the use of non-animal test methods for classification of health hazards

This informal document sets out the changes proposed in document ST/SG/AC.10/C.4/2021/5. New text, including existing text moved to a new location within Chapter 3.2, is shown in blue. For clarity deleted text is shown in ~~strikethrough~~.

“CHAPTER 3.2
SKIN CORROSION/IRRITATION

3.2.1 Definitions and general considerations

3.2.1.1 *Skin corrosion* refers to the production of irreversible damage to the skin; namely, visible necrosis through the epidermis and into the dermis occurring after exposure to a substance or mixture.

Skin irritation refers to the production of reversible damage to the skin occurring after exposure to a substance or mixture.

3.2.1.2 To classify, all available and relevant information on skin corrosion/irritation is collected and its quality in terms of adequacy and reliability is assessed. ~~Wherever possible classification should be based on data generated using internationally validated and accepted methods, such as OECD Test Guidelines or equivalent methods~~. Classification should be based on mutually acceptable data generated using methods that are validated according to international procedures. These include both OECD guidelines and equivalent methods (see 1.3.2.4.3). Sections 3.2.2.1 to ~~3.2.2.6~~ 3.2.2.7 provide classification criteria for the different types of information that may be available.

3.2.1.3 A *tiered approach* (see 3.2.2.~~7~~8) organizes the available information into levels/tiers and provides for decision-making in a structured and sequential manner. Classification results directly when the information consistently satisfies the criteria. However, where the available information gives inconsistent and/or conflicting results within a tier, classification of a substance or a mixture is made on the basis of the weight of evidence within that tier. In some cases when information from different tiers gives inconsistent and/or conflicting results (see 3.2.2.~~7~~8.3) or where data individually are insufficient to conclude on the classification, an overall weight of evidence ~~approach~~ assessment is used (see 1.3.2.4.9, 3.2.2.7 and 3.2.5.3.1).

3.2.1.4 Guidance on the interpretation of criteria and references to relevant guidance documents are provided in 3.2.5.3.

3.2.2 Classification criteria for substances

Substances can be allocated to one of the following three categories within this hazard class:

(a) Category 1 (skin corrosion)

This category may be further divided into up to three sub-categories (1A, 1B and 1C) which can be used by those authorities requiring more than one designation for corrosivity.

Corrosive substances should be classified in Category 1 where sub-categorization is not required by a competent authority or where data are not sufficient for sub-categorization.

When data are sufficient, and where required by a competent authority, substances may be classified in one of the three sub-categories 1A, 1B or 1C.

(b) Category 2 (skin irritation)

(c) Category 3 (mild skin irritation)

This category is available for those authorities that want to have more than one skin irritation category (e.g. for classifying pesticides).

3.2.2.1 ***Classification based on human data*** ***(Tier 1 in Figure 3.2.1)***

Existing reliable and good quality human data on skin corrosion/irritation should be given high weight where relevant for classification (see 3.2.5.3.2) and should be the first line of evaluation, as this gives information directly relevant to effects on the skin. Existing human data could be derived from single or repeated exposure(s), for example in occupational, consumer, transport or emergency response scenarios and epidemiological and clinical studies in well-documented case reports and observations (see 1.1.2.5 (c), 1.3.2.4.7 and 1.3.2.4.9). 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.

3.2.2.2 ***Classification based on standard animal ~~test~~ data*** ***(Tier 1 in Figure 3.2.1)***

OECD Test Guideline 404 is the currently available and internationally ~~validated and~~ accepted animal test method for classification as skin corrosive or irritant (see Tables 3.2.1 and 3.2.2, respectively) and is the standard animal test. The current version of OECD Test Guideline 404 uses a maximum of 3 animals. Results from animal studies conducted under previous versions of OECD Test Guideline 404 that used more than 3 animals are also considered standard animal tests when interpreted in accordance with 3.2.5.3.3.

3.2.2.2.1 *Skin corrosion*

3.2.2.2.1.1 A substance is corrosive to skin when it produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least one tested animal after exposure for up to 4 hours.

3.2.2.2.1.2 For those authorities wanting more than one designation for skin corrosion, up to three sub-categories are provided within the corrosion category (Category 1, see Table 3.2.1): sub-category 1A, where corrosive responses are noted following up to 3 minutes exposure and up to 1 hour observation; sub-category 1B, where corrosive responses are described following exposure greater than 3 minutes and up to 1 hour and observations up to 14 days; and sub-category 1C, where corrosive responses occur after exposures greater than 1 hour and up to 4 hours and observations up to 14 days.

Table 3.2.1: Skin corrosion category and sub-categories

	Criteria
Category 1	Destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least one tested animal after exposure ≤ 4 h
Sub-category 1A	Corrosive responses in at least one animal following exposure ≤ 3 min during an observation period ≤ 1 h
Sub-category 1B	Corrosive responses in at least one animal following exposure > 3 min and ≤ 1 h and observations ≤ 14 days
Sub-category 1C	Corrosive responses in at least one animal after exposures > 1 h and ≤ 4 h and observations ≤ 14 days

3.2.2.2.2 *Skin irritation*

3.2.2.2.2.1 A substance is irritant to skin when it produces reversible damage to the skin following its application for up to 4 hours.

3.2.2.2.2.2 An irritation category (Category 2) is provided that:

(a) recognizes that some test materials may lead to effects which persist throughout the length of the test; and

(b) acknowledges that animal responses in a test may be variable.

An additional mild irritation category (Category 3) is available for those authorities that want to have more than one skin irritation category.

3.2.2.2.2.3 Reversibility of skin lesions is another consideration in evaluating irritant responses. When inflammation persists to the end of the observation period in 2 or more test animals, taking into consideration alopecia (limited area), hyperkeratosis, hyperplasia and scaling, then a material should be considered to be an irritant.

3.2.2.2.2.4 Animal irritant responses within a test can be variable, as they are with corrosion. A separate irritant criterion accommodates cases when there is a significant irritant response but less than the mean score criterion for a positive test. For example, a test material might be designated as an irritant if at least 1 of 3 tested animals shows a very elevated mean score throughout the study, including lesions persisting at the end of an observation period of normally 14 days. Other responses could also fulfil this criterion. However, it should be ascertained that the responses are the result of chemical exposure. Addition of this criterion increases the sensitivity of the classification system.

3.2.2.2.2.5 An irritation category (Category 2) is presented in Table 3.2.2 using the results of animal testing. Authorities (e.g. for classifying pesticides) also have available a less severe mild irritation category (Category 3). Several criteria distinguish the two categories (Table 3.2.2). They mainly differ in the severity of skin reactions. The major criterion for the irritation category is that at least 2 of 3 tested animals have a mean score of ≥ 2.3 and ≤ 4.0. For the mild irritation category, the mean score cut-off values are ≥ 1.5 and < 2.3 for at least 2 of 3 tested animals. Test materials in the irritation category are excluded from the mild irritation category.

Table 3.2.2: Skin irritation categories [a,b]

Categories	Criteria
Irritation (Category 2) (applies to all authorities)	(a) Mean score of ≥ 2.3 and ≤ 4.0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or (b) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or (c) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.
Mild irritation (Category 3) (applies to only some authorities)	Mean score of ≥ 1.5 and < 2.3 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions (when not included in the irritant category above).

