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Discussion Guide
Skin Corrosion/Irritation, Eye Damage/Irritation & Skin Sensitization Hazard Classes

This guide has been prepared to facilitate the technical discussions of the PSWG regarding the implementation of the Globally Harmonized System (GHS) in Canada. The following document describes (1) differences between the GHS and PMRA's current approach (2) and the potential impact of the implementation of GHS. This discussion guide is not intended to be comprehensive but presents an approach that is considered viable at this time.

Background

Current PMRA criteria are based on physico-chemical properties as well as biological response data (largely animal data). However, criteria for both are not integrated and occasionally consultation within PMRA is required to determine appropriate hazard labelling. Signal word assignment is based on the biological response and/or the physico-chemical properties depending on the more severe hazard level. However, the criteria for symbol selection as outlined in the Pesticide Registration Handbook reference physico-chemical properties only. With the adoption of the GHS, there would be an integration of physico-chemical properties and biological response data for selection of the appropriate signal word and hazard symbol. When differences occur in the classification outcome of a product based on the biological and the physico-chemical criteria, the more severe hazard level would be communicated.

The following guide addresses the implementation of GHS from the perspective of the biological response criteria. Refer to **Appendix 1** for a table which summarizes the impact of the GHS implementation. **Appendix 2** and **3** provide details regarding the scoring approach used to determine the appropriate level of hazard as well as a visual representation of the differences between the GHS criteria, signal words, hazard statements and hazard symbols, and the existing labelling system used at PMRA.

Classification criteria for mixtures

Under the GHS, end-use products (mixtures) are classified according to the same criteria as active ingredients (substances), and when data are available for the complete mixture, classification will always be based on that information. When data are not available for the complete mixture, bridging principles are then applied. If this approach is not viable, the GHS specifies methods to estimate the potential hazard of a mixture to the skin or eyes.

Pesticide petitioners usually generate test data on the active ingredient as well as the end-use products or they bridge to the database of other similar products in order to identify the hazards and determine the appropriate hazard labelling.

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PMRA will consider the bridging approach in the absence of toxicological data.

1. Skin Corrosion/Irritation

Refer to **Appendix 2** for details regarding the scoring approach used to determine the appropriate level of hazard as well as a visual representation of the differences between the GHS criteria, signal words, hazard statements and hazard symbols and the existing labelling system used at PMRA.

The slight differences between the criteria used by the PMRA and those identified by the GHS are not expected to change the classification outcome to any significant extent.

The GHS criteria used to classify a chemical as Corrosive (Skin category 1A, 1B, 1C) appear to encompass PMRA's current criteria for requiring the signal word CORROSIVE on a pesticide label for both physico-chemical properties and biological criteria. Under the GHS, pesticides classified under category 1 will require the corrosive symbol, signal word and hazard statement "DANGER causes severe skin burns and eye damage". The more irritating pesticides which, on the basis of animal Draize tests, currently require a signal word and phrase only (DANGER, WARNING or CAUTION SKIN IRRITANT) would now require a symbol (!) under GHS category 2 and the signal word and hazard statement "WARNING causes skin irritation". Pesticides classified under GHS category 3 would only require the signal word and hazard statement "WARNING causes mild skin irritation"

The adoption of GHS for Skin Corrosion/Irritation:

Rationale: Harmonize skin corrosion/irritation hazard communication to the greatest extent possible between sectors within Canada and NAFTA countries.

Impact: As indicated above, labelling (signal word, hazard symbol) changes will be required where applicable and the bridging approach may be used as an alternative to toxicological data for mixtures.

2. Eye Damage/Irritation

Refer to **Appendix 3** for details regarding the scoring approach used to determine the appropriate level of hazard as well as a visual representation of the differences between the GHS criteria, signal words, hazard statements and hazard symbols and the existing labelling system used at PMRA.

The slight differences between the criteria used by the PMRA and those identified by the GHS are not expected to change the classification outcome to any significant extent.

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The PMRA currently requires signal words and hazard statements to designate the levels of eye hazard: one for irreversible effects (DANGER CORROSIVE TO EYES) and three levels for reversible effects (DANGER, WARNING or CAUTION EYE IRRITANT). The GHS consists of 3 comparable levels. Under the GHS, pesticides producing irreversible effects to the eye would belong to category 1 (irreversible effects) and be labelled with the corrosive symbol and signal word and hazard statement "DANGER causes severe eye damage". Pesticides which produce reversible eye effects would be in category 2 and, depending on the time required for reversal of effects, could be classified either as category 2A (reversal within 21 days) or category 2B (reversal within 7 days). Under the GHS, pesticides classified in category 2A would require the exclamation point symbol with the signal word and hazard statement "WARNING causes serious eye irritation" whereas products in category 2B would only require the signal word and hazard statement "WARNING causes eye irritation."

The adoption of GHS for Eye Damage/Irritation:

Rationale: Harmonize eye damage/irritation hazard communication to the greatest extent possible between sectors within Canada and NAFTA countries.

Impact: As indicated above, labelling (signal word, hazard symbol) changes will be required where applicable and the bridging approach may be used as an alternative to toxicological data for mixtures.

