Committee of Experts on the Transport of Dangerous Goods and on the Globally Harmonized System of Classification and Labelling of Chemicals

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Updating of the Globally Harmonized System of Classification and Labelling of Chemicals (GHS): Health hazards

Proposal for the editorial revision of Chapter 3.2 (track-changes)

Submitted by the expert from Germany on behalf of the informal correspondence group on the editorial revision of chapters 3.2 and 3.3

This document contains the text of Chapter 3.2 as amended in accordance with the proposed list of amendments in document ST/SG/AC.10/C.4/2012/12, as agreed by the informal correspondence group. Amendments are shown in visible mode ("track-changes").

The full text of Chapter 3.2 as amended (i.e. with all the suggested changes accepted) is circulated as INF.3/Add.1.

"**CHAPTER 3.2**

SKIN CORROSION/IRRITATION

3.2.1 Definitions and general considerations

3.2.1.1 *Skin corrosion* is the production of irreversible damage to the skin; namely, visible necrosis through the epidermis and into the dermis, following the application of a test substance for up to 4 hours[1]. Corrosive reactions are typified by ulcers, bleeding, bloody scabs, and, by the end of observation at 14 days, by discolouration due to blanching of the skin, complete areas of alopecia, and scars. Histopathology should be considered to evaluate questionable lesions.

Skin irritation is the production of reversible damage to the skin following the application of a test substance for up to 4 hours[1].

3.2.1.2 In a tiered approach, emphasis should be placed upon existing human data, followed by existing animal data, followed by *in vitro* data and then other sources of information. Classification results directly when the data satisfy the criteria. In some cases, classification of a substance or a mixture is made on the basis of the weight of evidence within a tier. In a total weight of evidence approach all available information bearing on the determination of skin corrosion/irritation is considered together, including the results of appropriate validated *in vitro* tests, relevant animal data, and human data such as epidemiological and clinical studies and well-documented case reports and observations (see Chapter 1.3, para. 1.3.2.4.9).

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 (see Table 3.2.1)

(b) Category 2 (skin irritation) (see Table 3.2.2)

(c) Category 3 (mild skin irritation)

This category is available for those authorities (e.g. pesticides) that want to have more than one skin irritation category (see Table 3.2.2).

~~3.2.2.1 The harmonized system includes guidance on the use of data elements that are evaluated before animal testing for skin corrosion and irritation is undertaken. It also includes hazard categories for corrosion and irritation.~~

~~3.2.2.2 Several factors should be considered in determining the corrosion and irritation potential of substances before testing is undertaken. Solid substances (powders) may become corrosive or irritant when moistened or in contact with moist skin or mucous membranes. Existing human experience and data including from single or repeated exposure and animal observations and data should be the first line of analysis, as they give information directly relevant to effects on the skin. In some cases enough information may be available from structurally related compounds to make~~

[1] *This is a working definition for the purpose of this document.*

classification decisions. Likewise, pH extremes like ≤ 2 and ≥ 11.5 may indicate skin effects, especially when buffering capacity is known, although the correlation is not perfect. Generally, such agents are expected to produce significant effects on the skin. It also stands to reason that if a substance is highly toxic by the dermal route, a skin irritation/corrosion study may not be practicable 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 are made of skin irritation/corrosion in acute toxicity studies and are observed up through the limit dose, additional testing would not be needed, provided that the dilutions used and species tested are equivalent. *In vitro* alternatives that have been validated and accepted may also be used to help make classification decisions.

All the above information that is available on a chemical should be used in determining the need for *in vivo* skin irritation testing. Although information might be gained from the evaluation of single parameters within a tier (see 3.2.2.3), e.g. caustic alkalis with extreme pH should be considered as skin corrosives, there is merit in considering the totality of existing information and making an overall weight of evidence determination. This is especially true when there is information available on some but not all parameters. Generally, primary emphasis should be placed upon existing human experience and data, followed by animal experience and testing data, followed by other sources of information, but case-by-case determinations are necessary.

3.2.2.3 A *tiered approach* to the evaluation of initial information should be considered, where applicable (Figure 3.2.1), recognizing that all elements may not be relevant in certain cases.