[a] *Grading criteria are understood as described in OECD Test Guideline 404.*

[b] *Evaluation of a 4, 5 or 6-animal study should follow the criteria given in 3.2.5.3.3.*

3.2.2.3 *Classification based on in vitro/ex vivo data (Tier 2 in Figure 3.2.1)*

3.2.2.3.1 The currently available individual *in vitro/ex vivo* test methods address either skin irritation or skin corrosion, but do not address both endpoints in one single test. Therefore, classification based solely on *in vitro/ex vivo* test results may require data from more than one method. For authorities implementing Category 3 it is important to note that the currently available internationally validated and accepted *in vitro/ex vivo* test methods do not allow identification of substances classified as Category 3.

3.2.2.3.2 ~~Wherever possible classification should be based on data generated using internationally validated and accepted *in vitro/ex vivo* test methods, and the classification criteria provided in these test methods needs to be applied.~~ *In vitro/ex vivo* data can only be used for classification when the tested substance is within

the applicability domain of the test method(s) used. Additional limitations described in the published literature should also be taken into consideration.

3.2.2.3.3 *Skin corrosion*

3.2.2.3.3.1 Where tests have been undertaken in accordance with OECD test guidelines 430, 431, or 435, a substance is classified for skin corrosion in Category 1 (and, where possible and required into sub-categories 1A, 1B or 1C) based on the criteria in Table 3.2.6 (see 3.2.5.3.4).

3.2.2.3.3.2 Some *in vitro/ex vivo* methods do not allow differentiation between sub-categories 1B and 1C (see Table 3.2.6). Where sub-categories are required by competent authorities and existing *in vitro/ex vivo* data cannot distinguish between the sub-categories, additional information has to be taken into account to differentiate between these two sub-categories. Where no or insufficient additional information is available, Category 1 is applied.

3.2.2.3.3.3 A substance identified as not corrosive should be considered for classification as skin irritant.

3.2.2.3.4 *Skin irritation*

3.2.2.3.4.1 Where classification for corrosivity can be excluded and where tests have been undertaken in accordance with OECD Test Guideline 439, a substance should be considered for classification as skin irritant in Category 2 based on the criteria in Table 3.2.7 (see 3.2.5.3.4).

3.2.2.3.4.2 Where competent authorities adopt Category 3, it is important to note that currently available *in vitro/ex vivo* test methods for skin irritation (e.g. OECD Test Guideline 439) do not allow for classification of substances in Category 3. ~~In this situation, if the classification criteria for either category 1 or 2 are not fulfilled, additional information is required to differentiate between category 3 and no classification.~~

3.2.2.3.5 *No classification for effects on the skin*

3.2.2.3.5.1~~4.3~~ Where competent authorities do not adopt Category 3, a negative result in an ~~internationally accepted and validated~~ *in vitro/ex vivo* test method for skin irritation that is validated according to international procedures, e.g. OECD Test Guideline 439, can be used to conclude as not classified for skin irritation. Where competent authorities adopt Category 3, additional information is required to differentiate between Category 3 and no classification.

3.2.2.4 *Classification based on other~~, existing~~ animal skin data ~~in animals~~ (Tier 3 in Figure 3.2.1)*

Other existing skin data in animals may be used for classification, but there may be limitations regarding the conclusions that can be drawn (see 3.2.5.3.5). If a substance is highly toxic via the dermal route, an *in vivo* skin corrosion/irritation study may not have been conducted since the amount of test substance to be applied would considerably exceed the toxic dose and, consequently, would result in the death of the animals. When observations of skin corrosion/irritation in acute toxicity studies are made, these data may be used for classification, provided that the dilutions used and species tested are relevant. Solid substances (powders) may become corrosive or irritant when moistened or in contact with moist skin or mucous membranes. This is generally indicated in the standardised test methods. Guidance on the use of other existing skin data in animals including acute and repeated dose toxicity tests as well as other tests is provided in 3.2.5.3.5.

3.2.2.5 *Classification based on ~~chemical properties~~ extreme pH (pH ≤ 2 or ≥ 11.5) and acid/alkaline reserve (Tier 4 in Figure 3.2.1)*

In general, substances with an extreme pH (pH ≤ 2 or ≥ 11.5) are expected to cause significant s~~S~~kin effects ~~may be indicated by pH, extremes such as ≤ 2 and ≥ 11.5~~, especially when associated with significant acid/alkaline reserve ~~(buffering capacity)~~. ~~Generally, such substances are expected to produce significant effects on the skin. In the absence of any other information,~~ A substance with pH ≤ 2 or ≥ 11.5 is therefore considered ~~corrosive~~ to cause skin corrosion (~~Skin~~ Category 1) in this tier if it has a ~~pH ≤ 2 or a pH ≥ 11.5~~significant acid/alkaline reserve or if no data for acid/alkaline reserve are available. However, if consideration of acid/alkaline reserve suggests the substance may not be corrosive despite the ~~low or high~~ extreme pH value, the result is

considered inconclusive within this tier (see Figure 3.2.1). ~~this needs to be confirmed by other data, preferably from an appropriate validated *in vitro/ex vivo* test. Buffering capacity and pH can be determined by test methods including OECD Test Guideline 122.~~ A pH > 2 and < 11.5 is considered inconclusive and cannot be used for classification purposes. Acid/alkaline reserve and pH can be determined by different methods including those described in OECD Test Guideline 122 and Young et al. (1988), acknowledging that there are some differences between these methods (see 3.2.5.3.6). A competent authority may decide which criteria for significant acid/alkaline reserve can be applied.

3.2.2.6 ***Classification based on non-test methods (Tier 5 in Figure 3.2.1)***

3.2.2.6.1 Classification, including the conclusion not classified, can be based on non-test methods, with due consideration of reliability and applicability, on a case-by-case basis. Such methods include computer models predicting qualitative structure-activity relationships (structural alerts, SAR)~~;~~ or quantitative structure-activity relationships (QSARs)~~;~~, computer expert systems~~;~~, and read-across using analogue and category approaches.

3.2.2.6.2 Read-across using analogue or category approaches requires sufficiently reliable test data on similar substance(s) and justification of the similarity of the tested substance(s) with the substance(s) to be classified. Where adequate justification of the read-across approach is provided, it has in general higher weight than (Q)SARs.

3.2.2.6.3 Classification based on (Q)SARs requires sufficient data and validation of the model. The validity of the computer models and the prediction should be assessed using internationally recognized principles for the validation of (Q)SARs. With respect to reliability, lack of alerts in a SAR or expert system is not sufficient evidence for no classification.

3.2.2.7 ***Classification based on an overall weight of evidence assessment (Tier 6 in Figure 3.2.1)***

3.2.2.7.1 An overall weight of evidence assessment using expert judgement is indicated where none of the previous tiers resulted in a definitive conclusion on classification. In some cases, where the classification decision was postponed until the overall weight of evidence, but no further data are available, a classification may still be possible.

3.2.2.7.2 A substance with an extreme pH (pH ≤ 2 or ≥ 11.5) and non-significant acid/alkaline reserve (result considered inconclusive in Tier 4; see 3.2.2.7) and for which no other information is available, should be classified as skin corrosion Category 1 in this tier. If inconclusive information is also available from other tiers but the overall weight of evidence assessment remains inconclusive, the extreme pH (pH ≤ 2 or ≥ 11.5) result should take precedence and the substance should be classified as skin corrosion Category 1 in this tier independently of its acid/alkaline reserve. For mixtures, the approach is different and is detailed in 3.2.3.1.3.

