

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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Item 2 (d) of the provisional agenda

**Classification criteria and related hazard communication:
practical classification issues**

Thought starter on GHS cut off value/concentration limit for mixtures classification as serious eye damage: Review of science

**Transmitted by the expert from the United States of America on
behalf of the practical classification issues informal correspondence
group**

1. In order to initiate discussion, the International Association for Soaps, Detergents and Maintenance Products (A.I.S.E.) and Croplife International have developed the attached thought starter (see Annex) regarding the GHS cut-off value/concentration limit for mixtures classification as serious eye damage.
2. The Sub-committee is invited to:
 - (a) share any additional studies and papers that could be relevant to the above topic.
 - (b) comment on the preliminary assessment based on existing scientific evidence.
3. Comments and inputs should be sent to Roberto Scazzola roberto.scazzola@aise.eu and Phil Todd phil.todd@syngenta.com.

Annex

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. The additivity method is a non-testing approach to assess the potential of a formulation to cause eye damage. This is based on the hypothesis that the more irritating ingredients are present in the formulation, the more likely the formulation will be irritating.
3. In the tiered approach, the additivity method comes last in the hierarchy (Section 1.3.2.3.1); however, to avoid animal testing and due to the limitations of validated in vitro tests, it is frequently used in some product categories. Despite recent activities at OECD level (revision OECD TG 438, 27th June 2018) and ongoing efforts (non-animal methods ICG), presently there are no validated and internationally accepted in vitro test methods for identifying eye irritation Cat. 2 in OECD Guidance Document 263 for an integrated approach to address eye damage / irritation.
4. The Draize test (OECD test guidelines 405) assesses the changes in the eye following the application of a test substance to the anterior surface of the eye of rabbits. Although there are animal welfare considerations and criticism of its level of reproducibility (e.g. Luechtefeld *et al.*, 2017¹) and subjectivity (e.g. Roggeband *et al.*, 2000²), it still represents the reference test method to assess eye effects. Most of the test data assessed by this paper are related to Draize tests (see Annex I for details).
5. Cut off values/concentration limits of ingredients for mixture classification are provided in Table 3.3.3. For the sum of ingredients classified as Skin Category 1 and/or Eye Category 1, the concentration triggering classification of a mixture as “Serious eye damage” is 3%.
6. For some substances, for example surfactants, additivity might not apply (UN GHS 3.3.3.3.4 and EU CLP 3.3.3.3.4.1). Case-by-case, a 1% threshold approach (Table 3.3.4) may have to be used instead of the additivity method. For surfactant containing products, ECHA’s CLP Guidance applies additivity by default - whereas OSHA’s GHS Guidance adopts the conservative threshold approach when a surfactant is present, in absence of more data. In surfactant mixtures, due to mitigating effects between

¹ Luechtefeld T., Maertens A., Russo D.P., Rovida C., Zhu H. and Hartung T. (2017). *Analysis of Draize Eye Irritation Testing and its Prediction by Mining Publicly Available 2008–2014 REACH Data*. ALTEX. 2016 ; 33(2): 123–134. doi:10.14573/altex.1510053.

² Roggeband R., York M., Pericoi M. and Braun W. (2000) *Eye irritation responses in rabbit and man after single applications of equal volumes of undiluted model liquid detergent products*. Food Chem Toxicol. 38(8): 727-734.

surfactant classes³, additivity can lead to over-prediction. On the other hand, the presence of surfactants (or other substances such as solvents or lipids) may positively or negatively influence the potency of toxicants⁴. These potential inherent limitations of the additivity approach (independent of the cutoff/concentration limit) are implicitly addressed in the current assessment because the additivity approach is evaluated against classifications based on actual test data on mixtures.

7. A body of evidence has emerged pointing at a potential over-classification for serious eye damage Cat.1 by the additivity approach. A hypothesis to be assessed is whether this is driven by the cut off value/concentration limit (see [UN/SCEGHS/36/INF. 17](#)).

