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Guidance Document on Considerations for Waiving or Bridging of Mammalian Acute Toxicity Tests

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OECD Environment, Health and Safety Publications

Series on Testing and Assessment

No. 237

GUIDANCE DOCUMENT ON CONSIDERATIONS FOR WAIVING OR BRIDGING OF MAMMALIAN ACUTE TOXICITY TESTS

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT
Paris 2016

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FOREWORD

The project to develop this OECD Guidance Document was initiated by the United States and Canada to address animal welfare concerns in the area of acute toxicity testing by introducing considerations where a study may be waived. It was included in the work plan of the Test Guidelines Programme in April 2014.

The draft document was circulated on several occasions (November 2014, June 2015, November 2015 and January 2016) for review by nominated experts, by the Working Group of the National Coordinators to the Test Guidelines Programme (WNT), and by the Task Force on Hazard Assessment. The document was approved at the 28th Meeting of the WNT in April 2016. The Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology agreed to its declassification on 8 July 2016.

This document is published under the responsibility of the Joint Meeting of the chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology.

GUIDANCE DOCUMENT ON CONSIDERATIONS FOR WAIVING OR BRIDGING OF MAMMALIAN ACUTE TOXICITY TESTS

Disclaimer

The Globally Harmonized System of Classification and Labelling of Chemicals (GHS, 2015) 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 the 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 are encouraged to give consideration to the approaches outlined in this document as part of the weight of evidence in determining the need for a mammalian acute toxicity study and appropriate classification and/or labelling.

INTRODUCTION

1. The 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. In the context of this document, acute toxicity studies refer to studies involving a single exposure (i.e. a single exposure or multiple exposures within 24 hours) to a test chemical and include those assessing systemic toxicity as well as those assessing local irritation, corrosion or sensitization. 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 test chemical by a specific route. Another approach to reducing or eliminating animal testing is to use existing hazard information that is informative for the acute toxicity endpoint for the test chemical; this would include the use of hazard information for one or multiple similar test chemicals to characterize the hazard for another (often referred to as read-across) or for mixtures, the use of recognized calculation approaches and bridging concepts. Clarification of these approaches 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 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 could be extended to the assessment of other chemicals, formulations and biological materials on a case-by-case basis. The objective of this 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. Certain legislations (e.g., the REACH Regulation, EC No. 1907/2006) include the waivers addressed in this guidance document and provide some further possibilities for waivers or adaptations from the information requirements (ECHA, 2015). At the same time, other regulatory frameworks, such as those for the global transport sector, are focussed on intrinsic hazard with minimal consideration of how a product is used or an exposure occurs. Given that legislation and regulatory frameworks differ among OECD member countries, it is incumbent

upon national regulatory authorities to determine if this guidance document (or any part 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. Furthermore, this document is focussed on the use of acute toxicity testing for human health assessment; due consideration should be given to the waiving of studies that could have implications for other areas of assessment such as ecological hazard.

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., test chemicals 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. The scientific rationale for any expert judgement should be explicitly stated.

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 in order to account for animal welfare considerations, such as when the test chemical is corrosive. The added value of the toxicological information for risk management can be a further consideration in some cases. For example, ICH guidance has removed the requirement for traditional acute toxicity studies due to their limited value for predicting consequences of overdose in humans; ICH guidance points to dose-escalation studies or short duration dose-ranging studies as alternate sources for acute toxicity information (ICH reference here). However, this does not directly apply in cases where repeated dose toxicity studies are not available, and when information on acute toxicity may be relevant. 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.

7. Waivers justified on the basis of use and exposure conditions may be particularly applicable for pesticides and biocides but less so for test chemicals under the purview of hazard-based chemical legislation; for the latter, exposure-based waiving of testing may be less applicable. When exposure-based waivers are proposed, sufficient documentation is required to identify all potential exposure scenarios. While exposure-based waivers might be appropriate in the context of certain regulatory programs (e.g. pesticide regulation), those responsible for the conduct of acute studies must be cognizant of the needs of other regulatory sectors that could also be implicated.