3.2.2.~~7~~8 ***Classification in a tiered approach (Figure 3.2.1)***

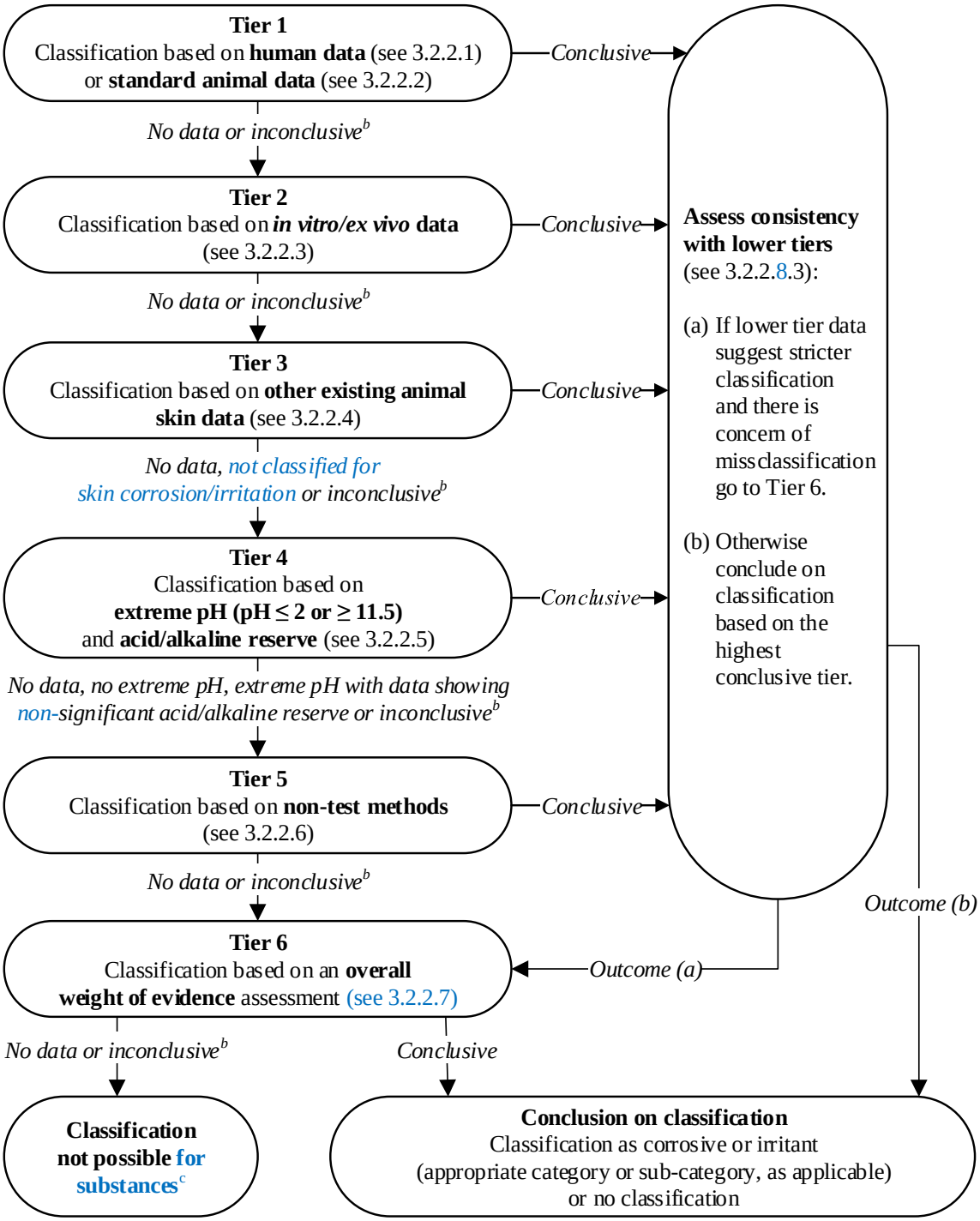
3.2.2.~~7~~8.1 A tiered approach to the evaluation of initial information should be considered, where applicable (Figure 3.2.1), recognising that not all elements may be relevant. However, all available and relevant information of sufficient quality needs to be examined for consistency with respect to the resulting classification.

3.2.2.~~7~~8.2 In the tiered approach (Figure 3.2.1), existing human and standard animal data form the highest tier, followed by *in vitro/ex vivo* data, other existing animal skin data ~~in animals~~, extreme pH and acid/alkaline reserve, and finally non-test methods~~and then other sources of information~~. Where information from data within the same tier is inconsistent and/or conflicting, the conclusion from that tier is determined by a weight of evidence ~~approach~~ assessment.

3.2.2.~~7~~8.3 Where information from several tiers is inconsistent and/or conflicting with respect to the resulting classification, information of sufficient quality from a higher tier is generally given a higher weight than information from a lower tier. However, when information from a lower tier would result in a stricter classification than information from a higher tier and there is concern for misclassification, then classification is determined by an overall weight of evidence ~~approach~~assessment. For example, having consulted the guidance in 3.2.5.3 as appropriate, classifiers concerned with a negative result for skin corrosion in an *in vitro/ex vivo* study when there is a positive result for skin corrosion in other existing skin data in animals would utilise an

overall weight of evidence ~~approach~~ assessment. The same would apply in the case where there is human data indicating skin irritation but positive results from an *in vitro/ex vivo* test for corrosion are also available.

Figure 3.2.1: Application of the tiered approach for skin corrosion and irritation[a]



[a] *Before applying the approach, the explanatory text in 3.2.2.~~7~~8 as well as the guidance in 3.2.5.3 should be consulted. Only adequate and reliable data of sufficient quality should be included in applying the tiered approach.*

[b] *Information may be inconclusive for various reasons, e.g.:*

- *The available data may be of insufficient quality, or otherwise insufficient/inadequate for the purpose of classification, e.g. due to quality issues related to experimental design and/or reporting;*