3. Skin Sensitization

The potential for skin sensitization is assessed by the PMRA and the hazard is communicated via the hazard statement "POTENTIAL SKIN SENSITIZER". However, no hazard symbol or signal word is used to communicate this hazard. PMRA currently applies this approach to both pesticide active ingredients (substances) and formulated products (mixtures).

The GHS cites the same test assays currently used by PMRA to assess this endpoint. Under the GHS, pesticides meeting the criteria for skin sensitization would require a symbol (!) as well as a signal word (WARNING) in addition to the hazard statement "May cause an allergic skin reaction".

The adoption of GHS for Skin Sensitization:

Rationale: Harmonize skin sensitization hazard communication to the greatest extent possible between sectors within Canada and NAFTA countries.

Impact: As indicated above, labelling (signal word, hazard symbol) changes will be required where applicable and the bridging approach may be used as an alternative to toxicological data for mixtures.

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Appendix 2: Skin Corrosion/ Irritation

GHS	Category 1A Corrosive  Danger Causes severe skin burns and eye damage Corrosive in ≥ 1/3 animals in ≤ 3 minutes (≤ 1 hour observation)	Category 1B Corrosive  Danger Causes severe skin burns and eye damage Corrosive in ≥ 1/3 animals in > 3 minutes - ≤ 1 hour (≤ days observation)	Category 1C Corrosive  Danger Causes severe skin burns and eye damage Corrosive in ≥ 1/3 animals in > 1 hour - ≤ hour - ≤ 4 hours (≤ 14 days observation)	Category 2 Irritant  Warning Causes skin Irritation Mean Draize score of ≥ 2.3 - < 4.0 for erythema/eschar or for oedema for 24, 48 and 72 hour assessments in at least 2/3 animals; grading on 3 consecutive days if reactions delayed - Persistence - Variability	Category 3 Mild Irritant (No symbol) Warning Causes mild skin irritation Mean Draize scores of ≥ 1.5 - < 2.3 for erythema/eschar or for oedema for 24, 48 and 72 hour assessments in at least 2/3 animals; grading on 3 consecutive days if reactions delayed (when not included in category 2)

Pesticides: Criteria using animal test data	DANGER SKIN IRRITANT Severely to extremely irritating Mean Draize score of ≥ 5.1 - 8.0 for erythema/eschar and for oedema for 24, 48 and 72 hour assessments for all animals on test (usually 6)	WARNING SKIN IRRITANT Moderately Irritating Mean Draize scores of ≥ 3.1 - 5.0 for erythema/eschar and for oedema for 24, 48 and 72 hour assessments for all animals on test (usually 6)	CAUTION SKIN IRRITANT Mildly Irritating Mean Draize score of ≥ 1.6 - 3.0 for erythema/eschar and for oedema for 24, 48 and 72 hour assessments for all animals on test (usually 6)

The PMRA and the GHS utilize the Draize scale of scoring (maximum of 8-points for skin reactions - 4 points for erythema/eschar response and 4 points for oedema response). Currently, the PMRA criteria are based on the average Draize scores for both erythema/eschar and oedema at specified time points whereas the GHS criteria are based on the average Draize scores for either erythema/eschar or oedema at the same time points

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Appendix 3: Serious Eye Damage/ Eye Irritation

GHS	Category 1 Irreversible Eye Effects  Danger Causes serious eye damage - in at least 1 animal, irreversible eye effects (or not expected to reverse) in 21 days, and/or - mean scores (24, 48, 72 hours) in 2/3 animals consisting of corneal opacity ≥ 3 and/or iritis ≥ 1.5	Category 2A Reversible - Irritating to Eyes  Warning Causes serious eye irritation - eye effects, which fully reverse in 21 days, characterized by at least 2/3 animals with - corneal opacity ≥ 1 and/or - iritis ≥ 1, and/or - conjunctival redness ≥ 2 - conjunctival oedema (chemosis) ≥ 2 - calculated as mean scores or grading at 24, 48 and 72 hours	Category 2B Reversible - Mildly Irritating to Eyes (No symbol) Warning Causes eye irritation - same criteria as for category 2A, however effects are fully reversible within 7 days

Pesticides: Criteria using animal test data	DANGER CORROSIVE TO EYES* Severely to extremely irritating (including irreversibility) Maximum average score of ≥ 50 - 110 for effects to cornea, iris and conjunctivae**	WARNING EYE IRRITANT Moderately irritating Maximum average score of ≥ 25 - 49 for effects to cornea, iris and conjunctivae	CAUTION EYE IRRITANT Mildly irritating Maximum average score of ≥ 15 - 24 for effects to cornea, iris and conjunctivae

* PMRA will consider use of DANGER EYE IRRITANT for pesticides with Maximum Average Scores > 50 - 80 if the response is severe (i.e. opacity) but does demonstrate complete recovery within the study observation period

** The treated eye of each animal is scored using the standard Draize scale (effects to cornea, iris and conjunctiva). These values are converted to an overall individual animal score based on a 110 point rating scale. The converted scores are averaged for each of the 24, 48 and 72 hour observation periods. The maximum average score is then compared against either the Draize (1944) rating guide or Kay and Calandra rating guide (1962) to determine the appropriate level of eye irritation hazard. The GHS criteria are based on the scores generated by effects in any or all areas of the eye at a specified time point.