Chapter 6:
SKIN CORROSION/IRRITATION

DEFINITIONS

1. Dermal Irritation is the production of reversible damage of the skin following the application of a test substance for up to 4 hours.

2. Dermal Corrosion is the production of irreversible damage of the skin; namely, visible necrosis through the epidermis and into the epidermis, following the application of a test substance for up to 4 hours. 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.

CLASSIFICATION CRITERIA FOR SUBSTANCES

Considerations

3. The harmonised system includes guidance for the use of initial considerations, that is those data elements that are evaluated before animal testing for dermal corrosion and irritation is undertaken. It also includes hazard classes for corrosion and irritation.

4. Several factors should be considered in determining the corrosion and irritation potential of chemicals before testing is undertaken. Existing human experience and data including from single or repeated exposure and animal observations and data should be the first line of analysis, as it gives information directly referable 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 $\leq$ 2 and $\geq$ 11.5, may indicate dermal 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 chemical is highly toxic by the dermal route, a dermal 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 dermal 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.

5. All the above information that is available on a chemical should be used in determining the need for in vivo dermal irritation testing. Although information might be gained from the evaluation of single parameters within a tier (e.g., caustic alkalies with extreme pH should be considered as dermal 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.

6. A tiered approach to the evaluation of initial information should be considered, where applicable (Figure 1), recognising that all elements may not be relevant in certain cases.

Figure 1: Tiered testing and evaluation of dermal corrosion and irritation potential (see also the "Testing and evaluation strategy for eye irritation/corrosion").

Step	Parameter	Finding	Conclusion
1a	Existing human or animal experience [g)]	→ Corrosive	→ Classify as corrosive [a)]
	↓ Not corrosive or no data		
1b	Existing human or animal experience [g)]	→ Irritant	→ Classify as irritant [a)]
	↓ Not irritant or no data		
1c	Existing human or animal experience	→ Not corrosive or irritant	→ No further testing
	↓ No data		
2a	Structure-activity relationships or structure-property relationships [b)]	→ Corrosive	→ Classify as corrosive [a)]
	↓ Not corrosive or no data		
2b	Structure-activity relationships or structure-property relationships [b)]	→ Irritant	→ Classify as irritant [a)]
	↓ Not irritating or no data		
3	pH with buffering [c)]	→ pH $\leq$ 2 or $\geq$11.5	→ Classify as corrosive [a)]
	↓ Not pH extreme or no data		
4	Existing dermal data in animals indicate no need for animal testing [d)]	→ Yes	→ Possibly no further testing may be deemed corrosive/ irritant
	↓ No indication or no data		
5	Valid and accepted in vitro dermal corrosion test [e)]	→ Positive response	→ Classify as corrosive [a)]
	↓		

Figure 1: Tiered testing and evaluation of dermal corrosion and irritation potential (see also the "Testing and evaluation strategy for eye irritation/corrosion").

Step	Parameter	Finding	Conclusion
	Negative response or no data ↓		
6	Valid and accepted in vitro dermal irritation test [f] ↓	→ Positive response	→ Classify as irritant [a]
	Negative response or no data ↓		
7	*In vivo* dermal corrosion test (1 animal) ↓	→ Corrosive response	→ Classify as corrosive [a]
	Negative response ↓		
8	*In vivo* dermal irritation test (3 animals total) [h] ↓	→ Irritant response	→ Classify as irritant [a]
	Negative response ↓	→ No further testing	→ Classify as irritant [a]
9	When it is ethical to perform human patch testing [g] ↓	→ Irritant response	→ Classify as irritant [a]
	Not as above	→ Non-irritant response	→ No further testing

a. Classify in the harmonised category, below.
b. Structure-activity and structure-property relationships are presented separately but would be conducted in parallel.
c. Measurement of pH alone may be adequate, but assessment of acid or alkali reserve is preferable; methods are needed to assess buffering capacity.
d. Pre-existing animal data should be carefully reviewed to determine if in vivo dermal corrosion/irritation testing is needed. As examples, testing may not be needed when a test material has not produced any dermal irritation in an acute dermal toxicity test at the limit dose, or produces very toxic effects in an acute dermal toxicity test. In the latter case, the material would be classed 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 dermal toxicity information that the reporting of 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.
e. Currently there are no internationally accepted validated in vitro methods of dermal corrosion, but a validation study on several methods has just been completed.
f. Presently there are no validated and internationally accepted in vitro test methods for dermal irritation.

g. This evidence could be derived from single or repeated exposures. There is no internationally accepted test method for human dermal irritation testing, but an OECD guideline has been proposed.
h. Testing is usually conducted in 3 animals, one coming from the negative corrosion test.