Figure 3.2.1: Tiered testing and evaluation of skin corrosion and irritation potential

Step	**Parameter**	**Finding**	**Conclusion**


1a
Existing human or animal experience (f)
Corrosive
Classify as corrosive (a)
Not corrosive or no data
1b
Existing human or animal experience (f)
Irritant
Classify as irritant (a)
Not irritant or no data
1c
Existing human or animal experience
Not corrosive or irritant
No further testing, not classified
No data
2a
Structure-activity relationships
Corrosive
Classify as corrosive (a)
Not corrosive or no data
2b
Structure-activity relationships
Irritant
Classify as irritant (a)
Not irritating or no data
3
pH with buffering (b)
pH ≤ 2 or ≥ 11.5
Classify as corrosive (a)
Not pH extreme or no data
4
Existing skin data in animals indicate no need for animal testing (c)
Yes
Possibly no further testing may be deemed corrosive/irritant
Not indication or no data
5
Valid and accepted *in vitro* skin corrosion test (d)
Positive response
Classify as corrosive (a)
Negative response or no data
6
Valid and accepted *in vitro* skin irritation test (e)
Positive response
Classify as irritant (a)
Negative response or no data
7
In vivo skin corrosion test (1 animal)
Positive response
Classify as corrosive (a)
Negative response
8
In vivo skin irritation test (3 animals total) (g)
Positive response
Classify as irritant (a)
Negative response
No further testing
No further testing, not classified
9
When it is ethical to perform human patch testing (f)
Positive response
Classify as irritant (a)
Not as above
Negative response
No further testing, not classified

~~*(a) Classify in the appropriate harmonized category, as shown in Table 3.2.1;*~~

~~*(b) Measurement of pH alone may be adequate, but assessment of acid or alkali reserve is preferable; methods are needed to assess buffering capacity;*~~

~~*(c) Pre-existing animal data should be carefully reviewed to determine if in vivo skin corrosion/irritation testing is needed. For example, testing may not be needed when a test material has not produced any skin irritation in an acute skin toxicity test at the limit dose, or produces very toxic effects in an acute skin toxicity test. In the latter case, the material would be classified as being very hazardous by the dermal route for acute toxicity; it is moot whether the material is also irritating or corrosive on the skin. It should be kept in mind in evaluating acute skin toxicity information that the reporting of skin lesions may be incomplete, testing and observations may be made on a species other than the rabbit, and species may differ in sensitivity in their responses;*~~

~~*(d) Examples of internationally accepted validated in vitro test methods for skin corrosion are OECD Test Guidelines 430 and 431;*~~

~~*(e) Presently there are no validated and internationally accepted in vitro test methods for skin irritation;*~~

~~*(f) This evidence could be derived from single or repeated exposures. There is no internationally accepted test method for human skin irritation testing, but an OECD guideline has been proposed;*~~

~~*(g) Testing is usually conducted in 3 animals, one coming from the negative corrosion test.*~~

3.2.2.1 Classification based on standard animal test data

~~3.2.2.4~~3.2.2.1.1 Skin ~~C~~ *corrosion*

~~3.2.2.4.1~~3.2.2.1.1.1 ~~A single harmonized corrosion category is provided in Table 3.2.1, using the results of animal testing.~~ A substance is corrosive to skin when it ~~is a test material that~~ produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least ~~1 of 3~~one tested animal~~s~~ after exposure for up to ~~a~~ 4 hours ~~duration~~. ~~Corrosive reactions are typified by ulcers, bleeding, bloody scabs and, by the end of observation at 14 days, by discoloration due to blanching of the skin, complete areas of alopecia and scars. Histopathology should be considered to discern questionable lesions.~~

3.2.2.1.1.2 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.

3.2.2.1.1.3 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 in accordance with the criteria in table 3.2.1.

3.2.2.~~4.2~~1.1.4 For those authorities wanting more than one designation for ~~corrosivity~~skin corrosion, up to three sub-categories are provided within the ~~corrosive~~ 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 between 3 minutes and 1 hour and observations up to 14 days; and sub-category 1C, where corrosive responses occur after exposures ~~between~~ 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[a]

~~Category 1: Corrosive~~	~~**Corrosive sub-categories**~~	~~Corrosive in ≥ 1 of 3 animals~~	
~~(applies to authorities not using sub-categories)~~	~~(only applies to some authorities)~~	~~**Exposure**~~	~~**Observation**~~

~~corrosive~~	~~1A~~	~~≤ 3 min~~	~~≤ 1 h~~
	~~1B~~	~~> 3 min ≤ 1 h~~	~~≤ 14 days~~
	~~1C~~	~~> 1 h ≤ 4 h~~	~~≤ 14 days~~

