

## **Draft Guidance Document on Waiving or Bridging of Mammalian Acute Toxicity Tests**

### **Disclaimer/Foreword**

The Globally Harmonized System of Classification and Labelling of Chemicals (GHS, 2013) has been cited throughout this document for context on classification and labelling but national authorities may have their own classification and labelling frameworks against which the waiver criteria can be applied. Elements of GHS have been included in Appendix 1 for ease of reference.

It is recognized that some approaches in this document under which a waiver may be justified (and classification and/or labelling proposed) are based on considerations not expressly addressed under the GHS. However, a basic tenet of the GHS is to give consideration to the totality of existing information and to use expert judgement in making a determination of the appropriate classification and labelling. Regulatory jurisdictions using the GHS for classification and labelling are strongly encouraged to give consideration to the approaches outlined in this document that extend beyond those specified under the GHS.

### **INTRODUCTION**

1. OECD Guidelines for the Testing of Chemicals are continually evolving to reflect changing assessment practices. Acute toxicity tests are an area of focus for developing alternative assays to address animal welfare concerns. One approach to minimizing the use of animals for acute toxicity testing is to consider waiving a study that may be required based on scientific criteria. These criteria include, but are not limited to, the consideration of physico-chemical properties of the test chemical or the potential for little or no exposure to that chemical by a specific route. Another approach to reducing or eliminating animal testing is to use existing hazard information for one compound to characterize the hazard for another (often referred to as bridging or read-across). Clarification of these two concepts is important to ensure that regulatory authorities are provided with the appropriate data required for decision-making and that reduced animal testing can be undertaken without compromising the integrity of the hazard information.
2. The origin of this document is based on guidance developed by the United States and Canada (U.S EPA 2012, Health Canada 2013) for pesticides. While this document is applicable to chemical pesticides, the principles articulated herein can be extended to the assessment of other chemicals, formulations and biological materials. The objective of the following document is to provide guidance and

criteria not only to those who are responsible for generating acute toxicity data, but also to those who are reviewing the data for classification and labelling purposes. This document may also have some value in other regulatory areas such as risk assessment, transport and storage. As legislation and regulatory frameworks differ among OECD member countries, it is incumbent upon national regulatory authorities to determine if this guidance document (or parts of it) has relevance to their programs. Likewise, stakeholders need to be aware of country-specific requirements.

3. The criteria outlined in this document are specific to acute toxicity testing (acute toxicity via the oral, dermal and inhalation route, eye and skin irritation and skin sensitization) and are not intended to be applicable to other areas of toxicity testing.
4. While every effort has been made to make this guidance document as comprehensive and up to date as possible, it is expected that there will also be cases where requests for waivers or bridging will fall outside the scope of this document and will require separate review and/or consultation with regulatory authorities (e.g., products containing particles in the nanoscale). Expert judgement is paramount in considering any waiver request and should take into account the context of all the available information.
5. For the purpose of this document, test chemical refers to active substance or end-use product (see specific guidance for end-use products later in the document). When extending the criteria to non-pesticides, active substance can be taken to be synonymous with a single substance or component and end-use product can be taken to be synonymous with a mixture of substances or components.

#### **WAIVER CRITERIA**

6. Generally, waivers are considered when there is little or no significant human exposure by a given route of exposure or when it is technically not possible to perform a study for a certain endpoint, such as not requiring an acute oral toxicity study when the test chemical exists as a vapour or gas. Waivers are also possible taking into account animal welfare considerations, such as when the test chemical is corrosive. Specific waiver criteria for each type of acute toxicity study are discussed below. Requests for a waiver of any acute toxicity data requirement or justification for bridging should be prepared in accordance with regulatory authority formatting requirements and should include a valid scientific rationale and documentation to support the request. All waiver requests should be considered on a case-by-case basis following a weight-of-evidence approach. The burden of proof lies entirely with the party requesting the waiver.

