

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

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Programme of work for the biennium 2019-2020

Proposal for a work item for biennium 2019-2020: review of the cut off value/concentration limit for mixtures classification as Serious eye damage

**Submitted by the International Association for Soaps, Detergents and
Maintenance Products (A.I.S.E.) and Croplife International**

Background

1. According to Section 3.3.3.3.2 “*The approach to classification of mixtures as 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 the additivity, such that each (...) ingredient contributes to the overall serious eye damage/eye irritation properties of the mixture in proportion to its potency and concentration*”.
2. Cut off values/concentration limits are therefore provided to determine if the mixture should be classified based on its ingredients (see table 3.3.3.).
3. During the preparation of the first version of GHS, OECD was tasked to develop draft criteria and it published in 2001 the “*Detailed Review Document on hazard classification systems for mixtures, ENV/JM/MONO(2001)10*”. That document highlighted that most used Cut off values/concentration limits in use to perform a mixture classification for Serious eye damage based on additivity were 10% (EU) and 1% (US).
4. The OECD drafting group on “skin and eye irritation/corrosion” reached a compromise to apply the cut off value/concentration limit of $\geq 3\%$ for Serious eye damage cat.1 and finalized its proposal in March 2001 (see ST/SG/AC.10/C.4/2001/4). This value was included in Chapter 3.3 of the GHS.

Discussion

5. At the thirty-fifth session the Sub-Committee of Experts on the GHS discussed informal paper INF.14 (35th session) on “*Hands-on experience with GHS Eye hazard classification for consumer products: challenges and opportunities*”. This paper highlighted potential challenges caused by the application of the cut off value/concentration limit of $\geq 3\%$ when using additivity for Serious eye damage to mixtures.
6. The GHS additivity method to determine hazard classification is an important tool in assigning hazard classifications for mixtures when data are available on ingredients but not

on the mixture. In the classification hierarchy, it offers a method of last resort in cases where there is an absence of appropriate in vivo or in vitro data.

7. The global move away from animal testing discourages the generation of new in vivo studies for eye effects.

8. Alternative in vitro methodologies for eye effects have been validated according to OECD criteria. However, predictivity of irritancy potential compared to existing animal or human data is not yet satisfactory to provide reliable hazard classification. Despite recent progresses (i.e. revision of OECD TG 438), these methods are frequently not yet accepted by competent authorities. Similarly, use of bridging principles and weight-of-evidence/expert judgement is hindered by a limited availability of suitable data.

9. Therefore, the additivity method is a highly practical and widely accepted method to derive a classification for the eye irritation/serious eye damage hazard class for products. Additivity should be used as a last resort in the tiered approach (Section 1.3.2.3.1), however, due to the above challenges, it has become mainstream.

10. In recent years, a body of evidence has emerged pointing at a potential over-classification for serious eye damage Cat.1 when using the additivity approach for mixtures; this conservatism seems to be mainly driven by the low cut off value/concentration limit applied for ingredients classified for Category 1 Eye Damage (see Annex I for further details):

- from scientific literature - Corvaro et Al., 2017 compared for over 200 agrochemical mixtures the GHS classification based on animal test and that obtained with the GHS additivity test. In the case of eye effects, additivity method overestimated classification with respect animal data (i.e. yielding a more severe GHS category) in 41.4% of cases. Similar results were also found by Cazelle et al. 2014 in the domain of cleaning products and detergents.
- from accidental human exposure – Two large Poison Control Centre studies across Europe on accidental human exposures to detergents and cleaning products (Hermanns-Clausen et al, 2015; Färber et al, 2016), reported that out of a total of 1,235 exposures, only two (2) cases of residual eye damage after 21 days had been recorded. In a further assessment of the cases above (see also informal document INF.14 (35th session)) it was found that of the 82% of all products that would be classified as Category 1 by the additivity method, nearly 90% resulted in no or minor symptoms following accidental human exposure.

11. When it is proportionate, classification information helps to clearly and effectively communicate the nature of hazard to product users and inform medical decision making in the event of accidental exposure. There is now evidence that over classification might occur, causing confusion amongst the target audience and potentially diluting the effectiveness of GHS.

12. Whilst a conservative approach is of merit in an absence of data; the unintended consequences of an overconservative classification and labelling approach are the following:

- Lack of differentiation in hazard communication - Application of the additivity method has resulted in mild products such hand dishwash detergents (designed for frequent household use without any special precaution) to carry the same hazard classification and pictogram as a truly corrosive to skin and eyes drain cleaner (designed for occasional use with several precautions).
- GHS users confusion - Consumer feedback (see informal document INF.5 (34th session) and also Baert, W., et Al, 2017) suggests that the wider public struggle to

differentiate the actual hazard posed by the product they are using based on the GHS pictogram.

- Emergency services difficulties - Over classification might interfere with effective medical intervention when accidental exposure occurs: misinforming medical practitioners can lead to over-prescription of curative measures, consuming resources and subjecting the patient to unnecessary treatment.

Proposal

13. In order to tackle the issues described above, it is proposed to insert a new work item for biennium 2019-2020 consisting of a potential review of cut off value/concentration limit of 3% for mixtures classification as Serious Eye Damage Cat.1 based on the latest scientific evidence.