8. At the 36th session of GHS, the Sub-Committee agreed to insert for the 2019-2020 working program the following working item: «*Review available scientific evidence on the use of 3% cut-off value/concentration limit in the additivity approach for mixture classification as Serious Eye Damage Category 1. The group can consider if a new cut-off value/concentration limit is appropriate and/or if additional guidance would be helpful when applying the additivity formula*».

Discussion

9. The scope of this review of science is to assess whether the cut off value/concentration limit of 3% for mixture classification as Serious eye damage Category 1 is fit for purpose.

10. To this extent, several recent scientific papers were assessed in which the eye hazard classification of mixtures obtained with test data is compared with the UN GHS additivity method.

11. This review provides an overview of scientific study data related to this matter. This includes assessments on several mixtures from 5 peer reviewed papers and one industry database and in vivo test data for dilutions of some single substances (1 paper and 1 technical report). Finally, an assessment of the symptoms following accidental human exposures reported by Poison Control Centres is also included.

12. In Annex 1, a summary is provided for each relevant paper. This includes full reference, brief summary, main findings and assessment of the results.

Methodology

13. Different classification models applied to the same mixture should ideally produce equivalent results. Nevertheless, the additivity approach can be seen as a 'safety net', and it can be argued that, to be adequately protective, it should to some

³ Paye M., Block C., Hamaide N., Hüttmann G., Kirkwood S., Lally C., Lloyd P. H., Makela P., Razenberg H. and Young R.(2006). *Antagonisms between Surfactants: The Case of Laundry Detergents. Tenside Surfactants Detergents: Vol. 43, No. 6, pp. 290-294.*

⁴ De Waard M.A. and Van Nistelrooy J.G.M (1982). *Antagonistic and synergistic activities of various chemicals on the toxicity of fenarimol to Aspergillus niduluns. Pest management science 13(3), pp. 279-286.*

extent be conservative compared to testing methods. Thus, the additivity method is expected to produce a low incidence of false negatives (under-classification versus data), and a higher but not excessive incidence of false positives (over-classification versus data) There is currently no guidance under GHS on what would be an acceptable level of false negative or positive classifications using additivity.

14. The hazard classification obtained by available test data on specific mixtures was compared with the hazard classification on the same mixtures by using the additivity approach (based on the concentration of the ingredients).

15. The metrics to assess the additivity method are:

- (a) false negatives rate = the proportion of mixtures calculated by the additivity method to be either Eye Irritant Cat. 2 or Non Classified, among the mixtures classified for Serious Eye Damage Cat. 1 based on conclusive test data.
- (b) false positives rate = the proportion of mixtures calculated by the additivity method to be Serious Eye Damage Cat. 1, among the mixtures classified as Eye Irritant Cat. 2 or Non Classified based on conclusive test data.
- (c) related metrics (not used herein) are specificity (1 - false positives rate), and sensitivity (1 - false negatives rate).
- (d) accuracy or concordance is determined as the proportion (among all mixtures) for which the additivity method leads to the same classification outcome (in terms of either “Cat. 1” versus “not Cat. 1”) as the conclusive test data.

16. This assessment focuses on the differentiation between classification as “Eye Category 1” (i.e. serious eye damage), and “Not Category 1” (i.e. Category 2 or Not Classified). The differentiation between Category 2 and Not Classified was not assessed.

Preliminary findings

17. Across the reviewed papers (Annex 1), it was possible to identify a rather large dataset of 447 mixtures for which the eye hazard classification is based on conclusive test data (304 classified as Not Cat. 1 and 143 as Cat.1).

18. For these mixtures, eye hazard classification as would be determined by additivity was also provided in the papers, or alternatively this could be calculated based on the reported information (i.e. applying the concentration of ingredients of a mixture as specified in Table 3.3.3 GHS).

19. Compared to the data-based classification, almost one out of two of the non-Cat1 tested products had a false positive Cat1 additivity outcome (143 out of 304, which is 47%). This is also explicitly indicated by Kurth et al. (2019): *“Due to the high false positive rate the CLP calculation method is prone to overestimating the potential for eye damage”*, by Corvaro et al. (2017): *“in the case of eye irritation the calculation method tends to overestimate classification (yielding a more severe GHS category)”*, as well as by Cazelle et al. (2014): *“EU CLP additivity approach for classification of*

mixtures was considerably less predictive, with a concordance of only 27%, and 100% over-predictions of non-Category 1 products.”