	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

[a] *The use of human data is ~~discussed~~ addressed in 3.2.2.2~~1~~ and in c~~C~~hapters 1.1 (para. 1.1.2.5 (c)) and 1.3 (para. ~~graph~~ 1.3.2.4.7).*

3.2.2.~~5~~1.2 *Skin ~~I~~irritation*

3.2.2.1.2.1 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.~~5.1~~1.2.2 An ~~single *irritant*~~ *irritation category (Category 2)* is provided ~~in Table 3.2.2~~ that:

~~(a) is centrist in sensitivity among existing classifications;~~

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

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

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

3.2.2.~~5.2~~1.2.3 Reversibility of skin lesions is another consideration in evaluating irritant responses. When inflammation persists to the end of the observation period in ~~2~~ two 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.~~5.3~~1.2.4 Animal irritant responses within a test can be ~~quite~~ 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.~~5.4~~1.2.5 An ~~single irritant~~ irritation category (Category 2) is presented in ~~the table~~ Table 3.2.2 using the results of animal testing. Authorities (e.g. for pesticides) also have available a less severe mild ~~irritant~~ irritation category (Category 3). Several criteria distinguish the two categories (see Table 3.2.2). They mainly differ in the severity of skin reactions. The major criterion for the ~~irritant~~ irritation category is that at least 2 of 3 tested animals have a mean score of ≥ 2.3 and ≤ 4.0. For the mild ~~irritant~~ 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 ~~irritant~~ irritation category ~~would be~~ are excluded from ~~being placed in~~ the mild ~~irritant~~ irritation category.

Table 3.2.2: Skin irritation categories [a, b, c]

Categories	Criteria
~~Irritant~~**Irritation** **(Category 2)** (applies to all authorities)	(1) Mean ~~value~~ 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 (2) 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 (3) 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 ~~irritant~~irritation **(Category 3)** (applies to only some authorities)	Mean score~~value~~ of ≥ 1.5 and < 2.3 for erythema/eschar or for oedema from gradings in at least 2 of 3 tested animals from grades 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] *The use of human data is ~~discussed~~ addressed in 3.2.2.2~~1~~ and in c~~C~~hapters 1.1 (para. 1.1.2.5 (c)) and 1.3 (para.~~graph~~ 1.3.2.4.7).*

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

[c] *Evaluation of a 4, 5 or 6-animal study should follow the criteria given in 3.2.5.3.*

3.2.2.2 Classification in a tiered approach

3.2.2.~~3~~2.1 A *tiered approach* to the evaluation of initial information should be considered, where applicable (Figure 3.2.1), recognizing that not all elements may ~~not~~ be relevant ~~in certain cases~~.

3.2.2.2.2 ~~Several factors should be considered in determining the corrosion and irritation potential of substances before testing is undertaken. Solid substances (powders) may become corrosive or irritant when moistened or in contact with moist skin or mucous membranes.~~ Existing human ~~experience~~ and animal data including information from single or repeated exposure ~~and animal observations and data~~ should be the first line of ~~analysis~~evaluation, as they give information directly relevant to effects on the skin.

~~In some cases enough information may be available from structurally related compounds to make classification decisions. Likewise, pH extremes like ≤ 2 and ≥ 11.5 may indicate skin effects, especially when buffering capacity is known, although the correlation is not perfect.~~

3.2.2.2.3 Acute dermal toxicity data may be used for classification. ~~Generally, such agents are expected to produce significant effects on the skin. It also stands to reason that i~~If a substance is highly toxic by the dermal route, a skin ~~irritation/~~corrosion/irritation study may not be practicable 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 are made of skin ~~irritation/~~corrosion/irritation in acute toxicity studies and are observed up through the limit dose, ~~additional testing would not be needed~~these data m ay be used for classification~~,~~ provided that the dilutions used and species tested are equivalent. ~~*In vitro* alternatives that have been validated and accepted may also be used to help make classification decisions.~~ Solid substances (powders) may become corrosive or irritant when moistened or in contact with moist skin or mucous membranes.

3.2.2.2.4 *In vitro* alternatives that have been validated and accepted ~~may also~~should be used to ~~help~~ make classification decisions.

