COMMITTEE OF EXPERTS ON THE TRANSPORT OF DANGEROUS GOODS AND ON THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS

Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals

Eighteenth session
Geneva, 9 – 11 December 2009
Item 2 (b) of the provisional agenda

UPDATING OF THE THIRD REVISED EDITION OF THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS (GHS)

Health hazards

Correspondence group on the revision of Chapters 3.2 and 3.3

Transmitted by the expert from Germany
on behalf of the informal correspondence group

Background

1. The programme of work for the biennium 2009-2010 includes the following item:

   - Editorially revise GHS Chapters 3.2 and 3.3 to improve clarify and enhance user-friendliness in the application of the criteria;

   - Examine whether particular criteria need further alignment/adjustment with respect to the internal consistency of Chapters 3.2 and 3.3 and develop proposals for any minor necessary amendments;

2. This paper updates the Sub-Committee on the correspondence group's ongoing work.

Activities

3. The correspondence group (CG) took up the work in February 2009. Up to now, four rounds of written commenting were carried out. The CG has had two face-to-face meetings at the 16th session of the UN SCE GHS. A comprehensive list of discussion points had been compiled, commented and discussed. On several points, a preliminary consensus could be achieved. The first aim is to sort out these issues where a direct consensus can be found (e.g. to achieve consistency in terminology within and between chapters 3.2 and 3.3). More complicate issues will have to be clarified during further discussions.

4. The current state of discussion is reported in the annexes which contain all current versions of the discussion papers distributed in the CG so far.

Annex 1

Paper 0:_Overview_status of work_september 2009.doc:

Correspondence group editorial revision of Chapters 3.2 and 3.3

Overview on the distributed discussion papers
(15 September 2009)

No.	Paper name	Content
a	02E92424.PDF	OECD SERIES ON TESTING AND ASSESSMENT Number 16 Detailed Review Document on Classification Systems for Skin Irritation/Corrosion in OECD Member Countries
b	02E92423.PDF	OECD SERIES ON TESTING AND ASSESSMENT Number 14 Detailed Review Document on Classification Systems for Eye Irritation/Corrosion in OECD Member Countries

No.	Paper name	Content	CG: what to do / which deadline?
1	1_Compiled Comments on UN GHS chapters 32_33_september 16 2009.doc	Compiled Comments of all discussion points; amended after 17th session	CG to discuss/agree at face to face meeting at the 18th session of UN SCE GHS

Papers 2-4 include and report the consequential changes of those points that were agreed by the CG at the 17th session.

No.	Paper name	Content	CG: what to do / which deadline?
2	2_GHS Chapter-3-2 rev3_CG_agreed edit2.doc	GHS Chapter-3-2 containing ONLY those changes agreed at 17th session (track changes)	CG to discuss/agree at face to face meeting at the 18th session of UN SCE GHS
3	3_Changes introduced into 3.2.doc	Paper listing the changes introduced into 'GHS Chapter-3-2 rev3_CG_agreed edit1.doc'	CG to discuss/agree at face to face meeting at the 18th session of UN SCE GHS
4	4_GHS Chapter-3-3 rev3_CG_agreed edit2.doc	GHS Chapter-3-3 containing ONLY those changes agreed at 17th session (track changes)	CG to discuss/agree at face to face meeting at the 18th session of UN SCE GHS
5	5_Changes introduced into 3.3.doc	Paper listing the changes introduced into 'GHS Chapter-3-3 rev3_CG_agreed edit1.doc'	CG to discuss/agree at face to face meeting at the 18th session of UN SCE GHS

Papers 6-9 are based on the previous papers GHS Chapter-3-2 rev3_3rd_change.doc and GHS Chapter-3-3 rev3_3rd_change.doc which have been circulated before but neither discussed nor agreed. They shall serve as discussion papers for the further alignment work on chapters 3.2 and 3.3.

They were prepared taking into account the following discussion points:

- Change of order of the text as proposed by US OSHA. Under GHS 3.2.1 and GHS 3.3.1. text complied from existing text in the GHS was added to make the general classification strategy clear (tiered approach vs. weight of evidence) as proposed by UK (S1 and E1 of '1_Compiled Comments on UN GHS chapters 32_33_september 16 2009.doc');

- The advice relating to testing strategy was deleted. It also became evident that the criteria text of GHS 3.2.2 vs. GHS 3.3.2 is inconsistent and needs alignment. These paragraphs are hard to survey in track change mode and are also supplied as 'clean' versions for better survey (papers 7 and 9 in table below);

- Figures 3.2.1 and 3.3.1 are deleted for better survey and because the CG concluded that they need amendment (AISE has drafted proposal, see papers 11 to 16);

- Moreover, a thought starter how to classify on the basis of tests with more than 3 animals has been added (paper 10).

No.	Paper name	Content	CG: what to do / which deadline?
6	6_GHS Chapter-3-2 rev3_4th_change_for discussion.doc	Discussion paper including changes to chapter 3.2 described above this table.	CG to discuss at face to face meeting at the 18th session of UN SCE GHS
7	7_GHS 3-2-2_4th_change_for discussion_clean.doc	GHS 3.3.2 copied from 'GHS Chapter-3-2 rev3_4th_change_for discussion.doc' but without track changes for better survey.	
8	8_GHS Chapter-3-3 rev3_4th_change_for discussion.doc	Discussion paper including changes to chapter 3.3 described above this table.	
9	9_GHS 3-3-2_4th_change_for discussion_clean.doc	GHS 3.3.2 copied from 'GHS Chapter-3-3 rev3_4th_change_for discussion.doc' but without track changes for better survey.	
10	10_skin_eye_evaluation data more than 3 animals_draft08Sept09.doc	Thought starter: Guidance on classification: how to use data from tests with more than 3 animals?	
11	11_Skin_corr_irrit_substances_CLP guidance_decision logic.doc	Decision logics skin substances; taken from RIP3.6 guidance on the European GHS regulation	
12	12_Skin_corr_irrit_mixtures_CLP guidance_decision logic.doc	Decision logics skin mixtures; taken from RIP3.6 guidance on the European GHS regulation	
13	13_Skin_corr_irrit_extreme pH_CLP guidance_decision logic.doc	Decision logics skin extreme pH; taken from RIP3.6 guidance on the European GHS regulation	
14	14_Serious Eye Dam_eye irrit_substances_CLP guidance_decision logic.doc	Decision logics eye substances; taken from RIP3.6 guidance on the European GHS regulation	
15	15_Serious Eye Dam_eye irrit_mixtures_CLP guidance_decision logic.doc	Decision logics eye mixtures; taken from RIP3.6 guidance on the European GHS regulation	
16	16_Serious Eye Dam_eye irrit_extreme pH_CLP guidance_decision logic.doc	Decision logics eye extreme pH; taken from RIP3.6 guidance on the European GHS regulation	

Annex 2

Paper 1_Compiled Comments on UN GHS chapters 32_33_september 2009.doc:

UN SCE GHS Correspondence group on GHS chapters 3.2 and 3.3

Commented compiled comments, 4th round of comments

(15 September 2009)

The issues below shaded in grey are those were a consensus was found at the CG meeting at the 17th session. These issues will be compiled in a first proposal to change the text in chapters 3.2 and 3.3.

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	**Comment/Motivation/Proposal**
Chapters 3.2 and 3.3: ISSUES AND COMMENTS RELATED to both chapters					
B1	**15/INF.5/3**	The GHS classification strategy is such that it uses all relevant existing data for classification purposes. The GHS does not generally aim at giving recommendations or advice on testing strategies. However, in the classification criteria text of the chapters skin corrosion/irritation and serious eye damage/eye irritation there are several elaborations on advice on testing strategy. Similar advice is not found in the GHS for any other hazard class. It should be discussed whether the chapters skin corrosion/irritation and serious eye damage/eye irritation would not be more user-friendly if the testing recommendations would be strongly reduced in the text on classification criteria. *(This point had also been addressed at the OECD workshop in Bern 2007: "For Skin Corrosion/Irritation and Serious Eye Damage/Eye Irritation [GHS Chapter 3.2], the flow chart 3.2.1 (and also 3.3.1) provides a mixture of test and classification strategy and is thus confusing for the self-classifier, e.g., there is no possibility to go for non-classification with a negative in vitro test.")* *Proposal 17.4.09:* amend the text to avoid wording on testing strategy and testing requirements as far as possible. *Amended proposal 29.05.09* Include advice on classification strategy and the correct consideration of all relevant information in the decision logics. **CG meeting conclusion at 17th UN SCE GHS session** Step 1) delete testing strategy advice from figs. 3.2.1 and 3.3.1. Amend figs. to current GHS requirements. WC (AISE) to draft proposal for figs. 3.2.1 and 3.3.1. Step 2) discuss where to place amended figs. 3.2.1 and 3.3.1 by taking into account the information covered in the decision logics		**Y: SDA, UK, exECB, BE, ECHA, FIN, BASF** **Neutral: AUS**	BE : the GHS generally does not contain information on testing strategies for other hazard classes because the situation is different. There are alternative tests available for skin corrosivity and as animal welfare is a concern in the GHS, such testing schemes starting with non-animal observations/measurements were included as part of the classification system (see general considerations: 1.3.2.4.6 Animal welfare). If we delete the testing strategy, we should try to reflect correctly the necessity to consider all the information available on the substance and to emphasize the necessity to consider non-animal observation/measurements, including in-vitro testing methods. All the experience gained in this field should not be lost. **ECHA:** However, any advice on classification strategy should be retained.
B2	**HFleig_31_3**	There are still a few remnants of Testing strategy or references to (e.g. 3.2.3.1.1 and 3.2.5.1/3.2.5.2/3.3.5.1....) **CG meeting conclusion at 17th UN SCE GHS session** delete testing strategy advice from criteria text in chapters 3.2 and 3.3		**Y: SDA** **Neutral: AUS**	**TG:** also 3.2.3.3.5 and 3.3.3.3.5, in 3.2.3.1.1 no change needed and in 3.2.5.2 not found. revised in GHS Chapter-3-2 rev3_2nd_change.doc and GHS Chapter-3-3 rev3_2nd_change.doc

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	**Comment/Motivation/Proposal**
Chapters 3.2 and 3.3: ISSUES AND COMMENTS RELATED to both chapters					
B3	**15/INF.5/4**	Moreover, the contents of figures 3.2.1 and 3.3.1 are unique for the hazard classes skin corrosion/irritation and serious eye damage/eye irritation; analogous figures are not found in the GHS for any other hazard class. Moreover, there is a partial overlap of these figures with the decision logics of skin corrosion/irritation and serious eye damage/eye irritation. This impairs the user-friendliness of the GHS as paralleling information located at different text passages has to be taken into account in the classification process.	Figs 3.2.1 and 3.3.1	**Y: UK, ECHA, SDA, DE, HFleig, exECB, AISE, BE, FIN, BASF** **Neutral: US OSHA, AUS** (agree with US OSHA comment)	**UK:** We agree that it is not necessary to include figures 3.2.1 and 3.3.1. They present a testing strategy that is not necessary for the GHS classification criteria and the bulk of the information is already contained within the text anyway. If the figures are deleted these points are no longer relevant. **ECHA**: it should be taken care that any guidance valuable for evaluation of data and classification is included in proper places of the text and not lost with the deletion. **HFleig**: like ECHA I think we should keep therefrom all valuable elements with respect to evaluation, especially clear hierarchy principles. There are e.g. also classification principles in the strategy (Figure 3.3.1 :1c) which cannot be found as such in the criteria: Skin irritant--> deemed to be Cat 2 Eye irritant without evaluation of effects on eyes). There are many substances classified as Skin irritants but not as Eye irritants. - Furthermore there are by now no validated OECD in vitro test methods exist for Eye testing (cf.3.3.3.1.) **US OSHA**: As a minimum, we need to ensure that there is consistency between what is presented in the explanatory text in 3.2.2 an 3.3.2, the figures (if they remain in some form) and the flow-diagram at the end of the chapters. 5/22/09-US OSHA: There is clearly a
	15/INF.5/5a	Figures 3.2.1 and 3.3.1: In both figures, the question is whether the steps 1a-c are needed; the strategy of data use (e.g. human data have precedence over animal data, if no data are available SAR may be applied) for classification is general advice and used for classification in each hazard class and does not need to be specifically mentioned in figures 3.2.1 and 3.3.1. Moreover, these points are already addressed in 3.2.2.2 and 3.3.2.4, respectively			
	15/INF.25/3.5	For skin corrosion/irritation and serious eye damage/eye irritation the flow diagrams 3.2.1 and 3.3.1 respectively address the hierarchy of data use (e.g. human data have precedence over animal data) in steps 1a – c for classification purposes. It is suggested that as this is a general strategy it does not need to be specifically mentioned here (Ref 3).			
	15/INF.25/3.6	Step 2 in flow diagram 3.2.1 for skin corrosion/irritation may not be needed, as the possibility to use SAR is already mentioned in the criteria text in 3.2.2.2 (Ref 3). (The same is also true for step 2 in flow diagram 3.3.1 for serious eye damage/eye irritation as the possibility to use SAR is already mentioned in the criteria text in 3.3.2.4). Proposal 17.4.09: delete Figures 3.2.1 and 3.3.1 *Amended proposal 29.05.09:* Discuss: WOE vs tiered approach/hierarchy **CG meeting conclusion at 17th UN SCE GHS session** See B2 with respect to figs 3.2.1 and 3.3.1 The hierarchy in data use is that human data have precedence over animal data, then comes other data. IN case the criteria cannot be directly applied, a weight of evidence approach considering all data has			

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	Comment/Motivation/Proposal
Chapters 3.2 and 3.3: ISSUES AND COMMENTS RELATED to both chapters					
		to be applied.			tension between WOE and the tiered evaluation. What is it about these hazard classes that lend them to a hierarchy of data evaluation? Human and animal data take precedence. Are all other data types equal for these classes or are some more 'valid' than others?
B4	**HFleig_31_3**	What kind of data are necessary to exonerate extreme pH with and without proof of buffer capacity? Proposal 17.4.09 amended and agreed at **CG meeting at 17th UN SCE GHS session**: following phrase copied from 3.2.3.1.2 to 3.2.2.2: "A mixture is considered corrosive (Skin Category 1) if it has a pH ≤ 2 or a pH ≥ 11.5. If consideration of alkali/acid reserve suggests the substance or mixture 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."	**3.2.2.~~5.1~~2**	**Y: BE, AUS** **N: BASF**	**TG: phrase copied from 3.2.3.1.2 to 3.2.2.2~~5.1~~: A mixture is considered corrosive (Skin Category 1) if it has a pH ≤ 2 or a pH ≥ 11.5.** BASF: 3.2.2.5.1 deals with irritation not corrosion. TG Response: 3.2.2.5.1 corr to 3.2.2.2
	US_1_4	Consistency between the chapters is important. **CG meeting conclusion at 17th UN SCE GHS session: agreement**		**Y: SDA**	
B5	**US_1_4**	We'll need to make sure we are working off the new bridging principles language agreed at the last S/C meeting (from the mixtures work). July 2009: Checked and done		**Y: SDA** **Neutral: AUS, BASF**	TG: the used text versions were supplied by the Secretariat after revision to represent rev.3 of UN GHS. Some minor points had to be and were inserted (will be included in the documents GHS Chapter-3-2 rev3_3rd_change.doc and GHS Chapter-3-3 rev3_3rd_change.doc distributed after the 17th session to the CG)

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	**Comment/Motivation/Proposal**
Chapters 3.2 and 3.3: ISSUES AND COMMENTS RELATED to both chapters					
B6	**15/INF.25/3.8** **15/INF.5/11** **FIN 17/3**	It is not clear which are the criteria when the additivity principle for corrosivity apply/do not apply, as there seems to be some conflict between paragraphs 3.2.3.3.3/Table 3.2.4 and 3.2.3.3.4. It is suggested that further guidance would be useful (Ref 4). *(Note: The same applies for serious eye damage/eye irritation).* To date there are no firm criteria or specific guidance when to apply the non-additivity approach in the process of classifying a mixture. We cannot assume that an average classifier of a mixture is able to judge in which case an additivity or non-additivity approach has to be chosen. Therefore we suggest to give more guidance for selection between additivity and non-additivity. Alternatively, it should be discussed whether and how the removal of the non-additivity approach as a whole from the chapters 3.2 and 3.3 could be envisaged without lowering the level of protection. Proposal 17.4.09: develop guidance **CG meeting conclusion at 17th UN SCE GHS session** Point needs further discussion Examples are considered to be helpful	3.2.3.3 (skin) 3.3.3.3 (eye)	**Y: HFleig, UK, exECB, AISE, BE, ECHA, FIN, BASF** **N: SDA,** **AUS**(agree with SDA)	**UK:** It would be useful to provide more information, both in the Purple Book and in associated guidance, as it is very unclear when the additivity approach should or should not be used. **SDA**: Paragraph 3.2.3.3.4 in combination with paragraphs 3.2.3.3.5 and 3.2.3.3.6 appear to provide sufficient guidance. Further guidance does not appear to be useful. 5/22/09-US OSHA: Example 5 of ST/SC/AC.10C.4/2008/23 was intended to assist with this concept. Is further guidance needed?
	~~15/INF.5/9~~	~~The term "structure- property relationship" is not commonly used and it is only used in the GHS chapters 3.2 and 3.3. It has got the same meaning like the more common term "structure-activity relationship". Instead, the term (Q)SAR is the term commonly used. The use of common terminology may be discussed.~~			~~Already solved. see UN GHS rev.3~~

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	**Comment/Motivation/Proposal**
Chapters 3.2 and 3.3: ISSUES AND COMMENTS RELATED to both chapters					
B7	**15/INF.25/3.11** **15/INF.5/12**	For eye irritation, classification criteria are provided in Table 3.3.1 and 3.3.2 for a 3-animal test. Clarification is required on how to interpret results for classification purposes when the test has not been conducted in 3 animals (Ref 4). *(Note: The same applies for skin irritation*[TG1]*).* Proposal 17.4.09: develop guidance **CG meeting conclusion at 17th UN SCE GHS session:** WC (AISE) to draft proposal		**Y: UK, SDA, US OSHA, HFLeig, exECB, AISE, BE, ECHA, FIN, AUS, BASF**	**UK:** Agree, there is currently nothing in the criteria for tests that don't use 3 animals; it would be useful to incorporate this information into the chapters. **SDA**: Clarification of how to use data when more than 3 animals were used would be helpful. Some guidance will be straight forward, such as use the same proportion of 2 out of 3 animals to classify when six animals are used (e.g., 4 out of 6 animals should lead to classification). U.S. EPA's guidance, which was presented at the OECD classification workshop in Bern, could be a helpful starting point.
B8	**15/INF.5/ Further issues b)** **FIN 17/3**	In the course of classifying for skin and eye irritation, ingredients which are skin or eye Cat.1 are weighted with a factor 10. This means that these ingredients are considered to be one order of magnitude more potent skin or eye irritants than Cat. 2 substances (see GHS tables 3.2.3 and 3.3.3). On the other hand, 3.2.3.3.1 and 3.3.3.3.1 set 1% for the " relevant ingredients"which have to be generally considered for classification which applies for both Cat. 2 and Cat. 1 skin and eye irritants. A possible solution would be to set 0. 1% as general " relevant ingredient" for Cat. 1 ingredients. The principle to weight the ingredients of Cat 1 by factor 10 (Tables 3.2.3 and 3.3.3; e.g. "(10 × Skin Corrosive Category 1A, 1B,1C) + Skin irritant Category 2") seems to be inconsistent in the light of a general limit for a "relevant ingredient" of 1%. For instance, if we multiply the >1% concentrations by factor 10, it will in every case drop in the >10%, Cat 2 (see Tables 3.2.3 and 3.3.3) for the mixture. However, this operation does not provide any added value because in the concentration range of 1-5%, Cat 2 for the mixture applies automatically; this originates from Cat 1-ingredients which are present in the mixture in a concentration over the "relevant ingredient"-level,		**Y: FIN, exECB, AISE, BE, ECHA** **Y**, but discuss**: UK** **N: SDA, , BASF, HFLeig, AUS**(needs more consideration)	**UK:** The weighting factor of 10 is confusing, especially as the cut-off for relevant ingredients is currently 1% (if a Cat 1 ingredient is present above 1% and <3% it is classified into Cat 2 anyway (table 3.3.3)). Lowering the cut-off for Cat 1 to 0.1% could be one way to make this clearer, although 3.3.3.1 does state that ingredients present at lower concentrations can be considered where still relevant for classification (e.g. corrosive substances). The approach needs more consideration, as it could result in more mixtures being classified as irritants than at present. **UK: additional comment** - lowering the cut-off to 0.1% would need careful consideration and may not be the best

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	Comment/Motivation/Proposal
Chapters 3.2 and 3.3: ISSUES AND COMMENTS RELATED to both chapters					
		but below 5%. Over 5% the mixture is classified again as Cat 1. Therefore, the statement in 3.2.3.3.2 "A weighting factor of 10 is used for corrosive components when they are present at a concentration below the generic concentration limit for classification with Category 1 (i.e. 5%), but are at a concentration that will contribute to the classification of the mixture as an irritant." needs further clarification and guidance. The same problem holds true for effects on the eye in 3.3.3.3. As a way forward one could imagine that if the limit for a "relevant ingredient" would be set down to 0.1%, the 10x rule could then reasonably take account of the sum of skin / eye Cat 1 and skin/eye Cat 2A/B ingredients. One could further discuss whether the lowering of the "relevant ingredient" to 0,1% could also cure the open issue pointed out in point 1. Proposal 17.4.09: discuss the lowering of the "relevant ingredient" to 0,1% for skin corrosives **CG meeting conclusion at 17th UN SCE GHS session.** Point needs further discussion Examples are considered helpful			approach. **SDA**: If a substance is corrosive, 1% is relevant as corrosive, and ten times more potent as irritant. As presented, the text and tables appear to appropriately consider corrosive or irritant substances and do not require future modifications. **AISE**: Agree that discussion on 3.2.3.3.1 / 3.3.3.1 would be useful but in terms of say introducing the specific concentration limit as an indicator as to whether an ingredient is relevant (i.e. SCL indicates ingredient is corrosive or irritant below 1%) rather than lowering the relevant ingredient level to 0.1% for all skin corrosives.
B9	**15/INF.5/ Further issues c)**	There is an inconsistency in the criteria for mixture classification (both skin and eye) in case the non-additivity approach applies. Imagine there is a mixture A containing one ingredient (a surfactant) with Skin Cat. 2 at 5%. This mixture does not contain any other skin irritant/corrosive ingredients. Mixture A will be classified as Skin Cat. 3. Imagine a second mixture B which is mixture A with another ingredient at 1.5%, classified as Skin Cat. 2. Imagine there is data showing non-additivity applies. Mixture B will be classified as Skin Cat. 2 as the concentration limit is 3% for non-additivity because of the 5% surfactant which warranted classification as Skin Cat. 3 in mixture A. **CG meeting conclusion at 17th UN SCE GHS session**		**Y: UK, exECB, ECHA, FIN** **Neutral: SDA, BASF** **Neutral: AUS** (agree with SDA comments)	**UK:** Again agree that clarification on the use of the additivity approach is required. It may be appropriate to include more information in both the Purple Book and in associated guidance documents. **SDA**. The classification tables and associated text based on % content and multiplication factors present numerous challenges for classifiers. They generally lead to incorrect classification – usually over classification. In view of developments of in vitro methods, bridging principals, and weight of

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	**Comment/Motivation/Proposal**
Chapters 3.2 and 3.3: ISSUES AND COMMENTS RELATED to both chapters					
		Very rare data constellation Point not discussed as considered not to be priority			evidence analysis, guidance on how to use these other approaches rather than the concentration limits and multiplication factors could be helpful. **FIN:** "Mixture A will not be classified as the concentration limit is 10%": Agree, not for Cat. 2, however should be classified as Cat. 3 (assuming, that the ingredient is to be classified according Table 3.2.3: Cat. 3: 1-10%). Response TG: Example corrected according to FIN comment.
B10	**US_1_4**	The footnotes under Tables 3.2.1 and 3.3.1 should both refer to paragraphs 1.1.2.5(c) in addition to 1.3.2.4.7. **CG meeting conclusion at 17th UN SCE GHS session:** agreed.	**Tables 3.2.1 and 3.3.1**	**Y:SDA, FIN** **Neutral: AUS**	
B11	**US_1_4**	Is guidance needed to explain what is meant by "human experience" and "animal observations" versus human or animal data? Human or animal "data" seems pretty clear. Proposal 17.4.09: avoid the terms "human experience" and "animal observations" where possible **CG meeting conclusion at 17th UN SCE GHS session** agreed		**Y:SDA, exECB, ECHA, FIN, AUS, BASF** **Neutral : BE**	**BE** : these terms were used to design something different. Sometimes the term "animal experience" was also used by opposition to the "animal testing data". If we delete the terms "human experience", "animal experience" and "animal observations" and use only the global terms "human data" and "animal data", the following question does not need to be discussed. **TG:** animal observation appears only once in the criteria text of chapter 3.2, and twice in the decision logics of 3.2 and 3.3, respectively.