20. On the other hand, 13.3% (19 out of 143) of the Cat.1 products based on conclusive test data had a false negative (Cat.2 or NC) outcome with the calculation method. It is important to put this percentage in the right context. *Luechtefeld et al. (2017)*⁵ assessed the Draize test and its predictivity when repeating the test on the same substance; they found that a Cat.1 Draize test outcome was reproducible only in 73% of the cases (27% false negative rate). In other words, when repeating a Draize test on the same substance originally classified as Serious eye damage Cat. 1, 27% of the cases the outcome was a less severe classification (16.5% Cat. 2 and 10.4% NC). Furthermore, a positive outcome of the Draize test does not necessarily correlate with a severe eye damage hazard for humans, but has the tendency to overpredict effects (cf. also paragraph 24). Thus, a false negative to predict the outcome of a Draize test does not automatically imply a false negative to predict severe eye damage in man.

21. The findings suggest that the outcome of the additivity method based on the cut off/concentration limit of 3% is often an over-classification when compared with the results of test data. *Kurth et al. (2019)*⁶ explicitly concluded that “...products which were classified by in vivo testing as eye damaging in Category 1 were well detected with the CLP calculation method. [...] but did not reliably distinguish between irritant and corrosive (Category 1 and 2) products.”

22. A limited number of substances has a very high eye irritation potential, leading to serious eye damage at concentrations below the current generic cut off/concentration limit of 3%; this is already considered under 3.3.3.3.4. To avoid systematic false negative predictions for mixtures containing such substances, it is important to distinguish and treat separately ingredients of a mixture when the additivity approach does not apply (Table 3.3.4.). On occasion reliable data may also show absence of effects above the generic cut-off values/concentration limits, in this case 3.3.3.3.5 applies.

23. Finally, the severity of observed eye effects following accidental human exposures recorded by four EU Poison Centres, was compared to the regulatory eye classification category of the products. The vast majority of exposures had caused only minor or no ocular symptoms, also for products classified as Category 1 (see [UN/SCEGHS/35/INF.14](#)). The very low incidence of severe ocular injuries due to chemical exposure was also found by a major study carried out in Switzerland (data related to a cohort 4.28 Million people): the incidence found in one year for all chemical eye injuries was 50 cases per 100 000 people; the incidence of severe eye injuries was much lower (0.02 cases per 100 000 people or 1 case per 5 000 000 people)⁷. The

⁵ *Luechtefeld T., Maertens A., Russo D.P., Rovida C., Zhu H. and Hartung T. (2017). Analysis of Draize Eye Irritation Testing and its Prediction by Mining Publicly Available 2008–2014 REACH Data. ALTEX. 2016; 33(2): 123–134. doi:10.14573/altex.1510053.*

⁶ *Kurth, D., Wend, K., Adler-Flindt, S. and Martin, S. (2019). A comparative assessment of the CLP calculation method and in vivo testing for the classification of plant protection products. Regulatory Toxicology and Pharmacology 101 (2019) 79–90.*

⁷ *Markus Tschopp, Peter Krahenbuhl, Christoph Tappeiner, Hugo Kupferschmidt, Serge Quarroz, David Goldblum, And Beatrice E. Frueh (2015). Incidence and causative agents of chemical eye injuries in Switzerland. Clinical Toxicology DOI: 0.3109/15563650.2015.1094702.*

magnitude of effects due to accidental exposures is not only determined by the intrinsic hazard but also by the exposure conditions and mitigating actions - for example immediate rinsing of the eyes following the accident. Nevertheless, also under controlled exposure situations, the classification based on the standard in vivo method (Draize, OECD 405) is over-predictive of effects in man (e.g. as reported in Beckley, 1965⁸; Lambert *et al.*, 1993⁹; Roggeband *et al.* 2000¹⁰). This aspect needs to be taken into consideration when assessing the calculation method relative to the Draize test.

