



**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****Twenty-first session**

Geneva, 27–29 June 2011

Item 2 (b) of the provisional agenda

**Updating of the Globally Harmonized System of Classification
and Labelling of Chemicals (GHS) – Health hazards****Skin corrosion/irritation and serious eye damage/eye
irritation – Guidance on evaluation of data from studies
conducted with more than three animals****Transmitted by the expert from Germany on behalf of the informal
correspondence group on the editorial revision of Chapters 3.2 and 3.3¹****Background**

1. Classification criteria for the skin and eye hazard classes are detailed in the GHS in terms of a three-animal test. It has been identified that some older test methods may have used up to six animals. However, the GHS does not specify how to classify based on existing data from tests with four, five or six animals.
2. The issue of how to classify based on existing data from studies with four or more animals was initially raised at the Organisation for the Economic Co-operation and Development (OECD) Workshop in July 2007 on the Application of GHS Classification Criteria to High Production Volume (HPV) Chemicals.
3. This issue was also discussed in the European Union REACH² Implementation Project (RIP) 3.6 Experts Group during development of guidance for the European Union GHS implementation legislation (the so-called Classification, Labelling and Packaging

¹ In accordance with the programme of work of the Sub-Committee for 2011-2012 approved by the Committee at its fifth session (refer to ST/SG/AC.10/C.4/40, annex II and ST/SG/AC.10/38, para.16).

² Regulation concerning the Registration, Evaluation, Autorisation and Restriction of Chemicals (Regulation (EC) No 1907/2006).

(CLP) Regulation³). The resultant approaches for skin and eye irritation have been included in the European Union CLP guidance document which has been published on the European Chemicals Agency (ECHA) website.

4. At the nineteenth session of the GHS Sub-Committee in July 2010, Germany and the International Association for Soaps, Detergents and Maintenance Products (AISE) submitted informal document INF.5 highlighting the need for guidance on the evaluation of data from studies with more than three animals.

5. Most experts were of the opinion that such guidance was needed and that it should preferably be included in the GHS via a new annex. The Sub-Committee agreed to extend the terms of reference for the informal correspondence group so that this group could continue to work on the required guidance.

6. The informal correspondence group has revisited possible location options for the required guidance and believe that such guidance would be better placed in the actual chapters. This could be achieved by adding a new sub-paragraph after the decision logic indicating that the “background guidance” is provided. A similar approach is already used in the carcinogenicity chapter and some physical hazard chapters. This approach keeps the guidance in the chapter, making it more accessible to classifiers but at the same time makes it clear that it is not part of the harmonised criteria.

7. The informal correspondence group would welcome the views of the Sub-Committee on the following proposal covering guidance on the evaluation of data from studies with more than three animals.

Proposal

8. In Chapter 3.2, amend the heading of current 3.2.5 to read: “Decision logic and guidance” and add a new sub-section 3.2.5.3 after the decision logics to read as follows:

“3.2.5.3 *Background guidance*”

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

3.2.5.3.2 Classification criteria based on a 3-animal test are detailed in 3.2.2.4 (skin corrosion) and 3.2.2.5 (skin irritation). Evaluation of a 4, 5 or 6-animal study should follow the criteria in the following paragraphs, depending on the number of animals tested. Scoring for erythema/eschar and oedema should be performed at 24, 48 and 72 hours after exposure or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions.

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

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

³ Regulation (EC) No. 1272/2008.

- (b) The substance or mixture is classified as skin irritation Category 2 if at least 4 out of 6 animals show a mean score per animal of $\geq 2.3 \leq 4.0$ for erythema/eschar or for oedema;
- (c) The substance or mixture is classified as skin irritation Category 3 if at least 4 out of 6 animals show a mean score per animal of $\geq 1.5 < 2.3$ for erythema/eschar or for oedema.

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

- (a) The substance or mixture is classified as skin corrosion Category 1 if destruction of skin tissue (that is, visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours in duration;
- (b) The substance or mixture is classified as skin irritation Category 2 if at least 3 out of 5 animals show a mean score per animal of $\geq 2.3 \leq 4.0$ for erythema/eschar or for oedema;
- (c) The substance or mixture is classified as skin irritation Category 3 if at least 3 out of 5 animals show a mean score per animal of $\geq 1.5 < 2.3$ for erythema/eschar or for oedema.