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	Comment/Motivation/Proposal
Chapters 3.2 and 3.3: ISSUES AND COMMENTS RELATED to both chapters					
B12	**US_1_4**	When does human experience or animal observation that may be positive trump animal data that is negative? Proposal 17.4.09: discuss point. **CG meeting conclusion at 17th UN SCE GHS session** See B3		**Y: SDA, HFLeig, BE, ECHA, FIN, AUS, BASF**	
B13	**15/INF.5/Further issues d)**	d) In case a substance is classified as skin Cat.1, a parallel classification with Eye Cat.1 is superfluous as this information is already included in the hazard statement for skin Cat. 1 (Causes severe skin burns and eye damage). **Already done in rev.3, see 1.4.10.5.3.3.**		**Y: UK, SDA, US OSHA, HFLeig, ex-ECB, AISE, ECHA, FIN, AUS, BASF**	**TG:** EU GHS regulation: "Skin corrosive substances shall be considered as leading to serious damage to the eyes as well (Category 1), while skin irritant substances may be considered as leading to eye irritation (Category 2) (added before last sentence in UN GHS 3.3.2.4)."
B14	**SDA_31_03**	As an initial step, we suggest that the decision logics be modified to remove the sub-bullets (e.g., a through f) in all the boxes in order to have the user focus on the text in chapters 3.2 and 3.3. As reminded in the GHS text, the decision logics are not part of the harmonized system. Although they are intended to be guidance, if they are not clear, then readers should rely on the text. Proposal 17.4.09: revise and amend all decision logics (especially as Figs. 3.2.1 and 3.3.1 will be deleted) **CG meeting conclusion at 17th UN SCE GHS session.** To be discussed together with B1.	Dec. logics 3.2 and 3.3	**Y: UK, HFleig; AISE, BE** **Neutral: AUS** (prefer not delete tables)	**AISE**: Suggest could also address the 'additivity does/doesn't apply' issue at the same time
B15	**HFleig_31_3**	Avoid " animal experience", better "data"(cf. ECHA).- **CG meeting conclusion at 17th UN SCE GHS session:** agreed.		**Y: SDA, AISE, ECHA, FIN, AUS**	**TG: 'animal experience'** appears once both in 3.2 and 3.3 in ..rev3_2nd change.doc.
B16	**HFleig_31_3**	Better "bases" than " caustic alkalis" **CG meeting conclusion at 17th UN SCE GHS session:** agreed	3.3.2.5	**Y: SDA, AISE, ECHA, FIN** **Neutral: AUS**	**TG: 'caustic alkalis'** appears once both in 3.2 and 3.3

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	Comment/Motivation/Proposal
Chapters 3.2 and 3.3: ISSUES AND COMMENTS RELATED to both chapters					
B17	**HFleig_31_3**	Better "chemicals" than "agents" **CG meeting conclusion at 17th UN SCE GHS session:** agreed. Take care whether "agents" refers to only to substances and not to mixtures.		**Y: SDA, ECHA, FIN, AUS**	**TG:** "agents" appears once both in 3.2 and 3.3 in ..rev3_2nd change.doc. general point. Also related to other hazard classes. Discuss separately? **IN:** We agreed in a way last meeting (UN/SCEGHS/16/INF.10) to use the term "chemicals" as a substitute for "substance", "mixture" or "substance and mixture", in case we want to capture them all. TG: "agents" appears in substance classification criteria part once both in 3.2 and 3.3 in ..rev3_2nd change.doc. Better to substitute "agent" with "substance"?
B18	**AISE_10_09**	Various forms of the term 'acid/alkaline reserve' (e.g. alkali/acid, acid/alkali) are used. Proposal: adopt 'acid/alkaline' as the standard terminology (this form is already used in some parts of Chapter 3.3).		**Y: UK, FIN, BE, ECHA, BASF, HFl**	
B19 (former S2)	**15/INF.5/10**	The last sentence in 3.2.3.1.2 reads as follows (similar for eye in 3.3.3.1): "If consideration of alkali/acid reserve suggests the substance or mixture 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." This sentence is only included in the chapter on mixture classification criteria. It is not included in the substance classification criteria. Thus, it is not clear whether it also relates to substance classification. Proposal 17.4.09 and 10.09.09: The respective sentences were added to 3.2.2.2 and 3.3.2.4 (see GHS Chapter-3-2 rev3_2nd_change.doc). See B4		**Y: SDA, HFleig, BE, AUS**	**UK: A negative result in an appropriate in vitro test that can reliably identify non corrosives/irritants should be sufficient for classification purposes without the need for confirmatory in vivo testing. If figure 3.2.1 is removed then the remaining text should allow for classification to be based on the appropriate in vitro testing only.** **SDA: The sentence on consideration of alkali/acid reserve should be added to the substance classification criteria. (See addition of that text in attached modified paragraph 3.2.2.2 in chapter 3.2.)**

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	Comment/Motivation/Proposal
Chapter 3.2 - ISSUES AND COMMENTS RELATED to Skin corrosion/irritation					
S1	**15/INF.5/ Further issues e)**	As we all know, the chapters are confusing as they discuss a weight-of-evidence approach for classification while also providing what appears to be a rigid hierarchy for existing data. It becomes very confusing to determine if there is a priority for human and animal data, and how weight-of-evidence is to be applied. In Chapter 3.2, Rev 2, the definitions for skin corrosion and irritation are set in paragraph 3.2.1 (and are supported by Tables 3.2.1 and 3.2.2). A point of confusion in this chapter is that Section 3.2.2 in the current version goes immediately to a discussion of weight of evidence and "Several factors that should be considered in determining the corrosion and irritation potential of chemicals..." and so on. It would make sense to remove this weight-of-evidence language from Section 3.2.2 and instead present Tables 3.2.1 and 3.2.2 which correspond to and support the definitions. The weight of evidence language and the tiered approach could follow in a new Section 3.2.3 and be entitled something like, "Weight of Evidence Approach When No Clear Data Exists for Substances" or "Classification criteria for substances using other data elements." This section would include all the factors listed in the current (Rev 2) paragraphs 3.2.2.2 and 3.2.2.3. Next is mixtures. Of course, when data is available for the complete mixture, it would be classified using the criteria for substances. Bridging Principles would not change. Classification of mixtures when data is only available for some ingredients, would also not change. That would complete the chapter. Proposal 17.4.09: Discuss issue at face to face meeting Possible solutions: i) keep order as is ii) change order as proposed by US OSHA and add a general introduction to the chapter **CG meeting conclusion at 17th UN SCE GHS session** Change order but take care that the order of precedence of data use is clear after this restructurisation.		**Y: SDA, BE, ECHA, FIN, AUS, BASF**	**UK:** as the chapters are now presented (docs GHS Chapter-3-2 rev3_1st_change.doc and GHS Chapter-3-3 rev3_1st_change.doc) they seem to suggest a preference for animal data over other data. For example the opening sentence in 3.2.2.2 states "Several factors should be considered in determining the corrosion and irritation potential of substances in case the criteria described above cannot be applied". This implies that you should consider the animal test data first, and then if that is not applicable look to other information, including human data. The text goes on to make it clear that there is a need to consider a weight-of-evidence approach even when test data are available e.g. the last paragraph in 3.2.2.2 states 'Generally, primary emphasis should be placed upon existing human experience and data, followed by animal experience and testing data' but perhaps more consideration needs to be given to the structure and presentation of these Chapters. In addition, the paragraphs under the heading 'Classification criteria for substances using other data elements' do not currently contain any criteria as such, i.e. they do not tell you how to classify a substance. For example, they do not set out the corrosive category that should be assigned to a substance with a pH of < 2.

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	Comment/Motivation/Proposal
Chapter 3.2 - ISSUES AND COMMENTS RELATED to Skin corrosion/irritation					
					SDA: The proposed revisions to Chapters 3.2 and 3.3 that appear to account for the proposal to restructure chapters 3.2 and 3.3 are appropriate. **BE:** we share the opinion of UK. This restructuration, like proposed, would place primary emphasis on animal testing data to classify substances when the criteria can be applied to these data. I can accept this proposal but to avoid any contradiction in the section renamed "Classification criteria for substances using other data elements" it would be necessary to revise some other parts of the text, e.g. at the end of the section, it is said that primary emphasis should be placed upon existing human experience and data, followed by animal experience and testing data. I suppose this should no more be the case as testing data will firstly be considered for the classification of the substance. n.b.: the title "corrosion" should not be deleted **ECHA:** We suggest that as analogous sentences the one in chapter 3.2 " 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." should replace the one in the revised chapter 3.3. We think that this issue would fit better under some kind of 'introduction' than

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	Comment/Motivation/Proposal
Chapter 3.2 - ISSUES AND COMMENTS RELATED to Skin corrosion/irritation					
					classification criteria in case the overall structure would however be changed as suggested. Keeping the current order of chapters the issues would be presented in a more logical order. In addition to that we are in favour of keeping the chapter headings, especially "Classification criteria for substances" because the criteria should not be linked to identification and evaluation of data. To our understanding the corrosion subheading should remain.
S2	**15/INF.5/10**	The last sentence in 3.2.3.1.2 reads as follows: "If consideration of alkali/acid reserve suggests the substance or mixture 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." This sentence is only included in the chapter on mixture classification criteria. It is not included in the substance classification criteria. Thus, it is not clear whether it also relates to substance classification. Proposal 17.4.09: This sentence was added to 3.2.2.2 (see GHS Chapter-3-2 rev3_2nd_change.doc). See B4		**Y: SDA, HFleig, BE, AUS**	**UK:** A negative result in an appropriate in vitro test that can reliably identify non corrosives/irritants should be sufficient for classification purposes without the need for confirmatory in vivo testing. If figure 3.2.1 is removed then the remaining text should allow for classification to be based on the appropriate in vitro testing only. **SDA**: The sentence on consideration of alkali/acid reserve should be added to the substance classification criteria. (See addition of that text in attached modified paragraph 3.2.2.2 in chapter 3.2.)
S3	**15/INF.25/3.9** **15/INF.5/8**	It is not clear in which subcategory a corrosive substance should be classified based on human data, extreme pH, in vitro or SAR results. It is suggested that the figures and related text be reconsidered to avoid inconsistencies (Ref 3). Proposal 17.4.09: add sentence: In case the available data/information are not sufficient to further divide into subcategories 1A, 1B, or 1C a corrosivity classification into category 1 without subcategorisation should be applied.		**Y: exECB, AISE, BE, ECHA, FIN, AUS** **Neutral: SDA** **N: BASF**	**UK:** Agree, no criteria are provided to allow for classification based on alternative information. It would be useful if additional information were included in the GHS text rather than guidance. **SDA**: From our experience, human data and extreme pH can only be used for determination of overall corrosivity, not to further divide a corrosivity classification into categories 1A, 1B, and

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	**Comment/Motivation/Proposal**
Chapter 3.2 - ISSUES AND COMMENTS RELATED to Skin corrosion/irritation					
		Proposal 29.5.09: Discuss point raised by BASF at face to face meeting **CG meeting conclusion at 17th UN SCE GHS session** Proposal 17.04. preliminary agreed but check the consequence for mixture classification: the note to table 3.2.3 may need some amendment.			1C. An SAR analysis, in some cases, can be correlated with 1A, 1B or 1C corrosives. **SDA can suggest alternative text.** **BASF:** will be difficult to transfer to transport classification (assignment of packing groups)
S4	**15/INF.5/5b** **15/INF.25/3.7**	Fig 3.2.1 indicates that even if a validated *in vitro* test for skin corrosion (in step 5) gives a negative result, then an *in vivo* skin corrosion test using one animal is required in step 7. This may be an unnecessary use of animals. The need for confirmatory *in vivo* testing should depend on whether a particular *in vitro* test can reliably identify non skin corrosives/irritants or not. Where an *in vitro* test can reliably identify both corrosives/irritants and non-corrosives/non-irritants confirmatory testing might not be necessary Flow diagram 3.2.1 for skin corrosion/irritation indicates that a negative response in a validated in vitro test(s) for corrosion and irritation requires in vivo testing. The informal working group should consider if the need for in vivo testing should depend on whether the in vitro test can reliably identify non corrosives/irritants or not. Where an in vitro test can reliably identify both corrosives/irritants and non corrosives/non irritants confirmatory testing might not be necessary. Therefore, further guidance or adjustments to the text of the GHS at some stage should be considered (Ref 3 and 4). Proposal 17.4.09: add sentence to the criteria that negative results from an OECD in vitro test lead to the decision "no classification" if the test has been validated accordingly.[TG2] **CG meeting conclusion at 17th UN SCE GHS session:** To be further discussed under B1		**Y: UK, HFleig, exECB, BASF, ECHA, AUS** (if *in vitro* test can reliably identify non corrosives/ irritants or not) **Neutral: SDA, FIN** **N:BE**	**UK:** A negative result in an appropriate in vitro test that can reliably identify non corrosives/irritants should be sufficient for classification purposes without the need for confirmatory in vivo testing. If figure 3.2.1 is removed then the remaining text should allow for classification to be based on the appropriate validated in vitro testing only. **UK:** Note for info - The OECD is currently discussing a draft *in vitro* skin irritation Test Guideline (TG). **exECB**: If the in vitro is validated for "non-classification". **BE :** the sentence can only be added when the OECD in vitro test can reliably identify both corrosives/irritants and non corrosives/non irritants. This is not yet the case for some tests (e.g. distinction between skin irr.cat.2 and skin irr. Cat.3 with the reconstructed human epidermis test).

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	Comment/Motivation/Proposal
Chapter 3.2 - ISSUES AND COMMENTS RELATED to Skin corrosion/irritation					
S5	**US_1_4**	Table 3.2.1 footnote (a) should make reference to paragraph 3.2.2.2 not 3.2.2.1. **CG meeting conclusion at 17th UN SCE GHS session:** agreed		**N: SDA, FIN** **Neutral: AUS**	**SDA:** If figure 3.2.1 is deleted this change is not necessary.
S6	**HFleig_31_3**	Could not be the sequence always Skin corrosion/Irritation, not sometimes this way then the other way around? Proposal 17.4.09: always use sequence 'corrosion/irritation' **CG meeting conclusion at 17th UN SCE GHS session:** agreed	3.2.3.1	**Y: SDA, BE, FIN, AUS**	**TG.** Easy to solve. Appears 9-times in chapter 3.2.
S7	**HFleig_31_3**	Do we need these §§? It is a general principle (establishing SCLs); a reference to 1.3.3.2 would be sufficient; in other appropriate hazard classes there is only the reference. **CG meeting conclusion at 17th UN SCE GHS session:** keep text as is.	3.2.3.3.5 and 3.2.3.3.6	**Y: SDA** (keep the paras) **Neutral:FIN**	
S8	**ECHA_31_3**	It is not clear from the text that it is possible to get some indication of irritating potential of a substance from both single and repeated exposure (human and animal data), footnote g. This is not ideally written in the "old" chapter 3.2.2.2 either. The 3rd sentence under 3.2.2.2 of the "old" text could e.g. be changed into "Existing human ~~experience~~ and animal data ~~and animal observations~~, including ~~data~~ information from single or repeated exposure should be the first line of analysis, as they give information directly relevant to effects on the skin." **CG meeting conclusion at 17th UN SCE GHS session:** discuss within context B1.	3.2.2.2	**Y: SDA, HFleig, AUS** **Neutral: FIN**	
S9	**ECHA_31_3**	The last sentence in footnote d) could be incorporated somewhere in the text : "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". **CG meeting conclusion at 17th UN SCE GHS session:** discuss within context B1.		**Y: HFleig** **N: SDA** **Neutral: FIN, AUS**	

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	Comment/Motivation/Proposal
Chapter 3.2 - ISSUES AND COMMENTS RELATED to Skin corrosion/irritation					
S10	**BE_10_09**	In 3.2.2.2, align the phrase "Likewise, pH extremes like ≤ 2 and ≥ 11.5 may indicate skin effects, especially when buffering capacity is known, although the correlation is not perfect. " to the respective sentence of chapter 3.3.		**Y: UK, FIN, ECHA, BASF, HFl**	
S11	ECHA_11_09	In 3.2.2.2, we suggest adding the sentence "Lack of reported skin corrosion/irritation in acute toxicity studies is not conclusive for non-classification." after the third last sentence. (cf. the "old" footnote d)			

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	**Comment/Motivation/Proposal**
Chapter 3.3	**ISSUES AND COMMENTS RELATED to Eye damage/irritation**				
E1		A similar approach could taken for this chapter. The definitions in 3.3.1 for "Serious eye damage" and "Eye irritation" are established and supported by paragraphs 3.3.2.8 and 3.3.2.9. To clarify the importance of the definitions and the use of existing data, the information in paragraphs 3.3.2.8 and 3.3.2.9 could be moved up to the beginning of the chapter and immediately follow Section 3.3.1. The new Section 3.3.2 could be entitled something along the lines of "Classification criteria for substances based on test data". The next section, Section 3.3.3, could be could be entitled "Classification criteria for substances using other data elements" (or something along those lines) and would adopt all of the language in current paragraph 3.3.2, including Figure 3.3.1. Of note is that Chapter 3.3 of Rev 2 states that the tiered approach in figure 3.3.1 is "good guidance on how to organize existing information..." indicating that the flow diagram in Figure 3.3.1 is not an "either/or" proposition. This language is not in Chapter 3.2, but it makes sense that the Figures 3.2.1 and 3.3.1 were intended to be applied similarly. Next is mixtures, and as for Chapter 3.2 and most others, when data is available for the complete mixture, it would be classified using the criteria for substances. Bridging Principles would not change. Classification of mixtures when data is only available for some ingredients, would also not change. That would complete this chapter and would emphasize the use of existing human and animal data, but maintain weight-of-evidence when needed.		**Y:SDA, HFleig, BE, ECHA, FIN, BASF** **Neutral: AUS** **Y: AUS** **Neutral: AUS**	**UK:** as the chapters are now presented (docs GHS Chapter-3-2 rev3_1st_change.doc and GHS Chapter-3-3 rev3_1st_change.doc) they seem to suggest a preference for animal data over other data. For example the opening sentence in 3.2.2.2 states "Several factors should be considered in determining the corrosion and irritation potential of substances in case the criteria described above cannot be applied". This implies that you should consider the animal test data first, and then if that is not applicable look to other information, including human data. The text goes on to make it clear that there is a need to consider a weight-of-evidence approach even when test data are available e.g. the last paragraph in 3.2.2.2 states 'Generally, primary emphasis should be placed upon existing human experience and data, followed by animal experience and testing data' but perhaps more consideration needs to be given to the structure and presentation of these Chapters. **SDA**: The proposed revisions to Chapters 3.2 and 3.3 that appear to account for the proposal to restructure chapters 3.2 and 3.3 are appropriate. **ECHA:** We suggest that as analogous sentences the one in chapter 3.2 " Generally, primary emphasis should be placed upon existing human experience

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	Comment/Motivation/Proposal
Chapter 3.3 ISSUES AND COMMENTS RELATED to Eye damage/irritation					
		Proposal 17.4.09: Discuss issue at face to face meeting Possible solutions: i) keep order as is ii) change order as proposed by US OSHA and add a general introduction to the chapter see S1			and data, followed by animal experience and testing data, followed by other sources of information, but case-by-case determinations are necessary." should replace the one in the revised chapter 3.3. We think that this issue would fit better under some kind of 'introduction' than classification criteria in case the overall structure would however be changed as suggested. Keeping the current order of chapters the issues would be presented in a more logical order. In addition to that we are in favour of keeping the chapter headings, especially "Classification criteria for substances" because the criteria should not be linked to identification and evaluation of data. To our understanding the corrosion subheading should remain.