3.2.2.2.5 Likewise, pH extremes like ≤ 2 and ≥ 11.5 may indicate skin effects, especially when associated with significant acid/alkaline reserve (buffering capacity). ~~is known, although the correlation is not perfect.~~ Generally, such ~~agents~~ substances are expected to produce significant effects on the skin. In the absence of any other information, a substance is considered corrosive (Skin Category 1) if it has a pH ≤ 2 or a pH ≥ 11.5. However, if consideration of acid/alkaline reserve suggests the substance may not be corrosive despite the low or high pH value, this needs to be confirmed by other data, preferably by data from an appropriate validated *in vitro* test.

3.2.2.2.6 In some cases ~~enough~~ sufficient information may be available from structurally related ~~compounds~~ substances to make classification decisions.

3.2.2.2.7 The tiered approach provides guidance on how to organize existing information on a substance and to make a weight of evidence decision about hazard assessment and hazard classification (ideally without conducting new animal tests). ~~All the above information that is available on a chemical should be used in determining the need for *in vivo* skin irritation testing.~~ Although information might be gained from the evaluation of single parameters within a tier (see 3.2.2.~~3~~2.1), ~~e.g. caustic alkalis with extreme pH should be considered as skin corrosives, there is merit in considering~~consideration should be given to the totality of existing information and making an overall weight of evidence determination. This is especially true when there is conflict in information available on some ~~but not all~~ parameters. ~~Generally, primary emphasis should be placed upon existing human experience and data, followed by animal experience and testing data, followed by other sources of information, but case by case determinations are necessary.~~

Figure 3.2.1: Tiered ~~testing and~~ evaluation ~~of~~for skin corrosion and irritation ~~potential~~

Step	Parameter		Finding		Conclusion
1a:	Existing human or animal skin corrosion/irritation data [a]	→	Skin corrosive	→	Classify as **skin corrosive** [b]
	↓ Not corrosive/No data				
1b:	Existing human or animal skin corrosion/irritation data [a]	→	Skin irritant	→	Classify as **skin irritant** [b]
	↓ Not irritant/No data				
1c:	Existing human or animal skin corrosion/irritation data [a]	→	Not a skin corrosive or skin irritant	→	**Not classified**
	↓ No/Insufficient data				
2:	Other, existing skin data in animals [c]	→	Yes; other existing data showing that substance may cause skin corrosion or skin irritation	→	May be deemed to be a **skin corrosive** [b] or a **skin irritant** [b]
	↓ No/Insufficient data				
3:	Existing *ex vivo/in vitro* data [d]	→	Positive: Skin corrosive	→	Classify as **skin corrosive** [b]
	↓	↘	Positive: Skin irritant	→	Classify as **skin irritant** [b]
	No/Insufficient data/Negative response				
4:	pH-Based assessment (with consideration of acid/alkaline reserve of the chemical) [e]	→	pH ≤ 2 or ≥ 11.5 with high acid/alkaline reserve or no data for acid/alkaline reserve	→	Classify as **skin corrosive**
	↓ Not pH extreme, no pH data or extreme pH with data showing low/no acid/alkaline reserve				
5:	Validated Structure Activity Relationship (SAR) methods	→	Skin corrosive	→	Deemed to be **skin corrosive** [b]
	↓	↘	Skin irritant	→	Deemed to be **skin irritant** [b]
	No/Insufficient data				
6:	Consideration of the total weight of evidence [f]	→	Skin corrosive	→	Deemed to be **skin corrosive** [b]
	↓	↘	Skin irritant	→	Deemed to be **skin irritant** [b]
7:	**Not classified**				

[a] Existing human or animal data could be derived from single or repeated exposure(s), for example in occupational, consumer, transport, or emergency response scenarios; or from purposely-generated data from animal studies conducted according to validated and internationally accepted test methods. 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;

~~(b)~~ [a] Classify in the appropriate ~~harmonized~~ category/sub-category, as ~~shown in Table 3.2.1~~applicable;

~~(c)~~ ~~Pre-~~All existing animal data should be carefully reviewed to determine if sufficient skin corrosion/irritation evidence is available~~in vivo skin corrosion/irritation testing is needed. For example, testing may not be needed when a test material has not produced any skin irritation in an acute skin toxicity test at the limit dose, or produces very toxic effects in an acute skin toxicity test. In the latter case, the material would be classified as being very hazardous by the dermal route for acute toxicity; it is moot whether the material is also irritating or corrosive on the skin. It should be kept in mind i~~In evaluating such data, however, the reviewer should bear in mind ~~acute skin toxicity information~~ that the reporting of ~~skin~~ dermal lesions may be incomplete, testing and observations may be made on a species other than the rabbit, and species may differ in sensitivity in their responses;