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

- (a) The substance or mixture is classified as skin corrosion Category 1 if destruction of skin tissue (that is, visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours in duration;
- (b) The substance or mixture is classified as skin irritation Category 2 if at least 3 out of 4 animals show a mean score per animal of $\geq 2.3 \leq 4.0$ for erythema/eschar or for oedema;
- (c) The substance or mixture is classified as skin irritation Category 3 if at least 3 out of 4 animals show a mean score per animal of $\geq 1.5 < 2.3$ for erythema/eschar or for oedema.”.

9. In Chapter 3.3, amend the heading of current 3.3.5 to read: “Decision logic and guidance” and add a new sub-section 3.3.5.3 after the decision logics to read as follows:

“3.3.5.3 Background guidance

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

3.3.5.3.2 Classification criteria based on a 3-animal test are detailed in 3.3.2.8 (serious eye damage) and 3.3.2.9 (eye irritation). Evaluation of a 4, 5 or 6 animal study should follow the criteria in the following paragraphs, depending on the number of animals tested. Scoring should be done at 24, 48 and 72 hours after instillation of the test material.

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

- (a) The substance or mixture is classified as serious eye damage Category 1 if:

- (i) at least one animal has any effects on the cornea, iris or conjunctiva that do not reverse or have not fully reversed within an observation period of normally 21 days; and/or
 - (ii) at least 4 out of 6 animals show a mean score per animal of ≥ 3 for corneal opacity and/or > 1.5 for iritis.
- (b) The substance or mixture is classified as eye irritation Category 2A if at least 4 out of 6 animals show a mean score per animal of:
- (i) ≥ 1 for corneal opacity and/or
 - (ii) ≥ 1 for iritis and/or
 - (iii) ≥ 2 for conjunctival redness and/or
 - (iv) ≥ 2 for conjunctival oedema (chemosis)
- and which fully reverses within an observation period of normally 21 days.
- (c) The substance or mixture is classified as mildly irritating to eyes (Category 2B) if the effects listed in sub-paragraph (b) above are fully reversible within 7 days of observation.

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

- (a) The substance or mixture is classified as serious eye damage Category 1 if:
- (i) at least one animal has any effects on the cornea, iris or conjunctiva that do not reverse within an observation period of normally 21 days; and/or
 - (ii) at least 3 out of 5 animals show a mean score per animal of ≥ 3 for corneal opacity and/or > 1.5 for iritis.
- (b) The substance or mixture is classified as eye irritation Category 2A if at least 3 out of 5 animals show a mean score per animal of:
- (i) ≥ 1 for corneal opacity and/or
 - (ii) ≥ 1 for iritis and/or
 - (iii) ≥ 2 for conjunctival redness and/or
 - (iv) ≥ 2 for conjunctival oedema (chemosis)
- and which fully reverses within an observation period of normally 21 days.
- (c) The substance or mixture is classified as mildly irritating to eyes (Category 2B) if the effects listed in sub-paragraph (b) above are fully reversible within 7 days of observation.

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

- (a) The substance or mixture is classified as serious eye damage Category 1 if:
- (i) at least one animal has any effects on the cornea, iris or conjunctiva that do not reverse within an observation period of normally 21 days; and/or

- (ii) at least 3 out of 4 animals show a mean score per animal of ≥ 3 for corneal opacity and/or > 1.5 for iritis.
 - (b) Classification as eye irritation Category 2A if at least 3 out of 4 animals show a mean score per animal of:
 - (i) ≥ 1 for corneal opacity and/or
 - (ii) ≥ 1 for iritis and/or
 - (iii) ≥ 2 for conjunctival redness and/or
 - (iv) ≥ 2 for conjunctival oedema (chemosis)and which fully reverses within an observation period of normally 21 days.
 - (c) The substance or mixture is classified as mildly irritating to eyes (Category 2B) if the effects listed in sub-paragraph (b) above are fully reversible within 7 days of observation.”.
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