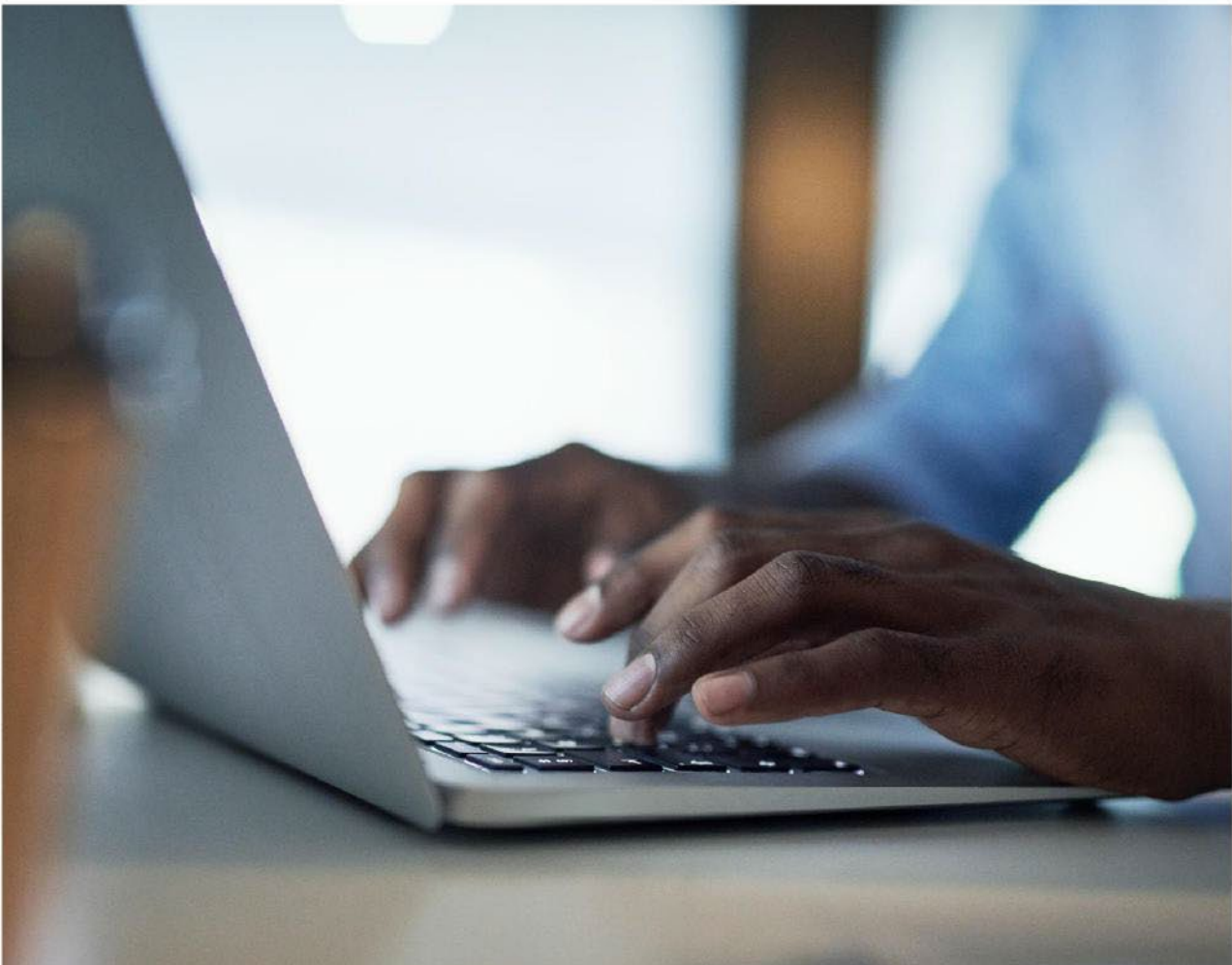


# Meeting the requirements for toxicological information for authorisation of Biocidal Products under GB BPR in light of Article 62: a guide for applicants

January 2024



*This document is an attempt to provide guidance in the interest of consistency. Please note, however, that the GB authority and applicants are not legally obliged to follow the approach set out in this document, since only the courts can give authoritative interpretations on the contents of the law.*