Corrosion

7. A single harmonised corrosion category is adopted using the results of animal testing. A corrosive is a test material that produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis) in ≥ 1 of 3 tested animals after exposure up to a 4 hour 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.

8. 6. For those authorities wanting more than one designation of corrosivity, up to three subclasses are adopted which divide up responses in the corrosive category (Category 1, see Table 1): **subcategory 1A** --where responses are noted following up to 3 minutes exposure and up to 1 hour observation; **subcategory 1B** --where responses are described following exposure between 3 minutes and 1 hour and observations up to 14 day; and **subcategory 1C** --where responses occur after exposures between 1 hour and 4 hours and observations up to 14 days.

Table 1. Skin corrosive category and subcategories. [a)]

Corrosive category (categ. 1)	**Potential corrosive Subcategories**	**Corrosive in ≥ 1 of 3 animals**	
(applies to authorities not using subcategories)	(only applies to some authorities)	**exposure**	**Observation**
corrosive	corrosive subcateg. 1A	≤ 3 minutes	≤ 1 hour
	corrosive subcateg. 1B	> 3 minutes -- ≤ 1 hour	≤ 14 days
	corrosive subcateg. 1C	> 1 hour -- ≤ 4 hours	≤ 14 days

a). In case human data is considered, the use of human data is discussed under "Considerations", above.

Irritation

9. A single irritant category is adopted that (a) is centrist in sensitivity among existing classifications, (b) recognises that some test materials may lead to effects which persist throughout the length of the test, and (c) acknowledges that animal responses in a test may be quite variable. The current EU 3-animal classification system is modified to generate the proposed position. An additional mild irritant category is available for those authorities that want to have more than one dermal irritant category.

10. Reversibility of dermal 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.

11. Animal irritant responses within a test can be quite variable, as they are with corrosion. A separate irritant criterion should be added to accommodate 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 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, the responses should be ascertained as being the result of chemical exposure. Addition of this criterion increases the sensitivity of the classification system beyond that of the current EU system.

12. To counterbalance the increases in sensitivity of a designation of an irritant position and to make room for a mild irritant category, the endpoint mean score for a positive animal response is raised from $\geq$ 2.0 under the current EU system to $\geq$ 2.3. From a training set of data, the proportion of positive tests for the total data base decreases from 0.59 for the current EU system to 0.34. The exact proportion of positive test materials in the proposed system is not known, but it would definitely be higher than 0.34 and, thus, closer to the proportion of positives in the current EU system. In addition, the proportion of positives will vary considerably with the composition of materials being tested. From the training set, about 0.34 of the chemicals are in the mild irritant category, and the total is the sum of the proportion of irritants and mild irritants, or 0.68 of the chemicals.

13. A single **irritant** category (Category 2) is adopted using the results of animal testing. Authorities (e.g., pesticides) also have available a less severe **mild irritant** category (Category 3). Several criteria distinguish the two categories (Table 2). They mainly differ in the severity of dermal reactions. The major criterion for the irritant category is that at least 2 tested animals have a mean score of $\geq$ 2.3 - $\leq$ 4.0. For the mild irritant category, the mean score cut-offs are $\geq$ 1.5 - < 2.3 for at least 2 tested animals. Test materials in the irritant category would be excluded from being placed in the mild irritant category.

Table 2. Skin irritant category and subcategory[a]

Categories	**Criteria**
Irritant (Category 2) (applies to all authorities)	(1) Mean value of $\geq$ 2.3 - < 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 dermal 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 (Category 3) (applies to only some authorities)	Mean value of $\geq$ 1.5 - < 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 dermal reactions (when not included in the irritant category above).

a. In case human data is considered, the use of human data is discussed under "Considerations", above.

CLASSIFICATION CRITERIA FOR MIXTURES

Classification of Mixtures When Data are Available for the Complete Mixture

14. The mixture will be classified using the criteria for substances, and taking into account the testing and evaluation strategies to develop data for these endpoints.