~~(d)~~ [b] Evidence from studies using validated protocols with isolated human/animal tissues or other, non-tissue-based, though validated, protocols should be assessed. Examples of internationally accepted, validated ~~in vitro~~ test methods for skin corrosion ~~are~~ include OECD Test Guideline~~s~~ 430 (Transcutaneous Electrical Resistance Test (TER)), ~~and~~ 431 (Human Skin Model Test), and 435 (Membrane Barrier Test Method). An example of a validated internationally accepted in vitro test method for skin irritation is OECD Test Guideline 439 (Reconstructed Human Epidermis Test Method);

~~(e) Presently there are no validated and internationally accepted in vitro test methods for skin irritation;~~

~~(f) This evidence could be derived from single or repeated exposures. There is no internationally accepted test method for human skin irritation testing, but an OECD guideline has been proposed;~~

~~(g) Testing is usually conducted in 3 animals, one coming from the negative corrosion test~~

~~(b)~~ [c] Measurement of pH alone may be adequate, but assessment of acid or alkali reserve (buffering capacity) ~~is~~ would be preferable. Presently, there is no validated and internationally accepted method for assessing this parameter; ~~methods are needed to assess buffering capacity;~~

[f] All information that is available should be considered and an overall determination made on the total weight of evidence. This is especially true when there is conflict in information available on some parameters. Expert judgment should be exercised prior to making such a determination. Negative results from applicable validated skin corrosion/irritation in vitro tests are considered in the total weight of evidence evaluation.

3.2.3 Classification criteria for mixtures

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

3.2.3.1.1 The mixture ~~will~~ should be classified using the criteria for substances, ~~and~~ taking into account the ~~testing and evaluation strategies to develop~~ tiered approach to evaluate data for thi~~s~~se hazard class~~es~~ (as illustrated in Figure 3.2.1).

3.2.3.1.2 ~~Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of chemicals that can give an accurate result for classification purposes, as well as being simple and relatively inexpensive~~

~~to perform.~~ When considering testing of the mixture, classifiers are encouraged to use a tiered weight of evidence ~~strategy~~ approach as included in the criteria for classification of substances for skin corrosion and irritation to help ensure an accurate classification, as well as to avoid unnecessary animal testing. In the absence of any other information, ~~A~~a mixture is considered corrosive (Skin Category 1) if it has a pH ≤ 2 or a pH ≥ 11.5. However, ~~I~~if consideration of ~~alkali/~~acid/alkaline reserve suggests the ~~substance or~~ mixture may not be corrosive despite the low or high pH value, ~~then further testing~~this needs to be ~~carried out to~~ confirmed by other data ~~this~~, preferably by data ~~use of~~ from an appropriate validated *in vitro* test.

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 ~~irritation/~~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 corrosivity/irritancy classification than the least corrosive/irritant original ingredient and which is not expected to affect the 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 ~~irritation/~~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 ~~toxicity~~ 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 ~~in the highest category~~ 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) ~~in the highest irritation category~~ without additional testing.

3.2.3.2.5 Interpolation within one ~~toxicity~~ 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 ~~irritation/~~corrosion/irritation ~~toxicity~~ 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 ~~irritation/~~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 ~~irritation/~~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 ~~toxicity~~ 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 ~~or corrosive~~ 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 ~~irritation/~~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 ~~irritation/~~corrosion/irritation.

3.2.3.3.2 In general, the approach to classification of mixtures as ~~irritant or~~ 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 ~~irritant or~~ 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 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 ~~an irritant or a~~ 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 ~~of~~ such substances are corrosive or irritant at concentrations < 1%. For mixtures containing strong acids or bases the pH should be used as classification criteria (see 3.2.3.1.2) since pH will be a better indicator of corrosion than the concentration limits ~~of~~ inTable 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 ~~strategy~~ 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**: ~~Only some authorities will use~~Where the sub-categories of skin Category 1 (corrosive) are used~~. In these cases~~, the sum of all ingredients of a mixture classified as skin Category 1A, 1B or 1C respectively, should each be ≥ 5% in order to classify the mixture as either skin ~~C~~sub-category 1A, 1B or 1C. ~~In case~~ Where the sum of the ~~skin Category~~ 1A ingredients is < 5% but the sum of ~~skin Category ingredients~~ 1A+1B ingredients is ≥ 5%, the mixture should be classified as ~~skin C~~sub-category 1B. Similarly, ~~in case~~ where the sum of ~~skin Category~~ 1A + 1B ingredients is < 5% but the sum of ~~Category~~ 1A + 1B + 1C ingredients is ≥ 5% the mixture ~~would~~ should be classified as ~~Category~~ 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 ~~for which~~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~~s for which additivity does not apply~~	≥ 1%	Category 1
Other irritant (Category 2/3) ingredient~~s for which additivity does not apply~~, 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 2 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.