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	**Comment/Motivation/Proposal**
Chapter 3.3 ISSUES AND COMMENTS RELATED to Eye damage/irritation					
E2	**15/INF.25/3.10**	Step 1c in flow diagram 3.3.1 for serious eye damage/eye irritation allows for classification in Category 2 if the substance is a skin irritant. Is there a valid correlation between these effects? (Ref 3)		**Y: SDA** **N,** but discuss: **UK**	**UK:** Our experience suggests that there is limited evidence for a correlation between skin irritation and eye irritation. **SDA**: From data we are aware of, most skin irritants are also eye irritants (about 80%).
	15/INF.5/5b	The adequacy of the flow chart for eye irritation may be questioned in step 1c, as classification for eye irritation based on human evidence of skin irritation may not generally be automatically advised. Recent data should be discussed whether a valid correlation between these effects can still be assumed. For instance, there is a review publication which came to the conclusion that there is no general correlation of skin and eye irritation and vice versa (Gerner et al. 2000. Development of a decision support system for the introduction of alternative methods into local irritancy/corrosivity testing strategies. Creation of fundamental rules for a decision support system. Altern Lab Anim. 28(5):665-98.) Proposal 17.4.09: further discuss the point **CG meeting conclusion at 17th UN SCE GHS session:** Preliminary agreement: The use of the term 'irritant' or 'irritation' is understood to relate to the respective chapter where the term is used, e.g. irritation in chapter 3.2 always means skin irritation.		**N:-Hfleig** **Neutral: FIN** **Discuss point: AUS, BE**	**HFleig:** There are enough examples showing there is no correlation. In addition, this statement is not in the criteria, rather only in the flow diagram, which is not criteria as such.

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	Comment/Motivation/Proposal
Chapter 3.3 ISSUES AND COMMENTS RELATED to Eye damage/irritation					
E3	**15/INF.5/6**	When classifying mixtures for eye (Category 2), according to the approach where additivity does not apply 'other irritant (Category 2) ingredients' have to be included in the process of classification (GHS table 3.3.4). It is not clear whether also skin irritants (Cat. 2) are to be subsumed in addition to the Category 2 eye irritants. Point related to point E2 above See E2		**Y: SDA, FIN, AUS** **N: BASF**	**UK:** Agree that this is not clear, but as the GHS currently advises that a skin irritant should also be classified as an eye irritant, the implication is that 'other irritants' includes skin irritants. However, as already mentioned, our experience shows that there is limited evidence for a link between skin and eye irritation. **SDA**: The original intent was to include eye irritants only. Those skin irritants classified as eye irritants were apparently included thereafter, though it may not have been thoroughly considered at the time. This issue could use discussion and clarification.

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	Comment/Motivation/Proposal
Chapter 3.3 ISSUES AND COMMENTS RELATED to Eye damage/irritation					
E4	**15/INF.5/715/I** **INF.25/3.12**	When classifying mixtures for eye (Category 2), there is no differentiation in mixture classification between Category 2A and 2B as it is the case for substances. If it is intended it might be clarified in the text. For serious eye damage/eye irritation there are differences between tables 3.3.2, 3.3.3, 3.3.4 and 3.3.5 (and text) and flow diagram 3.3.1 that should be reconciled i.e. there is inconsistency within each for the sub-division of Category 2 into Category 2A and 2B. One resolution could be to include categories 1, 2A and 2B in Table 3.3.3, or that only category 2B is included in the table with the explanation that category 2B can only be determined through test data and cannot be calculated. Other resolutions could be considered (Ref 2). Proposal 17.4.09: discuss at face-to-face meeting. **CG meeting conclusion at 17th UN SCE GHS session:** Further discussion needed.		**Y: SDA, HFleig, FIN, AUS (agree with UK comments)** **Y, but discuss: UK** **Neutral: BE**	**UK:** The chapter is not clear regarding its reference to Category 2A and 2B irritants. Tables 3.3.3 and 3.3.4 refer to a general Category 2, but there are no label elements for a general Category 2 in table 3.3.5. Consequently tables 3.3.3 and 3.3.4 need to make it clear whether a mixture should be classified in Cat 2A or 2B. However, this is not straight forward because for a mixture of Cat 2A and 2B substances it would not be possible to say which sub-category the mixture belonged to. Classification into Cat 2B is based on the duration of the effect which could not calculated for the mixture. In this case, only referring to Cat 2A in the table would be a way forward. However, if only category 2B ingredients were present in a mixture then the mixture could not be classified in Cat 2A. Perhaps referring only to one category in the table with an associated table note regarding the application of the other subcategory would be a way forward. Trying to include both Cat 2A and 2B in the table may make it over complicated. **SDA**: Category 2B is primarily included in the classification for pesticide regulatory authorities and is based mainly on test data. The issue could be fixed by deleting 2B from last row of Table 3.3.3. [FIN: agree to previous sentence] It could be helpful to consider clarifications in the text for differentiating between Categories 2A and 2B.

<table>
<tr><th>Ref. No</th><th>Issue Ref.</th><th>Comment/Proposal</th><th>GHS Ref.</th><th colspan="2">REACTIONS</th></tr>
<tr><th></th><th></th><th></th><th></th><th>Support (Y/N/Neutral)</th><th>Comment/Motivation/Proposal</th></tr>
<tr><td colspan="6">Chapter 3.3 ISSUES AND COMMENTS RELATED to Eye damage/irritation</td></tr>
<tr><td>E5</td><td>15/INF.5/Further issues a)</td><td>a) Can table 3.3.3 be simplified/amended?
i) In general, the additivity principle applies when classifying mixtures in case ingredients are present classified as skin Cat.1 AND eye Cat.1. If only skin Cat. OR eye Cat. 1 ingredients are present, those have to be considered. Thus, it is possible to combine the lines 2. "Eye effects Category 1 or Skin corrosive Category 1A, 1B, 1C" and 5. "Skin corrosive Category 1 + Eye Category 1".
ii) Moreover, the information in line 4. is included in line 6..
Rev'd GHS Table 3.3.3
<table>
<tr><td>Sum of ingredients classified as</td><td colspan="2">Concentration triggering classification of a mixture as</td></tr>
<tr><td></td><td>Irreversible eye effects</td><td>Reversible eye effects</td></tr>
<tr><td></td><td>Category 1</td><td>Category 2</td></tr>
<tr><td>Skin category 1 + eye category 1</td><td>≥ 3%</td><td>≥ 1% but < 3%</td></tr>
<tr><td>Eye Category 2/2A why not 2B?</td><td></td><td>≥ 10%</td></tr>
<tr><td>~~(10 × eye Category 1) + eye Category 2/2A~~</td><td></td><td>~~≥ 10%~~</td></tr>
<tr><td>~~Skin Category 1 + eye Category 1~~</td><td>~~≥ 3%~~</td><td>~~≥ 1% but < 3%~~</td></tr>
<tr><td>10 × (skin Category 1 + eye Category 1) + eye Category 2A/2B here 2B!</td><td></td><td>≥ 10%</td></tr>
</table>
CG meeting conclusion at 17th UN SCE GHS session: needs further discussion</td><td></td><td>Y: UK, SDA HFleig, AISE, FIN, AUS, BASF</td><td>UK: however, the issues regarding the application of Category 2A and 2B need to be resolved.

SDA: Category 2B is primarily included in the classification for pesticide regulatory authorities and is based mainly on test data. The issue could be fixed by deleting 2B from last row of Table 3.3.3. The proposed changes in (i) and (ii) and presented in Table 3.3.3 are appropriate. Regarding the question in Table 3.3.3 about whether or not to include 2B, it should not be included because it is not considered irritant by most authorities, with the exception of pesticides labelling. The clarity of the table would be improved by keeping all of the references to 2B out of the table. [FIN: agree to previous sentence]</td></tr>
<tr><td>E6</td><td>HFleig_31_3</td><td>Editorial: aIV: instillation or application, not installation
CG meeting conclusion at 17th UN SCE GHS session: agreed.</td><td>Table 3.3.2</td><td>Y: SDA, AUS</td><td></td></tr>
<tr><td>E7</td><td>HFleig_31_3</td><td>Better "classification..." than "hazard decisions".
CG meeting conclusion at 17th UN SCE GHS session: agreed.</td><td>3.3.2.4</td><td>Y: SD, FIN, AUS</td><td>TG: appears once in 3.3</td></tr>
</table>

Ref. No	Issue Ref.	Comment/Proposal	GHS Ref.	REACTIONS	
				Support (Y/N/Neutral)	Comment/Motivation/Proposal
Chapter 3.3 ISSUES AND COMMENTS RELATED to Eye damage/irritation					
E8	**HFleig_31_3**	Why "toxicity category" in the heading and in line 2: ; its the Serious eye damage/irritation category " **CG meeting conclusion at 17th UN SCE GHS session:** agreed. **Recognized after the meeting:** **TG:** general issue also for many other hazard classes. If re-termed better take "hazard category". Somebody to draft proposal ofr all hazard classes, no specific issue for this CG. If changed has to be changed consistently in whole GHS.	3.3.2.5.	**Y: SDA, AUS**	
E9	**AISE_10_09**	Align the text to consistently use the terms 'Serious eye damage / eye irritation' rather than for example 'serious eye damage/irritation' or 'irritation/serious eye damage' or serious ocular tissue damage.		**Y: UK, FIN, BE, ECHA, BASF, HFl**	
E10	ECHA_11_09	In 3.3.2.4, we would recommend to retain the two original sentences in 3.3.4.2 of the current GHS text related to extreme pH with minor modification and to incorporate the message of the "old" note (Step 3) in Figure 3.3.1. In other words, the text could be: "Likewise, pH extremes like * 2 and * 11.5, may produce significant effects on the eyes, especially when associated with significant buffering capacity. Such substances are expected to be corrosive (Category 1) and are therefore also expected to produce serious damage to eyes."			

Annex 3

Paper 2_GHS Chapter-3-2 rev3_CG_agreed edit2.doc:

"CHAPTER 3.2

SKIN CORROSION/IRRITATION

3.2.1 Definitions

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].

3.2.2 Classification criteria for substances

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 classification decisions. Likewise, pH extremes like ≤ 2 and ≥ 11.5 may indicate skin effects, especially when associated with significant buffering capacity ~~is known~~, although the correlation is not perfect. Generally, such ~~agents~~ substances are expected to produce significant effects on the skin. A substance is considered corrosive (Skin Category 1) if it has a pH ≤ 2 or a pH ≥ 11.5. If consideration of acid/alkaline reserve suggests the substance 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. It also stands to reason that if a substance is highly toxic by the dermal route, a skin ~~irritation/corrosion~~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~~corrosion/irritation 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~~bases 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.

---

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

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

Step	Parameter	Finding	Conclusion
1a	Existing human or animal ~~experience~~ data [f]	→ Corrosive	→ Classify as corrosive [a]
	↓ Not corrosive or no data		
1b	Existing human or animal ~~experience~~ data [f]	→ Irritant	→ Classify as irritant [a]
	↓ Not irritant or no data		
1c	Existing human or animal ~~experience~~data	→ 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
	↓ No 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		

(Cont'd on next page)

Figure 3.2.1 *(cont'd)*: **Tiered testing and evaluation of skin corrosion and irritation potential**

Step	Parameter	Finding	Conclusion
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~~ alkaline 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.

3.2.2.4 *Corrosion*

3.2.2.4.1 A single harmonized corrosion category is provided in Table 3.2.1, 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 at least 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.

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

[a] *The use of human data is discussed in 3.2.2.~~1~~2, in the Chapter 1.1 (para.* 1.1.2.5(c)), *and in Chapter 1.3 (para. 1.3.2.4.7).*

3.2.2.5 *Irritation*

3.2.2.5.1 A single *irritant category* is provided in Table 3.2.2 that:

(a) is centrist in sensitivity among existing classifications;

(b) recognizes 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. An additional mild irritant category is available for those authorities that want to have more than one skin irritant category.

3.2.2.5.2 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.

3.2.2.5.3 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 A single irritant category (Category 2) is presented in the table 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 3.2.2). They mainly differ in the severity of skin reactions. The major criterion for the irritant category is that at least 2 tested animals have a mean score of ≥ 2.3 ≤ 4.0. For the mild irritant category, the mean score cut-off values are ≥ 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 3.2.2 Skin irritation categories [a]

Categories	Criteria
Irritant **(Category 2)** (applies to all authorities)	(1) Mean value of ≥ 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 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 **(Category 3)** (applies to only some authorities)	Mean value of ≥ 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 skin reactions (when not included in the irritant category above).

[a] *The use of human data is discussed in 3.2.2.2~~1~~, in the Chapter 1.1 (para.* 1.1.2.5(c)), *and in the Chapter 1.3 (paragraph 1.3.2.4.7).*

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 be classified using the criteria for substances, and taking into account the testing and evaluation strategies to develop data for these hazard classes.

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 as included in the criteria for classification of substances for 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 ≤ 2 or a pH ≥ 11.5. If consideration of ~~alkali/acid~~acid/alkaline reserve suggests the ~~substance or~~ mixture 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.

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~~corrosion/irritation, 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 ~~irritation/corrosion~~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 toxicity 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 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 is concentrated and does not contain corrosive ingredients, the more concentrated untested mixture should be classified in the highest irritation category without additional testing.

3.2.3.2.5 *Interpolation within one toxicity category*

For three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and are in the same ~~irritation/corrosion~~skin corrosion/irritation toxicity 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 ~~irritation/corrosion~~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 ~~irritation/corrosion~~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 toxicity 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 mixture provided that the added propellant does not affect the 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~~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~~corrosion/irritation.

3.2.3.3.2 In general, the approach to classification of mixtures as irritant or corrosive 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 corrosive or irritant ingredient 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 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 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 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 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 3.2.3 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 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 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 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 the sub-categories 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 3.2.4: **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 2/3) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

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.

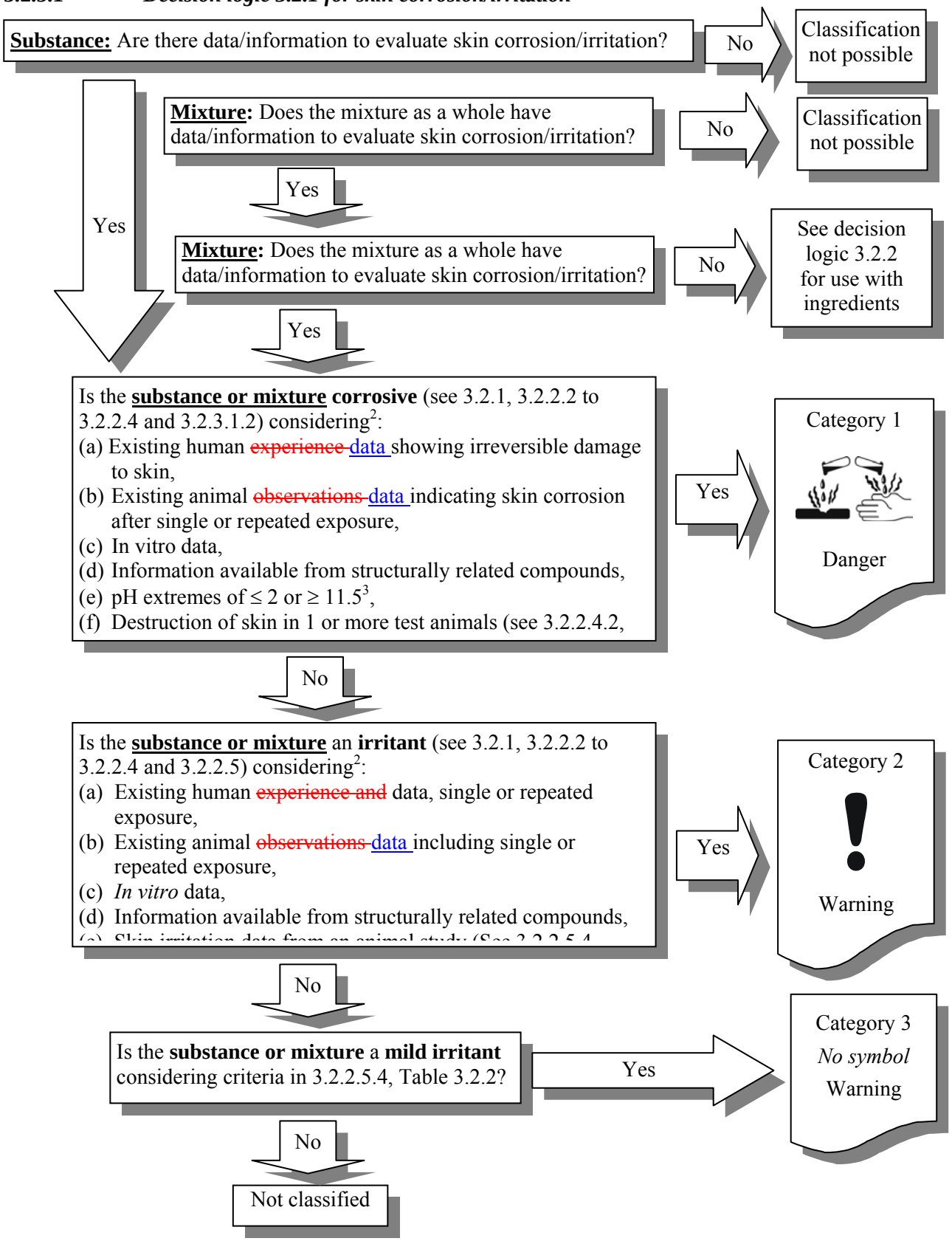
Table 3.2.5: Label elements for skin corrosion/irritation

	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*

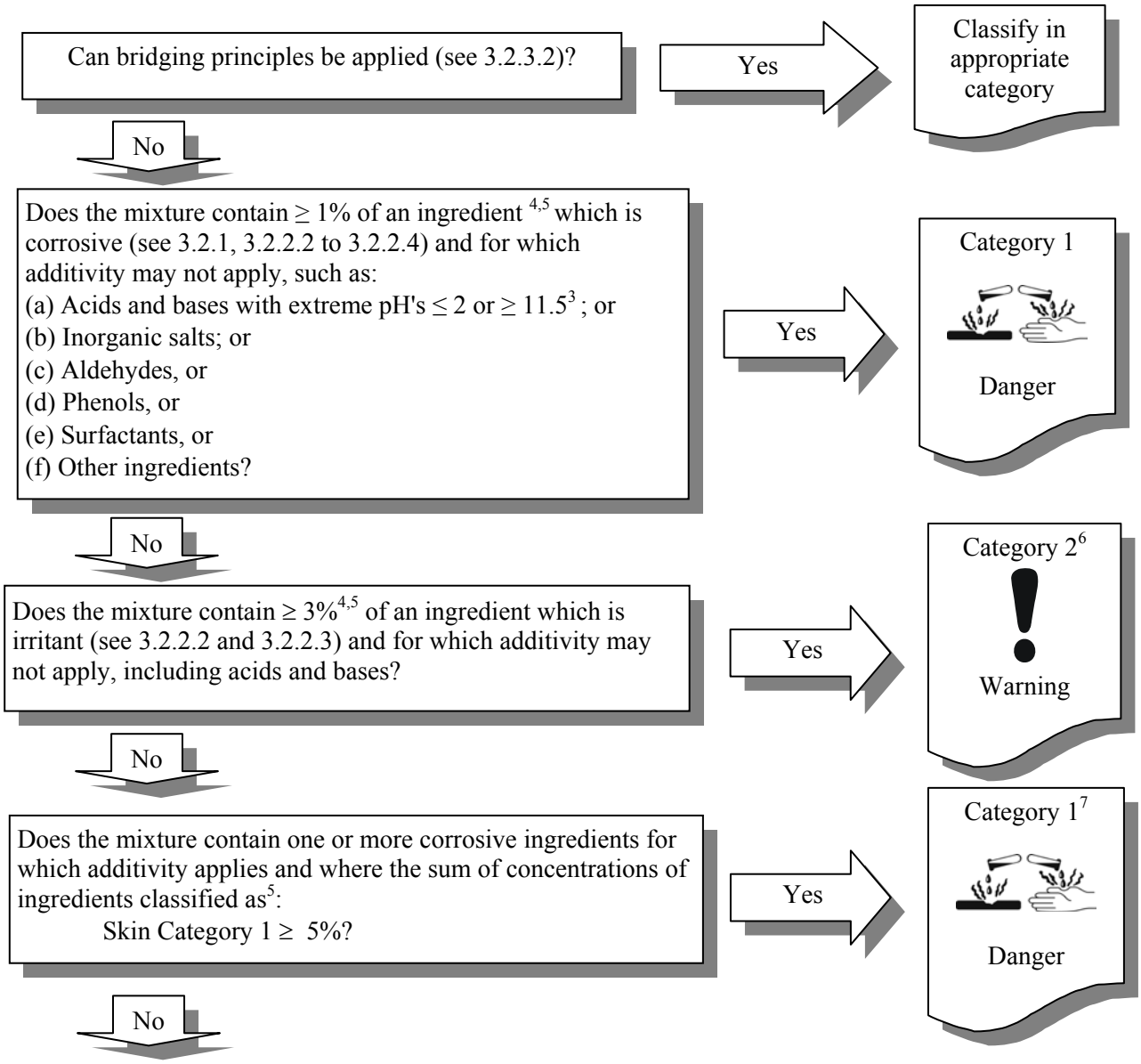


[2] *Figure 3.2.1 contains details for testing and evaluation.*

[3] *Including consideration of acid/~~alkali~~ alkaline reserve capacity, if appropriate.*

3.2.5.2 *Decision logic 3.2.2 for skin corrosion/irritation*

Classification of mixtures on the basis of information/data on ingredients



(Cont'd on next page)

---

[3] *Including consideration of acid/~~alkali~~ alkaline reserve capacity, if appropriate.*