15. Unlike other endpoints, there are alternative tests available for skin corrosivity of certain classes 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 manufacturers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for eye and skin corrosion and irritation to help ensure an accurate classification, as well as avoid unnecessary animal testing. A mixture is considered corrosive (Skin Category 1) if it has a pH of 2 or less or 11.5 or greater. If consideration of alkali/acid reserve suggests the substance or preparation may not be corrosive despite the low or high pH value, then further testing needs to be carried out to confirm this, preferably by use of an appropriate validated *in vitro* test.

Classification of Mixtures When Data are not Available for the Complete Mixture.

Bridging Principles

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

Dilution

17. If a 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 mixture may be classified as equivalent to the original mixture. Alternatively, the method explained in paragraphs 23-28 could be applied.

Batching

18. The irritation/corrosion potential of one production batch of a complex mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product and produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the toxicity of the batch has changed. If the latter occurs, new classification is necessary.

Concentration of Mixtures of the Highest Corrosion / Irritation Category

19. If a tested mixture classified in the highest subcategory for corrosion is concentrated, a more concentrated mixture should be classified in the highest corrosion subcategory without additional testing. If a tested mixture classified in the highest category for skin/eye irritation is concentrated and does not contain corrosive ingredients, a more concentrated mixture should be classified in the highest irritation category without additional testing.

20. If mixtures A and B are in the same irritation/corrosion toxicity category and mixture C is made in which the toxicologically active ingredients have concentrations intermediate to those in mixtures A and B, then mixture C is assumed to be in the same irritation/corrosion category as A and B. Note that the identity of the ingredients is the same in all three mixtures

Substantially Similar Mixtures

21. 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 irritation/corrosion 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 of B.

If mixture (i) is already classified by testing, mixture (ii) can be assigned in the same category.

Aerosols

22. An aerosol form of a mixture may be classified in the same hazard category as the tested non-aerosolised form of mixture provided that the added propellant does not affect the irritation or corrosive properties of the mixture upon spraying.

Classification of Mixtures When Data are Available for all Components or Only for Some Components of the Mixture.

23. In order to make use of all available data for purposes of classifying the skin irritation/corrosion hazards of the 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 of 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a presumption (e.g., in the case of corrosive ingredients) that an ingredient present at a concentration of less than 1% can still be relevant for classifying the mixture for skin irritation/corrosion.

24. In general, the approach to classification of mixtures as irritant or corrosive to skin when data are available on the components, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or irritant component contributes to the overall irritant or corrosive properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive components 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 components exceeds a threshold concentration limit.

25. Table 3 below provides the concentration limits to be used to determine if the mixture is considered to be an irritant or a corrosive for skin.

26. 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 paragraphs 24 and 25 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 paragraph 13) since pH will be a better indicator of corrosion than the concentration limits of Table 3. Mixtures containing corrosive or irritant ingredients that cannot be classified based on the additivity approach applied in Table 3 due to chemical characteristics that make this approach unworkable, the mixture will be classified as Skin Category 1 if it contains ≥ 1% of a corrosive ingredient and as Skin Category 2/3 when it contains ≥ 3% of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3 does not apply is summarised in Table 4 below.

27. 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 cut-off levels mentioned in Tables 3 - 4. In these cases the mixture could be classified according to that data (see also Chapter 3 – Use of Cut-Off Values). 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 levels mentioned in Tables 3 - 4, testing of the mixture may be considered. In those cases the tiered weight of evidence strategy should be applied as referred to in paragraph 15 and explained in detail in the chapter on classification of substances for skin hazards.

28. If there is data showing that (an) ingredient(s) may be corrosive or irritant at a concentration of < 1% (corrosive) or < 3% (irritant), the mixture should be classified accordingly (see also Chapter 3 – Use of Cut-Off Values).

Table 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	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 x Skin Category 1) + Skin Category 2		≥10%	≥1% but <10%
(10 x Skin Category 1) + Skin Category 2 + Skin Category 3			≥10%

Note to Table 3 : Only some authorities will use the subclasses of Skin Category 1 (corrosive). 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 Category 1A, 1B or 1C. In case the sum of the Skin Category 1A ingredients is < 5% but the sum of Skin Category ingredients 1A+1B is ≥ 5%, the mixture should be classified as Skin Category 1B. Similarly, in case the sum of Skin Category 1A+1B is < 5% but the sum of Category 1A+1B+1C is ≥ 5% the mixture would be classified as Category 1C.