- 85 7. Some waivers may be justified on the basis of use and exposure conditions; this  
86 may be particularly applicable for pesticides and biocides. For test chemicals  
87 under the purview of hazard-based chemical legislation, exposure-based waiving  
88 of testing may be less applicable. Where exposure-based waivers are proposed,  
89 sufficient documentation is required to identify all potential exposure scenarios.  
90
- 91 8. When a waiver is granted for an acute toxicity study, this should be identified  
92 when presenting the hazard profile for the test chemical in order to acknowledge  
93 that there is not a data gap for this study. Labelling language for acute hazards of  
94 active substances or end-use products should be reflective of the basis of the  
95 granted waiver. For example, the lack of acute inhalation hazard for a non-  
96 inhalable test chemical would be reflected through no requirement for label  
97 language regarding acute inhalation hazard. By contrast, if an acute dermal toxicity  
98 waiver is granted on the basis of the test chemical being corrosive, the label would  
99 need to reflect the potential for corrosivity of the test chemical by the dermal route.  
100 Where appropriate, labelling language for end-use products, for which acute  
101 studies have been waived, can be based on the inherent toxicological profiles of  
102 their single components.  
103
- 104 9. As an overarching criterion, in vivo animal studies should be waived where the  
105 results of validated in vitro tests or alternative approaches (such as read-across and  
106 (Q)SARs) are adequate to draw a conclusion regarding the classification of an  
107 acute hazard for a test chemical.  
108

## 109 **ACUTE ORAL TOXICITY**

- 110
- 111 10. An acute oral toxicity study may not be required if testing is not technically  
112 feasible or relevant such as when the test chemical is a gas or vapour at ambient  
113 temperature.  
114
- 115 11. Waivers will be considered for end-use products that are composed of non-friable  
116 material and are too large to be ingested; or where end-use product design prevents  
117 oral exposure. End-use products such as pet collars, plastic ear tags and tamper  
118 resistant roach traps and bait boxes often meet these criteria. Even though some  
119 end-use products may be too large to be ingested, there is still some concern for  
120 exposure (e.g. a child mouthing an end-use product or hand-to mouth contact  
121 following breakage). In this case, labelling should reflect the hazard potential of  
122 the active substance or other components of the end-use product.  
123
- 124 12. An acute oral toxicity study may be waived if the test chemical is corrosive to  
125 skin (GHS Category 1) based on in vivo, in vitro or other data or has a pH less  
126 than or equal to 2 or greater than or equal to 11.5 (OECD, 2014b). As the GHS  
127 corrosivity hazard statements only pertain to the skin, hazard statements that  
128 correspond to GHS Category 1 for acute toxicity via the oral route should be used  
129 for labelling.  
130

- 131 13. A waiver will be considered if the oral LD<sub>50</sub> of the test chemical is predicted to be  
132 greater than 2000 mg/kg bw (GHS Category 5 and the threshold for labelling)  
133 based on the results of a validated and/or accepted alternative test or test battery  
134 provided the test system was shown to have high sensitivity and the applicability  
135 domain is inclusive of the chemistry under investigation.