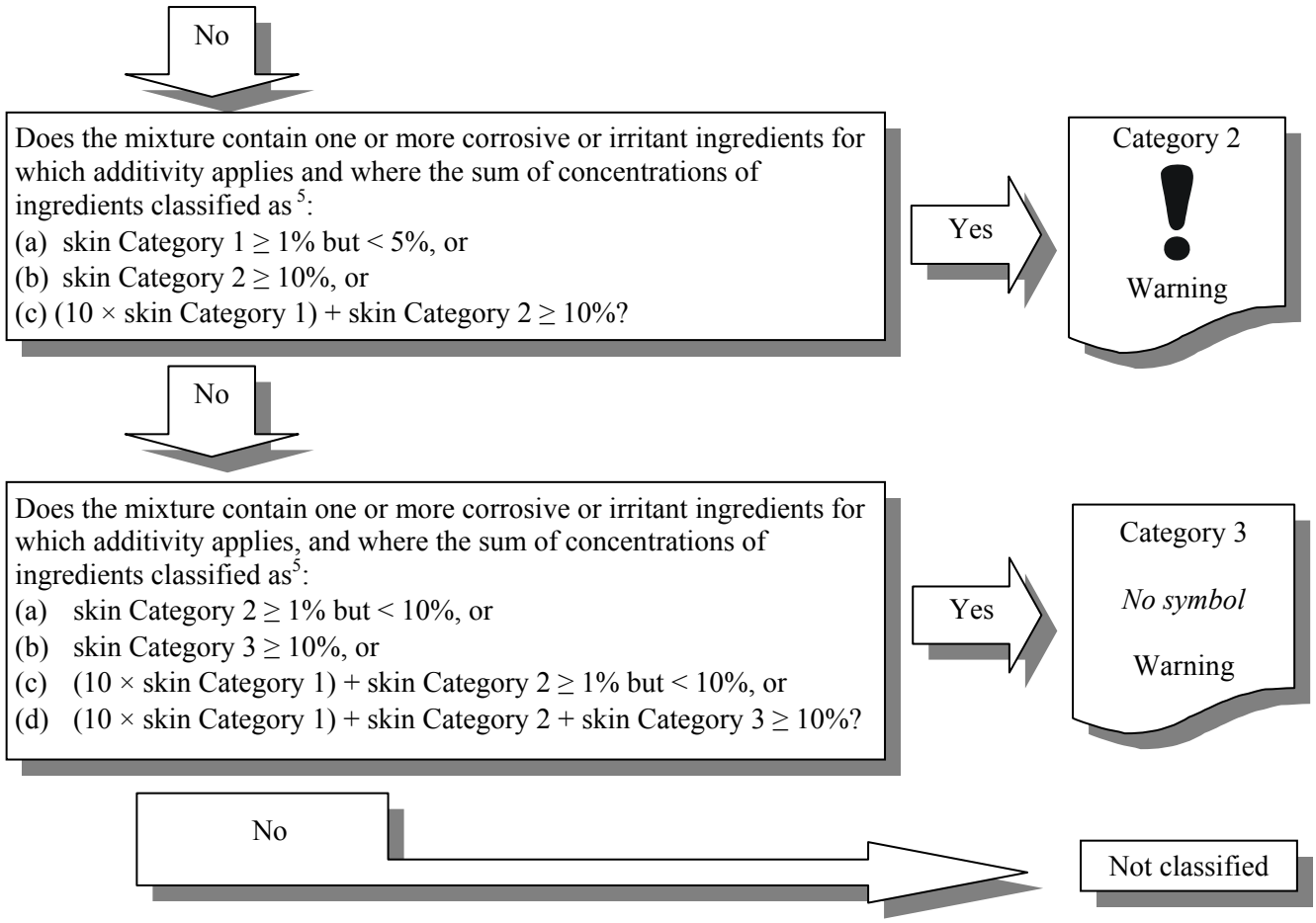
[4] *Or where relevant < 1 %, see 3.2.3.3.1.*

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

[6] *If the mixture also contains corrosive or irritant ingredient(s) for which additivity applies, move to the box below.*

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

Footnotes [5]



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

Annex 4

Paper 3_Changes introduced into 3.2.doc

Changes introduced into 3.2

Add the following text to 3.2.2.2. after the sixth sentence in this paragraph:

"A substance is considered corrosive (Skin Category 1) if it has a pH ≤ 2 or a pH ≥ 11.5. If consideration of acid/alkaline reserve suggests the substance 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. "

In 3.2.2.2, change "agent" to "substance"

Insert *", in the Chapter 1.1 (para.* 1.1.2.5(c)),*"* after 3.2.2.1 in footnote a to tables 3.2.1 and 3.2.2

Change in footnote b to figure 3.2.1 "alkali" to "alkaline"

Change 3.2.2.1 to 3.2.2.2 in footnote a to table 3.2.1

Delete in the third sentence of 3.2.2.2 "experience and" and "observations and"

In 3.2.3.1.2, last phrase substitute "alkali/acid" with „acid/alkaline" and delete "substance or".

In 3.2.5.1, in the fourth row of boxes from the top in the left column box substitute "experience" with "data" and "observations" with "data".

In 3.2.5.1, in the fifth row of boxes from the top in the left column box delete "experience and" and substitute "observations" with "data".

In the second last sentence of 3.2.2.2 delete "experience and" and "experience and testing".

In 3.3.2.5. second sentence substitute "caustic alkalis" with "bases".

Change "irritation/corrosion" to "corrosion/irritation" in 3.2.2.2 (twice), 3.2.3.2.1 (once), 3.2.3.3.1 (twice).

Change "irritation/corrosion" to "skin corrosion/irritation" in 3.2.3.2.3 (once), 3.2.3.2.5 (twice), 3.2.3.2.6 (once).

In the decision logics 3.2.1 and 3.2.2 (paragraphs 3.2.5.1 and 3.2.5.2), substitute "alkali" with "alkaline" in footnote 3.

Annex 5

Paper 4_GHS Chapter-3-3 rev3_CG_agreed edit2.doc

"CHAPTER 3.3
SERIOUS EYE DAMAGE /EYE IRRITATION

3.3.1 Definitions

Serious eye damage is the production of tissue damage in the eye, or serious physical decay of vision, following application of a test substance to the anterior surface of the eye, which is not fully reversible within 21 days of application[7] .

Eye irritation is the production of changes in the eye following the application of test substance to the anterior surface of the eye, which are fully reversible within 21 days of application[1].

3.3.2 Classification criteria for substances

3.3.2.1 A tiered testing and evaluation scheme is presented that combines pre-existing information on serious ~~ocular tissue~~eye damage and on eye irritation (including ~~data~~ information relating to historical human or animal ~~experience~~data) as well as considerations on structure-activity relationships (SAR) and the output of validated *in vitro* tests in order to avoid unnecessary animal testing.

3.3.2.2 The proposals for classification of serious eye damage/eye irritation ~~and serious damage to the eye~~ include elements that are harmonized and will be used by all authorities as well as optional sub-categories that will be applied by only some authorities (e.g. authorities classifying pesticides).

The harmonized system includes guidance on the data elements that must be evaluated before animal testing for eye damaging effects is undertaken. It also includes hazard categories for local lesions on the eyes.

3.3.2.3 Before there is any *in vivo* testing for serious eye damage/eye irritation, all existing information on a test material should be reviewed. Preliminary decisions can often be made from existing data as to whether a~~n agent~~ substance causes serious (i.e. irreversible) damage to the eyes. If a test material can be classified, no testing is required. A highly recommended way of evaluating existing information on agents or of approaching new uninvestigated substances, is to utilize a tiered testing strategy for serious eye damage and eye irritation.

3.3.2.4 Several factors should be considered in determining the serious eye damage or eye irritation potential of substances before testing is undertaken. Accumulated human and animal ~~experience~~ data should be the first line of analysis, as it gives information directly relevant to effects on the eye. In some cases enough information may be available from structurally related compounds to make ~~hazard~~ classification decisions. Likewise, pH extremes like ≤ 2 and ≥ 11.5, may produce serious eye damage, especially when associated with significant buffering capacity. ~~-~~Such ~~agents~~ substances are expected to produce significant effects on the eyes. A substance is considered to cause serious eye damage (Eye Category 1) if it has a pH ≤ 2 or ≥ 11.5. If consideration of acid/alkaline reserve suggests the substance may not have the potential to cause serious eye damage 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. Possible skin corrosion has to be evaluated prior to consideration of serious eye damage/eye irritation in order to avoid testing for local effects on eyes with skin corrosive substances. *In vitro* alternatives that have been validated and accepted may be used to make classification decisions.

3.3.2.5 All the above information that is available on a substance should be used in determining the need for *in vivo* eye irritation testing. Although information might be gained from the evaluation of

---

7 *This is a working definition for the purpose of this document.*

single parameters within a tier (e.g. ~~caustic alkalis~~bases with extreme pH should be considered as local 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 expert judgement, considering human ~~experience~~ data with the substance, followed by the outcome of skin irritation testing and of well validated alternative methods. Animal testing with corrosive substances should be avoided whenever possible.

3.3.2.6 A tiered approach to the evaluation of initial information should be considered where applicable, recognizing that all elements may not be relevant in certain cases. The tiered approach explained in Figure 3.3.1 was developed with contributions from (inter)national centres and committees for the testing and validation of alternatives to animal testing during a workshop in Solna, Sweden[8].

3.3.2.7 Where data needed for such a testing strategy cannot be required, the proposed tiered testing approach provides good guidance on how to organize existing information on a test material and to make a weight-of-evidence decision about hazard assessment and hazard classification (ideally without conducting new animal tests).

Figure 3.3.1: Testing and evaluation strategy for serious eye damage and eye irritation (see also: "Testing and evaluation strategy for skin irritation/corrosion" Figure 3.2.1)

Step	Parameter	Findings	Conclusions
1a	Data relating to historical human or animal ~~experience~~data	Serious eye damage	Category 1
		Eye irritant	Category 2
	No or don't know		
1b	Data relating to historical human or animal ~~experience~~data	Skin corrosive	No evaluation of effects on eyes; deemed to be Category 1
	No or don't know		
1c	Data relating to historical human or animal ~~experience~~data	Skin irritant	No evaluation of effects on eyes; deemed to be Category 2
	No or don't know		
2a	Structure activity relationships (SAR)	Severe damage to eyes	Category 1
	No or don't know		
2b	Structure activity relationships (SAR)	Eye irritant	No evaluation of effects on eyes; deemed to be Category 2
	No or don't know		

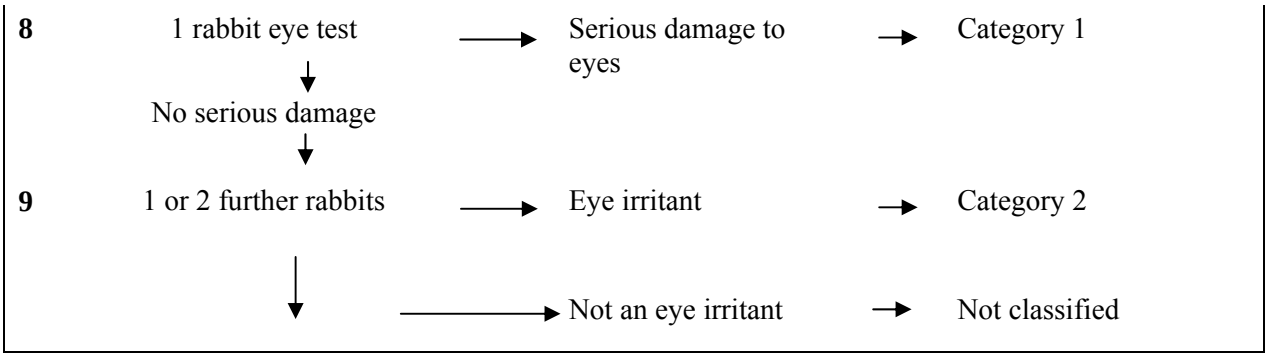
(Cont'd on next page)

[8] *OECD (1996). Final Report of the OECD Workshop on Harmonization of Validation and Acceptance Criteria for Alternative Toxicological Test Methods. Document ENV/MC/TG(96)9 (http://www.oecd.org/ehs/test/background.htm).*

Figure 3.3.1 *(cont'd)*: **Testing and evaluation strategy for serious eye damage and eye irritation (see also: "Testing and evaluation strategy for skin irritation/corrosion" Figure 3.2.1)**

Step	Parameter	Findings	Conclusions
2c	Structure activity relationships (SAR) →	Skin corrosive →	No evaluation of effects on eyes; deemed to be Category 1
	↓ No or don't know ↓		
3a	pH/acid or alkaline reserve ↓ →	pH ≥ 11.5 or pH ≤ 2 (considering acid or alkaline reserve) →	Category 1
3b	2 < pH < 11.5 (no buffering potential) ↓		
4	Other information indicating the material is a skin corrosive →	Yes →	No evaluation of effects on eyes; deemed to be Category 1
	↓ No ↓		
5	Is a valid *in vitro* test available to assess severe damage to eyes →	No →	Go to step 6
	↓		
5a	*In vitro* test for severe eye irritation →	Severe damage to eyes →	Category 1
	↓ Not a severe eye irritant ↓		
6	Is a valid *in vitro* test for eye irritation available → No →	- But *in vitro* test for severe eye irritancy was negative →	Go to step 8
	↓	- In the absence of any *in vitro* test →	Go to Step 7
	Yes ↓		
6a	*In vitro* eye irritation test →	Eye irritant →	Category 2
	↓ No indication of eye irritant properties ↓		
7	Experimentally assess skin corrosion potential (see Testing Strategy for Skin Irritation/Corrosion) →	Skin corrosive →	No evaluation of effects on eyes, deemed to be Category 1
	↓ Not corrosive ↓		

(Cont'd on next page)



NOTES to Figure 3.3.1:

Step 1a/b: *Data relating to historical human or animal ~~experience~~data: pre-existing information on eye irritation and skin corrosion are shown separately because evaluation of skin corrosion has to be considered if there is no information on local effects on eyes. Analysis of pre-existing ~~experience~~ data with the chemical may identify serious eye damage, corrosion and irritation potential for both skin and eye effects:*

(i) Step 1a - reliable determination of eye irritancy basing on human or animal ~~experience~~ data - depends on expert judgement: in most cases human ~~experience~~ data is based on accidental events and thus, the local effects detected after an accident have to be compared with classification criteria created for evaluation of animal test data;

(ii) Step 1b - evaluation of data on skin corrosivity - skin corrosive substances should not be instilled into the eyes of animals; such substances should be considered as leading to serious damage to the eyes as well (Category 1).

Step 2a/b/c: *SAR (Structure Activity Relationships) for eye irritation and skin corrosion are shown separately but in reality would probably be done in parallel. This stage should be completed using validated and accepted SAR approaches. The SAR analysis may identify serious eye damage, corrosion and irritation potential for both skin and eye effects:*

(i) Step 2a - reliable determination of eye irritancy only by theoretical evaluations - in most cases it will only be appropriate for substances that are homologous to ~~agents~~ substances with very well known properties;

(ii) Step 2c - theoretical evaluation of skin corrosivity - skin corrosive substances should not be instilled into the eyes of animals; such substances should be considered as leading to serious damage to the eyes as well (Category 1).

Step 3: *pH extremes like ≤ 2 and ≥ 11.5 may indicate strong local effects, especially in combination with assessment of acid or alkaline reserve, substances exhibiting such physico-chemical properties should be considered as leading to serious damage to eyes (Category 1).*

Step 4: *All attainable information should be used, including human ~~experience~~data. But this information should be restricted to that which pre-exists (e.g. the results of a skin LD_{50} test or historical information on skin corrosion).*

Step 5: *These must be alternative methods for the assessment of eye irritation/ or serious damage to eyes (e.g. irreversible corneal opacity) which have been validated in accordance with internationally agreed principles and criteria (see section 1.3.2 in Chapter 1.3).*

Step 6: *At present this step seems not to be achievable in the near future. Validated alternative methods for the reliable assessment of (reversible) eye irritation need to be developed.*

Step 7: *In the absence of any other relevant information, it is essential to obtain this via an internationally recognized corrosion/irritation test before proceeding to a rabbit eye irritation test. This must be conducted in a staged manner. If possible, this should be achieved using a validated, accepted in vitro skin corrosivity assay. If this is not available, then the assessment should be completed using animal tests (see the skin irritation/ corrosion strategy, section 3.2.2).*

Step 8: *Staged assessment of eye irritation in vivo. If in a limit test with one rabbit serious damage to eyes is detected no further testing is needed.*

Step 9: *Only two animals may be employed for irritation testing (including the one used for evaluation of possible serious effects) if these two animals give concordant clearly irritant or clearly non-irritant responses. In the case of different or borderline responses a third animal is needed. Depending on the result of this three-animal test, classification may be required or not.*

3.3.2.8 *Irreversible effects on the eye/serious damage to eyes (Category 1)*

A single harmonized hazard category is adopted for substances that have the potential to seriously damage the eyes. This hazard category - Category 1 (irreversible effects on the eye) - includes the criteria listed below. These observations include animals with grade 4 cornea lesions and other severe reactions (e.g. destruction of cornea) observed at any time during the test, as well as persistent corneal opacity, discoloration of the cornea by a dye substance, adhesion, pannus, and interference with the function of the iris or other effects that impair sight. In this context, persistent lesions are considered those which are not fully reversible within an observation period of normally 21 days. Hazard classification: Category 1 also contains substances fulfilling the criteria of corneal opacity ≥ 3 or iritis > 1.5 detected in a Draize eye test with rabbits, because severe lesions like these usually do not reverse within a 21 days observation period.

Table 3.3.1: Irreversible eye effects categories [a]

An eye irritant Category 1 (irreversible effects on the eye) is a test material that produces:
(a) at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or
(b) at least in 2 of 3 tested animals, a positive response of: (i) corneal opacity ≥ 3; and/or (ii) iritis > 1.5; calculated as the mean scores following grading at 24, 48 and 72 hours after instiallation of the test material.

~~[a] *The use of human data is discussed in "Purpose, scope and application" (para. 1.1.2.5 (c)) and "Classification of hazardous substances and mixtures" (para. 1.3.2.4.7).*~~

[a] *The use of human data is discussed in 3.3.2.4, in the Chapter 1.1 (para.* 1.1.2.5(c)*) and in the Chapter 1.3 (para. 1.3.2.4.7).*

3.3.2.9 *Reversible effects on the eye (Category 2)*

A single category is adopted for substances that have the potential to induce reversible eye irritation. This single hazard category provides the option to identify within the category a sub-category for substances inducing eye irritant effects reversing within an observation time of 7 days.

Those authorities desiring one single category for classification of "eye irritation" may use the overall harmonized Category 2 (irritating to eyes); others may want to distinguish between Category 2A (irritating to eyes) and Category 2B (mildly irritating to eyes).

Table 3.3.2: Reversible eye effects categories

An eye irritant Category 2A (irritating to eyes) is a test material that produces:
(a) at least in 2 of 3 tested animals a positive response of: (i) corneal opacity ≥ 1; and/or (ii) iritis ≥ 1; and/or (iii) conjunctival redness ≥ 2; and/or (iv) conjunctival oedema (chemosis) ≥ 2 calculated as the mean scores following grading at 24, 48 and 72 hours after ~~installation~~ instillation of the test material, and which fully reverses within an observation period of normally 21 days.
Within this category an eye irritant is considered **mildly irritating to eyes (Category 2B)** when the effects listed above are fully reversible within 7 days of observation.

For those substances where there is pronounced variability among animal responses, this information may be taken into account in determining the classification.

3.3.3 Classification criteria for mixtures

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

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

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 manufacturers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for skin corrosion and serious eye damage and eye irritation to help ensure an accurate classification, as well as avoid unnecessary animal testing. A mixture is considered to cause serious eye damage (Eye Category 1) if it has a pH ≤ 2 or ≥ 11.5. If consideration of ~~alkali/acid~~acid/alkaline reserve suggests the ~~substance or~~ mixture may not have the potential to cause serious eye damage 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.

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

3.3.3.2.1 Where the mixture itself has not been tested to determine its skin corrosivity or potential to cause serious eye damage or eye irritation, 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.

3.3.3.2.2 *Dilution*

If a tested mixture is diluted with a diluent which has an equivalent or lower classification for serious eye damage/eye ~~irritancy~~ irritation classification than the least damaging/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 3.3.3.3 could be applied.

3.3.3.2.3 *Batching*

The ~~irritation/~~serious eye damage/eye 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 of the untested batch has changed. If the latter occurs, a new classification is necessary.

3.3.3.2.4 *Concentration of mixtures of the highest serious eye damage/eye irritation category*

If a tested mixture classified in the highest category for serious eye damage is concentrated, the more concentrated untested mixture should be classified in the highest serious eye damage category without additional testing. If a tested mixture classified in the highest sub-category for ~~skin/~~eye irritation is concentrated and does not contain serious eye damage ingredients, the more concentrated untested mixture should be classified in the highest eye irritation category without additional testing.

3.3.3.2.5 *Interpolation within one toxicity category*

For three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and are in the same ~~irritation/~~serious eye damage/eye irritation toxicity 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 ~~irritation/~~serious eye damage/eye irritation category as A and B.

3.3.3.2.6 *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 ~~irritation/~~serious eye damage/eye 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 of B.

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

3.3.3.2.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested non-aerosolized form of mixture provided that the added propellant does not affect the irritation or corrosive properties of the mixture upon spraying[9].

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

3.3.3.3.1 In order to make use of all available data for purposes of classifying the ~~eye irritation/~~serious eye damage/eye irritation~~ing~~ properties 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 ≥ 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 eye irritation/serious eye damage.

3.3.3.3.2 In general, the approach to classification of mixtures as ~~eye irritant or~~ seriously damaging to the eye or eye irritant 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 corrosive or irritant ingredient 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 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 seriously damaging to the eye or eye irritant when the sum of the concentrations of such ingredients exceeds a threshold cut-off value/concentration limit.

3.3.3.3.3 Table 3.3.3 provides the cut-off value/concentration limits to be used to determine if the mixture should be classified as ~~an irritant or a~~ seriously damaging to the eye or an eye irritant.

3.3.3.3.4 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 3.3.3.3.1 and 3.3.3.3.2 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 3.3.3.1) since pH will be a better indicator of serious eye damage than the concentration limits of Table 3.3.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach applied in Table 3.3.3 due to chemical characteristics that make this approach unworkable, should be classified as Eye Category 1 if it contains ≥ 1% of a corrosive ingredient and as Eye Category 2 when it contains ≥ 3% of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3.3.3 does not apply is summarized in Table 3.3.4.

---

[9] *Bridging principles apply for the intrinsic hazard classification of aerosols, however, the need to evaluate the potential for "mechanical" eye damage from the physical force of the spray is recognized.*

3.3.3.3.5 On occasion, reliable data may show that the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic cut-off values/concentration limits mentioned in Tables 3.3.3 and 3.3.4. In these cases the mixture could be classified according to those data (see also 1.3.3.2 *"Use of cut-off values/Concentration limits"*). On occasion, when it is expected that the skin corrosion/irritation or the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic concentration/cut-off levels mentioned in Tables 3.3.3 and 3.3.4, testing of the mixture may be considered. In those cases, the tiered weight of evidence strategy should be applied as referred to in section 3.3.3, Figure 3.3.1 and explained in detail in this chapter.

3.3.3.3.6 If there are 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 1.3.3.2 *"Use of cut-off values/concentration limits"*).