8. When a waiver is granted for an acute toxicity study, this should be identified when presenting the hazard profile for the test chemical in order to acknowledge that there is not a data gap for this study. Labelling language for acute hazards of active substances or end-use products should be reflective of the

basis of the granted waiver. For example, the lack of acute inhalation hazard for a non-inhalable test chemical would be reflected through no requirement for label language regarding acute inhalation hazard. By contrast, if an acute dermal toxicity waiver is granted on the basis of the test chemical being corrosive, the label would need to reflect the potential for corrosivity of the test chemical by the dermal route. Where appropriate, labelling language for end-use products, for which acute studies have been waived, can be based on the inherent toxicological profiles of their single components or on the hazard identified through recognized calculation approaches.

9. As an overarching criterion, in vivo animal studies should be waived where the results of validated in vitro tests or alternative approaches (such as read-across and (Qauntitative) Structure-Activity relationships ((Q)SARs)) are adequate to draw a conclusion regarding the classification of an acute hazard for a test chemical.

ACUTE ORAL TOXICITY

10. An acute oral toxicity study may be waived if testing is not technically feasible or relevant such as when the test chemical is a gas or vapour at ambient temperature.

11. Waivers will be considered for end-use products that are composed of non-friable material and are too large to be ingested; or where end-use product design prevents oral exposure. End-use products such as pet collars, plastic ear tags and tamper resistant roach traps and bait boxes often meet these criteria. Even though some end-use products may be too large to be ingested, there is still some concern for exposure (e.g. a child mouthing an end-use product or hand-to mouth contact following breakage). In this case, labelling should reflect the hazard potential of the active substance or other components of the end-use product.

12. An acute oral toxicity study may be waived if the test chemical is corrosive to skin (GHS Category 1). The determination of corrosion is based on validated and/or accepted in vivo, in vitro or other data, or in the absence of any other information, when a test chemical has a pH less than or equal to 2 or greater than or equal to 11.5 together with high buffering capacity when relevant (OECD, 2014b). As the GHS corrosion hazard statements only pertain to the skin, hazard statements that correspond to GHS Category 1 for acute toxicity via the oral route should be used for labelling; where appropriate, it can be stated that acute oral toxicity is assumed based on the corrosive properties of the test chemical.

13. A waiver will be considered if the oral LD_{50} of the test chemical is predicted to be greater than 2000 mg/kg bw based on the results of a validated and/or accepted alternative test or test battery provided the test system was shown to have high sensitivity and the applicability domain is inclusive of the chemistry under investigation. Consideration of the results from reliable dose-escalation studies, short-duration range-finding studies or other repeat-dose oral toxicity studies may assist with a prediction of acute oral toxicity; test chemicals with a NOAEL of 1000 mg/kg bw/day or greater have been generally shown to have an acute oral LD50 above 2000 mg/kg bw (ECHA, 2015).

ACUTE DERMAL TOXICITY

14. A dermal toxicity study may be waived if the test chemical is corrosive or severely irritating to skin (GHS Category 1). The determination of corrosion is based on in validated and/or accepted vivo, in vitro or other data, or in the absence of any other information, when the test chemical has a pH less than or equal to 2 or greater than or equal to 11.5 together with high buffering capacity when relevant (OECD, 2014b).

15. Waivers will be considered for end-use products for which the product design prevents dermal exposure. Products such as roach traps and bait boxes that are tamper-resistant to children often meet these

criteria. In these cases, exposure is likely limited to situations where breakage occurs. Labelling should reflect the dermal hazard of the active substance or other components of the end-use product.