14. This activity could be carried out by an existing informal working group or, alternatively, by a newly established informal working group with the necessary expertise; this working group should report back to the Sub-Committee. Following, draft Terms of reference are proposed:

- Based on new available scientific evidence, it is considered appropriate to conduct a review of the GHS cut off value/concentration limit of 3% for mixtures classification as serious eye damage category 1 (review of science).
- Such a review should be based on the latest scientific evidence and assess whether the cut off value/concentration limit of 3% for serious eye damage category 1 hazard is still fit for purpose; if appropriate, the review could also recommend a new cut off value/concentration limit for serious eye damage category 1.

15. The outcome of this new work item will help ensure that the additivity method for eye effects remains a robust, effective and cost-efficient tool to produce proportionate hazard classifications that support hazard communication and safe use of chemicals within all target audience of the GHS.

16. A number of Sub-Committee members and Non-Governmental Organizations expressed a general support in principle of setting up a working group and participating in its activities.

17. The Sub-Committee is invited to consider the insertion of the above action item in the next biennium program of work.

Annex

Scientific evidence on a potential conservatism of the GHS additivity method

In the EU, prior to the introduction of the CLP Regulation, the classification of chemical mixtures was governed by the Dangerous Preparations Directive (DPD). The conventional calculation method was the primary determinant for classification - unless overruled by data. This was largely equivalent to the GHS calculation method, with the significant difference that the generic concentration limit of ingredients classified for serious eye damage (R41 - equivalent to Category 1) was 10%, while under GHS this was lowered to 3%. As the GHS threshold for Category 1 is more than 3 times lower than in the prior EU legislation, significant numbers of mixtures on the market before the transition to GHS have been reclassified as Category 1 for eye effects.

Corvaro et al. (2017), compared for over 200 agrochemical mixtures, the GHS classification based on animal test and that obtained with the GHS additivity test. In the case of eye effects, additivity method overestimated classification with respect animal data (i.e. yielding a more severe GHS category) in 41.4% of cases. In addition, it was found that among 85 preparations that would be classified as Category 1 for eye hazard using the GHS calculation method, only 27% were actually classified for serious eye damage based on the standard in vivo test data. This highlights not only a high level of conservatism but also significant over-prediction of hazard when using the GHS calculation method versus in vivo data.

Two large Poison Control Center studies across Europe on accidental human exposures to detergents and cleaning products (Hermanns-Clausen et al, 2015; Färber et al, 2016), reported that out of a total of 1,235 exposures, only two (2) cases of residual eye damage after 21 days had been recorded. This data demonstrates that severe eye damage occurs infrequently within this product category. In a further assessment of the cases with products where the regulatory classification could be retrieved (Scazzola et al., manuscript in preparation) it was found that of the 82% of all detergent and cleaning products that would be classified as Category 1 by the calculation method, nearly 90% resulted in no or minor symptoms following accidental human exposure. The calculation method was shown to be a poorer predictor of medically relevant effects (moderate severity or worse) than classification based on all available information (weight-of-evidence and expert judgment). Thus, symptoms observed following accidental human exposures to detergents and cleaning products indicate that Category 1 type effects (serious eye damage) occur extremely rarely, and that the calculation method is a poor predictor for moderate or severe effects.

On availability of non-animal tests

Several non-animal methods to assess eye irritation have been developed and validated over the past decade: OECD TG 438 (Isolated Chicken Eye - ICE test), OECD TG 437 (Bovine Corneal Opacity and Permeability - BCOP test), OECD TG 491 (Short time exposure - STE test), OECD TG 460 (Fluorescein Leakage - FL test), OECD TG 492 (Reconstructed human Cornea-like Epithelium - RhCE test). BCOP, ICE, STE and RhCE are validated to identify mixtures as “not classified”. However, currently none of the available animal alternative methods are accepted to conclusively support a Category 2 classification. Thus, for a majority of mixtures for consumer use (including detergents), for which the non-animal methods indicate eye irritation but no serious eye damage, the Category 2 classification cannot be determined based on the non-animal test data without a broader weight-of-evidence justification.

Negative implications of over-classification

In a consultation with Poison Control Centers (May 2016, during the annual EAPCCT conference), representatives reported that they have observed confusion among patients about the meaning of the various on-pack pictograms – especially the corrosive pictogram. Indeed, the use of this pictogram has been extended to Category 1 eye irritants under GHS, and this impact is increased because a higher proportion of products is classified as Category 1 under GHS. This change prevents PCCs from determining whether a product is corrosive based only on presence of the pictogram. This hinders communication to the PCC and decision making within the PCC, delay treatment and could lead to over-treatment if no further information about the involved product is readily available.

Consumer research (SynapsesQuali, 2016, Baert et al., 2017 see also [UN/SCEGHS/34/INF.5](#)) confirms that the general public is not able to differentiate between products that are corrosive to skin versus Category 1 eye irritants (based on the pictogram, but also not when reading the other label elements). After studying the GHS content, consumers found the label information to be quite similar for different product classifications. Contrary to their intuition, consumers believe the labels tell them that all products are equally hazardous. They feel misled due to this discrepancy between their experience and label information.

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