Table 4: Concentration of ingredients of a mixture for which 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) ingredients for which additivity does not apply	≥ 1%	Category 1
Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

HAZARD COMMUNICATION

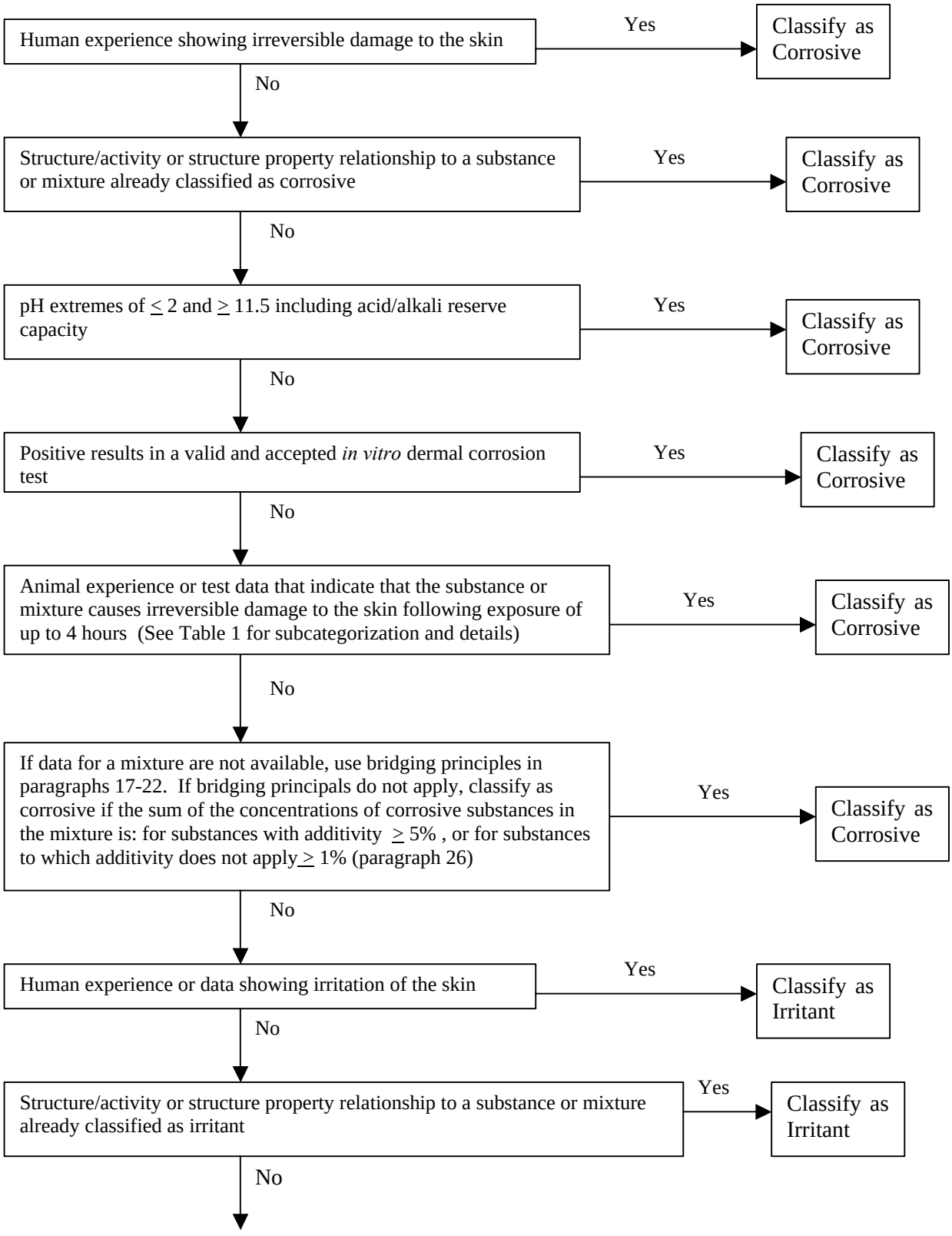
Allocation of Label Elements

29. General and specific considerations concerning labelling requirements are provided in Chapter 4. Annex 5 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. Additional reference sources providing advice on the use of precautionary information is also included.