16. A dermal toxicity study may be waived if the test chemical has shown no adverse effects in an acute oral toxicity test up to 2000 mg/kg bw . Reviews comparing the classification of oral and dermal hazards indicate that it is rare for the dermal test to yield a more severe classification (Thomas and Dewhurst, 2007; Creton et al., 2010; Seidle et al., 2011, Moore et al., 2013). Under this premise, the dermal toxicity of a test chemical meeting this criterion should not result in a more severe classification than the corresponding oral hazard and would be classified as a GHS Category 5 dermal hazard in those jurisdictions that require this classification or not classified in jurisdictions that have not adopted the concept of GHS Category 5 (ECHA, 2015; EPA, 2016).

17. Under the same premise articulated above (i.e., dermal toxicity is unlikely to result in a more severe classification than the corresponding oral hazard), a waiver may be considered if the oral LD_{50} of the test chemical is less than 300 mg/kg bw. Test chemicals meeting this criterion would be classified in the corresponding GHS category as the oral hazard (i.e., a Category 2 oral hazard would be classified as a Category 2 dermal hazard, a Category 3 oral hazard would be classified as a Category 3 dermal hazard etc.) As there is no difference between the symbol and signal word for labelling Category 1, 2 or 3 oral or dermal hazards, there is generally no need to conduct further animal testing to refine the classification.

18. A waiver may be considered where the oral LD_{50} range is between 300-2000 mg/kg bw and dermal penetration data indicates low dermal absorption (<10%) relative to oral absorption. In this case, the oral LD_{50} would equate to a dermal-equivalent value of 3000 mg/kg bw (oral value of 300 mg/kg bw ÷ 0.1 [i.e., 10% dermal absorption]) or greater and be classified according to the corresponding GHS category. Care must be taken with this approach to ensure that dermal absorption values have been appropriately determined taking into account the effects of dermal loading. Furthermore, this approach assumes high oral bioavailability; re-consideration of this approach may be necessary if available information indicates low oral bioavailability of the test chemical.

ACUTE INHALATION TOXICITY

19. An acute inhalation toxicity study may be waived 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 test chemicals are defined as having vapor pressures $<1 \times 10^{-5}$ kPa (7.5×10^{-5} mmHg) for indoor uses, and $<1 \times 10^{-4}$ kPa (7.5×10^{-4} mmHg) for outdoor uses at 20-30º 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 and 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 considered low as defined above.

20. Waivers for acute inhalation studies may be considered for test chemicals that are too large to be inhaled (e.g., granules) and do not readily crumble into inhalable 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 µm in diameter. Particles larger than 100 µm are less likely to be inhalable. Of those particles that are inhalable, the respirable fraction poses a particular hazard because they are small enough to reach the alveoli, the major site of absorption in the respiratory tract, as well as the tracheobronchial region. Respirable particles are generally defined as being smaller than 10 µm in

diameter for humans and approximately 1 μm for rodents (Vincent, 2005). It is important to note that an inhaled test chemical need not be respirable to pose a hazard. Many particles are readily absorbed in the nasal mucosa (e.g. cocaine) and/or can be ingested when particles deposited in the upper respiratory tract are carried by mucociliary transport to the hypopharynx and then swallowed.

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 μm 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 ≤2 μm with a geometric standard deviation (σg) of 3, OECD Guidance Document 39, 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/). Solid materials that are dissolved or suspended in liquid under conditions of use may need to be tested in this alternate physical state if it can result in human exposure.

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. The waiver request should include a clear description of the methods and equipment used in attempting 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 and other components of the end-use product or on the hazard identified through recognized calculation approaches.