*This document may be periodically reviewed in the light of experience.*

## Document history

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# Introduction

1. An applicant for authorisation of a Biocidal Product (BP) under GB Biocidal Products Regulation 528/2012 (GB BPR) is required to submit to HSE specific information on some aspects of the toxicity of the product: skin, eye, respiratory tract irritation potential, respiratory and skin sensitisation potential and acute oral, dermal and inhalation toxicity. Information on the dermal absorption of the active substance in the BP is also required.
2. GB BPR Annex III sets out the toxicological information that applicants must submit to support their applications for authorisation. The primary purpose of this information is to establish the toxicity of the BP after single exposures so that appropriate measures can be implemented to protect against any potential consequences arising from these forms of toxicity in those who might encounter the product: distributors, users, bystanders, residents, consumers or workers. In considering authorisation, other known information on the toxicology of the active substance(s) and co-formulants shall also be taken into account (for example, repeated-dose toxicity, carcinogenicity, reproductive toxicity; see paragraph 6 below in relation to information on co-formulants), but specific investigations of the BP as a whole for these potential effects are not required.
3. The information provided should also permit the applicant to propose a classification of the BP in accordance with Regulation (EC) No 1272/2008 (CLP) as it applies in GB, where appropriate (Annex III Para 2 of GB BPR). The label that ensues from the classification informs the BP's users of its hazards and of appropriate risk management measures.
4. GB BPR offers options, with associated criteria, for applicants to take in meeting the information requirements. Of particular importance is that, before conducting a study on vertebrate animals, applicants must consider if any existing information and other methods are available for use as acceptable substitutes for animal testing (e.g. calculation method of the CLP regulation as it applies in GB, bridging/read-across, *in vitro* tests, *in silico* predictions). For each test conducted on vertebrate animals, an explanation must be provided of why it was necessary and why alternative approaches were not appropriate, in accordance with the guidance on HSE's website ([Vertebrate testing - Biocides - HSE](#)). Article 62 (1) of GB BPR also stipulates that testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort.
5. Available toxicological data on co-formulants should be submitted and assessed by the applicant (section 8.7. of Annex III of GB BPR). This information shall include, but is not limited to: where applicable, registration numbers issued under Regulation (EC) No 1907/2006 (REACH) as it applies in GB; the study summaries included in

the REACH technical (registration) dossier; an SDS that complies with Article 31 of REACH as it applies in GB. A REACH-compliant SDS should also be submitted for the BP.

6. The information requirement for each aspect of toxicity listed in paragraph 2 above and the options for meeting the requirement are outlined below. These are presented in a tiered sequence to be consistent with the provisions of Article 62 (1) of GB BPR, i.e., to minimise unnecessary animal testing.
7. As science and technology develop, and new *in vitro* methods are validated and published by the OECD, these should be taken into account in meeting the data requirements, even though not mentioned in this document at the time of writing.

## Skin irritation

8. Sufficiently reliable information is required to establish the skin irritation potential (including reversibility) of the BP and enable the applicant to propose a classification, if appropriate.
9. The OECD has published an 'IATA' (integrated approach to testing and assessment) for skin corrosion and irritation<sup>1</sup>. This describes the use of existing test data, physicochemical properties and non-test methods (such as bridging and additivity) in a weight-of-evidence approach to decide upon the predicted irritative effects on human skin and the need for new tests.
10. The GB biocides regulatory regime recognises this OECD IATA and, therefore, there are multiple sequential ways in which this requirement for information on the skin irritation potential of the product might be satisfied:
  - a. by a consideration of the pH of the BP;
  - b. via findings of severe skin irritation or corrosion in an acute dermal study on the BP, if this study has been done and its conduct was justified;
  - c. by the "calculation method" – prediction of the skin irritation potential of the BP from the skin irritation data of its individual components;
  - d. by "bridging" – prediction of the skin irritation potential of the BP by reading across from such data available on another product of similar composition;
  - e. via the results of validated *in vitro* skin irritation / corrosion tests with the BP;
  - f. via the results of an existing skin irritation study on the BP that uses experimental animals.
11. Further details on the appropriate conditions for each approach (a – f) are given below. [Note that there are now internationally-recognised *in vitro* test methods for assessing skin irritation that can provide a full replacement for *in vivo* tests.]
12. If the pH of the BP to be authorised is  $\leq 2$  or  $\geq 11.5$ , it can be presumed that it will be

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<sup>1</sup> [OECD \(2014\). New guidance document on an integrated approach on testing and assessment \(IATA\) for skin corrosion and irritation. Series on testing and assessment No. 2003, ENV/JM/MONO\(2014\)19](#)

corrosive to skin – (a). No further tests are needed and the appropriate classification should be applied. In some cases, if it can be shown that the acid/alkaline reserve in combination with other sources of information (e.g. *in vitro* tests) justifies a lower classification (even where the formulation has a pH in the extreme ranges described above), this will be taken into account.