#### 136 ACUTE DERMAL TOXICITY

- 137  
138  
139 14. A dermal toxicity study may be waived if the test chemical is corrosive or severely  
140 irritating to skin (GHS Category 1) based on in vivo, in vitro or other data or has a  
141 pH less than or equal to 2 or greater than or equal to 11.5 (OECD, 2014b).  
142  
143 15. Waivers will be considered for end-use products for which the product design  
144 prevents dermal exposure. Products such as roach traps and bait boxes that are  
145 tamper-resistant to children often meet these criteria. In these cases, exposure is  
146 likely limited to situations where breakage occurs. Labelling should reflect the  
147 dermal hazard of the active substance or other components of the end-use product.  
148  
149 16. A dermal toxicity study may be waived if the test chemical has shown no toxicity  
150 in an acute oral toxicity test up to 2000 mg/kg bw (Category 5 hazard under GHS).  
151 Reviews comparing the classification of oral and dermal hazards indicate that it is  
152 rare for the dermal test to yield a more severe classification (Thomas and  
153 Dewhurst, 2007; Creton et al., 2010; Seidle et al., 2011, Moore et al., 2013). Under  
154 this premise, dermal toxicity of test chemical meeting this criterion should not  
155 result in a more severe classification than the corresponding oral hazard and would  
156 be classified as a Category 5 dermal hazard.  
157  
158 17. Under the same premise articulated above (i.e., dermal toxicity is unlikely to result  
159 in a more severe classification than the corresponding oral hazard), a waiver may  
160 be considered if the oral LD<sub>50</sub> of the test chemical is less than 300 mg/kg bw. Test  
161 chemicals meeting this criterion would be classified in the corresponding GHS  
162 category as the oral hazard (i.e., a Category 2 oral hazard would be classified as a  
163 Category 2 dermal hazard, a Category 3 oral hazard would be classified as a  
164 Category 3 dermal hazard etc.) As there is no difference between the symbol and  
165 signal word for labelling Category 1, 2 or 3 oral or dermal hazards, there is  
166 generally no need to conduct further animal testing to refine the classification.  
167  
168 18. A waiver may be considered where the oral LD<sub>50</sub> range is between 300-2000  
169 mg/kg bw and dermal penetration data indicates low dermal absorption (<10%)  
170 relative to oral absorption. In this case, the oral LD<sub>50</sub> would equate to a dermal-  
171 equivalent value of 3000 mg/kg bw (oral value of 300 mg/kg bw ÷ 10% dermal  
172 absorption) or greater and test chemicals meeting this criteria would be classified  
173 as a Category 5 dermal hazard according to GHS. Care must be taken with this  
174 approach to ensure that dermal absorption values have been appropriately  
175 determined taking into account the effects of loading.  
176

**Comment [CC1]:** Supporting analysis conducted by A.Lowit/ICCVAM and J.Mehta – add citations if/when they become available

## ACUTE INHALATION TOXICITY

19. An acute inhalation toxicity study may not be required for a test chemical if it demonstrates low volatility, is not aerosolized (i.e., generated as a mist, fog, spray, dust, smoke or fume), heated, evaporated, or otherwise made inhalable as a gas or vapour under conditions of use, storage, handling, or transport. Low-volatility products are defined as having vapor pressures  $<1 \times 10^{-5}$  kPa ( $7.5 \times 10^{-5}$  mmHg) for indoor uses, and  $<1 \times 10^{-4}$  kPa ( $7.5 \times 10^{-4}$  mmHg) for outdoor uses at 20-30° C (Whalan et al., 1998). Examples of test chemicals with low volatility include, but are not limited to, viscous liquids, waxes, resins, lotions, and caulks. A waiver request should report the vapor pressure for the test chemical and provide evidence that there is no substantial off-gassing. Where the waiver involves an end-use product with low volatility, labelling should reflect the inhalation hazard of the active substance or other components of the end-use product. A waiver may not be appropriate for a test chemical that is expected to be highly toxic via the inhalation route (based on available information) unless its volatility is extremely low.
20. Waivers for acute inhalation studies may be considered for test chemicals for which the particles are too large to be inhaled and the material cannot be broken down into inhalable-sized particles. Inhalable liquid and solid particles are capable of entering the human respiratory tract via the nose and/or mouth, and are generally defined as being smaller than 100  $\mu\text{m}$  in diameter. Particles larger than 100  $\mu\text{m}$  are less likely to be inhalable. Of those particles which are inhalable, respirable particles pose a particular hazard because they are small enough to reach the alveoli, the major site of absorption in the respiratory tract. It is important to note that an inhaled test chemical need not be respirable to pose a hazard since many chemicals are readily absorbed in the nasal mucosa (e.g. cocaine) and/or can result in oral ingestion due to mucociliary transport. Significant oral ingestion can also occur when animals are exposed in whole-body chambers due to the licking of particles deposited on the fur during grooming. For these reasons, a waiver may not be appropriate for test chemicals that are highly toxic by the oral route.
21. An aerosol for an end-use product or application method may be considered essentially non-inhalable provided  $>99\%$  of the particles by mass are  $>100 \mu\text{m}$  in diameter at the point where humans are exposed (Whalan et al., 1998). Waiver requests based on particle size should be accompanied by particle size distribution measurements performed in accordance with a standardized test method that provides reliable results.
22. Solid aerosol particles can be generated as dusts, fumes, smoke, and granules. When performing an inhalation toxicity study of a solid material, the test chemical may need to be crushed in a ball mill to achieve a respirable particle size (a mass median aerodynamic diameter (MMAD) of 1-4  $\mu\text{m}$ , OECD Guidance Document39, 2009). Requests for waivers on the basis of solid particle size should include evidence that the test chemical consists of large, non-inhalable particles

that are resistant to attrition. This can be accomplished by using the latest version of the American Society of Testing Materials (ASTM) Test Method E728-91-Standard Test Method for Resistance to Attrition of Granular Carriers and Granular Pesticides (<http://www.astm.org/>).