⁸ Beckley J.H. (1965) *Comparative eye testing: man vs. animal. Toxicology and Applied Pharmacology* 7: 93-101.

⁹ Lambert L.A., Chambers W.A., Green S., Gupta K.C., Hill R.N., Hurley P.M., Lee C.C., Lee J.K., Liu P.T., Lowther D.K., Roberts C.D., Seabaugh V.M., Springer J.A. and Wilcox N.L. (1993) *The use of low-volume dosing in the eye irritation test. Food Chem Toxicol.* 31(2): 99-103

¹⁰ Roggeband R., York M., Pericoi M. and Braun W. (2000) *Eye irritation responses in rabbit and man after single applications of equal volumes of undiluted model liquid detergent products. Food Chem Toxicol.* 38(8): 727-734.

Appendix

I. Relevant studies

A. Kurth, *et al.* (2019)

Kurth, D., Wend, K., Adler-Flindt, S. and Martin, S. (2019). A comparative assessment of the CLP calculation method and in vivo testing for the classification of plant protection products. Regulatory Toxicology and Pharmacology 101 (2019) 79–90.

Brief summary

The paper has been written by scientists of the German Federal institute for Risk Assessment (BfR). It assesses the predictivity of the calculation method for in vivo effects (including eye damage) for agrochemical mixtures (plant protection products). The question addressed is mainly whether the calculation method is conservative enough. To specifically focus on false negatives, the dataset was limited to in vivo classified products. Contrary to other endpoints, with regard to eye irritation, the calculation method underestimated the irritation potential in only 6% of plant protection products. Thus, the overall tone of the paper, indicating a risk for under-prediction, is reported to not apply to eye irritation.

Findings

n=168 all with conclusive test data – 90 with Draize test data on the exact formula (reported between brackets in the below table) and the other 78 with Draize data on a similar formula

<i>data sourced from Table 6 on p.86</i>		Calculation method	
		Cat1	Not Cat1
Test data	Cat1	61 (34)	8 (4)
	Not Cat1	66 (34)	33 (18)
Assessment Calculation vs test data (Cat1 vs No Cat1)		67% false positives (66 / [66+33])*	
		11.6% false negatives (8 / [61 + 8])	
		concordance 56% ([61 + 33] / 168)	

* Mixtures in the data set without any GHS hazard classification were excluded from the assessment. Thus, in this subset, the number of mixtures Not Cat1 based on test data may be lower than in the full data set. Via additivity, the excluded mixtures might be classified either Cat1 or Not Cat1 – which may eventually lead to a higher or lower false positives rate in the overall data set versus the subset. On the other hand, the false negatives assessment (which was the primary objective of the publication) is fully robust because it is derived only from the mixtures with a data based Cat1 classification (all of which are included).

Assessment

- *All in vivo findings are Draize test results, and thus conclusive to determine classification. The proportion of false positives for Cat1 (67%) is very high.*
- It is explicitly stated that the calculation method is prone to overestimating the potential for eye damage (Category 1), and that the high number of false positive and the comparably low number of false negative predictions indicates that the calculation method is more conservative for this endpoint.
- It is also concluded that within the dataset, the calculation method did not reliably distinguish between Category 1 and 2 products.
- Note that the false positives rate as reported in the paper itself (i.e. 40%) was not calculated in a standard way, it is rather a 'proportion of overpredictions'. This different approach was applied because the actual false positives rate of the total data set cannot be determined from the subset used in the assessment (cf. above).

B. Corvaro, *et al.* (2017)

Corvaro, M., Gehen, S. Andrews, K., Chatfield, R., Macleod, F. and Mehta, J. (2017). A retrospective analysis of in vivo eye irritation, skin irritation and skin sensitisation studies with agrochemical formulations: Setting the scene for development of alternative strategies. Regulatory Toxicology and Pharmacology 89 (2017) 131-147.