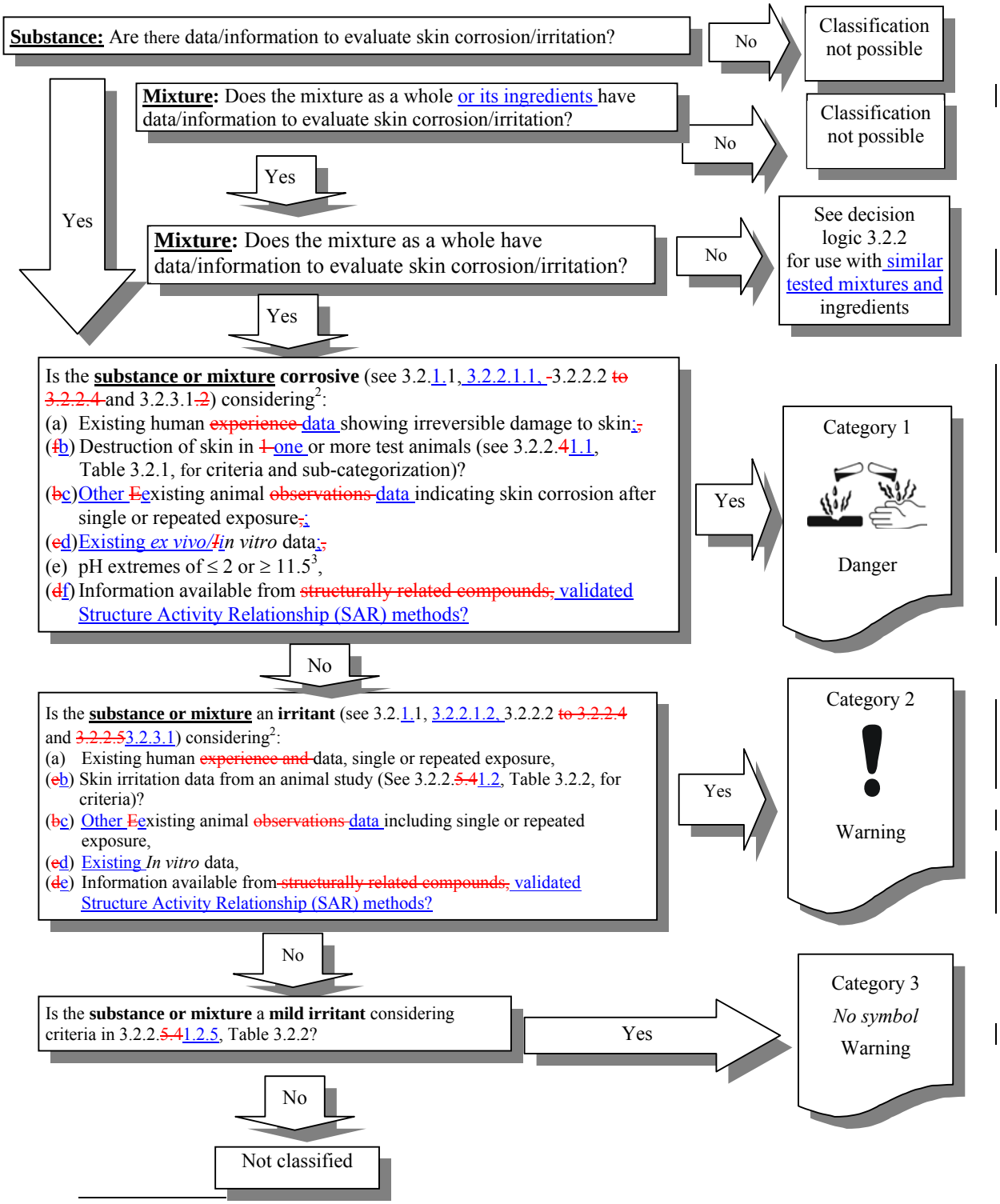
Table 3.2.5: Label elements for skin corrosion/irritation

	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 logic

The decision logic which follows is not part of the harmonized classification system but is 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 logic.