23. Liquid aerosols can be generated as mists and fogs by spraying, nebulization, and by the pouring of liquids. For pesticides, waiver rationales based on the use of medium or coarse spray nozzles that result in large droplets (100 – 500 µm diameter) are generally insufficient as it has been shown that within seconds of leaving a nozzle, large droplets of an aqueous mix can rapidly shrink to a size that is inhalable and often respirable (Matthews, 2008). Consideration should be made for the likelihood that liquid particles may shrink due to evaporation and therefore may become inhalable. Waivers will not be granted for liquid aerosols on the basis of large particle size unless it can be demonstrated that large droplets do not shrink to an inhalable size (i.e., < 100 µm).
24. A waiver for an acute inhalation toxicity study may be considered if a test chemical cannot be generated as a gas, vapour, or aerosol in sufficient concentration to elicit animal toxicity in the optimal conditions of an inhalation chamber. Extraordinary measures are not required. The waiver request should include a clear description of the methods and equipment used to generate an inhalable concentration of the product. An example of a waiver candidate under this criterion is pesticidal paint (*e.g.*, antifouling paint) that may clog the airways of animals and that may be impractical to generate as a respirable aerosol in an inhalation chamber. In this case, labelling should reflect the inhalation hazard of the active substance or other components of the end-use product.
25. There are several toxicokinetic reasons why the inhalation route is the most toxic route for many chemicals: i) the lungs have a huge alveolar surface area where chemicals are rapidly transported across the thin alveolar membrane into the blood stream; ii) all orally administered chemicals make a first pass through the liver (via hepatic portal circulation) where most are detoxified, but inhaled chemicals immediately enter the blood stream, bypassing the metabolic protection of the liver; and iii) stomach acid converts many ingested chemicals into less toxic moieties. The only route that provides faster systemic exposure is intravenous injection. Because of these significant toxicokinetic differences, a waiver for an acute inhalation toxicity study may be considered for test chemicals that are classified as Category 1 or 2 for acute oral or dermal toxicity according to GHS. Under these conditions, a test chemical would be classified as a Category 1 inhalation hazard according to GHS. As there is no difference between the symbol and signal word for labelling Category 1 and 2 inhalation hazards, there is generally no need to conduct further animal testing to refine the classification.
26. OECD inhalation test guidelines and Guidance Document 39 require the testing of corrosive chemicals at targeted concentrations that are low enough to not cause marked pain and distress, yet sufficient to extend the concentration-response curve

**Comment [CC2]:** Reference UK-led OECD project work on fixed dose procedure when available.

to levels that reach the regulatory and scientific objectives of the test. This can be accomplished by using a dilution of the test chemical, preferably using water as the diluent. Particular attention should be paid to portal-of-entry effects. Experience has shown that chemicals that are corrosive to the eyes and skin are not always corrosive to the respiratory tract and often demonstrate low inhalation toxicity. Nevertheless, an inhalation toxicity study may be waived if the test chemical is corrosive to skin (GHS Category 1) based on in vivo, in vitro or other data or has a pH less than 2 or greater than 11.5 (OECD, 2014). As the GHS corrosivity hazard statements only pertain to the skin, hazard statements that correspond to GHS Category 1 for acute toxicity via the inhalation route should be used for labelling.