25. There are several toxicokinetic reasons why the inhalation route is the most toxic route for many chemicals: a) the lungs have a huge alveolar surface area where chemicals are rapidly transported across the thin (0.5 μm) alveolar membrane into the blood stream; b) 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; c) stomach acid converts many ingested chemicals into less toxic moieties; there is no analogous process in the lungs; and d) many chemicals can reach the brain within a few seconds of being inhaled into the lungs; intravenous injection is the only route that provides faster systemic exposure. 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 the GHS. Under these conditions, a test chemical would be classified as a Category 1 inhalation hazard according to the 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. The OECD inhalation test guidelines and Guidance Document 39 recommend that corrosive test chemicals should be assessed and tested following expert judgement on a case-by-case basis and where testing corrosive chemicals is required, it should be carried out at targeted concentrations that are low enough to not cause marked pain and distress, yet sufficient to extend the concentration-response curve 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 minimal inhalation toxicity (see OECD Guidance Document 39 for further discussion). Rodents exposed at test chemical concentrations that cause sensory irritation of the upper or lower respiratory tract may experience reflex bradypnea or a Paintal (C-fiber stimulation) reflex, respectively. These protective reflexes can result in marked decreases in body temperature, minute volume and test chemical exposure; and thus toxicity may be significantly less than if the animals were breathing normally. Further information on these reflexes can be found in OECD Guidance Document 39. In addition to the appropriate acute inhalation classification and labelling indicated for a diluted preparation of a corrosive test chemical, consideration should be given to retaining a corrosion hazard statement such as “corrosive” or “corrosive to the respiratory tract” for the undiluted test chemical.

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 labelling of the test chemical. Moreover, consideration should be given to the totality of existing information in making an overall weight of evidence determination as it relates to skin irritation/corrosion.

28. A skin corrosion/irritation study may not be required if the test chemical is known to be potentially corrosive to skin via evaluation of other data. The determination of corrosion is based on validated and/or accepted in vivo, in vitro or other data, or in the absence of any other information, when a test chemical has a pH less than or equal to 2 or greater than or equal to 11.5 together with high buffering capacity when relevant (OECD, 2014b). Such test chemicals will be considered as Category 1 dermal corrosives under the GHS for labelling purposes. It cannot be ruled out that some test chemicals may be over-predicted based solely on pH considerations. Accordingly, using the acid/alkali reserve method, especially for classification of mixtures containing acidic or alkaline substances (Young at el, 1988), or testing with in vitro methods can be performed as an alternate approach for test chemicals with strong acidity or alkalinity. Where sub-categorization is required by a regulatory sector, further information may be necessary.

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 the GHS (i.e., dermal toxicity ≤ 200 mg/kg bw). Observations of skin corrosion or irritation in the acute toxicity studies (including skin sensitization studies) can be used to inform whether the test chemical would be considered as a Category 1 dermal corrosive or Category 2 dermal irritant under the GHS for labelling purposes. Alternatively, in vitro tests for skin irritation or skin corrosion could be performed. Where sub-categorization is required by a regulatory sector, further information may be necessary.

31. Waiving may be possible when it is technically not feasible 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 and other components of the end-use product or on the hazard identified through recognized calculation approaches.

32. For end-use products containing strong dyes or pigments that may complicate interpretation of skin corrosion/irritation data, hazard 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) or sub-categories of Category 1 skin corrosives. Alternatively a waiver may be considered if supported by a screening study 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 and other components of the end-use product. It may also be an acceptable approach to remove the colorant from the product to be tested if it can be shown that the colorant is neither an irritant nor is anticipated to contribute to the irritation of the product.

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 labelling of the test chemical. Moreover, consideration should be given to the totality of existing information in making a weight of evidence determination.

34. A study assessing serious eye damage or eye irritation may be waived if the test chemical is corrosive to skin (GHS Category 1). The determination of corrosion is based on validated and/or accepted in vivo, in vitro or other data, or in the absence of any other information, when a test chemical has a pH less than 2 or greater than 11.5 together with high buffering capacity when relevant (OECD, 2014b). In this case, the test chemical should be considered in GHS Category 1 for serious eye damage. In fact, the potential for eye damage is reflected in the GHS hazard statement for a test chemical that is corrosive to skin which states “Causes severe skin burns and eye damage”.

35. A study assessing serious eye damage or eye irritation may be waived 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 the GHS (i.e., dermal toxicity ≤ 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 feasible 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 and other components of the end-use product or on the hazard identified through recognized calculation approaches.

