

ANNEX 2B

ANNEX 3

CRITERIA FOR CLASSIFICATION OF TEST SUBSTANCES WITH EXPECTED LD₅₀ VALUES EXCEEDING 2000 MG/KG WITHOUT THE NEED FOR TESTING.

Criteria for hazard Category 5 are intended to enable the identification of test substances which are of relatively low acute toxicity hazard but which, under certain circumstances may present a danger to vulnerable populations. These substances are anticipated to have an oral or dermal LD₅₀ in the range of 2000-5000 mg/kg or equivalent doses for other routes. Test substances could be classified in the hazard category defined by: 2000mg/kg <LD₅₀ < 5000mg/kg (Category 5 in the GHS) in the following cases:

- a) if directed to this category by any of the testing schemes of Annex 2, based on mortality incidences
- b) if reliable evidence is already available that indicates the LD⁵⁰ to be in the range of Category 5 values; or other animal studies or toxic effects in humans indicate a concern for human health of an acute nature.
- c) through extrapolation, estimation or measurement of data if assignment to a more hazardous class is not warranted, and
 - reliable information is available indicating significant toxic effects in humans, or
 - any mortality is observed when tested up to Category 4 values by the oral route, or
 - where expert judgement confirms significant clinical signs of toxicity, when tested up to Category 4 values, except for diarrhoea, piloerection or an ungroomed appearance, or
 - where expert judgement confirms reliable information indicating the potential for significant acute effects from the other animal studies.

TESTING AT DOSES ABOVE 2000 MG/KG

Exceptionally, and only when justified by specific regulatory needs, the use of an additional upper fixed dose level of 5000 mg/kg may be considered. Recognising the need to protect animal welfare, testing at 5000 mg/kg is discouraged and should only be considered when there is a strong likelihood that the results of such a test would have a direct relevance for protecting animal or human health (9).

Sighting Study

The decision rules governing the sequential procedure presented in Annex 1 are extended to include a 5000 mg/kg dose level. Thus, when a sighting study starting dose of 5000 mg/kg is used outcome A (death) will require a second animal to be tested at 2000 mg/kg; outcomes B and C (evident toxicity or no toxicity) will allow the selection of 5000 mg/kg as the main study starting dose. Similarly, if a starting dose other than 5000 mg/kg is used then testing will progress to 5000 mg/kg in the event of outcomes B or C at 2000 mg/kg; a subsequent 5000 mg/kg outcome A will dictate a main study starting dose of 2000 mg/kg and outcomes B and C will dictate a main study starting dose of 5000 mg/kg.

Main Study

The decision rules governing the sequential procedure presented in Annex 2 are extended to include a 5000 mg/kg dose level. Thus, when a main study starting dose of 5000 mg/kg is used, outcome A (≥ 2 deaths) will require the testing of a second group at 2000 mg/kg; outcome B (evident toxicity and/or ≤ 1 death) or C (no toxicity) will result in the substance being

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unclassified according to GHS. Similarly, if a starting dose other than 5000 mg/kg is used then testing will progress to 5000 mg/kg in the event of outcome C at 2000 mg/kg; a subsequent 5000 mg/kg outcome A will result in the substance being assigned to GHS Category 5 and outcomes B or C will lead to the substance being unclassified.