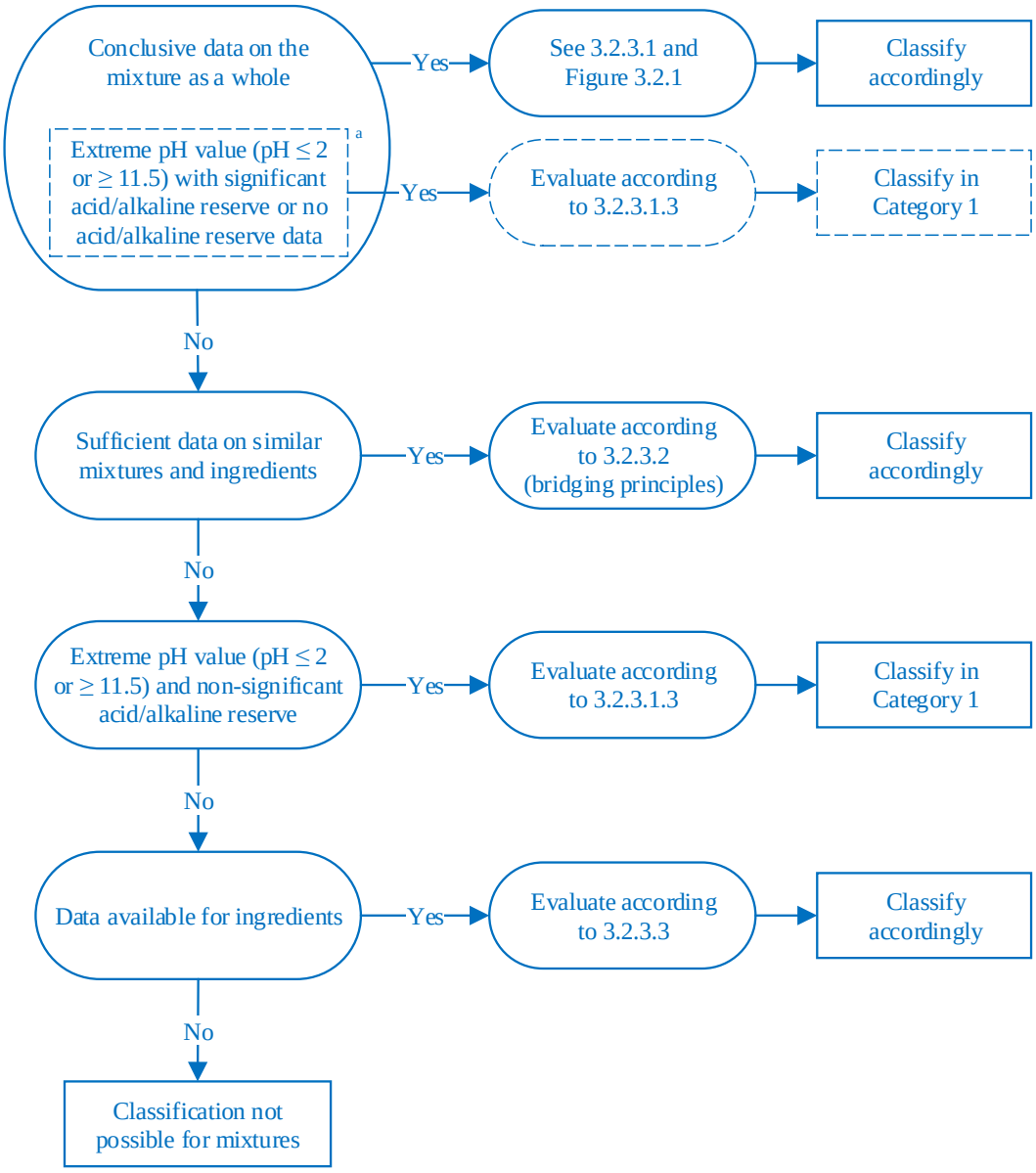
- *The available data may be insufficient to conclude on the classification, e.g. they might be adequate to demonstrate irritancy, but inadequate to demonstrate absence of corrosivity;*
- *Where competent authorities make use of the mild skin irritation Category 3, the available data may not be capable of distinguishing between Category 3 and Category 2, or between Category 3 and no classification;*
- *The method used to generate the available data may not be suitable for concluding on no classification (see 3.2.2. and 3.2.5.3 for details). Specifically, in vitro/ex vivo and non-test methods need to be validated explicitly for this purpose.*

[c] *For mixtures, the flow chart in Figure 3.2.2 should be followed.*

3.2.3 Classification criteria for mixtures

The approach to classification for skin corrosion/irritation is tiered and is dependent upon the amount of information available for the mixture itself and for its ingredients. The flow chart of Figure 3.2.2 below outlines the process to be followed.

Figure 3.2.2: Tiered approach to classification of mixtures for skin corrosion/irritation



[a] *The dashed boxes represent an individual tier within conclusive data on the mixture as whole. However, in contrast to substances, mixtures having an "extreme pH value (pH ≤ 2 or ≥ 11.5) and non-significant acid/alkaline reserve" but no other conclusive data on the mixture as a whole, or no conclusive weight of evidence assessment from all available data on the mixture as whole, are not conclusive within the tiers for conclusive data on the mixture as a whole. Such mixtures should be first evaluated according to the bridging principles before the extreme pH value is considered as conclusive for classification.*

3.2.3.1 *Classification of mixtures when data are available for the complete mixture*

3.2.3.1.1 In general, the mixture should be classified using the criteria for substances, taking into account the tiered approach to evaluate data for this hazard class (as illustrated in Figure 3.2.1) and 3.2.3.1.2 and 3.2.3.1.3 below. If classification is not possible using the tiered approach, then the approach described in 3.2.3.2 (bridging principles), or, if that is not applicable 3.2.3.3 (~~calculation method~~classification based on ingredients) should be followed.

3.2.3.1.2 *In vitro/ex vivo* ~~data generated from validated~~ test methods validated according to international procedures may not have been validated using mixtures; although these methods are considered broadly applicable to mixtures, they can only be used for classification of mixtures when all ingredients of the mixture fall within the applicability domain of the test method(s) used. Specific limitations regarding applicability domains are described in the respective test methods, and should be taken into consideration as well as any further information on such limitations from the published literature. Where there is reason to assume or evidence indicating that the applicability domain of a particular test method is limited, data interpretation should be exercised with caution, or the results should be considered not applicable.

3.2.3.1.3 ~~In the absence of any other information,~~A mixture with an extreme pH (pH ≤ 2 or ≥ 11.5) is considered corrosive (~~Skin~~ Category 1) in Tier 4 if it has a ~~pH ≤ 2 or a pH ≥ 11.5~~significant acid/alkaline reserve or if no data for acid/alkaline reserve are available. However, if consideration of acid/alkaline reserve suggests the mixture[a] may not be corrosive despite the ~~low or high~~ extreme pH value, ~~this needs to be confirmed by other data, preferably from an appropriate validated *in vitro/ex vivo* test.~~ the result is considered inconclusive within Tier 4 (see Figure 3.2.1). If the overall weight of evidence assessment remains inconclusive or no data other than pH and acid/alkaline reserve are available, mixtures with an extreme pH (pH ≤ 2 or ≥ 11.5) and non-significant acid/alkaline reserve should be assessed using the bridging principles described in 3.2.3.2. If the bridging principles cannot be applied, mixtures with an extreme pH (pH ≤ 2 or ≥ 11.5) and non-significant acid/alkaline reserve should be classified as skin Category 1 (see Figure 3.2.2). A pH > 2 and < 11.5 is considered inconclusive and cannot be used for classification purposes. Acid/alkaline reserve and pH can be determined by different methods including those described in OECD Test Guideline 122 and Young et al. (1988), acknowledging that there are some differences between these methods (see 3.2.5.3.6). A competent authority may decide which criteria for significant acid/alkaline reserve can be applied.

3.2.3.2 *Classification of mixtures when data are not available for the complete mixture: bridging principles*

3.2.3.2.1 Where the mixture itself has not been tested to determine its skin corrosion/irritation potential, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following agreed bridging principles. This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without the necessity for additional testing in animals.

3.2.3.2.2 *Dilution*

If a tested mixture is diluted with a diluent which has an equivalent or lower skin corrosivity/irritancy classification than the least skin corrosive/irritant original ingredient and which is not expected to affect the skin corrosivity/irritancy of other ingredients, then the new diluted mixture may be classified as equivalent to the original tested mixture. Alternatively, the method explained in 3.2.3.3 could be applied.

3.2.3.2.3 *Batching*

The skin corrosion/irritation potential 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 manufacturer, unless there is reason to believe there is significant variation such that the skin corrosion/irritation potential of the untested batch has changed. If the latter occurs, a new classification is necessary.

3.2.3.2.4 *Concentration of mixtures of the highest corrosion/irritation category*

If a tested mixture classified in the highest sub-category for skin corrosion is concentrated, the more concentrated untested mixture should be classified in the highest corrosion sub-category without additional testing. If a tested mixture classified for skin irritation (Category 2) is concentrated and does not contain skin corrosive ingredients, the more concentrated untested mixture should be classified for skin irritation (Category 2) without additional testing.

3.2.3.2.5 *Interpolation within one hazard category*

For three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and are in the same skin corrosion/irritation hazard category, and where untested mixture C has the same toxicologically active ingredients as mixtures A and B but has concentrations of toxicologically active ingredients intermediate to the concentrations in mixtures A and B, then mixture C is assumed to be in the same skin corrosion/irritation category as A and B.

3.2.3.2.6 *Substantially similar mixtures*

Given the following:

(a) Two mixtures: (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) Data on skin corrosion/irritation 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 skin corrosion/irritation potential of B.