3.2.5.1 *Decision logic 3.2.1 for skin corrosion/irritation*

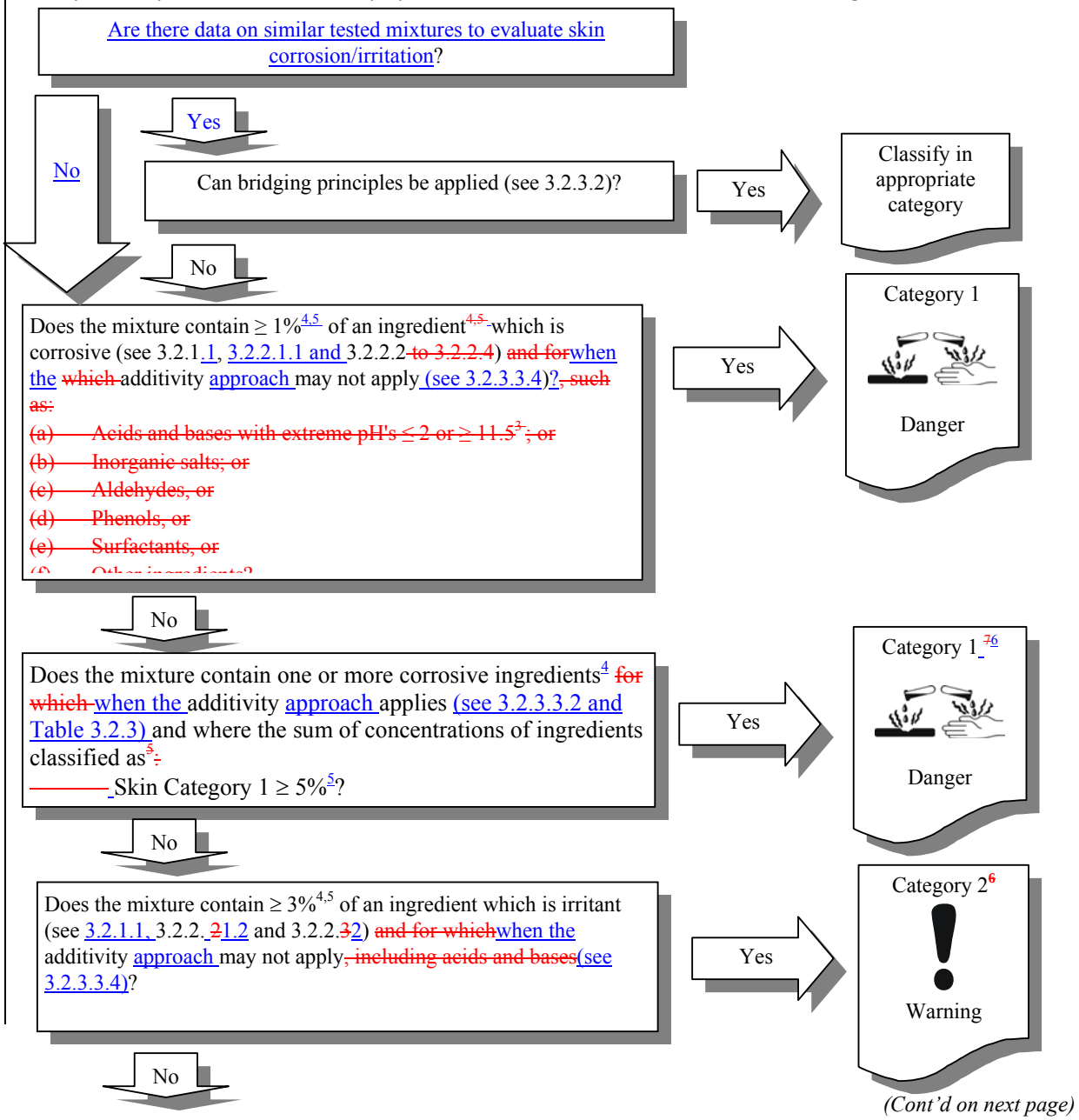


[2] *Taking into account consideration of the total weight of evidence as needed.*