Brief summary

For eye irritation, this paper retrospectively evaluates the predictivity of the calculation method versus existing eye irritancy studies in animals, in a database of 210 agrochemical formulations. These are all studies of acceptable quality, submitted to pesticide registration authorities as part of the product authorisation process. For identifying the correct category (Cat1, Cat2 or NC) the predictivity of the calculation method was 51%. It is reported that the over-prediction may lead to a false risk perception in the population of concern. However, when a negative is obtained via calculation, this is highly likely to be a true negative (negative predictive value of 88%).

Findings

n=210 all with conclusive test data

data sourced from Fig. 5 (E) on p.139		Calculation method	
		Cat1	Not Cat1
Test data	Cat1	23	6
	Not Cat1	62	119

Assessment Calculation vs test data (Cat1 vs No Cat1)	34% false positives (62 / [62 + 119])
	20.7% false negatives (6 / [23 + 6])
	concordance 68% ([23 + 119] / 210)

Assessment

- All in vivo findings are Draize test results, and thus conclusive to determine classification. The proportion of false positives for Cat1 is notable (34%).
- The false negatives rate is lower (21%) than the false positives rate.
- The calculation method is identified as suitable in case of negative results (thanks to the high negative predictivity) but for positive calculation results follow-up is recommended due to the high over-prediction rate.
- Note that the proportion of “overestimated classification” as reported in the paper is a different metric than the rate of false positives.

C. A.I.S.E. data (Cazelle, *et al.* 2014, 2015 and DetNet)

Cazelle, E., Eskes, C., Hermann, C., Jones, P., McNamee, P., Prinsen, M., Taylor, H. and Wijnands, M. (2014). Suitability of histopathology as an additional endpoint to the Isolated Chicken Eye Test for classification of non-extreme pH detergents^{SEP} and cleaning products. *Toxicology in Vitro* 28 (2014) 657–666.

Cazelle, E., Eskes, C., Hermann, C., Jones, P., McNamee, P., Prinsen, M., Taylor, H. and Wijnands, M. (2015). Suitability of the isolated chicken eye test for classification of extreme pH detergents and cleaning products. *Toxicology in Vitro* 29 (2015) 609–616.

A.I.S.E. (2019). *DetNet: Detergent Industry Network for CLP Classification*. An A.I.S.E. initiative. www.det-net.eu.

Brief summary

Cazelle *et al.* (2014) assesses the use of histopathology as an additional endpoint to the Isolated Chicken Eye (ICE) in vitro test to identify Category 1 (serious eye damage) in non-extreme pH detergents and cleaning products. Histopathology criteria were shown to significantly increase the overall sensitivity for Category 1 identification whilst maintaining a good concordance overall. This was also compared to the calculation method, that was found to be considerably less predictive, with a concordance of only

27%, and 100% over-predictions of non-Category 1 products. Cazelle *et al.* (2015) focuses on extreme pH detergents and cleaning products. The standard ICE led to good concordance with available in vivo data. Histopathology did not improve this, but rather, it reduced specificity. In comparison, the calculation method was found to be considerably less predictive, with a concordance of 61% and over-prediction for non-Category 1 products by 50%.

The DetNet database (A.I.S.E., 2019) contains multiple reference formulas with conclusive in vivo or in vitro test data, as well as the composition information necessary to apply the additivity method in comparison.

Findings

- (a) Cazelle *et al.* (2014): n=30 of which 16 have conclusive test data *
- (b) Cazelle *et al.* (2015): n=18 of which 9 have conclusive test data *
- (c) DetNet: n=17 with conclusive test data * [excluding duplication with Cazelle *et al.* (2014, 2015)]

	Calculation method (incl. extreme pH rule)	
	Cat1	Not Cat1
(a) data sourced from Table 7 p.662 (b) data sourced from Table 7 p.614 (c) data extracted from DetNet		
Test data	Cat1	n=33 (a) 13 (8 LVET, 5 ICE+HP) (b) 6 (5 Draize, 1 LVET) (c) 14 (8 LVET, 5 ICE+HP, 1 BCOP)
	Not Cat1	n=1 (a) 0 (b) 0 ** (c) 1 (BCOP)
		n=6 (a) 3 (Draize) (b) 3 (Draize) (c) 0
		n=2 (a) 0 (b) 0 ** (c) 2 (Draize)