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

3.2.3.2.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested non-aerosolized form of the mixture provided that the added propellant does not affect the skin corrosion/irritation properties of the mixture upon spraying.

3.2.3.3 *Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture*

3.2.3.3.1 In order to make use of all available data for purposes of classifying the skin corrosion/irritation hazards of mixtures, the following assumption has been made and is applied where appropriate in the tiered approach:

The "relevant ingredients" of a mixture are those which are present in concentrations ≥ 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases), unless there is a presumption (e.g. in the case of corrosive ingredients) that an ingredient present at a concentration < 1% can still be relevant for classifying the mixture for skin corrosion/irritation.

3.2.3.3.2 In general, the approach to classification of mixtures as corrosive or irritant to skin when data are available on the ingredients, but not on the mixture as a whole, is based on the theory of additivity, such that

each skin corrosive or irritant ingredient contributes to the overall corrosive or irritant properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive ingredients when they are present at a concentration below the concentration limit for classification with Category 1 but are at a concentration that will contribute to the classification of the mixture as an irritant. The mixture is classified as corrosive or irritant to skin when the sum of the concentrations of such ingredients exceeds a cut-off value/concentration limit.

3.2.3.3.3 Table 3.2.3 below provides the cut-off value/concentration limits to be used to determine if the mixture is considered to be corrosive or irritant to the skin.

3.2.3.3.4 Particular care must be taken when classifying certain types of chemicals such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in 3.2.3.3.1 and 3.2.3.3.2 might not work given that many such substances are corrosive or irritant at concentrations < 1%. For mixtures containing strong acids or bases the pH should be used as the classification criterion~~criteria~~ (see 3.2.3.1.3~~2~~) since extreme pH will be a better indicator of corrosion than the concentration limits in Table 3.2.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach shown in Table 3.2.3~~,~~ due to chemical characteristics that make this approach unworkable, should be classified as skin corrosion Category 1 if it contains ≥ 1% of a corrosive ingredient and as skin irritation Category 2 or Category 3 when it contains ≥ 3% of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3.2.3 does not apply is summarized in Table 3.2.4 below.

3.2.3.3.5 On occasion, reliable data may show that the skin corrosion/irritation of an ingredient will not be evident when present at a level above the generic concentration limits/cut-off values mentioned in Tables 3.2.3 and 3.2.4. In these cases the mixture could be classified according to those data (see also *Classification of hazardous substances and mixtures – Use of cut-off values/Concentration limits* (1.3.3.2)). On occasion, when it is expected that the skin corrosion/irritation of an ingredient will not be evident when present at a level above the generic concentration cut-off values mentioned in Tables 3.2.3 and 3.2.4, testing of the mixture may be considered. In those cases the tiered weight of evidence approach should be applied as described in 3.2.3 and illustrated in Figure 3.2.1.

3.2.3.3.6 If there are data showing that (an) ingredient(s) may be corrosive or irritant to skin at a concentration of < 1% (corrosive) or < 3% (irritant), the mixture should be classified accordingly (see also *Classification of hazardous substances and mixtures – Use of cut-off values/Concentration limits* (1.3.3.2)).

Table 3.2.3: Concentration of ingredients of a mixture classified as skin Category 1, 2 or 3 that would trigger classification of the mixture as hazardous to skin (Category 1, 2 or 3)

Sum of ingredients classified as:	**Concentration triggering classification of a mixture as:**		
	Skin corrosive	**Skin irritant**	
	Category 1 (see note below)	**Category 2**	**Category 3**
Skin Category 1	≥ 5%	≥ 1% but < 5%	
Skin Category 2		≥ 10%	≥ 1% but < 10%
Skin Category 3			≥ 10%
(10 × skin Category 1) + skin Category 2		≥ 10%	≥ 1% but < 10%
(10 × skin Category 1) + skin Category 2 + skin Category 3			≥ 10%

NOTE: *Where the sub-categories of skin Category 1 (corrosive) are used, the sum of all ingredients of a mixture classified as sub-category 1A, 1B or 1C respectively, should each be ≥ 5% in order to classify the mixture as either skin sub-category 1A, 1B or 1C. Where the sum of 1A ingredients is < 5% but the sum of 1A+1B ingredients is ≥ 5%, the mixture should be classified as sub-category 1B. Similarly, where the sum of 1A + 1B ingredients is < 5% but the sum of 1A + 1B + 1C ingredients is ≥ 5% the mixture should be classified as sub-category 1C. Where at least one relevant ingredient in a mixture is classified as Category 1 without sub-*

categorisation, the mixture should be classified as Category 1 without sub-categorisation if the sum of all ingredients corrosive to skin is ≥ 5%.

Table 3.2.4: **Concentration of ingredients of a mixture when the additivity approach does not apply, that would trigger classification of the mixture as hazardous to skin**

Ingredient:	Concentration	Mixture classified as: Skin
Acid with pH ≤ 2	≥ 1%	Category 1
Base with pH ≥ 11.5	≥ 1%	Category 1
Other corrosive (Category 1) ingredient	≥ 1%	Category 1
Other irritant (Category 2/3) ingredient, including acids and bases	≥ 3%	Category 2/3

3.2.4 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard communication: Labelling* (Chapter 1.4). Annex 1 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. The table below presents specific label elements for substances and mixtures that are classified as irritating or corrosive to the skin based on the criteria set forth in this chapter.

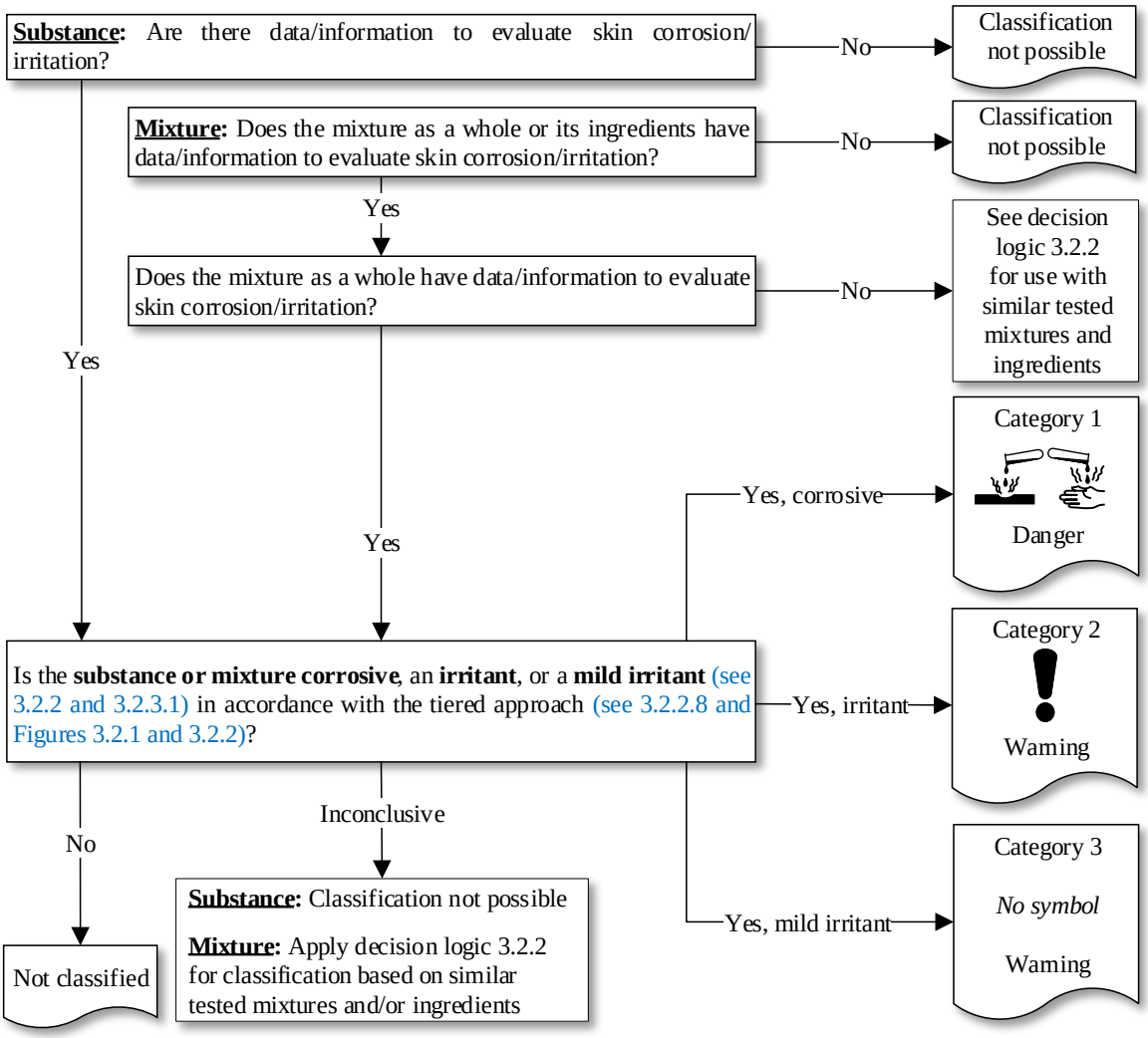
Table 3.2.5: Label elements for skin corrosion/irritation