Table 3.3.3: Concentration of ingredients of a mixture classified as skin Category 1 and/or eye Category 1 or 2 that would trigger classification of the mixtures as hazardous to the eye (Category 1 or 2)

Sum of ingredients classified as	**Concentration triggering classification of a mixture as**	
	Irreversible eye effects	**Reversible eye effects**
	Category 1	**Category 2**
Eye or skin Category 1	≥ 3%	≥ 1% but < 3%
Eye Category 2/2A		≥ 10%
(10 × eye Category 1) + eye Category 2/2A		≥ 10%
Skin Category 1 + eye Category 1	≥ 3%	≥ 1% but < 3%
10 × (skin Category 1 + eye Category 1) + eye Category 2A/2B		≥ 10%

Table 3.3.4: Concentration of ingredients of a mixture for which the additivity approach does not apply, that would trigger classification of the mixture as hazardous to the eye

Ingredient	**Concentration**	**Mixture classified as: Eye**
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

3.3.4 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.

Table 3.3.5: Label elements for serious eye damage/eye irritation[a]

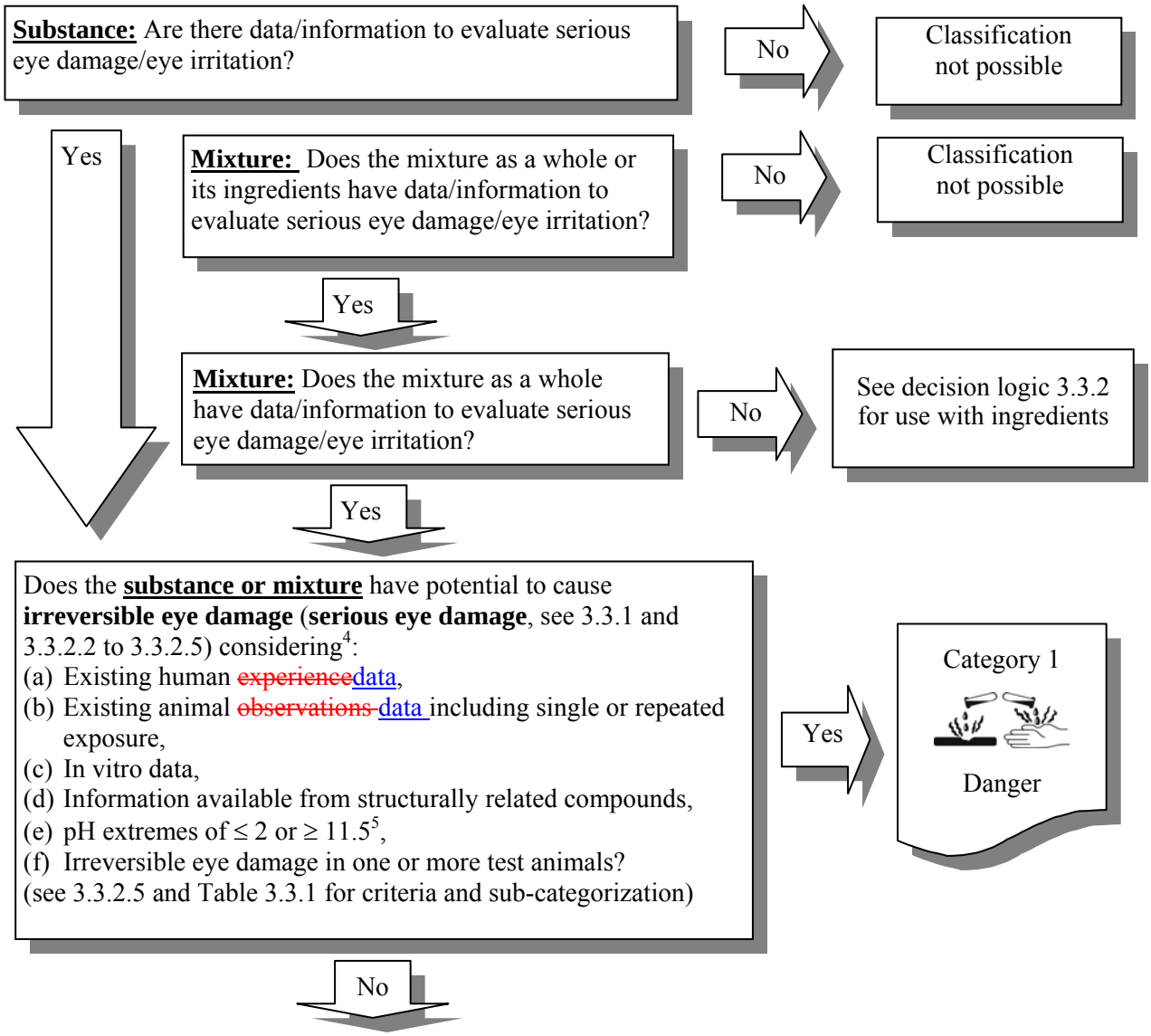
	Category 1	**Category 2A**	**Category 2B**
Symbol	Corrosion	Exclamation mark	*No symbol*
Signal word	Danger	Warning	Warning
Hazard statement	Causes serious eye damage	Causes serious eye irritation	Causes eye irritation

[a] In case a chemical is classified as skin Cat.1, labelling for serious eye damage/eye irritation should be omitted as this information is already included in the hazard statement for skin Cat. 1 (Causes severe skin burns and eye damage).

3.3.5 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.

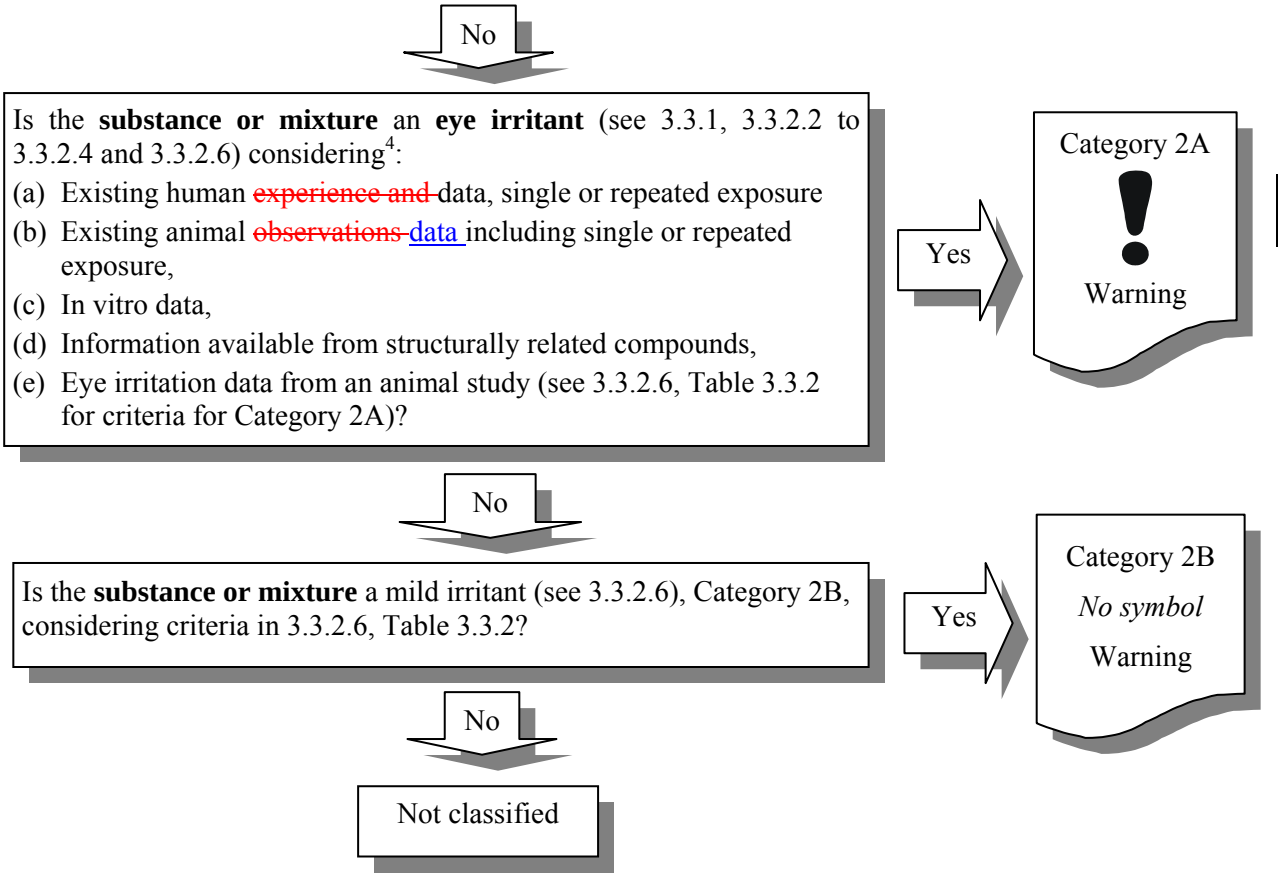
3.3.5.1 *Decision logic 3.3.1 for serious eye damage/eye irritation*



(Cont'd on next page)

[10] *Figure 3.3.1 contains details for testing and evaluation.*

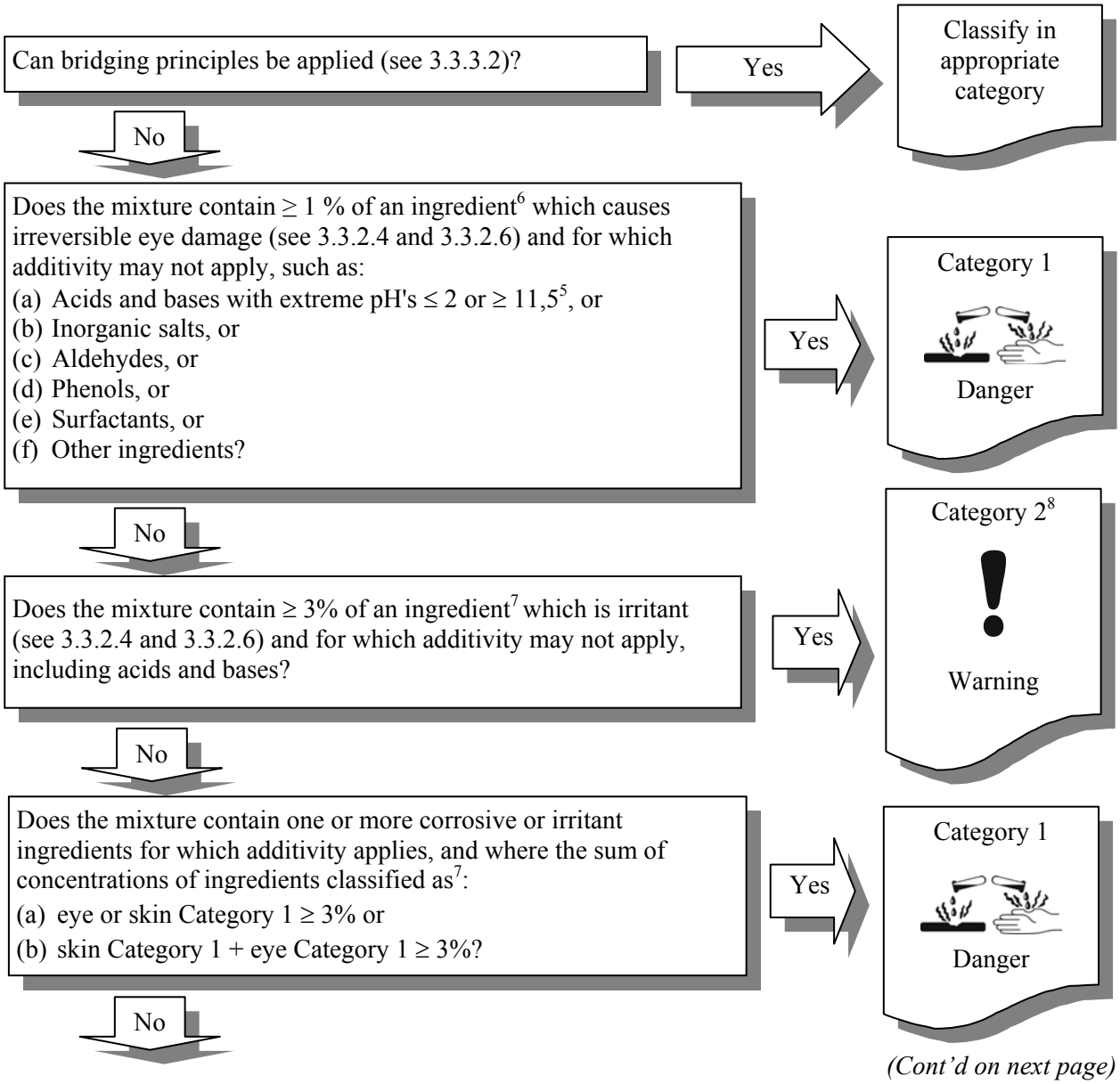
[11] *Including consideration of acid/~~alkali~~ alkaline reserve capacity, if appropriate.*



[4] *Figure 3.3.1 contains details for testing and evaluation.*

3.3.5.2 *Decision logic 3.3.2 for serious eye damage/eye irritation*

Classification of mixtures on the basis of information/data on ingredients



(Cont'd on next page)

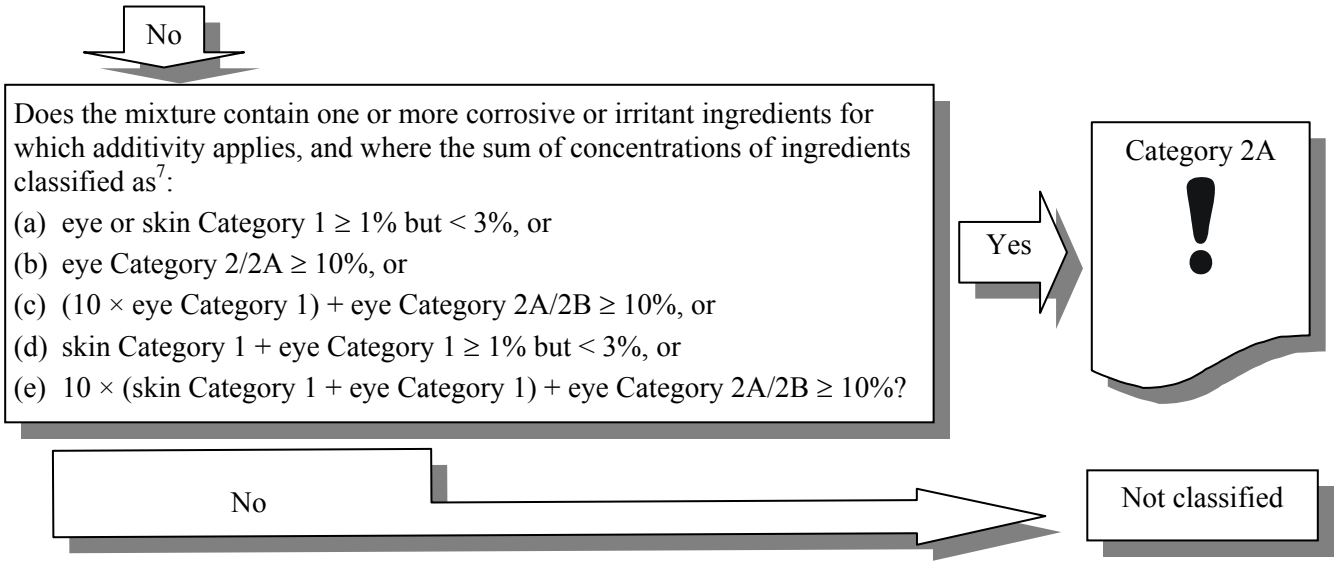
---

[5] *Including consideration of acid/~~alkali~~ alkaline reserve capacity, if appropriate.*

[12] *Or where relevant < 1 %, see 3.3.3.3.1.*

[13] *For specific concentration limits, see 3.3.3.3.4. See also Chapter 1.3, para. 1.3.3.2 for "The Use of cut-off values/concentration limits".*

[14] *If the mixture also contains other corrosive or irritant ingredient(s) for which additivity applies move to the box below.*



[7] *For specific concentration limits, see 3.3.3.3.4. See also Chapter 1.3, para. 1.3.3.2 for "The Use of cut-off values/concentration limits".*

Annex 6

Paper 5_Changes introduced into 3.3.doc:

Changes introduced into 3.3

In 3.3.2.1, first phrase substitute “serious ocular tissue damage” with “serious eye damage”.

In 3.3.2.1, substitute “data” with “information” and “experience” with “data”.

In 3.3.2.2, first phrase substitute “eye irritation and serious damage to the eye” with “serious eye damage/eye irritation”.

In 3.3.2.3 second sentence substitute “an agent” with “a substance”.

In 3.3.2.4, first sentence insert “eye” before “irritation”. In the second sentence substitute “experience” with “data”. In the third sentence substitute “hazard” with “classification”. In the fifth sentence substitute “agents” with “substances”. After the fifth sentence insert the sentence:
“A substance is considered to cause serious eye damage (Eye Category 1) if it has a pH ≤ 2 or ≥ 11.5. If consideration of acid/alkaline reserve suggests the substance may not have the potential to cause serious eye damage 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. “

In 3.3.2.5, third last sentence substitute “caustic alkalis” with “bases” and in second last sentence substitute “experience” with “data”.

In tables 3.3.1 and 3.3.2, substitute “installation” with “instillation”.

Substitute footnote a in table 3.3.1 with the following text: “[a] *The use of human data is discussed in 3.3.2.4, in the Chapter 1.1 (para.* 1.1.2.5(c)), *and in the Chapter 1.3 (para. 1.3.2.4.7).“*

In 3.3.3.1, substitute “alkali/acid” with “acid/alkaline” and delete “substance or”.

In 3.3.3.2.1, insert “eye” before “irritation”.

In 3.3.3.2.2, substitute “irritancy” with “irritation”.

In 3.3.3.2.3, substitute “irritation/serious eye damage” with “serious eye damage/eye irritation”. Delete “skin/” and insert “eye” before “irritation” in the last phrase of 3.3.3.2.4.

In the title of paragraph 3.3.3.2.4, insert “eye” before “irritation”.

In 3.3.3.2.5, substitute twice “irritation/serious eye damage” with “serious eye damage/eye irritation”.

In 3.3.3.2.6, substitute “irritation/serious eye damage” with “serious eye damage/eye irritation”.

In 3.3.3.3.1, substitute “eye irritation/serious eye damaging properties” with “serious eye damage/eye irritation”.

In 3.3.3.3.2, substitute “eye irritant or seriously damaging to the eye” with “seriously damaging to the eye or eye irritant”.

In 3.3.3.3.3, substitute “an irritant or a seriously damaging to the eye” with “as seriously damaging to the eye or an eye irritant”.

In 3.3.5.1, in the fourth row of boxes from the top in the left column box substitute “experience” with “data” and “observations” with “data”. In the third last row of boxes in the left column box delete “experience and” and substitute “observations” with “data”

Insert a footnote a to table 3.3.5 with the following text:
[a] In case a chemical is classified as skin Cat.1, labelling for serious eye damage/eye irritation should be omitted as this information is already included in the hazard statement for skin Cat. 1 (Causes severe skin burns and eye damage).

In the decision logics 3.3.1 and 3.3.2 (paragraphs 3.3.5.1 and 3.3.5.2), footnotes 5, substitute “alkali” with “alkaline”, respectively.

Annex 7

Paper 6_GHS Chapter-3-2 rev3_4th_change_for discussion.doc:

"CHAPTER 3.2
SKIN CORROSION/IRRITATION

3.2.1 Definitions and general considerations

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].

In a tiered approach, emphasis should be placed upon existing human data, followed by animal data, followed by other sources of information. Classification results directly when the data satisfy the criteria. In case the criteria cannot be directly applied, classification of a substance or a mixture is made on the basis of the total weight of evidence (see 1.3.2.4.9). This means that all available information bearing on the determination of toxicity is considered together, including the results of valid *in vitro* tests, relevant animal data, and human experience such as epidemiological and clinical studies and well-documented case reports and observations.

Classification criteria for substances: animal test data

3.2.2.4 [TG3] *Corrosion*

3.2.2.4.1 A single harmonized corrosion category is provided in Table 3.2.1, 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 at least 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.

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

---

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

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

[a] *The use of human data is discussed in 3.2.2.1 and in Chapter 1.3 (para. 1.3.2.4.7).*

3.2.2.5 ***Irritation***

3.2.2.5.1 A single *irritant category* is provided in Table 3.2.2 that:

(a) is centrist in sensitivity among existing classifications;

(b) recognizes 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. An additional mild irritant category is available for those authorities that want to have more than one skin irritant category.

3.2.2.5.2 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.

3.2.2.5.3 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 A single irritant category (Category 2) is presented in the table 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 3.2.2). They mainly differ in the severity of skin reactions. The major criterion for the irritant category is that at least 2 tested animals have a mean score of ≥ 2.3 ≤ 4.0. For the mild irritant category, the mean score cut-off values are ≥ 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 3.2.2 Skin irritation categories [a]

Categories	Criteria
Irritant **(Category 2)** (applies to all authorities)	(1) Mean value of ≥ 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 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 **(Category 3)** (applies to only some authorities)	Mean value of ≥ 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 skin reactions (when not included in the irritant category above).

[a] *The use of human data is discussed in 3.2.2.1 and in the Chapter 1.3 (paragraph 1.3.2.4.7).*

3.2.2[TG4] **Classification criteria for substances: ~~-~~ further data elements**

~~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 in case the criteria described above can not be applied (refer to section above) before testing is undertaken. Solid substances (powders) may become corrosive or irritant when moistened or in contact with moist skin or mucous membranes~~. [SDA5]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 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~~ substances are expected to produce significant effects on the skin. A substance is considered corrosive (Skin Category 1) if it has a pH ≤ 2 or a pH ≥ 11.5. If consideration of alkali/acid reserve suggests the substance or mixture 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. It also stands to reason that 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 corrosion/irritation~~/corrosion~~ in acute toxicity studies and are observed up through the limit dose, ~~additional testing would not be needed,~~these data may 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~~should 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.[SDA6]

~~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~~bases 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 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.~~ [TG7]

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.

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 be classified using the criteria for substances, and taking into account the testing and evaluation strategies to develop data for these hazard classes.

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 as included in the criteria for classification of substances for 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 ≤ 2 or a pH ≥ 11.5. If consideration of alkali/acid reserve suggests the substance or mixture 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.