### SKIN CORROSION/IRRITATION

27. In vivo animal studies should be waived where the results of validated and/or accepted in vitro tests are adequate to draw a conclusion on the appropriate classification and risk assessment of the test chemical.
28. A skin corrosion/irritation study may not be required if the test chemical is corrosive to skin based on in vivo, in vitro or other data or has a pH less than or equal to 2 or greater than or equal to 11.5 (OECD, 2014b). Such test chemicals will be considered as Category 1 (or sub-categories 1A, 1B or 1C if required) dermal corrosives under GHS for labelling purposes. It cannot be ruled out that some test chemicals may be over-predicted based solely on pH considerations. Accordingly, testing with in vitro methods can be performed as an alternate approach for test chemicals with strong acidity or alkalinity.
29. A skin corrosion/irritation study may not be required if the test chemical is spontaneously flammable in air or water at room temperature. No classification for skin corrosion or irritation is required.
30. A skin corrosion/irritation study may be waived where the test chemical has been classified as a Category 1 or 2 acute dermal hazard under GHS (i.e., dermal toxicity  $\leq 200$  mg/kg bw). Such test chemicals will be considered as Category 1 dermal corrosives under GHS for the labelling purposes. Alternatively, in vitro tests for skin irritation or skin corrosion could be performed.
31. Waiving may be possible when it is technically not possible to turn the test chemical into an accessible form for a skin corrosion/irritation test. Where relevant and technically possible, in vitro testing could be considered. For end-use products meeting this criterion, the skin corrosion/irritation potential can be considered from the corrosion/irritation potential of the active substance or other components of the end-use product.
32. Waivers may be considered for end-use products containing strong dyes or pigments that may complicate interpretation of skin corrosion/irritation data. In

such situations, a screening study should be conducted in an appropriate test species in order to determine the degree of adherence and/or dermal staining. All observations made during this screening study should be included in the waiver request. For end-use products meeting this criterion, the skin corrosion/irritation potential can be considered from the corrosion/irritation potential of the active substance or other components of the end-use product. Alternatively, it can be informed by validated and/or accepted in vitro methods such as those using reconstructed human epidermis and HPLC/UPLC spectrophotometry to address color interference (OECD, 2013, OECD, 2014a). These latter methods can be used to identify GHS Category 1 skin corrosives, Category 2 skin irritants, and non-classified chemicals (OECD 2014b), but may pose problems in classifying mild irritants (GHS Category 3).

#### **SERIOUS EYE DAMAGE/EYE IRRITATION**

33. In vivo animal studies should be waived where the results of validated and/or accepted in vitro tests are adequate to draw a conclusion on the appropriate classification and risk assessment of the test chemical.
34. A study assessing serious eye damage or eye irritation may not be required if the test chemical is corrosive to skin (GHS Category 1) based on in vivo, in vitro or other data or has a pH less than 2 or greater than 11.5 (OECD, 2012). In this case, the test chemical should be considered in GHS Category 1 for serious eye damage.
35. A study assessing serious eye damage or eye irritation may not be required if the test chemical is spontaneously flammable in air at room temperature. No classification for serious eye damage or eye irritation is required.
36. A study assessing serious eye damage or eye irritation may be waived where the test chemical has been classified as a Category 1 or 2 acute dermal hazard under GHS (i.e., dermal toxicity  $\leq 200$  mg/kg bw). Such test chemicals will be considered in GHS Category 1 for serious eye damage for the labelling purposes. Alternatively, in vitro tests for serious eye damage or eye irritation could be performed.
37. Waiving may be possible when it is technically not possible to turn the test chemical into a suitable form for a test for serious eye damage or eye irritation. Prior to considering a waiver based on the inability to turn the test chemical into a suitable form for testing, consideration should be given as to whether the test chemical can be more appropriately tested in an in vitro system. For end-use products meeting this criterion, the potential for serious eye damage or eye irritation can be considered from the serious eye damage or irritation potential of the active substance or other components of the end-use product.
38. Waivers may be appropriate for test chemicals composed of granules or pellets that are very large (unable to be retained in the eye) or non-friable (as



demonstrated by an attrition study), if the material retains its physical form under application conditions (i.e., it is not dispersed in water prior to application). Size range of the granules which compose the product should be documented and submitted as part of the request.