LVET = Low Volume Eye Test, BCOP = Bovine Corneal Opacity test, in vitro test

* To note: only mixtures with stand-alone test data that are conclusive according to current regulatory guidance are included in the above table: i.e. Draize (all outcomes), LVET (only Cat1), ICE (Cat1 or NC) and BCOP (Cat1 or NC) are included. Consequently, LVET studies with Cat. 2 or NC outcomes were not included in the current assessment, nor were in vitro studies with a Cat. 2 outcome.

** all extreme pH products resulted in a calculated Cat.1 classification based on the extreme pH rule

Assessment Calculation vs test data (Cat1 vs No Cat1)	75% false positives (6 / [6 + 2])
	2.9% false negatives (1 / [33 + 1])
	concordance 83.3% ([33 + 2] / 42)

Assessment

- *Across the A.I.S.E. data on detergents and cleaning products, the false positives rate is very notable (65%) while the false negatives rate is an order of magnitude lower (2.9%). In Cazelle et al. (2014, 2015), the calculation method is explicitly identified as poorly predictive of the in vivo classification.*
- The false positives and false negatives rates indicate that the substantial presence of surfactants in these products did not lead to the additivity method being insufficiently conservative, and thus, suggests that presence of surfactants does not require using the 1% threshold approach in lieu of additivity by default.
- To note: a majority of the available test data (both in the Cazelle et al. papers and in DetNet) has a non-Cat.1 outcome that is not conclusive in isolation (i.e. LVET Cat.2 or NC, ICE Cat.2, BCOP Cat.2). While these data can be considered in a weight of evidence assessment to determine classification, they could not be included in the current assessment of the additivity method. Consequently, the subsample used in the current assessment is not representative of the total detergent and cleaning products category, but is biased towards a higher proportion of products with a Cat.1 classification. Consequently, the false positives assessment is not applicable to the entire category. On the other hand, the false negatives assessment is robust because it focuses only on the subset of products with a data based Cat.1 classification.

D. Kolle, et al. (2017)

Kolle, S.N., Van Cott, A., van Ravenzwaay, B. and Landsiedel, R. (2017). Lacking applicability of in vitro eye irritation methods to identify seriously eye irritating agrochemical formulations: Results of bovine cornea opacity and permeability assay, isolated chicken eye test and the EpiOcular™ ET-50 method to classify according to UN GHS. Regulatory Toxicology and Pharmacology 85 (2017) 33-47.

Brief summary

This paper assesses the predictivity of three in vitro eye irritation tests for Cat1 eye damage as determined by the standard animal test, for 27 agrochemical formulations. This indicates a lack of applicability of the three in vitro methods to reliably predict UN GHS Cat 1 of agrochemical formulations. In addition, the calculation method was evaluated - this showed good predictivity for non-irritants; however, the additivity approach was not capable of identifying the hazard of severe eye damage (Cat1) in this data set.

Reported data

UN GHS category (based on the standard Draize test) is reported for each individual tested mixture (n=27). Results of the calculation method are not reported, but for each mixture the % of ingredients classified as Cat1 is provided. 16 mixtures have $\geq 3\%$ of Cat1 ingredients, thus (unless there would be a higher SCL for some of these ingredients) we can estimate these to result in Cat1 in the calculation method. 9 of these

16 mixtures had a Draize result not Cat1. To note, surfactant level (total) is also reported.