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, 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 irritation/corrosion 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 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 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 is concentrated and does not contain corrosive ingredients, the more concentrated untested mixture should be classified in the highest irritation category without additional testing.

3.2.3.2.5 *Interpolation within one toxicity category*

For three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and are in the same irritation/corrosion toxicity 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 irritation/corrosion 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 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) 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 mixture provided that the added propellant does not affect the 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 hazards of mixtures, the following assumption has been made and is applied where appropriate in a ~~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.

3.2.3.3.2 In general, the approach to classification of mixtures as irritant or corrosive 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 corrosive or irritant ingredient 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 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 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 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 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 3.2.3 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 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 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 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 the sub-categories 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 3.2.4: **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 2/3) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

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.

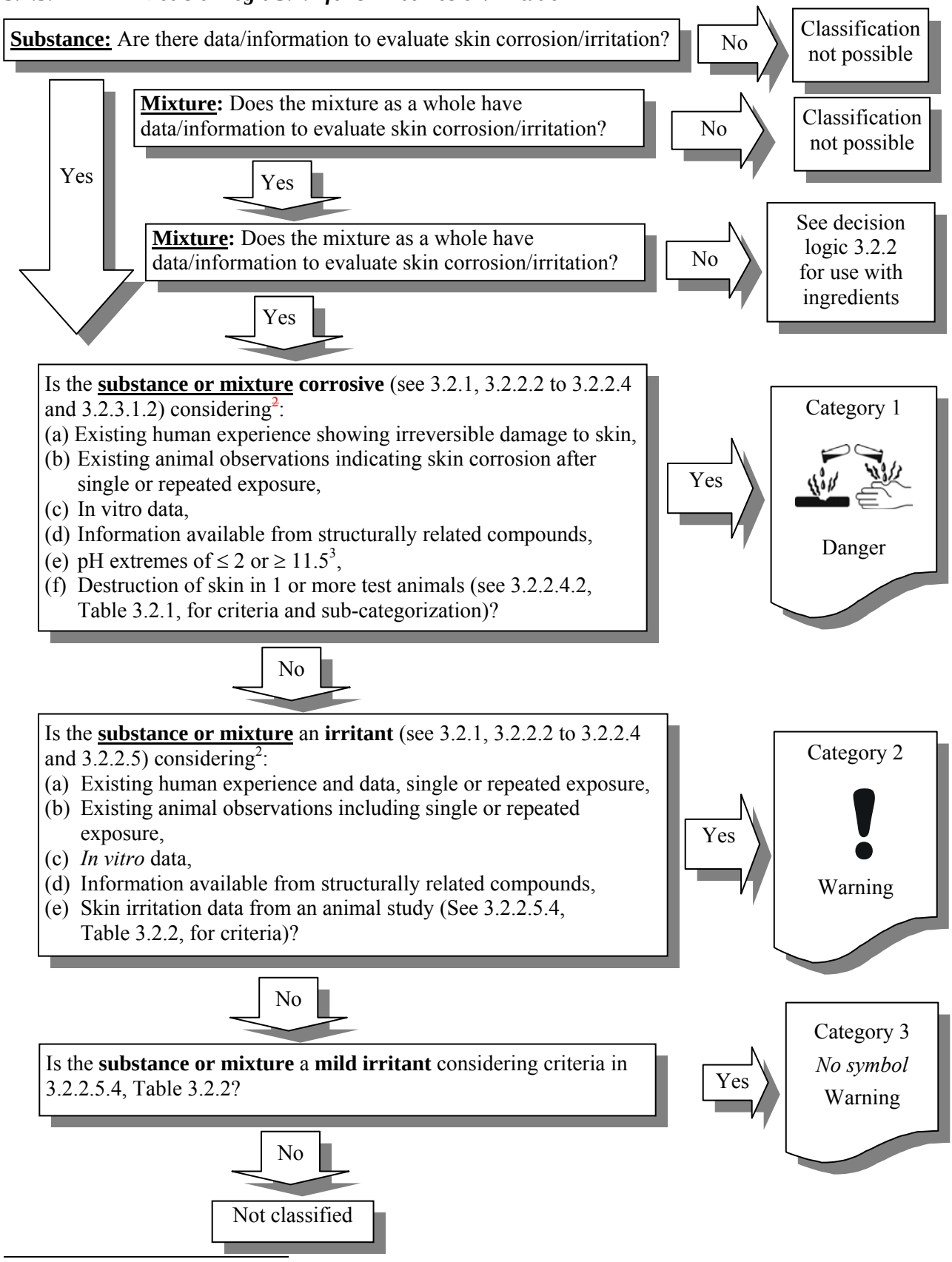
Table 3.2.5: Label elements for skin corrosion/irritation

	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*

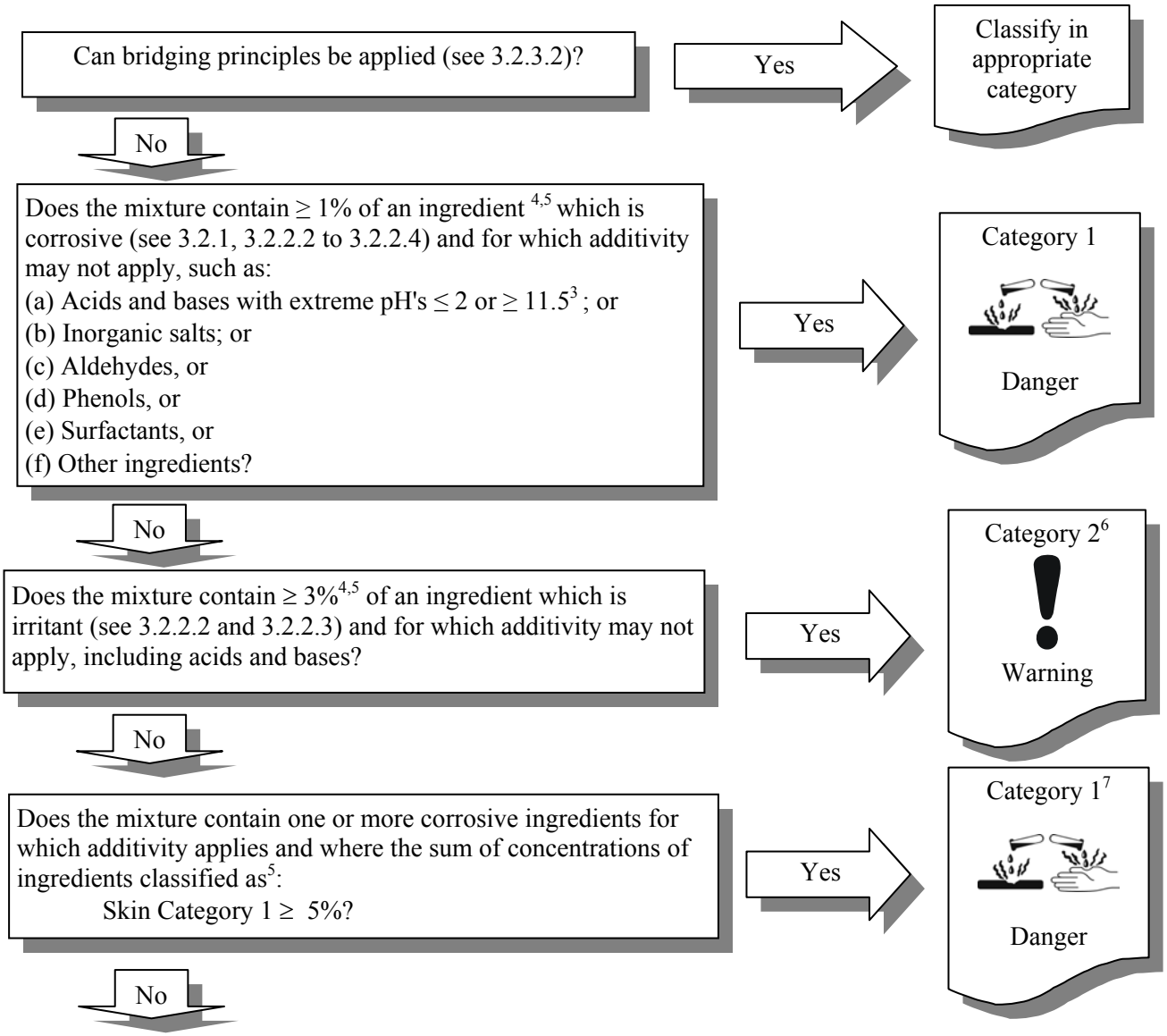


2 *Figure 3.2.1 contains details for ~~testing and~~ evaluation.*

3 *Including consideration of acid/alkali reserve capacity, if appropriate.*

3.2.5.2 ***Decision logic 3.2.2 for skin corrosion/irritation***

Classification of mixtures on the basis of information/data on ingredients



(Cont'd on next page)

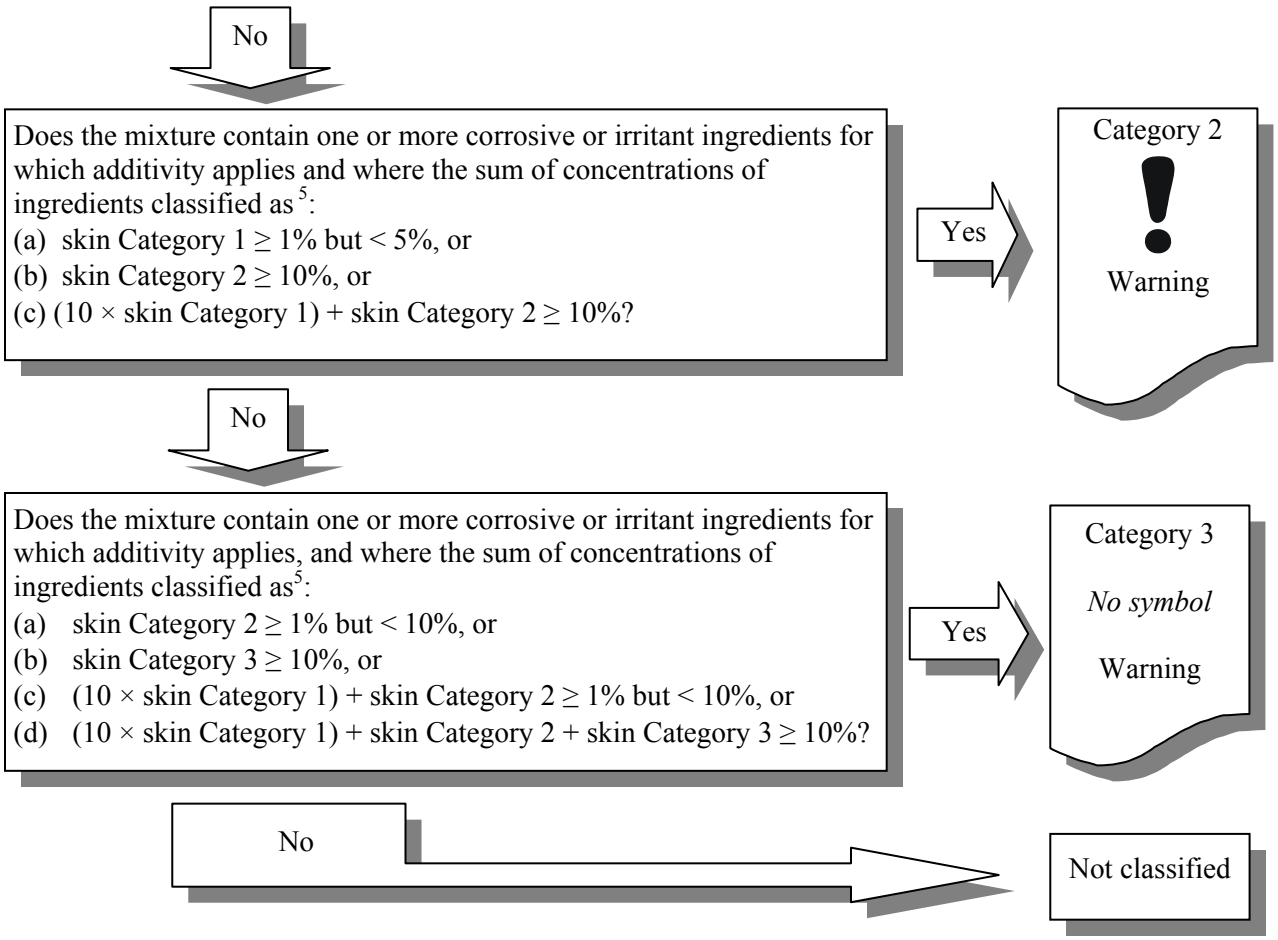
[3] *Including consideration of acid/alkali reserve capacity, if appropriate.*

[4] *Or 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 use of cut-off values/concentration limits".*

[6] *If the mixture also contains corrosive or irritant ingredient(s) for which additivity applies, move to the box below.*

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



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

Annex 8

Paper 7_GHS 3-2-2_4th_change_for discussion_clean.doc:

3.2.2[TG8] **Classification criteria for substances: further data elements**

3.2.2.2 Existing human data including from single or repeated exposure and animal 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 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 substances are expected to produce significant effects on the skin. A substance is considered corrosive (Skin Category 1) if it has a pH ≤ 2 or a pH $\geq$ 11.5. If consideration of alkali/acid reserve suggests the substance or mixture 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. It also stands to reason that if a substance is highly toxic by the dermal route, a skin 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 corrosion/irritation in acute toxicity studies and are observed up through the limit dose, these data may be used for classification provided that the dilutions used and species tested are equivalent. *In vitro* alternatives that have been validated and accepted should be used to make classification decisions. Solid substances (powders) may become corrosive or irritant when moistened or in contact with moist skin or mucous membranes.[SDA9]

Although information might be gained from the evaluation of single parameters within a tier (see 3.2.2.3), e.g. bases 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 conflict in information available on some parameters.

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.

Annex 9

Paper 8_GHS Chapter-3-3 rev3_4th_change_for discussion.doc

"CHAPTER 3.3
SERIOUS EYE DAMAGE /EYE IRRITATION

3.3.1 Definitions and general considerations

Serious eye damage is the production of tissue damage in the eye, or serious physical decay of vision, following application of a test substance to the anterior surface of the eye, which is not fully reversible within 21 days of application[21] .

Eye irritation is the production of changes in the eye following the application of test substance to the anterior surface of the eye, which are fully reversible within 21 days of application[1].

In a tiered approach, emphasis should be placed upon existing human data, followed by animal data, followed by other sources of information. Classification results directly when the data satisfy the criteria. In case the criteria cannot be directly applied, classification of a substance or a mixture is made on the basis of the total weight of evidence (see 1.3.2.4.9). This means that all available information bearing on the determination of toxicity is considered together, including the results of valid *in vitro* tests, relevant animal data, and human experience such as epidemiological and clinical studies and well-documented case reports and observations.

Classification criteria for substances: animal test data

3.3.2.8[TG10] ***Irreversible effects on the eye/serious damage to eyes (Category 1)***

A single harmonized hazard category is adopted for substances that have the potential to seriously damage the eyes. This hazard category - Category 1 (irreversible effects on the eye) - includes the criteria listed below. These observations include animals with grade 4 cornea lesions and other severe reactions (e.g. destruction of cornea) observed at any time during the test, as well as persistent corneal opacity, discoloration of the cornea by a dye substance, adhesion, pannus, and interference with the function of the iris or other effects that impair sight. In this context, persistent lesions are considered those which are not fully reversible within an observation period of normally 21 days. Hazard classification: Category 1 also contains substances fulfilling the criteria of corneal opacity ≥ 3 or iritis > 1.5 detected in a Draize eye test with rabbits, because severe lesions like these usually do not reverse within a 21 days observation period.

Table 3.3.1: Irreversible eye effects categories [a]

An eye irritant Category 1 (irreversible effects on the eye) is a test material that produces:
(a) at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or
(b) at least in 2 of 3 tested animals, a positive response of: (i) corneal opacity ≥ 3; and/or (ii) iritis > 1.5; calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.

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

[a] *The use of human data is discussed in "Purpose, scope and application" (para. 1.1.2.5 (c)) and "Classification of hazardous substances and mixtures" (para. 1.3.2.4.7).*

3.3.2.9 *Reversible effects on the eye (Category 2)*

A single category is adopted for substances that have the potential to induce reversible eye irritation. This single hazard category provides the option to identify within the category a sub-category for substances inducing eye irritant effects reversing within an observation time of 7 days.

Those authorities desiring one single category for classification of "eye irritation" may use the overall harmonized Category 2 (irritating to eyes); others may want to distinguish between Category 2A (irritating to eyes) and Category 2B (mildly irritating to eyes).

Table 3.3.2: Reversible eye effects categories

An eye irritant Category 2A (irritating to eyes) is a test material that produces:
(a) at least in 2 of 3 tested animals a positive response of: (i) corneal opacity ≥ 1; and/or (ii) iritis ≥ 1; and/or (iii) conjunctival redness ≥ 2; and/or (iv) conjunctival oedema (chemosis) ≥ 2 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of normally 21 days.
Within this category an eye irritant is considered **mildly irritating to eyes (Category 2B)** when the effects listed above are fully reversible within 7 days of observation.

For those substances where there is pronounced variability among animal responses, this information may be taken into account in determining the classification.

3.3.2 [TG11] Classification criteria for substances: further data elements

~~3.3.2.1 A tiered testing and evaluation scheme is presented that combines pre-existing information on serious ocular tissue damage and on eye irritation (including data relating to historical human or animal experience) as well as considerations on structure-activity relationships (SAR) and the output of validated *in vitro* tests in order to avoid unnecessary animal testing.~~

~~3.3.2.2 The proposals for classification of eye irritation and serious damage to the eye include elements that are harmonized and will be used by all authorities as well as optional sub-categories that will be applied by only some authorities (e.g. authorities classifying pesticides).~~

~~The harmonized system includes guidance on the data elements that must be evaluated before animal testing for eye damaging effects is undertaken. It also includes hazard categories for local lesions on the eyes.~~

3.3.2.3 ~~Before there is any *in vivo* testing for serious eye damage/eye irritation, all existing information on a test material should be reviewed. Preliminary decisions can often be made from existing data as to whether an agent causes serious (i.e. irreversible) damage to the eyes. If a test material can be classified, no testing is required. A highly recommended way of evaluating existing information on agents or of approaching new uninvestigated substances, is to utilize a tiered testing strategy for serious eye damage and eye irritation.~~

[TG12]

3.3.2.4 ~~Several factors should be considered in determining the serious eye damage or irritation potential of substances in case the criteria described above can not be applied (refer to section above). When animal test data are not available or useful a~~~~Accumulated~~Existing human and animal ~~experience~~ data should be the first line of analysis, as ~~it~~ they give~~s~~ information directly relevant to effects on the eye. ~~-~~In some cases enough information may be available from structurally related compounds to make ~~hazard~~ classification decisions. ~~-~~Likewise, pH extremes like ≤ 2 and ≥ 11.5, may produce serious eye damage, especially when ~~analysed with associated with significant~~ buffering capacity is known.~~-~~ Such ~~agents~~ substances are expected to produce significant effects on the eyes. Possible skin corrosion has to be evaluated prior to consideration of serious eye damage/eye irritation in order to avoid testing for local effects on eyes with skin corrosive substances. *In vitro* alternatives that have been validated and accepted ~~may~~ should be used to make classification decisions.

3.3.2.5 ~~All the above information that is available on a substance should be used in determining the need for *in vivo* eye irritation testing. ~~Although information might be gained from the evaluation of single parameters ~~within a tier (~~e.g. ~~caustic alkalis~~bases with extreme pH should be considered as local 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 conflict in information available on some ~~but not all~~ parameters. ~~-Generally, primary emphasis should be placed upon expert judgement, considering human experience with the substance, followed by the outcome of skin irritation testing and of well validated alternative methods.[TG13]~~ Animal testing with corrosive substances should be avoided whenever possible.

3.3.2.6 A tiered approach to the evaluation of initial information should be considered where applicable (Figure 3.3.1), recognizing that all elements may not be relevant in certain cases. ~~The tiered approach explained in Figure 3.3.1 was developed with contributions from (inter)national centres and committees for the testing and validation of alternatives to animal testing during a workshop in Solna, Sweden[22].~~

~~3.3.2.7 Where data needed for such a testing strategy cannot be required, the proposed tiered testing approach provides good guidance on how to organize existing information on a test material and to make a weight-of-evidence decision about hazard assessment and hazard classification (ideally without conducting new animal tests).~~

[TG14]

3.3.3 Classification criteria for mixtures

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

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

---

[22] *OECD (1996). Final Report of the OECD Workshop on Harmonization of Validation and Acceptance Criteria for Alternative Toxicological Test Methods. Document ENV/MC/TG(96)9 (http://www.oecd.org/ehs/test/background.htm).*

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 manufacturers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for skin corrosion and serious eye damage and eye irritation to help ensure an accurate classification, as well as avoid unnecessary animal testing. A mixture is considered to cause serious eye damage (Eye Category 1) if it has a pH ≤ 2 or ≥ 11.5. If consideration of alkali/acid reserve suggests the substance or mixture may not have the potential to cause serious eye damage 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.

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

3.3.3.2.1 Where the mixture itself has not been tested to determine its skin corrosivity or potential to cause serious eye damage or irritation, 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.

3.3.3.2.2 *Dilution*

If a tested mixture is diluted with a diluent which has an equivalent or lower classification for serious eye damage/irritancy classification than the least damaging/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 3.3.3.3 could be applied.

3.3.3.2.3 *Batching*

The irritation/serious eye damage 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 of the untested batch has changed. If the latter occurs, a new classification is necessary.

3.3.3.2.4 *Concentration of mixtures of the highest serious eye damage/ irritation category*

If a tested mixture classified in the highest category for serious eye damage is concentrated, the more concentrated untested mixture should be classified in the highest serious eye damage category without additional testing. If a tested mixture classified in the highest sub-category for skin/eye irritation is concentrated and does not contain serious eye damage ingredients, the more concentrated untested mixture should be classified in the highest irritation category without additional testing.

3.3.3.2.5 *Interpolation within one toxicity category*

For three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and are in the same irritation/serious eye damage toxicity 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 irritation/serious eye damage category as A and B.

3.3.3.2.6 *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 irritation/serious eye damage 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) or (ii) is already classified by testing, the other mixture can be assigned in the same hazard category.

3.3.3.2.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested non-aerosolized form of mixture provided that the added propellant does not affect the irritation or corrosive properties of the mixture upon spraying[23].