13. If an acute dermal toxicity study on the BP resulted in severe skin irritation or corrosion, further information to assess skin irritation potential is not needed – (b). See paragraphs 24 – 26 for the conditions that apply to the use of results from tests on experimental animals. [Note that this could apply also in bridging from local skin effects seen in an acute dermal study on a similar product.]
14. Beyond (a) and (b), there are options for the applicant to use alternative approaches to the skin irritation assessment that are recognised under the CLP Regulation (1272/2008) as it applies in GB; i.e., without undertaking an *in vivo* skin irritation test on the BP for which authorisation is being sought.
15. One such approach is the calculation method – (c). If this approach is used, section 8.1 of Annex III of GB BPR states that the applicant shall justify that it is appropriate and shall provide information on the skin irritation potential of **all relevant** components of the BP.
16. The calculation method involves a prediction of the toxicity of a whole mixture from a consideration of the toxicity of its individual components. If this approach is used, under paragraph 8.5 of Annex III of GB BPR, the applicant must provide the calculations. Given the duty under section 62 (1) of GB BPR to test on animals only where no other methods are available, the use of an alternative approach is encouraged by HSE. The skin irritation potential of all components of the BP must be provided or reliably predicted. Under Annex 1 to Regulation (EC) No 1272/2008 (as it applies in GB) “all components” means the relevant ingredients of a mixture, i.e. those that are present in concentrations of 1% or greater, unless there is a reason to suspect that an ingredient present at a concentration of less than 1% is still relevant for classifying the mixture for skin irritation. Ingredients that are presumed not to be skin irritants (for example, water, sugar or common food ingredients, such as xanthan gum) would not be considered relevant for classifying the mixture for skin irritation<sup>2</sup>. Information on the skin irritation potential of a component should be obtained from its safety data sheet (SDS). Its harmonised classification should also be checked, as, if available and if more severe, it has

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<sup>2</sup> Please refer to [section 3 of Annex I to the CLP Regulation \(1272/2008\)](#) as it applies in GB and the associated [Guidance on the Application of the CLP Criteria](#) for information on the levels of components that should be taken into account in the consideration of mixture toxicity; i.e., generic concentration limits, specific concentration limits, cut-off levels for inclusion of a component in calculations.

precedence over the SDS self-classification. The most recent version of the SDS should be used, which should be compliant with the SDS stipulations of REACH (as it applies in GB); Article 31 (9) of REACH (as it applies in GB) specifies under what circumstances suppliers must update their SDS. HSE interpret the lack of skin irritation classification (in section 2 of the SDS or in the harmonised entry) as lack of hazard and not as an unknown (data gap). With classification information (or lack thereof) of all relevant components, a calculation of the predicted skin irritation can be made.

17. Another alternative is the bridging approach, in which an applicant will rely upon skin irritation data generated in an existing study on vertebrate animals or with *in vitro* test systems conducted with another closely-related formulation – (d).
18. As outlined below (paragraphs 24 – 26) for a skin irritation study on the specific BP for which authorisation is sought, the same principle applies to using “bridging” data from a test on a different substance – if the test that generated the data to be used for bridging was commissioned after 1 September 2013 (implementation date of the BPR), and not previously evaluated;

- Under EU BPR prior to 1<sup>st</sup> January 2021
- Evaluated under GB BPR after 31<sup>st</sup> December 2020;

the applicant would be required to explain why it was necessary to rely on the results of an *in vivo* test for the purposes of an authorisation application. On receipt of an application in which the bridging approach is used, HSE will give consideration to the legitimacy of the bridging argument, based on the chemical composition of the BP for which authorisation is sought and the material on which skin irritation data has been generated. Where the test that generated the data to be used for bridging has previously been evaluated under the BPR as specified above, no such justification is required to re-use the test data.

19. Another approach is to undertake new tests on the BP concerned. At the time the BPR was written, outlining the data requirements, the EU Test Method Regulation (EC No 440/2008) as it applies in GB described a sequential test strategy for the assessment of acute dermal irritation and corrosion; this strategy recommended that *in vitro* tests be conducted before any tests are undertaken on live animals but did not recognise negative results from the non-animal tests as being conclusive – in other words, tests in animals were required to confirm a negative result. The same strategy was adopted in the data requirements for BP (GB BPR).
20. In 2014, the OECD published an IATA for skin corrosion and irritation (guidance document 203). The IATA can be applied to both individual substances and mixtures. If a weight-of-evidence analysis of existing test data, physico-chemical properties and non-test methods (such as bridging and additivity) is inconclusive

with regards to skin irritation potential, the IATA describes the test methods that can be used to generate more data.