	Category 1			Category 2	Category 3
	1 A	1 B	1 C		
Symbol	Corrosion	Corrosion	Corrosion	Exclamation mark	*No symbol*
Signal word	Danger	Danger	Danger	Warning	Warning
Hazard statement	Causes severe skin burns and eye damage	Causes severe skin burns and eye damage	Causes severe skin burns and eye damage	Causes skin irritation	Causes mild skin irritation

3.2.5 Decision logics and guidance

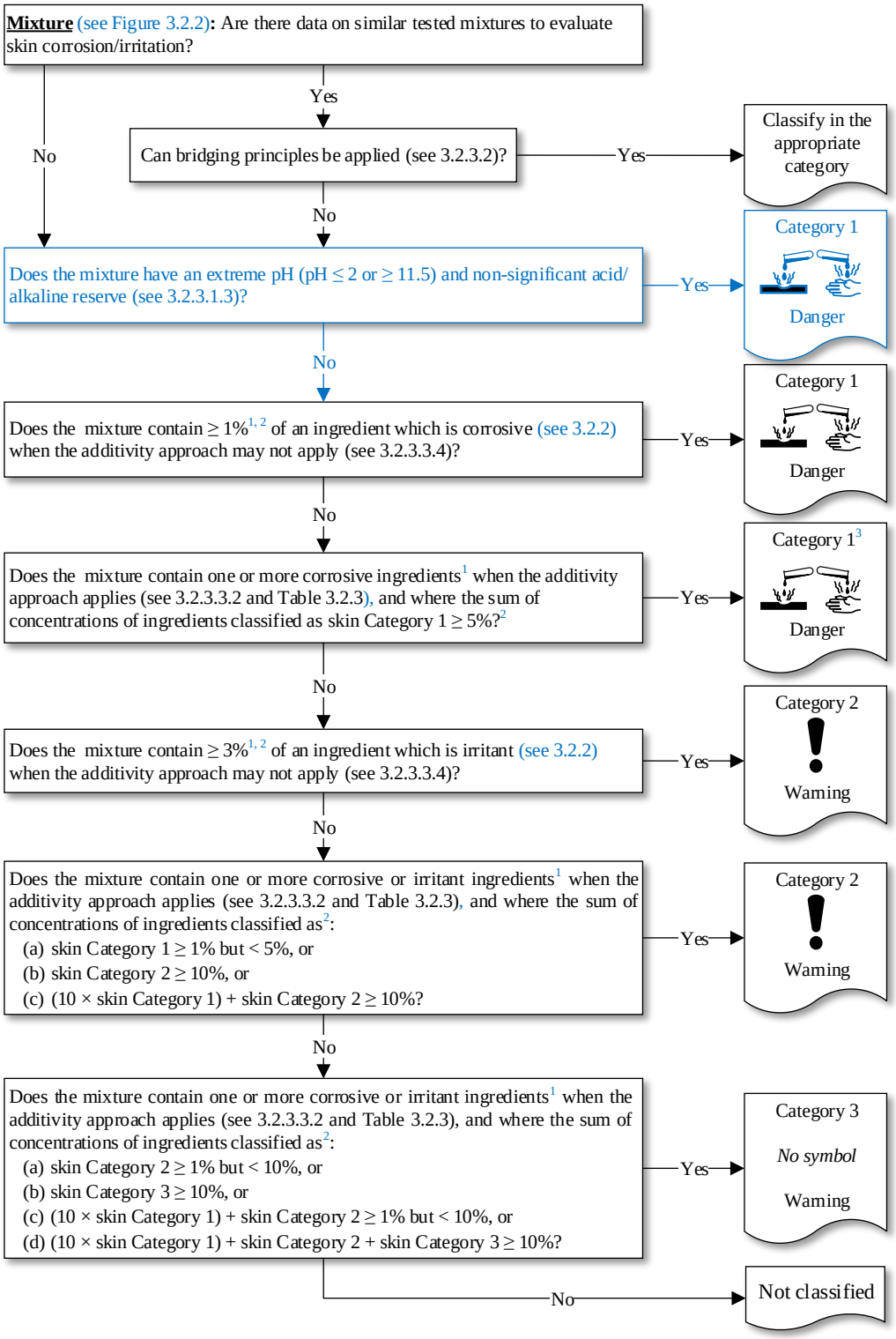
The decision logics which follow are not part of the harmonized classification system but are provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logics.

3.2.5.1 *Decision logic 3.2.1 for skin corrosion/irritation*



3.2.5.2 *Decision logic 3.2.2 for skin corrosion/irritation*

Classification of mixtures on the basis of information/data on similar tested mixtures and/or ingredients



[1] *Where relevant < 1%, see 3.2.3.3.1.*

[2] *For specific concentration limits, see 3.2.3.3.5 and 3.2.3.3.6. See also Chapter 1.3, paragraph 1.3.3.2 ~~for~~ "Use of cut-off values/concentration limits".*

[3] *See note to Table 3.2.3 for details on use of Category 1 sub-categories.*

3.2.5.3 *Background guidance*

3.2.5.3.1 *Relevant guidance documents*

Helpful information on the strengths and weaknesses of the different test and non-test methods, as well as useful guidance on how to apply a weight of evidence ~~approach~~assessment, is provided in OECD Guidance Document 203 on an integrated approach on testing and assessment (IATA) for skin corrosion and irritation.

3.2.5.3.2 *Guidance on the use of human data for classification as skin corrosion or skin irritation*

3.2.5.3.2.1 Human data generally refers to two types of data: prior human experience (e.g. published case studies from occupational, consumer, transport, emergency response scenarios, epidemiological studies) or from human tests (e.g. clinical trials, dermal patch test). Relevant, reliable and good quality human data is generally given high weight for classification. However, human data may have limitations. Further details on the strengths and limitations of human data for skin irritation/corrosion can be found in OECD Guidance Document 203 (section III. A, Part 1, Module 1).