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

3.3.3.3.1 In order to make use of all available data for purposes of classifying the eye irritation/serious eye damaging properties of the mixtures, the following assumption has been made and is applied where appropriate ~~in the~~ a 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 eye irritation/serious eye damage.

3.3.3.3.2 In general, the approach to classification of mixtures as eye irritant or seriously damaging to the eye 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 corrosive or irritant ingredient 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 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 seriously damaging to the eye or eye irritant when the sum of the concentrations of such ingredients exceeds a threshold cut-off value/concentration limit.

3.3.3.3.3 Table 3.3.3 provides the cut-off value/concentration limits to be used to determine if the mixture should be classified an irritant or a seriously damaging to the eye.

---

[23] *Bridging principles apply for the intrinsic hazard classification of aerosols, however, the need to evaluate the potential for "mechanical" eye damage from the physical force of the spray is recognized.*

3.3.3.3.4 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 3.3.3.3.1 and 3.3.3.3.2 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 3.3.3.1) since pH will be a better indicator of serious eye damage than the concentration limits of Table 3.3.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach applied in Table 3.3.3 due to chemical characteristics that make this approach unworkable, should be classified as Eye Category 1 if it contains ≥ 1% of a corrosive ingredient and as Eye Category 2 when it contains ≥ 3% of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3.3.3 does not apply is summarized in Table 3.3.4.

3.3.3.3.5 On occasion, reliable data may show that the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic cut-off values/concentration limits mentioned in Tables 3.3.3 and 3.3.4. In these cases the mixture could be classified according to those data (see also 1.3.3.2 *"Use of cut-off values/Concentration limits"*). On occasion, when it is expected that the skin corrosion/irritation or the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic concentration/cut-off levels mentioned in Tables 3.3.3 and 3.3.4, testing of the mixture may be considered. In those cases, the ~~tiered weight of evidence~~ strategy should be applied as referred to in section 3.3.3, Figure 3.3.1 and explained in detail in this chapter.

3.3.3.3.6 If there are 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 1.3.3.2 *"Use of cut-off values/concentration limits"*).

Table 3.3.3: Concentration of ingredients of a mixture classified as skin Category 1 and/or eye Category 1 or 2 that would trigger classification of the mixtures as hazardous to the eye (Category 1 or 2)

Sum of ingredients classified as	**Concentration triggering classification of a mixture as**	
	Irreversible eye effects	**Reversible eye effects**
	Category 1	**Category 2**
Eye or skin Category 1	≥ 3%	≥ 1% but < 3%
Eye Category 2/2A		≥ 10%
(10 × eye Category 1) + eye Category 2/2A		≥ 10%
Skin Category 1 + eye Category 1	≥ 3%	≥ 1% but < 3%
10 × (skin Category 1 + eye Category 1) + eye Category 2A/2B		≥ 10%

Table 3.3.4: Concentration of ingredients of a mixture for which the additivity approach does not apply, that would trigger classification of the mixture as hazardous to the eye

Ingredient	**Concentration**	**Mixture classified as: Eye**
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

3.3.4 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.

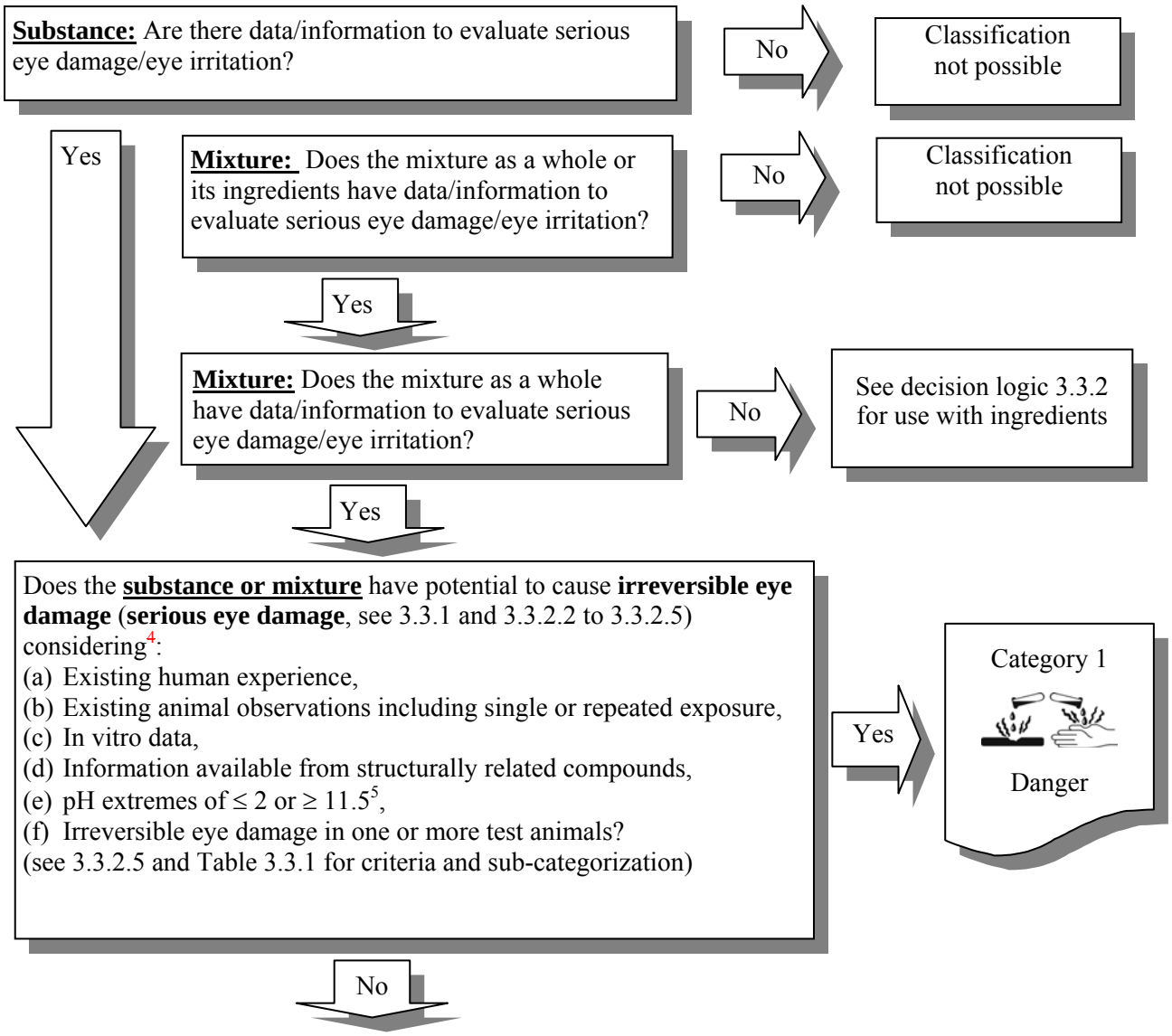
Table 3.3.5: Label elements for serious eye damage/eye irritation

	Category 1	**Category 2A**	**Category 2B**
Symbol	Corrosion	Exclamation mark	*No symbol*
Signal word	Danger	Warning	Warning
Hazard statement	Causes serious eye damage	Causes serious eye irritation	Causes eye irritation

3.3.5 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.

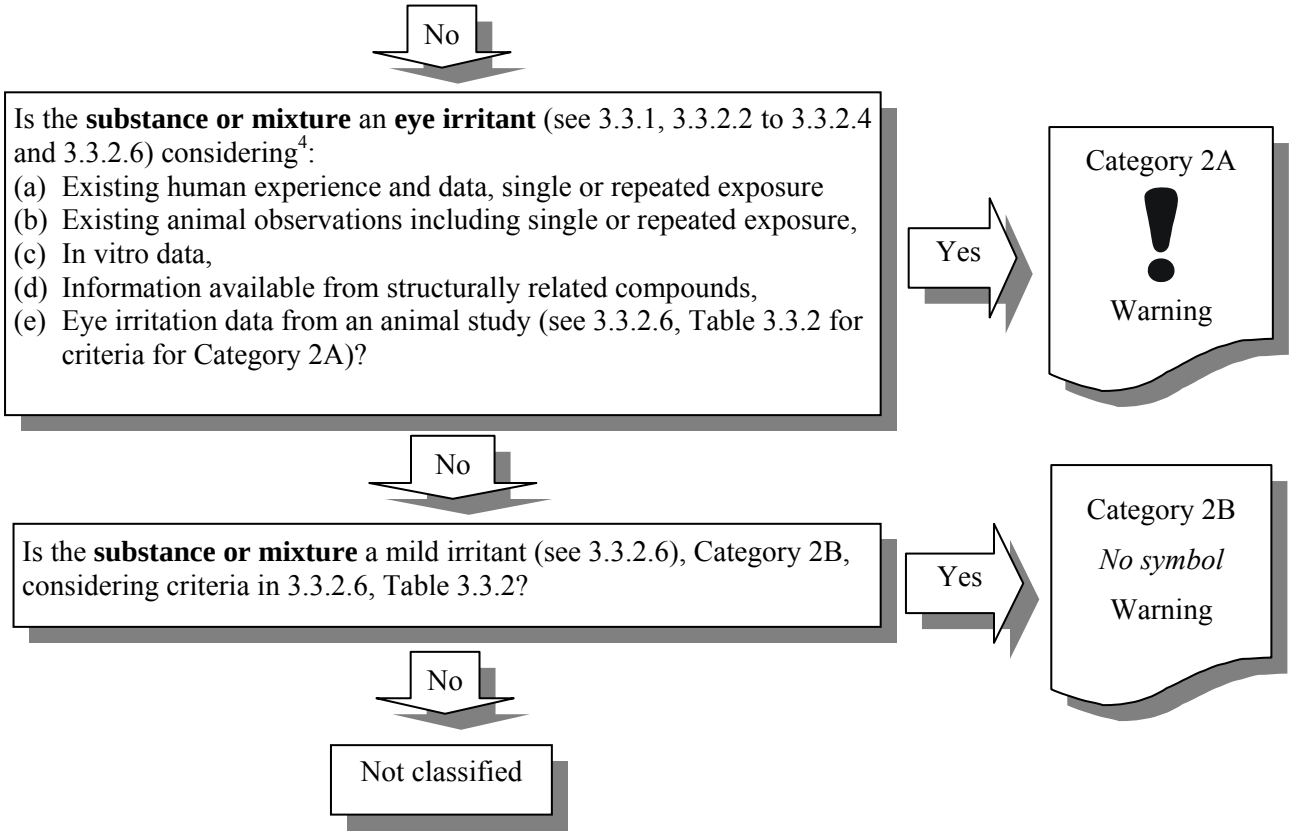
3.3.5.1 *Decision logic 3.3.1 for serious eye damage/eye irritation*



(Cont'd on next page)

[24] *Figure 3.3.1 contains details for ~~testing and~~ evaluation.*

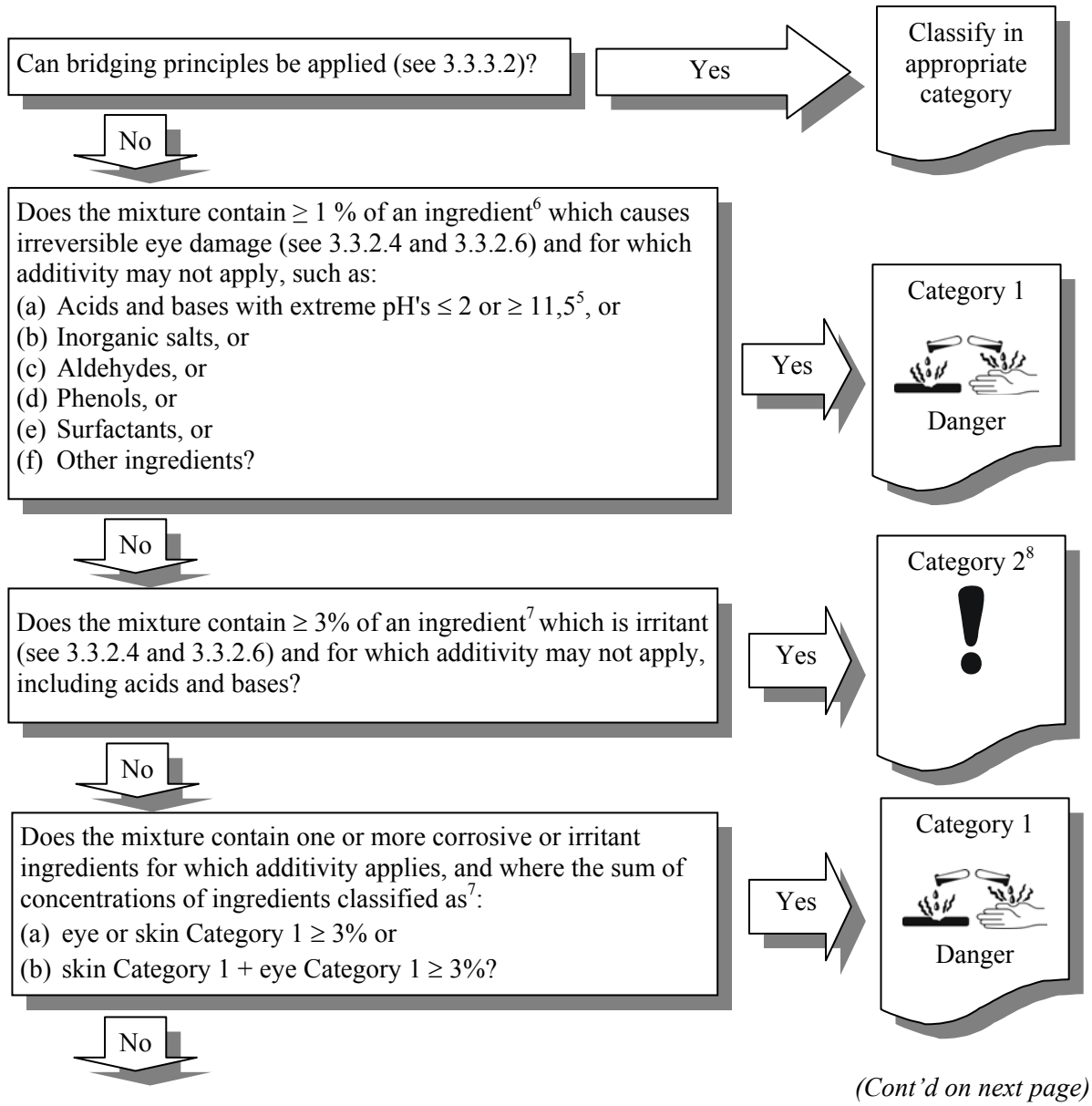
[25] *Including consideration of acid/alkali reserve capacity, if appropriate.*



[4] *Figure 3.3.1 contains details ~~for testing and~~ evaluation.*

3.3.5.2 *Decision logic 3.3.2 for serious eye damage/eye irritation*

Classification of mixtures on the basis of information/data on ingredients



(Cont'd on next page)

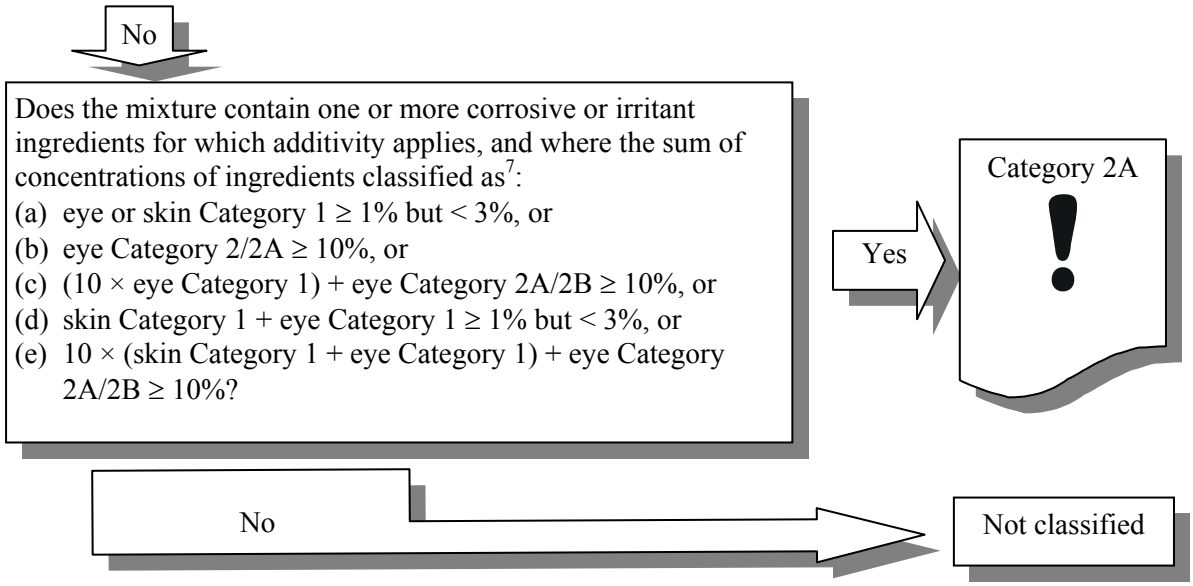
---

[5] *Including consideration of acid/alkali reserve capacity, if appropriate.*

[26] *Or where relevant < 1 %, see 3.3.3.3.1.*

[27] *For specific concentration limits, see 3.3.3.3.4. See also Chapter 1.3, para. 1.3.3.2 for "The Use of cut-off values/concentration limits".*

[28] *If the mixture also contains other corrosive or irritant ingredient(s) for which additivity applies move to the box below.*



[7] *For specific concentration limits, see 3.3.3.3.4. See also Chapter 1.3, para. 1.3.3.2 for "The Use of cut-off values/concentration limits".*

Annex 10

Paper 9_GHS 3-3-2_4th_change_for discussion_clean.doc

3.3.2[TG15] **Classification criteria for substances: further data elements**

[TG16]3.3.2.4 Existing human and animal data should be the first line of analysis, as they give information directly relevant to effects on the eye. 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 produce serious eye damage, especially when buffering capacity is known. Such substances are expected to produce significant effects on the eyes. Possible skin corrosion has to be evaluated prior to consideration of serious eye damage/eye irritation in order to avoid testing for local effects on eyes with skin corrosive substances. *In vitro* alternatives that have been validated and accepted should be used to make classification decisions.

3.3.2.5 Although information might be gained from the evaluation of single parameters e.g. bases with extreme pH should be considered as local 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 conflict in information available on some parameters. Animal testing with corrosive substances should be avoided whenever possible.

3.3.2.6 A tiered approach to the evaluation of initial information should be considered where applicable (Figure 3.3.1), recognizing that all elements may not be relevant in certain cases.

Annex 11

Paper 10_skin_eye_evaluation data more than 3 animals_draft08Sept09.doc

DRAFT/version 08 Sept 2009

Thought starter

Skin/Eye Irritation: Evaluation of data from tests conducted with more than 3 animals

1. Issue

Classification criteria for skin and eye effects are detailed in GHS in terms of a 3-animal test. However, some older test methods may have used up to 6 animals. GHS does not specify how to classify existing data based on such tests with 4, 5 or 6 animals.

2. Background

This issue was initially raised at the OECD Workshop in July 2007 on the Application of GHS Classification Criteria to HPV Chemicals. At this Workshop, Amy Rispin (US EPA) gave a presentation on the guidance developed by ICCVAM to classify for eye irritation based on data from tests with more than 3 animals.

This issue was also discussed in the EU RIP 3.6 Experts Group during development of guidance for the EU GHS implementation legislation (the so called CLP Regulation (EC) No. 1272/2008). The resultant approaches for skin and eye irritation have been included in the EU CLP guidance document which has just been published on the ECHA website.

The agreed EU approach to the evaluation of existing test data with more than 3 animals is as follows:

2.1 *Skin Irritation*

(a) Option 1

The overall average over all animals will be used. In this case Skin Irritant Category 2 is assigned if the overall average for erythema/eschar or for oedema is 2.3 or above.

For example, a substance was tested for skin irritation/corrosion according to OECD TG 404. Contact time was 4 hours. No effects were seen after a contact time of 3 min and one hour. The following scores were obtained:

Animal Nr	Degree of erythema after …[observation time]						Degree of oedema after …[observation time]					
	1h	24h	48h	72h	7d	14d	1h	24h	48h	72h	7d	14d
1	3	3	2	2	1	0	2	3	2	2	1	0
2	3	2	2	2	1	0	2	2	2	2	1	0
3	2	2	1	1	1	0	2	2	2	2	1	0
4	2	2	1	1	1	0	2	2	2	2	1	0

Evaluation was made based on the arithmetic mean of all animals.

The arithmetic mean after 24/48/72 hours for erythema M_E= 21:12 = 1.8; and for oedema M_O = 25:12 = 2.1. Both values are below 2.3, i.e. no classification is warranted for skin irritation.

This approach has been common practice under the EU Dangerous Substances Directive and was included in the EU CLP guidance document for the sake of flexibility (i.e. reduces the need for revisiting all the original test reports and re-calculating the means - overall arithmetic mean versus per animal mean).

(b) Option 2

The average score is determined per animal. In this case Skin Irritant Category 2 is assigned if 4 of 6 rabbits show a mean score of 2.3 or above. Likewise, if the test was performed with 4 or 5 animals, for at least 3 individuals the mean score must exceed the value of 2.3 to classify as Skin Irritant Category 2.

For example, a substance was tested on acute skin irritation / corrosion according to OECD TG 404. Contact time was 4 hours. No effects were seen after a contact time of 3 min and one hour. The following scores were obtained after a contact time of 4 hours:

Animal Nr	Degree of erythema after … [observation time]						Degree of oedema after … [observation time]						Positive responder	
	1h	24h	48h	72h	7d	14d	1h	24h	48h	72h	7d	14d	Erythe-ma	Oede-ma
1	3	3	2	2	1	0	2	3	2	2	1	0	Yes	Yes
2	3	2	2	2	1	0	2	2	2	2	1	0	No	No
3	2	2	1	1	1	0	2	2	2	2	1	0	No	No
4	2	2	1	1	1	0	2	2	2	2	1	0	No	No

Evaluation was made based on the average score per animal.

Only 1/4 of the animals reached the cut-off value of 2.3, i.e. only animal No 1 is a positive responder. No classification is warranted with regard to skin irritation.

The more stringent result has to be used if the evaluation according to the method shown in option 1 is different to that under option 2.

2.2 Serious eye damage/eye irritation

(a) *In the case of a study with **6** rabbits the following applies:*

Classification as Serious eye damage Category 1 if at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or

at least 4 out of 6 rabbits show a mean score of ≥ 3 for the cornea and/or ≥ 1.5 for the iris.