Findings

n=27 all with conclusive test data

data sourced from Table 8 on p.44		Calculation method*	
		Cat1	Not Cat1
Test data	Cat1	7	4
	Not Cat1	9	7

* based on the reported percentage of Cat1 ingredients in Table 8 of the paper (mixture deemed to be Cat1 by additivity if the total percentage of Cat1 ingredients is $\geq 3\%$)

Assessment Calculation vs test data (Cat1 vs No Cat1)	56.3% false positives ($9 / [9 + 7]$)
	36.4% false negatives ($4 / [7+4]$)
	concordance 51.9% ($[7+7]/27$)

Assessment

- *All in vivo findings are Draize test results, and thus conclusive to determine classification. The proportion of false positives for Cat1 is high at 56%. But also the false negatives rate is high (36%).*
- The calculation method was found to be not capable of identifying Cat1 eye irritants.
- Many of the included agrochemical formulas contain high surfactant levels, which increases the cross-sector applicability.
- For the calculation method the outcome is not reported for individual mixtures, reproducing this required assumption of “no SCL”.

E. Scazzola, et al. (2019)

Scazzola, R., Boeije, G., Bøtker Pedersen, E., Brenneman, W., Cagáňová, B., Celentano, A., De Coninck, E., Desel, H., Ebbenhøj, N., Färber, E., Sesana, F. and Zacharov, S. (2019). Eye hazard classification according to UN GHS / EU CLP and the severity of eye symptoms caused by accidental exposures to detergents and cleaning products. Regulatory Toxicology and Pharmacology 105 (2019), 69-76.

Brief summary

The severity of observed eye effects following accidental human exposures with detergents recorded by four EU Poison Centres, was compared to the regulatory eye classification category of the products. Irrespective of the classification, the vast majority of exposures caused only minor or no symptoms. Still, classification using the weight of evidence approach based on all available information was found to be more predictive of medically relevant symptoms than the approach based on the calculation method. The latter led to a poorer differentiation between products that are deemed to

be irritating versus those products potentially causing serious eye damage. See also [UN-SCEGHS-35-INF14](#)

Reported data

The paper reports the severity of effects and the product classification (based on different regulatory schemes) for nearly 200 accidental eye exposures that happened across 4 European countries. A statistical assessment is included that assesses the predictivity of classification for medically relevant effects (= 'moderate' severity or worse)

Findings

90% of the exposures did not cause symptoms with worse than minor severity. For the subgroup of products with the highest hazard classification, irrespective of the applied classification scheme, moderate or severe effects (with PSS \geq 2) were rarely incurred (less than 15% of the exposures). This shows that, for at least a substantial proportion of these products, the hazards suggested by the high classification level did not materialise following accidental exposure. When only applying the calculation approach, a much larger proportion of products was to be classified for serious eye damage Category 1 (82% rather than 52%). This led to a poorer differentiation between products, as demonstrated by the high percentage of Category 1 products associated with only minor (or no) symptoms.

Assessment

- The study reports on a substantial number of actual human exposures, covering a large geographical area. Classification based on the calculation method was found to be poorly predictive of the occurrence of medically relevant effects.
- The observed clinical effects and their severity are not only determined by the intrinsic eye irritation hazard of the involved products but also by the first-aid response that was administered (usually rinsing happened shortly after exposure, possibly mitigating the severity of the effects). Nevertheless, the findings do not contradict the hypothesis that the classification by the calculation method is overly conservative relative to actual hazard.

II. Supplementary information (about human exposure and individual substances)

A. Tschopp, et al. 2015

Markus Tschopp, Peter Krahenbuhl, Christoph Tappeiner, Hugo Kupferschmidt, Serge Quarroz, David Goldblum, And Beatrice E. Frueh (2015). Incidence and causative agents of chemical eye injuries in Switzerland. Clinical Toxicology

DOI: 10.3109/15563650.2015.1094702

ABSTRACT: Chemical eye injuries are ophthalmological emergencies with a high risk of secondary complications and severe visual loss. Only limited epidemiological data for such injuries are available for many countries. Patients and methods: We performed two independent studies. The cause of chemical eye injuries was assessed with a prospective questionnaire study. Questionnaires were sent to all ophthalmologists in Switzerland. A total of 163 patients (205 eyes) were included, between December 2012 and October 2014. Independent of the questionnaire study, the incidence of chemical eye injuries was assessed with a retrospective cohort study design using the database of the mandatory accident insurance. Results: Ophthalmological questionnaires revealed that plaster/cement (20.5%), alkaline (12.2%) and acid (10.2%) solutions caused the highest number of chemical injuries. Only 2% of all injuries were classified as grade III and none as grade IV (Roper-Hall classification). The official toxicological information phone-hotline was contacted in 4.3% of cases. Using data from the accident insurance, an incidence of chemical eye injuries of about 50/100 000/year was found in the working population. Conclusion: Here, we present data on the involved agents of chemical eye injuries in Switzerland, and also the incidence of such injuries in the working population. This may also help to assess the need for further education programs and to improve and direct preventive measures.