3.2.5.3.2.2 Generally, Human Patch Tests (HPT) are performed to discriminate between irritant and non-irritant substances. Application of a corrosive substance to human skin is generally avoided. Therefore, another test is normally performed in advance to exclude corrosivity. The HPT alone does not normally discriminate between irritant and corrosive substances. In rare circumstances, there may be HPT data that can be used for classification as corrosive (e.g. application of an HPT after a false negative *in vitro* test). However, the combination of an HPT and sufficient other information on skin corrosion can be used for classification within a weight of evidence assessment.

3.2.5.3.2.3 Some competent authorities do not allow HPT testing solely for hazard identification (see 1.3.2.4.7) while some competent authorities recognize the use of HPT for classification as skin irritant.

3.2.5.3.2.4 Specific criteria for HPT results leading to classification as Category 2 (skin irritation), Category 3 (mild irritation) or not classified, have not been established at the international level. Therefore, the results of an HPT are generally used within a weight of evidence assessment. However, some competent authorities may provide specific guidance. A clearly negative result in an HPT with a sufficient number of volunteers after exposure to the undiluted substance for 4 hours can justify no classification.

3.2.5.3.2.5 Human case reports may be used for classification as corrosive if irreversible damage to the skin was observed. There are no internationally accepted classification criteria for irritation. Therefore, where competent authorities have not provided specific guidance on this matter, expert judgement may be required to evaluate whether the exposure duration and any available long-term follow-up information are sufficient to allow for a conclusion on classification. Cases resulting in irritation or no effects may not be conclusive on their own but can be used in a weight of evidence assessment.

3.2.5.3.3 *Classification based on standard animal tests with more than 3 animals*

3.2.5.3.3.1 Classification criteria for the skin and eye hazard classes are detailed in the GHS in terms of a 3-animal test. It has been identified that some older test methods may have used up to 6 animals. However, the GHS criteria do not specify how to classify based on existing data from tests with more than 3 animals. Guidance on how to classify based on existing data from studies with 4 or more animals is given in the following paragraphs.

3.2.5.3.3.2 Classification criteria based on a 3-animal test are detailed in 3.2.2.2. Evaluation of a 4, 5 or 6-animal study should follow the criteria in the following paragraphs, depending on the number of animals tested. Scoring for erythema/eschar and oedema should be performed at 24, 48 and 72 hours after exposure or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions.

3.2.5.3.3.3 In the case of a study with 6 animals the following principles apply:

(a) The substance or mixture is classified as skin corrosion Category 1 if destruction of skin tissue (that is, visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours in duration;

(b) The substance or mixture is classified as skin irritation Category 2 if at least 4 out of 6 animals show a mean score per animal of ≥ 2.3 and ≤ 4.0 for erythema/eschar or for oedema;

(c) The substance or mixture is classified as skin irritation Category 3 if at least 4 out of 6 animals show a mean score per animal of ≥ 1.5 and < 2.3 for erythema/eschar or for oedema.

3.2.5.3.3.4 In the case of a study with 5 animals the following principles apply:

(a) The substance or mixture is classified as skin corrosion Category 1 if destruction of skin tissue (that is, visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours in duration;

(b) The substance or mixture is classified as skin irritation Category 2 if at least 3 out of 5 animals show a mean score per animal of ≥ 2.3 and ≤ 4.0 for erythema/eschar or for oedema;

(c) The substance or mixture is classified as skin irritation Category 3 if at least 3 out of 5 animals show a mean score per animal of ≥ 1.5 and < 2.3 for erythema/eschar or for oedema.

3.2.5.3.3.5 In the case of a study with 4 animals the following principles apply:

(a) The substance or mixture is classified as skin corrosion Category 1 if destruction of skin tissue (that is, visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours in duration;

(b) The substance or mixture is classified as skin irritation Category 2 if at least 3 out of 4 animals show a mean score per animal of ≥ 2.3 and ≤ 4.0 for erythema/eschar or for oedema;

(c) The substance or mixture is classified as skin irritation Category 3 if at least 3 out of 4 animals show a mean score per animal of ≥ 1.5 and < 2.3 for erythema/eschar or for oedema.

3.2.5.3.4 *Classification criteria based on in vitro/ex vivo data*

Where *in vitro/ex vivo* tests have been undertaken in accordance with OECD test guidelines 430, 431, 435 and/or 439, the criteria for classification in Category 1 (and, where possible and required into sub-categories 1A, 1B or 1C) for skin corrosion and in Category 2 for skin irritation are set out in Tables 3.2.6 and 3.2.7.

Table 3.2.6: Skin corrosion criteria for *in vitro/ex vivo* methods

Category	OECD Test Guideline 430 (Transcutaneous Electrical Resistance test method)	OECD Test Guideline 431 Reconstructed human Epidermis test methods: Methods 1, 2, 3, 4 and 5 as numbered in Annex 2 of OECD Test Guideline 431			OECD Test Guideline 435 Membrane barrier test method	
	Using rat skin discs corrosive chemicals are identified by their ability to produce a loss of normal *stratum corneum* integrity. Barrier function of the skin is assessed by recording the passage of ions through the skin. The electrical impedance of the skin is measured using transcutaneous electrical resistance (TER). A confirmatory test of positive results using a dye-binding step that assesses if an increase in ionic permeability is due to the physical destruction of the *stratum corneum* is performed in case of a reduced TER (less than or around 5 kΩ) in the absence of obvious damage. The criteria are based on the mean TER value in kΩ and sometimes on dye content.	Four similar methods where the test chemical is applied topically to a three-dimensional reconstructed human epidermis (RhE) which closely mimics the properties of the upper parts of human skin. The test method is based on the premise that corrosive chemicals are able to penetrate the *stratum corneum* by diffusion or erosion and are cytotoxic to the cells in the underlying layers. Tissue viability is assessed by enzymatic conversion of the dye MTT into a blue formazan salt that is quantitatively measured after extraction from the tissues. Corrosive chemicals are identified by their ability to decrease tissue viability below defined threshold values. The criteria are based on the percent tissue viability following a defined exposure period.			An *in vitro* membrane barrier test method comprising a synthetic macromolecular bio-barrier and a chemical detection system (CDS). Barrier damage is measured after the application of the test chemical to the surface of the synthetic membrane barrier. The criteria are based on the mean penetration/breakthrough time of the chemical through the membrane barrier.	
					Type 1 chemicals (high acid/alkaline reserve)	Type 2 chemicals (low acid/alkaline reserve)
1	(a) mean TER value ≤ 5 kΩ and the skin discs are obviously damaged (e.g. perforated), or (b) mean TER value ≤ 5 kΩ, and (i) the skin discs show no obvious damage (e.g. perforation), but (ii) the subsequent confirmatory testing of positive results using a dye binding step is positive.	Method 1 < 35% after 3, 60 or 240 min exposure	Methods 2, 3, 4, 5 < 50% after 3 min exposure; or ≥ 50% after 3 min exposure and < 15% after 60 min exposure		≤ 240 min	≤ 60 min
1A	Not applicable	Method 1 < 35% after 3 min exposure	Method 2 < 25% after 3 min exposure	Method 3 < 18% after 3 min exposure	Method 4 < 15% after 3 min exposure	0-3 min.	0-3 min
1B		≥ 35% after 3 min exposure and < 35% after 60 min exposure or ≥ 35% after 60 min exposure and < 35% after 240 min exposure	≥ 25% after 3 min exposure and fulfilling criteria for Category 1	≥ 18% after 3 min exposure and fulfilling criteria for Category 1	≥ 15% after 3 min exposure and fulfilling criteria for Category 1	> 3 to 60 min.	> 3 to 30 min
1C						> 60 to 240 min.	> 30 to 60 min
Not classified as skin corrosive	(a) the mean TER value > 5 kΩ, or (b) the mean TER value ≤ 5 kΩ, and (i) the skin discs show no obvious damage (e.g. perforation), and (ii) the subsequent confirmatory testing of positive results using a dye binding step is negative	≥ 35% after 240 min exposure	≥ 50% after 3 min exposure and ≥ 15% after 60 min exposure			> 240 min.	> 60 min