Classification as Eye irritation Category 2 if at least 4 out of 6 rabbits show a mean score of
≥ 1 for the cornea and/or
≥ 1 for the iris and/or
≥ 2 for conjunctival erythema and/or
≥ 2 for conjunctival swelling.

(b) *In the case of a study with **5** rabbits the following applies:*

Classification as Serious eye damage Category 1 if at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or

at least 3 out of 5 rabbits show a mean score of ≥ 3 for the cornea and/or ≥ 1.5 for the iris.

Classification as Eye irritation Category 2 if at least 3 out of 5 rabbits show a mean score of
≥ 1 for the cornea and/or
≥ 1 for the iris and/or
≥ 2 for conjunctival erythema and/or
≥ 2 for conjunctival swelling.

(c) *In case of a study with **4** rabbits the following applies:*

Classification as Serious eye damage Category 1 if at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or

at least 3 out of 4 rabbits show a mean score of ≥ 3 for the cornea and/or ≥ 1.5 for the iris.

Classification as Eye irritation Category 2 if at least 3 out of 4 rabbits show a mean score of
≥ 1 for the cornea and/or
≥ 1 for the iris and/or
≥ 2 for conjunctival erythema and/or
≥ 2 for conjunctival swelling.

3. Way forward

The Correspondence Group may wish to consider using a similar approach in the GHS for the evaluation of existing data from studies with more than 3 animals.

The Correspondence Group may also wish to consider including an additional approach for the evaluation of eye effects based on overall mean scores (similar to option 1 for the evaluation of skin irritation).

Annex 12

Paper 11_Skin_corr_irrit_substances_CLP guidance_decision logic.doc:

SKIN CORROSION/IRRITATION

Decision logic for classification of substances

(extract from guidance document dated August 2009 for EU CLP Regulation)

Step		
1a	Is the substance an organic hydro peroxide or an organic peroxide? **YES** ➔ **NO** ↓	Consider to classify as – corrosive (Skin Corr. 1B) if the substance is a hydro peroxide, or – irritating (Skin Irrit. 2) if the substance is a peroxide. OR Provide evidence for the contrary and proceed to step 1b
1b	Is the pH of the substance ≤ 2 or ≥ 11.5? **YES** ➔ **NO** ↓	Consider to classify as corrosive. – Where classification is based upon consideration of pH alone (i.e. buffering capacity is not known), Skin Corr. 1A should be applied. – Where consideration of alkali/acid reserve suggests that the substance is not corrosive, this has to be confirmed (preferably by use of an appropriate *in vitro* test). Proceed to step 1c
1c	Are there other physical or chemical properties that indicate that the substance is irritating / corrosive? **YES** ➔ **NO** ↓	Use this information for weight of evidence (WoE) determination (step 7). Proceed to step 2
2	Are there adequate existing human data which provide evidence that the substance is corrosive or irritant? **YES** ➔ **NO** ↓	Classify accordingly.
3	Are there data from existing studies *on irritation and corrosion* in laboratory animals, which provide sound conclusive evidence that the substance is a corrosive, irritant or non-irritant? **YES** ➔ **NO** ↓	Classify accordingly (either Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification).
4a	Has the substance proven to be a corrosive, irritant or non-irritant in a suitable acute dermal toxicity test? **YES** ➔ **NO** ↓	If test conditions are consistent with OECD TG 404, classify accordingly (Skin Corr. 1A/ 1B/1C or Skin Irrit. 2 or no classification) If test conditions are not consistent with OECD TG 404, use this information in the WoE determination (step 7) and proceed to step 4b

Step		
4b	Has the substance proven to be a corrosive or an irritant in sensitisation studies or after repeated exposure? **YES ➔** NO **↓**	Classification cannot be considered directly. Use this information for WoE determination (step 7). Proceed to step 5a
5a	Are there structurally related substances (suitable "read-across" or grouping), which are classified as corrosive (Skin Cat. 1) on the skin, or do suitable (Q)SAR methods indicate corrosive potential of the substance? **YES ➔** **NO** **↓**	Consider to classify as Skin Corr. 1. Proceed to step 5b
5b	Are there structurally related substances (suitable "read-across" or grouping), which are classified as irritant on the skin (Skin Cat. 2), or do suitable (Q)SAR methods indicate the presence of irritating potential of the substance? **YES ➔** **NO** **↓**	Consider to classify as Skin Irrit. 2. Proceed to step 6a
6a	Has the substance demonstrated corrosive properties in an OECD adopted *in vitro* test? **YES ➔** **NO** **↓**	Classify as corrosive. If discrimination between Skin Corr. 1A/1B/1C is not possible, Skin Corr. 1 must be chosen.
6b	Are there acceptable data from a validated *in vitro* test (adopted by OECD or not), which provide evidence that the substance is an irritant or non-irritant? **YES ➔** **NO** **↓**	Consider to classify accordingly (Skin Irrit. 2 or no classification). Proceed to step 6c
6c	Are there data from a suitable *in vitro* test, which provide sound conclusive evidence that the substance is an irritant? **YES ➔** **NO** **↓**	Consider to classify as Skin Irrit. 2 Proceed to step 7
7	Taking all existing and relevant data (steps 1-6) into account, is there sufficient information to make a decision on classification? **YES ➔** **NO** **↓**	Classify accordingly (Skin Corr. 1A or Skin Corr. 1B or Skin Corr. 1C or Skin Irrit. 2 or no classification)
Unable to classify substance for skin corrosion/irritation		Decision to undertake generation of new test data should be made in compliance with REACH and Article 8 of CLP. It is recommended that IR/CSA R.7.2.6 should also be considered.

Annex 13

Paper 12_Skin_corr_irrit_mixtures_CLP guidance_decision logic.doc

SKIN CORROSION/IRRITATION

Decision logic for classification of mixtures
(extract from guidance document dated August 2009 for EU CLP Regulation)

1. When data are available for the complete mixture		
1a	Is the pH of the mixture ≤ 2 or ≥ 11.5? **YES** ➔ **NO** 🡻	Consider to classify as corrosive. – Where classification is based upon consideration of pH alone (i.e. buffering capacity is not known), Skin Corr. 1A should be applied. – Where consideration of alkali/acid reserve suggests that the substance is not corrosive, this has to be confirmed (preferably by use of an appropriate *in vitro* test). Proceed to step 1b.
1b	Are there other physical or chemical properties that indicate that the mixture is corrosive/irritating? **YES** ➔ **NO** 🡻	Use this information for WoE analysis (step 6). Proceed to step 2
2	Is there adequate existing human experience which provides evidence that the mixture is corrosive or irritant? **YES** ➔ **NO** 🡻	Classify accordingly (Skin Corr. 1 or Skin Irrit. 2).
3	Are there data from existing studies *on irritation and corrosion* in laboratory animals, which provide sound conclusive evidence that the mixture is corrosive, irritant or non-irritant? **YES** ➔ **NO** 🡻	Classify accordingly (Skin Corr. 1A or Skin Corr. 1B or Skin Corr. 1C or Skin Irrit. 2 or no classification).
4a	Has the mixture proven to be a corrosive, irritant or non-irritant in a suitable acute dermal toxicity test? **YES** ➔ **NO** 🡻	– If test conditions are consistent with OECD TG 404, classify accordingly (Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification). – If test conditions are not consistent with OECD TG 404, use this information in the WoE determination (step 6) and proceed to step 4b
4b	Has the mixture proven to be a corrosive or an irritant in sensitisation studies or after repeated exposure? **YES** ➔ **NO** 🡻	Classification cannot be considered directly. Use this information for WoE determination (step 6). Proceed to step 5a

5a	Has the mixture demonstrated corrosive properties in an OECD adopted *in vitro* test? **YES ➔** **NO** **↓**	Classify as corrosive. If discrimination between Skin Corr. 1A/1B/1C is not possible, Skin Corr. 1 must be chosen.
5b	Are there acceptable data from a validated *in vitro* test (adopted by OECD or not), which provide evidence that the mixture is an irritant or non-irritant? **YES ➔** **NO** **↓**	Consider to classify accordingly (Skin Irrit. 2 or no classification). Proceed to step 5c
5c	Are there data from a suitable *in vitro* test, which provide sound conclusive evidence that the mixture is an irritant? **YES ➔** **NO** **↓**	Consider to classify as Skin Irrit. 2. Proceed to step 6
6	Taking all existing and relevant data (steps 1-5) into account including potential synergistic/antagonistic effects and bioavailability, is there sufficient information to make a decision on classification? **YES ➔** **NO** **↓**	Classify accordingly (Skin Corr. 1A or Skin Corr. 1B or Skin Corr. 1C or Skin Irrit. 2 or no classification**)**
2. When data are not available for the complete mixture: bridging principles		
7a	Are existing sufficient skin corrosion/irritation data available on similar tested mixtures and on the individual ingredients? **NO ➔** **YES** **↓**	Proceed to step 8
7b	Can bridging principles be applied? **YES ➔** **NO** **↓**	Classify in appropriate category (Skin Corr. 1A or Skin Corr. 1B or Skin Corr. 1C or Skin Irrit. 2 or no classification)
3. When data are available for all components or only for some components of the mixture		
8a	Is pH of the mixture ≤ 2 or ≥ 11.5? **YES ➔** **NO** **↓**	Follow decision logic in Section 3.2.3.2.1.1 and classify accordingly.
8b	Is there any indication that the additivity principle does not apply? **YES ➔** **NO** **↓**	Annex I, section. 3.2.3.3.4 and Table 3.2.4 may apply. Take into account relevant ingredients (Annex I, 3.2.3.3.1. and SCLs as appropriate. Classify in appropriate category (Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification)
	Annex I, section 3.2.3.3.2 and Table 3.2.3 applies. Take into account relevant ingredients (Annex I, 3.2.3.3.1. and SCLs as appropriate. Classify in appropriate category (Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification)	Where the mixture is classified as corrosive but the data used for classification does not allow differentiation between the skin corrosion subcategories 1A/1B/1C, then the mixture should be assigned Skin corrosion Category 1.

Annex 14

Paper 13_Skin_corr_irrit_extreme pH_CLP guidance_decision logic.doc

SKIN CORROSION/IRRITATION

Mixtures with extreme pH
(extract from guidance document dated August 2009 for EU CLP Regulation)

As a general rule, mixtures with a pH of ≤ 2 or ≥ 11.5 should be considered as corrosive. However, assessment of the buffering capacity of the mixture indicated by its acid or alkali reserve should be considered. If the additional consideration of the acid/alkaline reserve according to Young *et a*l. (1987, 1994) suggests that classification for corrosion or even irritation may not be warranted, then further *in vitro* testing to confirm final (or no) classification shall be carried out. The consideration of acid/alkali reserve should not be used alone to exonerate mixtures from classification.

Where the mixture has an extreme pH value but the only corrosive/irritant ingredient present in the mixture is an acid or base with an assigned SCL (either in CLP Annex VI or set by supplier), then the mixture should be classified according to the SCL. In this instance, pH of the mixture should not be considered a second time since it would have already been taken into account when deriving the SCL for the substance.

If this is not the case, then the steps to be taken into consideration when classifying a mixture with pH ≤ 2 or ≥ 11.5 are described in the following decision logic:

Mixture without *in vivo* data on skin corrosion or relevant data from similar tested mixtures, **pH is ≤ 2 or ≥ 11.5**	
Does the acid alkaline reserve indicate that the mixture may not be corrosive? **NO** ➔ **YES** 🡻	Classify as corrosive, Skin Corr. Cat. 1A.
Is the mixture tested in an OECD adopted *in vitro* test for skin corrosion? **NO** ➔ **YES** 🡻	Classify as corrosive, Skin Corr. Cat. 1A.
Does the mixture demonstrate corrosive properties in an OECD adopted *in vitro* test? **YES** ➔ **NO** 🡻	Classify as corrosive. If discrimination between Skin Corr. 1A/1B/1C is not possible, Skin Corr. 1 must be chosen.
Apply methods in Annex I, sections 3.2.3.3.2 (Table 3.2.3) / 3.2.3.3.4 (Table 3.2.4) ➔ (When validated *in vitro* skin irritation test methods are available, these may be used to generate data to classify the mixture instead of using the summation method.)	Classify accordingly.

The mixture must be classified as Skin corrosion Category 1 should the supplier decide not to carry out the required confirmatory testing.

It is also important to note that the pH-acid/alkali reserve to change classification from corrosive to irritant or from irritant to not classified assumes that the potential corrosivity or irritancy is due to the effect of the ionic entities. When this is not the case, especially when the mixture contains non-ionic (non-ionisable) substances themselves classified as corrosive or irritant, then the pH-reserve method cannot be a basis for modifying the classification but should be considered in a weight of evidence analysis.

Annex 15

Paper 14_Serious Eye Dam_eye irrit_substances_CLP guidance_decision logic.doc

SERIOUS EYE DAMAGE / EYE IRRITATION

Decision logic for the classification of substances

(extract from guidance document dated August 2009 for EU CLP Regulation)

Step		
0	Is the substance classified as a skin corrosive? **YES** ➔ **NO** ↓	When classified as Skin Corr. 1, the risk of severe damage to eyes is considered implicit. No need to proceed.
1a	Is the substance an organic hydro peroxide or an organic peroxide? **YES** ➔ **NO** ↓	– Consider to classify as serious eye damage (Eye Dam. 1) if the substance is a hydro peroxide, or – eye irritating (Eye Irrit. 2) if the substance is a peroxide. OR Provide evidence for the contrary and proceed to step 1b
1b	Is the pH of the substance ≤ 2 or ≥ 11.5? **YES** ➔ **NO** ↓	– Where classification is based upon consideration of pH alone (i.e. buffering capacity not known), Eye Dam. 1 should be applied. When assigned Skin Corr. 1, the risk of severe damage to eyes is considered implicit. – Where consideration of the alkali/alkaline reserve suggests that the substance is not corrosive, this has to be confirmed (preferably by use of an appropriate *in vitro* test). Proceed to step 1c
1c	Are there other physical or chemical properties that indicate that the substance has the potential to cause serious eye damage or is irritating to the eye? **YES** ➔ **NO** ↓	Use this information for weight of evidence (WoE) determination (step 6). Proceed to step 2
2	Is there adequate existing human experience which provides evidence that the substance has the potential to cause serious eye damage or is irritating to the eye? **YES** ➔ **NO** ↓	Classify accordingly (Eye Dam. 1 or Eye Irrit. 2).
3	Are there data from existing studies *on eye irritation* in laboratory animals, which provide sound conclusive evidence that the substance has the potential to cause serious eye damage, is an eye irritant or non-irritant? **YES** ➔ **NO** ↓	Classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification).

Step		
4	Are there structurally related substances (suitable "read-across" or grouping), which are classified as serious eye damage or eye irritant, or do valid QSAR methods indicate the presence/absence of serious eye damage/eye irritation potential of the substance? **YES** ➔ **NO** ↓	Consider to classify accordingly (Eye Dam. 1 or Eye Irrit. 2). If discrimination between Eye Dam. 1 and Eye Irrit. 2 is not possible, Eye Dam. 1 must be chosen. Proceed to step 5a
5a	Are there data from a validated *in vitro* test (adopted by OECD or not), which provide evidence that the substance is an eye irritant or non-irritant? **YES** ➔ **NO** ↓	Consider to classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification). If discrimination between Eye Dam. 1 and Eye Irrit. 2 is not possible, Eye Cat. 1 must be chosen. Proceed to step 5b
5b	Are there acceptable data from a suitable *in vitro* test, which provide evidence that the substance is a severe eye irritant? **YES** ➔ **NO** ↓	Consider to classify as Eye Dam. 1. Proceed to step 6
6	Taking all existing and relevant data) into account, is there sufficient information to make a decision on classification? **YES** ➔ **NO** ↓	Classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification).
	Unable to classify substance for serious eye damage/eye irritation	Decision to undertake generation of new test data should be made in compliance with REACH and Article 8 of the CLP. It is recommended that ECHA guidance R.7.2.6 should also be considered.

Annex 16

Paper 15_Serious Eye Dam_eye irrit_mixtures_CLP guidance_decision logic.doc

SERIOUS EYE DAMAGE / EYE IRRITATION

Decision logic for the classification of mixtures

(extract from guidance document dated August 2009 for EU CLP Regulation)

1. When data are available for the complete mixture		
0	Is the mixture classified as a skin corrosive? **YES** ➔ **NO** ↓	When assigned Skin Corr. 1, the risk of severe damage to eyes is considered implicit. No need to proceed.
1a	Is the pH of the mixture ≤ 2 or ≥ 11.5? **YES** ➔ **NO** ↓	– Where classification is based upon consideration of pH alone (i.e. buffering capacity not known), Eye Dam. 1 should be applied. When assigned Skin Corr. 1, the risk of severe damage to eyes is considered implicit. – Where consideration of the acid/alkaline reserve suggests that the substance is not corrosive, this has to be confirmed (preferably by use of an appropriate in vitro test). Proceed to step 1b.
1b	Are there other physical or chemical properties that indicate that the mixture has the potential to cause serious eye damage or is irritating to the eye? **YES** ➔ **NO** ↓	Use this information for weight of evidence (WoE) determination (step 6). Proceed to step 2.
2	Are there adequate existing human experience data which provide evidence that the mixture has the potential to cause serious eye damage or is irritating to the eye? **YES** ➔ **NO** ↓	Classify accordingly (Eye Dam. 1 or Skin Irrit. 2).
3	Are there data from existing studies *on eye irritation* in laboratory animals, which provide sound conclusive evidence that the mixture has the potential to cause serious eye damage, is an eye irritant or non-irritant? **YES** ➔ **NO** ↓	Classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification).
4a	Are there data from a validated *in vitro* or *ex vivo* test (adopted by OECD or not), which provide evidence that the mixture is an eye irritant or non-irritant? **YES** ➔ **NO** ↓	Consider to classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification). If discrimination between Eye Dam. 1 and Eye Irrit. 2 is not possible, Eye Dam. 1 must be chosen. Proceed to step 4b
4b	Are there acceptable data from a suitable *in vitro* test, which provide evidence that the mixture is an irritant to the eye? **YES** ➔ **NO** ↓	Consider to classify accordingly (Eye Dam. 1 or Eye Irrit. 2). If discrimination between Eye Dam. 1 and Eye Irrit. 2 is not possible, Eye Dam. 1 must be chosen. Proceed to step 5

5	Taking all existing and relevant data (steps 1-4) into account including potential synergistic/antagonistic effects and bioavailability, is there sufficient information to make a decision on classification? **YES** ➔ **NO** ↓	Classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification)
2. When data are not available for the complete mixture: bridging principles		
6a	Are existing eye irritation data available on similar tested mixtures and on the individual ingredients? **NO** ➔ **YES** ↓	Proceed to step 7a
6b	Can bridging principles be applied? **YES** ➔ **NO** ↓	Classify in appropriate category (Eye Dam. 1 or Eye Irrit. 2 or no classification)
3. When data are available for all components or only for some components of the mixture		
7a	Is pH of the mixture ≤ 2 or ≥ 11.5? **YES** ➔ **NO** ↓	Follow decision logic in Section 3.3.3.2.1.1 and classify accordingly.
7b	Is there any indication that the additivity principle does not apply? **YES** ➔ **NO** ↓	Section 3.3.3.3.4 and Table 3.3.4 may apply. Take relevant ingredients (Annex I, 3.2.3.3.1) and SCLs into account, as appropriate. Classify in appropriate category (Eye Dam. 1 or Eye Irrit. 2 or no classification)
	Section. 3.3.3.3.2 and Table 3.3.3 applies. Take relevant ingredients (Annex I, 3.2.3.3.1) and SCLs into account, as appropriate. Classify in appropriate category (Eye Dam. 1 or Eye Irrit. 2 or no classification).	

Annex 17

Paper 16_Serious Eye Dam_eye irrit_extreme pH_CLP guidance_decision logic.doc

SERIOUS EYE DAMAGE / EYE IRRITATION

Mixtures with extreme pH (extract from guidance document dated August 2009 for EU CLP Regulation)

Where the mixture has an extreme pH value but the only corrosive/irritant ingredient present in the mixture is an acid or base with an assigned SCL (either CLP Annex VI or set by supplier), then the mixture should be classified accordingly. In this instance, pH of the mixture should not be considered a second time since it would have already been taken into account when deriving the SCL for the substance.

If this is not the case, then the steps to be taken into consideration when classifying a mixture with pH ≤ 2 or ≥ 11.5 are described in the following decision logic:

Mixture not classified as Skin Corr. 1 and without *in vivo* data on serious eye damage/eye irritation or relevant data from similar tested mixtures. **pH is ≤ 2 or ≥ 11.5**	
Does the acid/alkaline reserve indicate that the mixture may not be corrosive? **NO** ➔ **YES** ↓	Classify as serious eye damaging, Eye Dam. 1.
Is the mixture tested for serious eye damaging properties in an accepted *in vitro* test? **NO** ➔ **YES** ↓	Classify as serious eye damaging, Eye Dam. 1.
Does the mixture demonstrate serious eye damaging properties in an accepted *in vitro* test? **YES** ➔ **NO** ↓	Classify as serious eye damaging, Eye Dam. 1.
Apply methods in Annex I, 3.3.3.3.2 (Table 3.3.3) / 3.3.3.3.4 (Table 3.3.4) ➔ (When validated *in vitro* eye irritation test methods are available, these may be used to generate data to classify the mixture instead of using the summation method.)	Classify accordingly.

If consideration of extreme pH and acid/alkaline reserve indicates the mixture may not have the potential to cause serious eye damage, then the supplier should carry out further testing to confirm this (Annex I, Section 3.3.3.2.1). The mixture must be classified as Serious eye damage Category 1 if the supplier decide not to carry out the required confirmatory testing.

If further testing confirms that the mixture should not be classified for serious eye damage effects, then the supplier should assess the mixture for eye irritation either using *in vitro* eye irritation test methods when available or the summation method.

It must be note that the pH-acid/alkali reserve method assumes that the potential corrosivity or irritancy is due to the effect of the ionic entities. When this is not the case, especially when the mixture contains non-ionic (non-ionisable) substances themselves classified as corrosive or irritant, then the pH-reserve method cannot be a basis for modifying the classification.

Where the mixture has an extreme pH value and contains some other corrosive/irritant ingredients (some of which may have SCLs assigned) in addition to an acid or base with or without an assigned SCL, then the mixture shall follow the procedure described in the decision logic.