[3] *Not applicable if consideration of pH and acid/alkaline reserve indicates substance or mixture may not be corrosive and confirmed by other data, preferably by data from an appropriate validated in vitro test.*

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

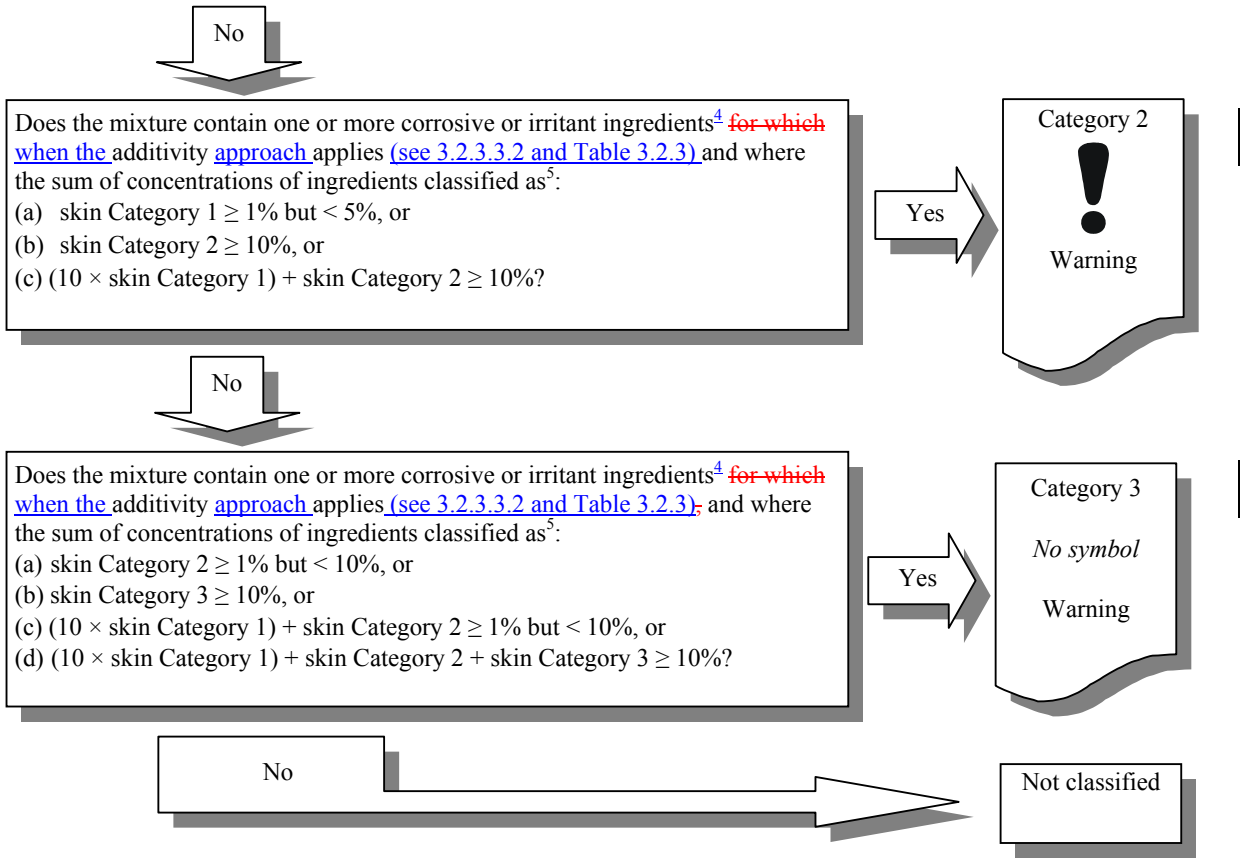


(Cont'd on next page)

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

[5] *For specific concentration limits, see 3.2.3.3.6. See also Chapter 1.3, para. 1.3.3.2 for "The u Use of cut-off values/concentration limits".*

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



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

[5] *For specific concentration limits, see 3.2.3.3.6. See also Chapter 1.3, para. 1.3.3.2 for "The uUse of cut-off values/concentration limits".*

3.2.5.3 *Background guidance*

3.2.5.3.1 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.

3.2.5.3.2 Classification criteria based on a 3-animal test are detailed in 3.2.2.1. 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 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.

3.2.5.3.4 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.

3.2.5.3.5 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.