Table 3.2.7 Skin irritation criteria for *in vitro* methods

Category	**OECD Test Guideline 439** **Reconstructed Human Epidermis test methods**
	Four similar methods (1-4) where the test chemical is applied topically to a three-dimensional reconstructed human epidermis (RhE) which closely mimics the properties of the upper parts of human skin. Tissue viability is assessed by enzymatic conversion of the dye MTT into a blue formazan salt that is quantitatively measured after extraction from the tissues. Positive chemicals are identified by their ability to decrease tissue viability below defined threshold levels. The criteria are based on mean percent tissue viability after exposure and post-treatment incubation.
1 or 2	Mean percent tissue viability (≤) 50%. ***Note:*** *The RhE test methods covered by this test guideline cannot resolve between GHS categories 1 and 2. Further information on skin corrosion will be required to decide on its final classification (see also the OECD Guidance Document 203).*
2	Mean percent tissue viability ≤ 50% and the test chemical is found to be noncorrosive (e.g., based on Test Guideline 430, 431 or 435)
Not classified as skin irritant or Category 3	Mean percent-tissue viability > 50% ***Note:*** *The RhE test methods covered by this test guideline cannot resolve between GHS optional Category 3 and not classified as skin irritant. Further information on skin irritation is required for those authorities that want to have more than one skin irritation category.*

3.2.5.3.5 *Guidance on the use of other existing skin data in animals for classification as skin corrosion or skin irritation*

3.2.5.3.5.1 General approach

All existing other animal data should be carefully reviewed and only used if they are conclusive for classification. In evaluating other existing skin data in animals, however, it should be recognized that the reporting of dermal lesions may be incomplete, testing and observations may be made in a species other than the rabbit, and species may differ in sensitivity in their responses. In general skin thickness decreases with body weight. However, other factors also affect species variability. In addition, for most of these tests, irritating and corrosive effects need to be avoided. Therefore, these effects may only be observed in range finding studies using a small number of animals with limited observations and reporting.

3.2.5.3.5.2 Other data limitations and consequences for classification

3.2.5.3.5.2.1 Acute dermal toxicity tests, repeated dose animal studies, skin sensitisation studies and skin absorption studies may all differ from the standard in vivo acute dermal irritation/corrosion test (e.g. OECD Test Guideline 404) with regard to exposure duration, area dose, the use of dissolved substances, level of occlusion, patch type, scoring and follow-up of the skin lesions and the test species.

3.2.5.3.5.2.2 Destruction of the skin in any acute dermal toxicity test (e.g. OECD Test Guideline 402) should be considered for classification as corrosive (Category 1 or sub-category 1A, 1B or 1C where possible and required). Skin irritation in an acute dermal study in rabbits fulfilling the criteria in Table 3.2.2, should be considered for classification as irritant if the exposure conditions are such that corrosive effects can be excluded. Skin irritation in an acute dermal study in other species should be considered as not conclusive, as these species may be less or more sensitive than rabbits. Such data should be taken into account in a weight-of-evidence assessment. The absence of skin irritation should also be considered as not conclusive and taken into account in a weight-of-evidence assessment.

3.2.5.3.5.2.3 Repeated dose dermal studies (e.g. OECD test guidelines 410 and 411) can be used to classify as corrosive when destruction of the skin is observed after the initial exposures. However, normally such exposures are avoided and corrosive effects may only be observed in the range-finding studies. Moreover, sub-categorisation for corrosion will rarely be possible due to a longer time period between start of exposure and first observation. The observation of skin irritation or the absence of skin irritating effects should be considered as not conclusive. Skin effects only observed after multiple exposures may indicate skin sensitisation rather than skin irritation.

3.2.5.3.5.2.4 In skin sensitisation studies in guinea pigs (e.g. OECD Test Guideline 406), severely irritating and corrosive exposure must be avoided. Therefore, such effects are normally only observed in range-finding studies. The range-finding results, with the exception of intradermal exposure in the maximisation test, can be used to classify as corrosive when destruction of the skin is observed. The presence or absence of skin irritation in a skin sensitisation study should be considered as not conclusive by itself as the species tested may be more or less sensitive than rabbits, but signs of irritation should be taken into account in a weight of evidence assessment.

3.2.5.3.5.2.5 Irritation data from the Local Lymph Node Assay (e.g. OECD test guidelines 429, 442A and 442B) should normally not be used for classification as the test substance is applied to the dorsum of the ear by open topical application, and in some cases specific vehicles for enhancement of skin penetration are used. Further, due to the proportional increase of skin thickness associated with increased body weight, the skin thickness of mice deviates significantly from that of rabbits and humans.

3.2.5.3.5.2.6 In skin absorption studies (e.g. OECD Test Guideline 427), corrosive exposure conditions are generally avoided as this affects the absorption. Therefore, information on skin effects from these studies does not allow classification directly but may be considered within a weight of evidence approach. However, information on the dermal absorption may be taken into account in a weight-of-evidence assessment as a high dermal absorption in combination with additional evidence for high cytotoxicity may indicate irritation or corrosivity.

3.2.5.3.6 *Guidance on the use of pH and acid/alkaline reserve for classification as skin corrosion*

3.2.5.3.6.1 Methods to determine the pH value such as OECD Test Guideline 122 and the method described by Young et al. (1988) differ in the concentration of the substance or mixture for which the pH is determined and include values of 1%, 10% and 100%. These methods also differ in the way the acid/alkaline reserve is determined, namely up to a pH of 7 for both acids and bases (OECD Test Guideline 122) or up to a pH of 4 for acids and a pH of 10 for bases (Young et al., 1988). Furthermore, there are differences between OECD Test Guideline 122 and Young et al. (1988) in the units used to express the acid/alkaline reserve.

3.2.5.3.6.2 Criteria to identify substances and mixtures requiring classification in Category 1 based on pH and acid/alkaline reserve have been developed for effects on the skin (Young et al., 1988). These criteria were developed using a combination of pH and acid/alkaline reserve values that were determined in a specific way (Young et al., 1988). Therefore, these criteria may not be directly applicable when other test concentrations or methods are used to measure pH and acid/alkaline reserve. Furthermore, the calibration and validation of these criteria was based on a limited dataset for effects on the skin. Thus, the predictive value of the combination of pH and acid/alkaline reserve for classification in Category 1 for effects on the skin is limited, especially for substances and mixtures with an extreme pH but a non-significant acid/alkaline reserve. The criteria developed by Young et al. (1988) for classification in Category 1 may be used as a starting point for determining whether a substance or a mixture has a significant acid/alkaline reserve or a non-significant acid/alkaline reserve. A competent authority may decide which criteria for significant acid/alkaline reserve can be applied.

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* *References:*

Young, J.R., M.J. How, A.P. Walker, and W.M. Worth. 1988. Classification as corrosive or irritant to skin of preparations containing acidic or alkaline substances, without testing on animals. Toxicol. In Vitro, 2(1): 19-26. doi: 10.1016/0887-2333(88)90032-x.