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. Consideration should be given to realistic foreseeable end-use scenarios. For example, if it is shown that sweaty hands could enable the transfer of a residue from a treated fabric to the eyes, appropriate classification and labelling of the eye irritation potential of the treated fabric should be considered.

DERMAL SENSITIZATION

40. In vivo animal studies should be waived where the results of a recognized combination of validated and/or accepted in vitro tests (e.g., OECD Test Guideline 442D, 2015a) or in chemico tests (e.g., OECD Test Guidelines 442C, 2015b) covering the key mechanistic events as described in the adverse outcome pathway for skin sensitization (OECD, 2013) 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.

41. A dermal sensitization study may be waived on an end-use product if it is corrosive to the skin at the most dilute use concentration recommended on the product label. The determination of corrosion is based on validated and/or accepted in vivo, in vitro or other data, or in the absence of any other information, when a test chemical has a pH less than 2 or greater than 11.5 together with high buffering capacity when relevant (OECD, 2014b). For chemicals that may be used in an end-use product, information on their sensitizing potential may be needed.

42. A dermal sensitization study may be waived if the test chemical is spontaneously flammable in air at room temperature. No classification for dermal sensitization is required.

43. Waiving may be feasible 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.

44. 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 or validated and/or accepted in vitro assays, should be pursued that are not compromised by the presence of dyes or pigments. It may also be an acceptable approach to remove the colorant from the product to be tested if it can be shown that the colorant is neither a sensitizer nor is anticipated to contribute to the sensitization potential of the product.

45. A dermal sensitization study may be waived for an end-use product if any of the components of that product are known sensitizers based on test data. Such end-use products should be classified as a Category 1 skin sensitizer. However, the GHS and some regulatory frameworks may make this classification dependent on the concentration of the component(s) of concern in the end-use product.

46. If in vivo testing is required by a regulatory jurisdiction, a preferred method would be one that is consistent with replacement, reduction and refinement of animal testing, such as the Local Lymph Node Assay (provided that the test chemical is not prone to false positives or negatives by virtue of its chemical properties).

END-USE PRODUCTS

47. 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 and classifying mixtures for acute toxicity, irritation, corrosion or sensitizationcan be found under GHS (Chapter 3.1.3, 3.2.3, 3.3.3 and 3.4.3 Classification Criteria for Mixtures).

GRANULAR END-USE PRODUCTS

48. 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.

49. 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 or not classified under the GHS, the end-use product may be classified as a Category 5 hazard or not classified, as determined by recognized calculation approaches. 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.

50. If the acute toxicity profile of the active substance(s) and other components of the end-use product are classified as GHS Category 1 through 3, calculations that bridge downward from these categories (i.e., lower the hazard classification) will be considered if there are valid data available on the components (including the granular inert carrier) to generate an acute toxicity estimate. If data are not available, bridging downward will generally not be considered and hazard labelling would have to reflect that of the active substance and components of the end-use product.

51. Irritation studies (skin and eye) can be waived for the granular end use-products described above. Labelling for irritation potential for the end-use product would need to conform to irritation labelling used for the active substance or reflect the known irritation of components contained in the end-use product.

52. If a granular end-use product contains any component that is a known sensitizer, the product generally would be labelled as a sensitizer. If the components in the product are all known to be negative for dermal sensitization, a dermal sensitization study may be waived and the product will not be considered a dermal sensitizer.