39. Full consideration of the conditions of use is necessary prior to determining the applicability of a waiver and the resulting labelling. For instance, while treated fabric may not come into direct contact with eyes, the possibility exists that sweaty hands could transfer residues from treated clothing to the eyes. In this case, a study for serious eye damage or eye irritation may be waived for the treated fabric but the fabric would require labelling based on the serious eye damage or eye irritation potential of the active substance or other components of the end-use product.

#### **DERMAL SENSITIZATION**

40. A dermal sensitization study may not be required on an end-use product if it is corrosive to the skin at the most dilute use concentration recommended on the product label based on in vivo, in vitro or other data or a pH less than 2 or greater than 11.5. For chemicals that may be used in an end-use product, information on their sensitizing potential may be needed.
41. A dermal sensitization study may not be required if the test chemical is spontaneously flammable in air at room temperature. No classification for dermal sensitization is required.
42. Waiving may be possible when it is technically not possible to turn the test chemical into an accessible form for a dermal sensitization test. For end-use products meeting this criterion, the dermal sensitization potential can be considered from the sensitization potential of the active substance or other components of the end-use product.
43. In general, waivers will not be considered for end-use products with dyes and pigments on the basis that these components will interfere with interpretation of results in guinea pig sensitization models. Alternate methods, such as the local lymph node assay, should be pursued that are not compromised by the presence of dyes or pigments.
44. In vivo animal studies should be waived where the results of validated and/or accepted in vitro or in chemico tests covering the key mechanistic events as described in the adverse outcome pathway for skin sensitization are adequate to draw a conclusion on the appropriate classification and risk assessment of the test chemical. Where potency considerations are required by a regulatory jurisdiction, it would be necessary for alternative in vitro assays to address such considerations.
45. A dermal sensitization study may not be required for an end-use product if one of the components of that product is a known sensitizer based on test data. Such end-

use products should be classified as a Category 1 skin sensitizer. However, some regulatory frameworks may make this classification dependent on the concentration of the components in the end-use product.

46. Waivers may be considered for a dermal sensitization study on an end-use product if that product contains only components that are non-sensitizers and there is low likelihood for interaction between the components. Data demonstrating the lack of sensitization potential of the components would need to be made available to support such a waiver. In this case, the end-use product would be labelled as a non-sensitizer.

47. If in vivo testing is required by a regulatory jurisdiction, a preferred method would be one that optimally reflects the 3R considerations, such as the Local Lymph Node Assay.

## END-USE PRODUCTS

48. Testing on an end-use product may not need to be conducted if there are valid data available on each of the components in the product sufficient to allow classification of the product according to recognized calculation approaches, and synergistic effects among any of the components are not expected. Data demonstrating the toxic potential of the components would need to be made available to support such a waiver. Guidance on generating an acute toxicity estimate can be found under GHS (Chapter 3.1.3 Classification Criteria for Mixtures).

## GRANULAR END-USE PRODUCTS

49. For the purposes of this guidance, granular end-use products are limited to those products composed of a high percentage (generally greater than 90%) of granular inert carrier(s) (corn cobs, clay, limestone, sand, food) and a minimal amount of sticker/binder (generally 5% or less of the formulation). Rodenticide baits are excluded from the data waiver/bridging approach outlined below since experience has shown that rodenticide baits are often more toxic than would be predicted using the bridging method.

50. Acute toxicity studies (acute oral, dermal or inhalation toxicity studies) can be waived for granular end-use products that comply with the description above. If the acute toxicity profile of the active substance(s) and other components of the end-use product (excluding the granular inert carrier) are classified as Category 4 or 5 hazards under GHS, the end-use product may be classified as a Category 5 hazard. This extrapolation for acute systemic toxicity is based on the principle of dilution. The assumption is that the inert carrier does not contribute to the toxicity, and thus acts as a diluent.

