Critical Review of the UN GHS decision criteria for chemicals causing irreversible effects on the eye/serious damage to the eye: Cosmetics Europe Analysis

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Introduction

A thorough understanding of which effects assessed in the in vivo Draize eye test are responsible for driving UN-GHS classification is critical for an appropriate selection of chemicals to be used in the development and/or evaluation of in vitro methods and for properly assessing test method predictive capacity and limitations. For this reason, Cosmetics Europe has compiled a database of Draize eye test Reference Database (DRD) from external labs that were created to support post validation activities. The key goals for compiling the DRD were: (1) to enable a comprehensive analysis and understanding regarding in vivo drivers of classification based on the Draize eye test, (2) to further evaluate the variability of the Draize eye test based on data obtained from repeat studies, (3) to make available an extensive list of chemicals with TG 405 in vivo data, beyond those generally used historically, for further method development and validation, and (4) to provide guidance for selecting reference chemicals based on understanding similar toxic effects that drive classification in the in vivo rabbit Draize eye test. The work presented here describes one part of the overall analysis which is focused on Category 1 (Cat 1) studies classified based on persistence of effects in the majority/majority of animals (77 studies) and on concentration (IC50 < 10 μg/ml). Furthermore, data on chemicals tested in multiple in vivo studies were analyzed to determine the concordance of classification between repeat studies and the consistency for drivers of classification.

Strategy for Developing the DRD

The DRD was primarily compiled using different sources of historic test data in the Draize eye test database at TOXnet, CERHR, Laboratory data from in vivo Draize test studies performed by external labs in which the tests were performed according to specific guidelines (CODEx and OECD TG 405). According to the classification systems, there are several criteria derived from the 4-acetyl scissor effects assessed for the Draize eye test, namely corneal opacity (D14), corneal erosion (D7), conjunctival hyperemia (D7), and conjunctival chemosis (D7). These criteria are defined in the guidelines and lead to a single or multiple drivers of classification. These criteria of classification are defined in Table 1. Full identification of all drivers of classification must be determined in the DRD and are represented in the developed database by species and concentration. Furthermore, the concentrations and species are represented as a series of concentrations and/or species by concentration, allowing for the driver appearing in the majority of animals and/or in more repeat studies, to be selected. Through this, it is possible to develop a consistent, readily accessible, and easily interpretable database for use by the cosmetics industry, regulatory bodies, and other stakeholders.

Results: Distribution According to Drivers of Classification

Table 1: List of drivers of classification; chemical drivers and biological drivers for the chemical selection by classification. This table also contains the percentage of animals and number of studies across all major drivers of classification as according to the categories.

Results: Studies Classified Cat 1 Based on Persistence

Table 2: Summary data showing the number and distribution of chemicals over the sensitivity to category 1 drivers of classification. The major classification drivers include corneal opacity (D14), corneal erosion (D7), conjunctival hyperemia (D7), and conjunctival chemosis (D7).

Table 3: Table showing the distribution of chemicals over the sensitivity to category 1 drivers of classification. The major classification drivers include corneal opacity (D14), corneal erosion (D7), conjunctival hyperemia (D7), and conjunctival chemosis (D7).

Results: Studies Classified Cat 1 Based on CO = 4

Table 4: Table showing the distribution of chemicals over the sensitivity to category 1 drivers of classification. The major classification drivers include corneal opacity (D14), corneal erosion (D7), conjunctival hyperemia (D7), and conjunctival chemosis (D7).

Conclusions:

UN-GHS classification criteria define that a Cat 1 classification can be triggered based on tissue effects observed in a single animal. It is questionable whether such results should lead to a Cat 1 classification, especially in case of delayed effects observed in a single animal in the absence of any other Cat 1 triggering effects. On the basis of the analysis provided here, implementation of the following recommendations should thus be considered:

- CR and CC scores of less than 3 in 1 or 2 studies should be recognized as fully reversed and should not drive a Cat 1 classification in the absence of any other Cat 1 triggering results.
- CR and CC scores of less than 3 in 1 or 2 studies should be recognized as partially reversed and should not drive a Cat 1 classification in the absence of any other Cat 1 triggering results.
- CR and CC scores of fully reversed in multiple 2 studies should not trigger a Cat 1 classification in the absence of any other Cat 1 triggering effects.

Overall, based on this analysis we suggest that chemicals identified as Cat 1 on the basis of the effects described above should not be included in validation studies of alternative methods. Such chemicals could lead to a revision of test results of an alternative method when validation criteria such as the absence of undetected Cat 1 chemicals is used, and in our opinion, would not be scientifically justifiable. Therefore, the establishment of validity criteria and chemicals selection should be carefully considered before validating the results.

References: Barron et al. "Cosmetics Europe compilation of historical versus eye damage trials in vivo data analyzed by drivers of classification to support the selection of chemicals for development and evaluation of alternative methods: the Draize eye test Reference Database (DRD)." Arch. Toxicol. 2016; in press.