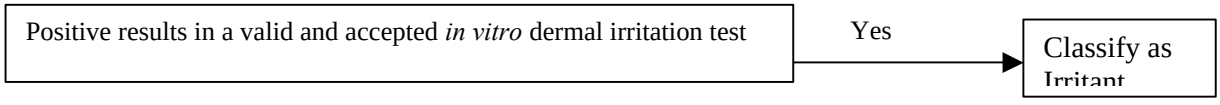
Table 5: Label elements for Skin corrosion/irritation.

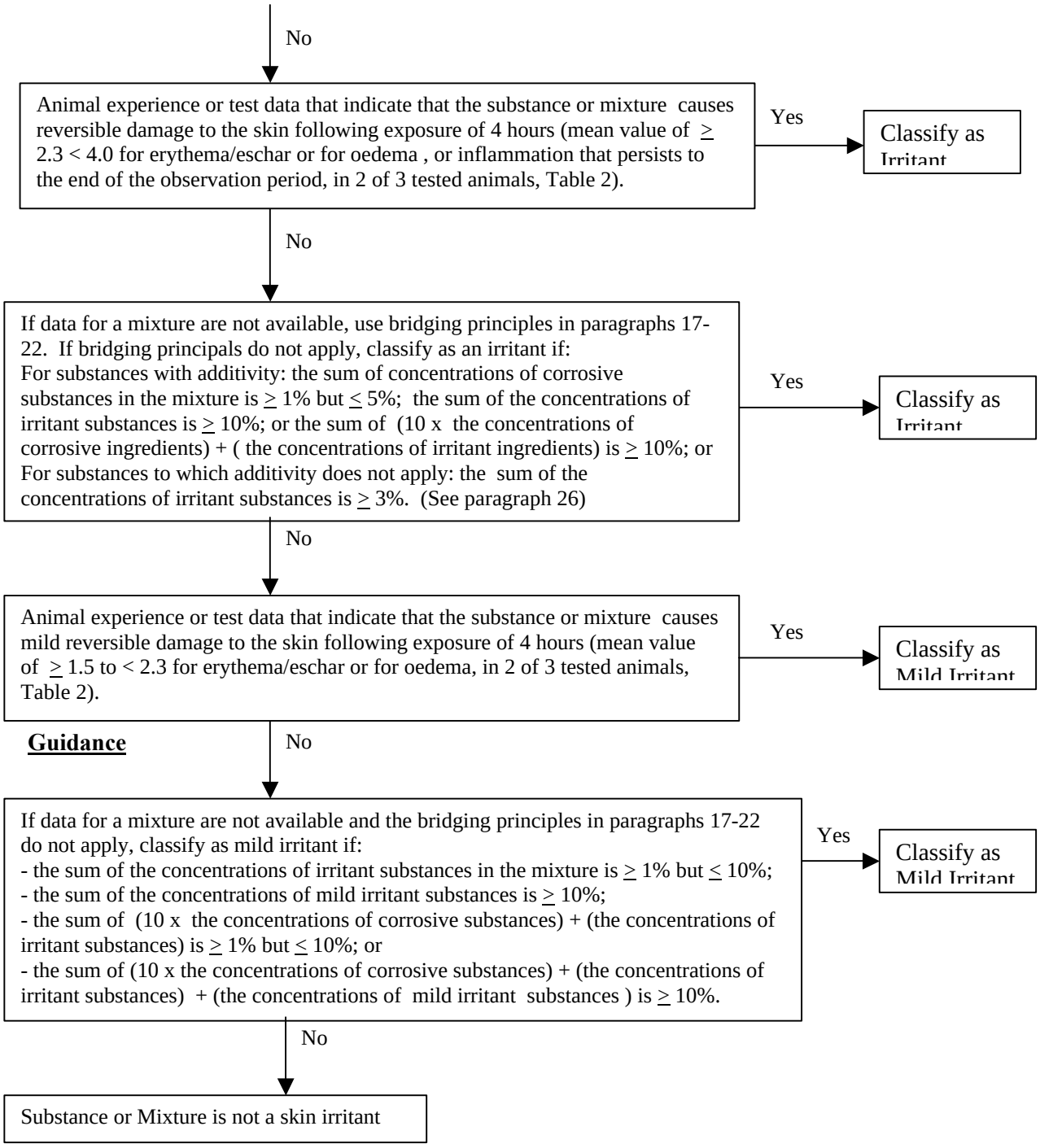
	Category 1			**Category 2**	**Category 3**
	1A	1B	1C		
Symbol	Corrosion	Corrosion	Corrosion	Exclamation mark	No symbol is used
Signal Word	Danger	Danger	Danger	Warning	Warning
Hazard Statement	Causes severe skin burns and eye damage	Causes severe skin burns and eye damage	Causes severe skin burns and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