- 452 51. If the acute toxicity profile of the active substance(s) and other components of the  
453 end-use product are classified as Category 1 through 3, calculations that bridge  
454 downward from these categories (i.e., lower the hazard classification) will be  
455 considered if there are valid data available on the components (including the  
456 granular inert carrier) to generate an acute toxicity estimate. If data are not  
457 available, bridging downward will generally not be considered and hazard  
458 labelling would have to reflect that of the active substance and components of the  
459 end-use product.
- 460
- 461 52. Irritation studies (skin and eye) can be waived for the granular end use-products  
462 described above. Labelling for irritation potential for the end-use product would  
463 need to conform to irritation labelling used for the active substance or reflect the  
464 known irritation of components contained in the end-use product.
- 465
- 466 53. If a granular end-use product contains any component that is a known sensitizer,  
467 the product generally would be labelled as a sensitizer. If the components in the  
468 product are all known to be non-dermal sensitizers, a dermal sensitization study  
469 may be waived and the product will not be considered a dermal sensitizer.
- 470

#### 471 **BRIDGING OF DATA FOR ACUTE TOXICITY**

472

- 473 54. Bridging (or read-across) refers to the use of an existing data set to characterize  
474 the hazard for another chemical for which there are little or no existing data. End-  
475 use products of unknown hazard may be similar in composition and form to one or  
476 more other products with an existing complete acute toxicity data base. In these  
477 situations, a complete or partial acute toxicity profile can be constructed for the  
478 product of unknown hazard depending on the applicability of available data. Each  
479 specific hazard determination eliminates the need to conduct the associated acute  
480 toxicity study on the end-use product. The underlying logic for each determination  
481 is, in most cases, based on expert scientific judgment.
- 482
- 483 55. Determining the similarity of products involves a comparison of the product  
484 chemistry and product formulation data (including the percentage of active  
485 substance(s) as well as other components). Examples of dissimilar products from a  
486 toxicological perspective include (but are not limited to): changes in the identity of  
487 the non-active components; significant changes in the percentage of active  
488 substance; new formulation type; and, significant changes in the proportion of  
489 non-active components.
- 490
- 491 56. Where a product is considered to be toxicologically comparable to another product  
492 with valid acute data, the classification and hazard labelling should be identical  
493 between the two products.
- 494
- 495 57. Bridging acute toxicity study results from a product containing a lower  
496 concentration of an active substance to a product containing a higher concentration  
497 of the active substance is generally not recommended, as the classification of

toxicity could be underestimated. Products containing a higher concentration of active substance may be used to support products containing a lower concentration of active substance; however, precautionary labelling would reflect that of the product with the high concentration.

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## APPENDIX 1

Table 1. GHS Criteria for Acute Toxicity via the Oral, Dermal and Inhalation Route.

| GHS CATEGORY | SYMBOL               | SIGNAL WORD | HAZARD STATEMENT   | ORAL LD <sub>50</sub> (mg/kg bw) | DERMAL LD <sub>50</sub> (mg/kg bw) | INHALATION LC <sub>50</sub> (mg/L or ppm)  |
|--------------|----------------------|-------------|--|----------------------------------|------------------------------------|--|
| 1            | Skull and Crossbones | Danger      | Fatal (select: if swallowed, in contact with skin or if inhaled)   | ≤ 5                              | ≤ 50                               | ≤ 0.05 mg/L (dust, mist)<br>≤ 0.5 mg/L (vapour)<br>≤ 100 ppm (gas)   |
| 2            | Skull and Crossbones | Danger      | Fatal (select: if swallowed, in contact with skin or if inhaled)   | 5 < 50                           | 50 < 200                           | 0.05 < 0.5 mg/L (dust, mist)<br>0.5 < 2.0 mg/L (vapour)<br>100 < 500 ppm (gas)   |
| 3            | Skull and Crossbones | Danger      | Toxic (select: if swallowed, in contact with skin or if inhaled)   | 50 < 300                         | 200 < 1000                         | 0.5 < 1.0 mg/L (dust, mist)<br>2.0 < 10.0 mg/L (vapour)<br>500 < 2500 ppm (gas)  |
| 4            | Exclamation Mark     | Warning     | Harmful (select: if swallowed, in contact with skin or if inhaled) | 300 < 2000                       | 1000 < 2000                        | 1.0 < 5.0 mg/L (dust, mist)<br>10.0 < 20.0 mg/L (vapour)<br>2500 < 5000 ppm (gas)  |
| 5            | None                 | None        | None   | 2000 ≤ 5000                      | 2000 ≤ 5000                        | ≥ 5.0 mg/L (dust, mist)<br>≥ 20.0 mg/L (vapour)<br>≥ 5000 ppm (gas)<br>AND: any mortality at Cat 4, indication of human effects, significant signs at Cat 4, indication from other studies |
| Unclassified | None                 | None        |  | > 5000                           | > 5000                             | None of the above  |