B. Barroso, et al. (2016)

Barroso, J., Pfannenbecker, U., Adriaens, E., Alépée, N., Cluzel, M., De Smedt, A., Hibatallah, J., Klaric, M., Mewes, K.R., Millet, M., Templier, M. and McNamee, P. (2016). Cosmetics Europe compilation of historical serious eye damage/ eye irritation in vivo data analysed by drivers of classification to support the selection of chemicals for development^{SEP} and evaluation of alternative methods/strategies: the Draize eye test Reference Database (DRD). Arch Toxicol 91 (2017) 521–547.

This paper reports on the compilation of a database of Draize data by Cosmetics Europe, the Draize eye test Reference Database. This contains 681 independent in vivo studies on 634 individual chemicals representing a wide range of chemical classes. An evaluation of the various in vivo drivers of classification was performed to establish which of these are most important from a regulatory point of view. The analyses suggest the need for a critical revision of the UN GHS / EU CLP decision criteria for the Cat 1 classification of chemicals.

The paper focuses on Draize data for individual chemical substances, mixtures are not within its scope. Furthermore, the paper mainly reports aggregated findings across the database, and no individual data points.

The main relevance of the reported findings is to assess the suitability of in vivo Draize data for the validation of in vitro alternative methods. Current classification criteria are assessed in detail and limitations are identified. It is emphasized that the way the Draize eye test data are interpreted is very conservative and may over-predict the true irritation potential of chemicals. The scope is limited to substances. The paper did not assess mixtures and hence, also not the calculation method.

C. ECETOC (1998)

ECETOC (1998). Eye Irritation: Reference Chemicals Data Bank (Second Edition). Technical Report nr. 48(2). June 1998.

This report provides Draize data on 132 individual chemicals (assessed in 149 in vivo studies). Some of these were tested in dilutions (<10%).

The paper focuses on Draize data for individual chemical substances, mixtures are not within its scope. Full raw data are reported, hence a detailed assessment against classification criteria is possible.

The report provides the data. There is no assessment of classification criteria. The calculation method is not a topic that is covered in this paper. A number of substances were tested at <10%. In principle these may be used as “mixture” data. The classification should be determined based on the detailed test results as reported. Among the 9 individual substances tested in dilution, 2 substances have a Cat1 conclusion at a concentration below 10%.

D. EU CLP Regulation Annex VI

CLP Annex VI is considered in an unofficial Excel table (available on <http://echa.europa.eu>) containing the substances with harmonised classification and labelling. In the version covering up until the 9th Adaptation to Technical Progress (in force from March 1st 2018), this Excel table contains 4249 entries. 12.4% (526 entries) are classified as Eye Damage Cat. 1 and an additional 8.8% (374 entries) are classified as Skin Corrosive Cat. 1. Hence, in total 21.2% of the substances in Annex VI will contribute in the additivity method to the classification for Eye Damage Cat. 1:

- 12.2% (n=518) are Eye Dam. 1 without SCL - thus their contribution is determined by the Eye GCL.
- <0.2% (n=8) are Eye Dam. 1 with SCL - thus their contribution is not determined by the Eye GCL of 3%. Importantly, for none of these substances, the SCL is <3%.
- 7.9% (n=335) are Skin Corr. 1 (not Eye Dam. 1) without SCL - thus their contribution is determined by the Eye GCL.
- <1% (n=32) are Skin Corr. 1 (not Eye Dam. 1) with an SCL. - thus their contribution is not determined by the Eye GCL of 3%. For 8 of these substances, the SCL is <3%.