

Regulatory Developments: UN Publishes GHS Rev 10

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Government Regulation

On July 27, 2023, the United Nations (UN) [published an electronic version](#) of the tenth revision (Rev 10) of the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) available for free for consultation purposes. The amendments to the ninth revision of the GHS (Rev 9) include the classification procedure for desensitized explosives (Chapter 2.17); the use of non-animal testing methods for classification of health hazards, in particular: skin corrosion/irritation (Chapter 3.2), serious eye damage/eye irritation (Chapter 3.3), and respiratory or skin sensitization (Chapter 3.4); further rationalization of precautionary statements to improve users' comprehensibility while taking into account usability for labeling practitioners; and the review of Annexes 9 and 10 to ensure alignment of the classification strategy, guidance, and tools on metals and metal compounds with the provisions for long-term aquatic classification toxicity in Chapter 4.1.

The most significant changes are in Chapters 3.3 and 3.4. The changes focus heavily on guidance for the use of non-animal test methods and how to apply a weight of evidence assessment. These additions/revisions allow the user additional insight on how to utilize multiple data endpoints to determine if the criteria are met. The revisions include the following new subchapters:

Chapter 3.3

- Subchapter 3.3.2.1 revisions include the re-naming of this subchapter to “Classification based on human data.” Rev 10 amends the content to address human data and states that existing reliable and good quality human data on serious eye damage/eye irritation should be given high weight where relevant for classification and should be the first line of evaluation. According to Rev 10, existing human data could be derived from single or repeated exposure(s).
- Subchapter 3.3.2.3, “Classification based on defined approaches,” is new to Rev 10 and states that defined approaches consist of a rule-based combination of data obtained from a predefined set of different information sources. Rev 10 indicates that defined approaches “can be useful strategies of combining data for classifying substances and mixtures.” Rev 10 notes that data from a defined approach can only be used for classification when the tested substance is within the applicability domain of the defined approach used.
- Subchapter 3.3.2.4, “Classification based on *in vitro/ex vivo* data,” is new to Rev 10 and

includes references to revised/added figures to assist. Table 3.3.6 provides insight for currently available Organization for Economic Cooperation and Development (OECD) test guidelines and indicates how these are to be assessed for this endpoint.

- Subchapter 3.3.2.5, “Classification based on conclusive human data, standard animal data, or *in vitro/ex vivo* data for skin corrosion,” is new to Rev 10. This addition provides details on classification for this hazard class when substances classified as corrosive to skin (skin Category 1) based on conclusive human data, standard animal data, or *in vitro/ex vivo* data for skin corrosion according to the criteria in Chapter 3.2 are also deemed as inducing serious eye damage (eye Category 1). Rev 10 states that skin irritation (skin Category 2), mild skin irritation (skin Category 3), and no classification for skin irritation, as well as human patch data, cannot be used alone to conclude on eye irritation or no classification for effects on the eye, but “may be considered in an overall weight of evidence assessment.”
- 3.3.2.6, “Classification based on other existing animal skin or eye data,” is new to Rev 10 and states that other existing skin or eye data in animals may be used for classification, but there may be limitations regarding the conclusions that can be drawn.
- 3.3.2.7, “Classification based on extreme pH (pH \leq 2 or \geq 11.5) and acid/alkaline reserve,” is new, but the concept is not. Rev 10 provides new guidance on how to address extreme pH and states that a substance with pH \leq 2 or \geq 11.5 is considered to cause serious eye damage (Category 1) in this tier if it has a significant acid/alkaline reserve or if no data for acid/alkaline reserve are available.
- 3.3.2.8, “Classification based on non-test methods for serious eye damage/eye irritation or for skin corrosion,” is new to Rev 10. This subchapter explores computer models, structure-activity relationships, read-across, and other approaches to address classification in this hazard class.
- 3.3.2.9, “Classification based on an overall weight of evidence assessment,” is new to Rev 10 and provides guidance on using a weight of evidence with expert judgment approach. This subchapter includes additional figures to illustrate the process.
- 3.3.5.3, “Background guidance,” is revised in Rev 10. This subchapter provides insight into the integrated approach on testing and assessment (IATA) and includes valuable information on strengths and weaknesses for this hazard class. The addition of Table 3.3.6 provides a useful tool in navigating the complexities of the *in vitro/ex vivo* methods.

Chapter 3.4

- 3.4.2.2.4, “Classification based on defined approaches,” is revised in Rev 10. Subchapter 3.4.2.2.4.1 states that defined approaches consist of a rule-based combination of data obtained from a predefined set of different information sources. Rev 10 notes that data from a defined approach can only be used for classification when the tested substance is within the applicability domain of the defined approach used. Additional limitations described in the published literature should also be taken into consideration.
- 3.4.2.2.5, “Classification based on *in chemico/in vitro* data,” is new to Rev 10. Subchapter 3.4.2.2.5.1 states that the currently available *in chemico/in vitro* methods address specific biological mechanisms leading to the acquisition of skin sensitization. Individual test methods

that are validated according to international procedures and are accepted as stand-alone methods can be used to conclude on the classification in tier 1.

- 3.4.2.2.6, “Classification based on non-test methods,” is new to Rev 10. Subchapter 3.4.2.2.6.1 states that classification, including the conclusion not classified, can be based on non-test methods, with due consideration of reliability and applicability, on a case-by-case basis.
- 3.4.2.2.7, “Classification in a tiered approach,” is new to Rev 10 and according to Subchapter 3.4.2.2.7.1, a tiered approach to the evaluation of information should be considered, where applicable, recognizing that not all tiers, as well as information within a tier, may be relevant. New figures are included to assist with application of the tiered approach.
- 3.4.5.3, “Background guidance,” is new to Rev 10. It includes detailed explanations and guidance on understanding the value of the individual *in chemico* and *in vitro* methods compared to the *in vivo* methods. Table 3.4.7 provides criteria for defined approaches and additional insight to assist with navigation of the skin sensitization endpoint.

Commentary

The most relevant revisions and additions to Rev 10 relate to the non-animal method approaches for serious eye damage/irritation and skin sensitization endpoints. The inclusion of several new/revised figures and tables will allow users to navigate this space more efficiently. The continued use and development of these non-animal methods in the registration and evaluation of chemicals created a gap in criteria-based approaches to classification and labeling. The revisions and additions in Rev 10 and previous revised editions are now addressing these developments. The use of non-animal methods is a useful tool for any stakeholder in this space, even if the jurisdiction you are operating within is not yet aligned with these revisions.

The UN GHS sub-committee continues to clarify physical hazard classes with revisions to Chapter 2.17, Desensitized Explosives. Rev 9 included revisions to Chapter 2.1, Explosives, and Rev 10 further clarifies the exclusion of desensitized explosives from Chapter 2.1. These hazard classes appear to be a priority within the sub-committee, which aims to establish consistent approaches and address transport configurations.

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