Decision Logic for skin Corrosion/irritation:



Continuation - Decision Logic for skin Corrosion/irritation:





Classification and Labelling Summary for Skin Corrosion/irritation

If the substance or mixture meets one of the following criteria, classify and use corresponding communication elements. If the criteria are not met then the substance or mixture need not be classified.

Class	**Criteria** (See Figure 1 for detailed decision tree).	**Hazard Communication Elements**

Category 1 Corrosive Some authorities use sub-categories A, B, and C; see Table 1	• Human experience showing irreversible damage to the skin; • Structure/activity or structure property relationship to a substance or mixture already classified as corrosive; • pH extremes of ≤ 2 and ≥ 11.5 including acid/alkali reserve capacity; • Positive results in a valid and accepted *in vitro* dermal corrosion test; or • Animal experience or test data that indicate that the substance/mixture causes irreversible damage to the skin following exposure of up to 4 hours (See Table 1 for subcategorization and details) If data for a mixture are not available, use bridging principles in paragraphs 17-22. If bridging principals do not apply, classify as corrosive if the sum of the concentrations of corrosive substances in the mixture is ≥ 5% (for substances with additivity), or ≥ 1% (for substances to which additivity does not apply). See paragraph 26..	*Signal Word*	Danger (all subcategories A, B, or C)
		Symbol	Corrosive symbol (all subcategories A, B, or C)
		Hazard Statement	Causes severe skin burns and eye damage (all subcategories A, B, or C)
Category 2 Irritant (applies to all authorities)	• Human experience or data showing reversible damage to the skin following exposure of up to 4 hours; • Structure/activity or structure property relationship to a substance or mixture already classified as an irritant; • Positive results in a valid and accepted *in vitro* dermal irritation test; or • Animal experience or test data that indicate that the substance/mixture causes reversible damage to the skin following exposure of up to 4 hours , mean value of ≥ 2.3 < 4.0 for erythema/eschar or for oedema , or inflammation that persists to the end of the observation period, in 2 of 3 tested animals (Table 2). If data for a mixture are not available, use bridging principles in paragraphs 17-22. If bridging principals do not apply, classify as an irritant if: • For substances with additivity: the sum of concentrations of corrosive substances in the mixture is ≥ 1% but ≤ 5%; the sum of the concentrations of irritant substances is ≥ 10%; or the sum of (10 x the concentrations of corrosive ingredients) + (the concentrations of irritant ingredients) is ≥ 10%; or • For substances to which additivity does not apply: the sum of the concentrations of irritant substances is ≥ 3%. (See paragraph 26)	*Signal Word*	Warning
		Symbol	Exclamation mark
		Hazard Statement	Causes skin irritation
Category 3 Mild Irritant (applies to some authorities)	• Animal experience or test data that indicates that the substance/mixture causes reversible damage to the skin following exposure of up to 4 hours, mean value of ≥ 1.5 < 2.3 for erythema/eschar in 2 of 3 tested animals (See Table 2) If data for a mixture are not available and the bridging principles in paragraphs 17-22 do not apply, classify as mild irritant if: • the sum of the concentrations of irritant substances in the mixture is ≥ 1% but ≤ 10%; • the sum of the concentrations of mild irritant substances is ≥ 10%; • the sum of (10 x the concentrations of corrosive substances) + (the concentrations of irritant substances) is ≥ 1% but ≤ 10%; or • the sum of (10 x the concentrations of corrosive substances) + (the concentrations of irritant substances) + (the concentrations of mild irritant substances) is ≥ 10%.	*Signal Word*	Warning
		Symbol	None
		Hazard Statement	Causes mild skin irritation

EXAMPLES:

Will be provided later this week.