BRIDGING OF DATA FOR ACUTE TOXICITY

53. Bridging (or read-across) refers to the use of an existing data set to characterize the hazard for another chemical for which there are little or no existing data. Test chemicals of unknown hazard may be similar in composition and form to one or more other chemicals with an existing complete acute toxicity data base. In these situations, it may be possible to construct a complete or partial acute toxicity profile for the test chemical of unknown hazard depending on the applicability of available data. Each specific hazard characterization eliminates the need to conduct the acute toxicity study associated with that hazard. The underlying logic for each determination is, in most cases, based on expert scientific judgment. Further guidance on read-across methodology is available (OECD, 2014c)

54. For end-use products, determining the similarity of products involves a comparison of the product chemistry and product formulation data (including the percentage of active substance(s) as well as other components). Examples where similarity of products needs careful examination from a toxicological perspective include (but are not limited to): changes in the identity of the non-active components; significant changes in the percentage of active substance; new formulation type; and, significant changes in the proportion of non-active components. Bridging principles for classification of potentially similar mixtures are outlined in GHS for each endpoint and include the principles of dilution, batching, concentration of mixtures in the highest sub/category, interpolation within one sub/category and substantially similar mixtures.

55. Where a test chemical is considered to be toxicologically comparable to another test chemical with valid acute data, the classification and hazard labelling should be identical for the two test chemicals.

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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_{50} (mg/kg bw)	DERMAL LD_{50} (mg/kg bw)	INHALATION LC_{50} (mg/L or ppm)[1]
1	Skull and Crossbones	Danger	Fatal (select: if swallowed, in contact with skin or if inhaled)	≤ 5	≤ 50	≤ 0.05 mg/L (dust, mist) ≤ 0.5 mg/L (vapour) ≤ 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) 0.5 < 2.0 mg/L (vapour) 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) 2.0 < 10.0 mg/L (vapour) 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) 10.0 < 20.0 mg/L (vapour) 2500 < 20000 ppm (gas)
5	None	Warning	May be harmful (select: if swallowed, in contact with skin or if inhaled)	2000 ≤ 5000	2000 ≤ 5000	Not specified (consult GHS)
Unclassified	None	None		> 5000	> 5000	None of the above

[1]Based in a 4-hour exposure period.

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 **OR** in vitro skin corrosion test positive results **OR** Corrosive* in ≥ 1/3 (or 1/6) animals
2	Exclamation Mark	Warning	Causes skin irritation	in vitro skin irritation test positive results **OR** MS** in ≥ 2/3 (or 4/6) animals of: ≥ 2.3 to ≤ 4.0 for erythema/eschar or edema (if delayed effect: calculate MS from 3 consecutive days after onset of reaction); **OR** inflammation persisting to 14 days in ≥ 2 animals; **OR** in cases of extreme variability of response definite positive effects in one animal.
3	None	Warning	Causes mild skin irritation	MS** in ≥ 2/3 (or 4/6) animals of ≥ 1.5 to < 2.3 for erythema/eschar or edema (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 **OR** in vitro eye damage test positive results **OR** ≥ 1 animal with effects remaining at 21 days; **AND/OR** MS* in ≥ 2/3 (or 4/6) animals of: ≥ 3 corneal opacity; **AND/OR** ≥ 1.5 iritis
2A	Exclamation Mark	Warning	Causes serious eye irritation	in vitro eye irritation test positive results **OR** classification as Category 2 skin irritant **OR** Effects which fully reverse in 21 days **AND:** MS* in ≥ 2/3 (or 4/6) animals of: ≥ 1 corneal opacity; **AND/OR** ≥ 1 iritis; **AND/OR** ≥ 2 conjunctival redness; **AND/OR** ≥ 2 chemosis
2B	None	Warning	Causes eye irritation	Effects which fully reverse in 7 days **AND**: MS* in ≥ 2/3 (or 4/6) animals of: ≥ 1 for corneal opacity; **AND/OR** ≥ 1 for iritis; **AND/OR** ≥ 2 for conjunctival redness; **AND/OR** ≥ 2 for chemosis
Unclassified	None	None	None	None of the above
SKIN SENSITIZATION				
1 (1A and 1B)	Exclamation Mark	Warning	May cause allergic skin reaction	Positive results from animal test **AND/OR** human evidence 1A: High frequency of occurrence in humans and/or a high potency in animals; severity of reaction may be considered 1B: Low to moderate frequency of occurrence in humans and/or a low to moderate 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).