Table 2. GHS Criteria for Corrosion, Irritation and Sensitization.

| GHS CATEGORY              | SYMBOL           | SIGNAL WORD | HAZARD STATEMENT                        | CRITERIA   |
|---------------------------|------------------|-------------|---|--|
| SKIN CORROSION/IRRITATION |                  |             |   |  |
| 1                         | Corrosion        | Danger      | Causes severe skin burns and eye damage | pH ≤ 2.0 or pH ≥ 11.5 <b>OR</b><br>in vitro skin corrosion test positive results <b>OR</b><br>Corrosive* in ≥ 1/3 (or 2/6) animals   |
| 2                         | Exclamation Mark | Warning     | Causes skin irritation                  | in vitro skin irritation test positive results <b>OR</b><br>MS** in ≥ 2/3 (or 4/6) animals of:<br>≥ 2.3 to ≤ 4.0 for erythema/eschar or edema<br>(if delayed effect: calculate MS from 3 consecutive days after onset of reaction); <b>OR</b><br>inflammation persisting to 14 days in ≥ 2 animals;<br><b>OR</b> extreme variability of response |
| 3                         | None             | Warning     | Causes mild skin irritation             | MS** in ≥ 2/3 (or 4/6) animals of:<br>≥ 1.5 to < 2.3 for erythema/eschar or edema<br>(if delayed effect: calculate MS from 3 consecutive days after onset of reaction)   |
| Unclassified              | None             | None        | None                                    | None of the above  |
| EYE DAMAGE AND IRRITATION |                  |             |   |  |
| 1                         | Corrosion        | Danger      | Causes serious eye damage               | pH < 2.0 or pH > 11.5 <b>OR</b><br>in vitro eye damage test positive results <b>OR</b><br>≥ 1 animal with effects remaining at 21 days;<br><b>AND/OR</b><br>MS* in ≥ 2/3 (or 4/6) animals of:<br>≥ 3 corneal opacity; <b>AND/OR</b><br>≥ 1.5 iritis  |
| 2A                        | Exclamation Mark | Warning     | Causes serious eye irritation           | in vitro eye irritation test positive results <b>OR</b><br>classification as Category 2 skin irritant <b>OR</b><br>Effects which fully reverse in 21 days <b>AND</b> :<br>MS* in ≥ 2/3 (or 4/6) animals of:<br>≥ 1 corneal opacity; <b>AND/OR</b> ≥ 1 iritis; <b>AND/OR</b> ≥ 2 conjunctival redness; <b>AND/OR</b> ≥ 2 chemosis                 |
| 2B                        | None             | Warning     | Causes eye irritation                   | Effects which fully reverse in 7 days <b>AND</b> :<br>MS* in ≥ 2/3 (or 4/6) animals of:<br>≥ 1 for corneal opacity; <b>AND/OR</b> ≥ 1 for iritis;<br><b>AND/OR</b> ≥ 2 for conjunctival redness; <b>AND/OR</b> ≥ 2 for chemosis  |
| Unclassified              | None             | None        | None                                    | None of the above  |
| SKIN SENSITIZATION        |                  |             |   |  |
| 1<br>(1A and 1B)          | Exclamation Mark | Warning     | May cause allergic skin reaction        | Positive results from animal test <b>AND/OR</b> human evidence<br>1A: High frequency of occurrence in humans and/or a high potency in animals; severity of reaction may be considered<br>1B: Low to moderate frequency of occurrence in humans and/or a high potency in animals; severity of reaction may be considered                          |
| Unclassified              | None             | None        | None                                    | Negative animal test results   |

\* Corrosive = destruction of skin tissue (visible necrosis, ulcers, bleeding, bloody scabs and at 14 days, discolouration due to blanching of the skin)

\*\*MS = Mean Score (of 24, 48 and 72 hours).