

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

Nineteenth session

Geneva, 30 June – 2 July 2010

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

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 and the representative of the
International Association for Soaps, Detergents and Maintenance
Products (AISE) on behalf of the correspondence group on the editorial
revision of chapter 3.2 and 3.3**

I. Introduction

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 existing data based on such tests with four, five or six animals.

II. Background

2. The issue of how to classify existing data based on studies with four or more animals was initially raised at the OECD workshop on the application of GHS classification criteria to high production volume chemicals, which was held in Bern in July 2007. At this workshop, Amy Rispin from the United States' Environmental Protection Agency (US EPA) gave a presentation on the guidance developed by the Interagency Coordination Committee on the Validation of Alternative Methods (ICCVAM) to classify for eye irritation based on data from tests with more than three animals (the presentation can be found in Annex I to this document).

3. This issue was also discussed in the European Union REACH¹ implementation Project (RIP) 3.6 Expert Group during the development of guidance for the European Union GHS implementation legislation (the so-called "CLP Regulation": Regulation (EC) No. 1272/2008). The resultant approaches for skin and eye irritation have been included in the EU CLP guidance document which has been published on the European Chemicals Agency (ECHA) website.

¹ Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

4. Details of the agreed EU approach to the evaluation of existing test data with more than three animals are given in Annex II to this document.

III. Way forward

5. The correspondence group believes that introduction of guidance on the evaluation of existing studies with more than three animals would enhance the GHS text.

6. The correspondence group is currently considering the possibility of using an approach similar to that adopted by the EU, for the GHS. However, it is recognized that any GHS text on this topic would also need to include skin irritation Category 3 and eye irritation Category 2B.

7. The correspondence group is planning to bring forward a proposal for guidance on the evaluation of existing studies with more than three animals to the Sub-Committee at the twentieth session. In the mean time, the correspondence group would welcome input/direction from the Sub-Committee on the final location of this guidance:

- Should it be added to the relevant sections of Chapters 3.2 and 3.3 or included as a new standalone Annex to the GHS (i.e. Annex 11)?
- Other options e.g. posted on the United Nations Economic Commission for Europe (UNECE) website?

Annex I

Presentation by Amy Rispin at the OECD workshop on the application of GHS classification criteria to high production volume chemicals (Bern, July 2007)

Guidance Developed by
ICCVAM (U.S.) to Classify for
Eye Irritation

Amy S. Rispin
United States Environmental Protection
Agency



Criteria for GHS Classification for Eye Irritation are Based on Testing with 3 Rabbits:

- Table 3.3.1 Irreversible eye effects categories
- Table 3.3.2 Reversible eye effects categories



Internationally Harmonized Classification and Labeling will Lead to Re-Classification of Existing Products

- Older test methods used up to 6 rabbits.
- ICCVAM recently classified chemicals based on previous test results. These chemicals serve as *reference standards* for development of in vitro alternative assays for eye irritation.



GHS Classification for Tests Using 4-6 Rabbits

- Number of Rabbits
 - Sequential testing of rabbits until response is confirmed (typically, up to 3 rabbits)



GHS Classification for Tests Using 4-6 Rabbits

- Observation Times (after treatment)
 - 1, 2, 3 days (if effects induced, observation until reversal or Day 21, whichever comes first)



GHS Classification for Tests Using 4-6 Rabbits

- Basis for a Positive Response
 - Individual rabbit values averaged over Days 1, 2, and 3 (mean score used to classify)



GHS Classification for Tests Using 4-6 Rabbits

- Category 2 (Reversible Eye Effects)
(follow rules sequentially)
 - (1) Eye Irritant Category 2A – At least 2 of 3 (or 4 of 6; 3 of 4; 4 of 5) rabbits have individual animal mean values where ≥ 1 Opacity < 3 , ≥ 1 Iritis ≥ 1.5 , Redness ≥ 2 , and/or Chemosis ≥ 2 and the effect reverses > 7 days but < 21 days.



GHS Classification for Tests Using 4-6 Rabbits

- Category 2 (Reversible Eye Effects)
(follow rules sequentially)
 - (2) Eye Irritant Category 2B – At least 2 of 3
(or 4 of 6; 3 of 4; 4 of 5) rabbits have
individual animal mean values where ≥ 1
Opacity < 3 ; ≥ 1 Iritis ≥ 1.5 , Redness ≥ 2 ,
and/or Chemosis ≥ 2 and the effect reverses
by 7 days



Annex II

Extract from EU guidance: evaluation of existing test data with more than three animals

Skin irritation

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).

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	Erythema	Oedema
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.

Serious eye damage/eye irritation

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.

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.

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.