21. The recommended test method(s) to generate more data depend in part upon the skin irritation classification categories and sub-categories of the United Nations Globally Harmonised System (GHS) that have been adopted into regional implementing legislation. In the EU's implementing legislation, the CLP Regulation (1272/2008) as it applies in GB, the categories used for skin corrosion are category 1 (sub-categories 1A, 1B, 1C) or non-corrosive; and for skin irritation, category 2 or not classified. By following the tiered strategy in the IATA, *in vitro* test methods, either singly or in combination, can be used to predict the skin irritation potential of substances and mixtures and determine an appropriate classification under CLP (as it applies in GB). All these methods have OECD test guidelines and regulatory acceptance.
22. Therefore, in GB these *in vitro* tests can now be used to fully replace tests on experimental animals, provided the test material is within the scope and applicability domain of the methods used and there are no chemical-specific limitations to those methods (for example, the testing of gases and aerosols is not possible) – (e).
23. Another approach to meeting the information requirement is to use the results of an existing skin irritation study on the BP in experimental animals – (f). See paragraphs 24 – 26 for the conditions that apply to the use of results from tests on experimental animals. Of particular importance in justifying the use of results from a study on animals is the lack of availability of validated *in vitro* alternatives at the time the test was conducted or uncertainties in the outcome of the calculation method of the CLP Regulation, as it applies in GB.
24. As the implementation date for the BPR was 1 September 2013, a justification for the use of a test on vertebrate animals that was commissioned after that date is required – regardless of the purpose for which the study was originally undertaken.
25. If the approach taken is to use the results of a skin irritation study on the BP in experimental animals and a justification for this approach has not been provided, or is considered by HSE to be insufficient, the application will be rejected at the sift stage. HSE will also consider investigating whether there has been a contravention of Article 62(1) of GB BPR.
26. So, although information on the skin irritation potential is required relating to the concerned BP is required, this should not be generated by experimental animal testing on BPs for which the if available alternatives are appropriate. Whilst the data requirement in GB BPR mentions the use of information from skin irritation studies on experimental animals, the science has progressed and there are now OECD test guidelines for *in vitro* tests that can fully replace *in vivo* tests for regulatory purposes. Therefore, we would now expect there to be few, if any, instances when new *in vivo*

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skin irritation tests on BPs are necessary or justifiable.

## Eye irritation

27. Sufficiently reliable information is required to establish the eye irritation potential (including reversibility) of the BP and enable the applicant to propose a classification, if appropriate.
28. GB BPR requires that a weight-of-evidence approach be applied to assess the eye damage and irritation potential before tests on animals are undertaken with the BP to be authorised.
29. There are multiple sequential ways in which this requirement for information on the potential of the BP to be able to produce serious eye damage and irritation might be satisfied:
  - a. by a consideration of the pH of the BP;
  - b. by a consideration of the skin corrosion potential (predicted or observed) of the BP;
  - c. by the “calculation method” – prediction of the eye irritation / damage potential of the BP from data on the eye irritation of its individual components;
  - d. by “bridging” – prediction of the eye irritation / damage potential of the BP by reading across from such data available on another product of similar composition;
  - e. via the results of validated *in vitro* and *ex vivo* eye irritation / corrosion tests with the BP, either alone or in combination;
  - f. via the results of an existing eye irritation study on the BP that uses experimental animals.
30. Further details on the appropriate conditions for each approach are given below (a – f). [Note that there are now internationally-recognised *in vitro* and *ex vivo* test methods for assessing eye irritation / damage that can provide a full replacement for *in vivo* tests.]
31. If the pH of the BP to be authorised is  $\leq 2$  or  $\geq 11.5$ , it can be presumed that it will cause serious eye damage. No further tests are needed and the appropriate classification should be applied.
32. If the available information indicates that the BP is corrosive to skin, it can be presumed that the BP will cause serious eye irritation / damage; further information to assess the eye irritation / damage potential is then not needed. See the principles described in paragraphs 24 – 26 for the conditions that apply to the use of results

from tests on experimental animals.

33. Beyond (a) and (b), there are options for the applicant to use alternative approaches to the eye irritation / damage assessment that are recognised under the CLP Regulation (1272/2008) as it applies in GB; i.e. without undertaking an *in vivo* eye irritation test on the BP for which authorisation is being sought.
34. One such approach is the calculation method, as applicable – (c). If this approach is used, section 8.2 of Annex III of GB BPR states that the applicant shall justify that it is appropriate and shall provide information on the eye irritation / damage potential of all **relevant components** of the BP. See the principles described in paragraph 16 for other conditions that apply to the use of this approach.
35. Another alternative is the bridging approach, in which an applicant will rely upon eye irritation / damage data generated in an existing study on vertebrate animals or with *in vitro* test systems conducted with another closely-related formulation – (d). The principles and conditions for the use of this approach are outlined in paragraph 18.
36. Another approach is to undertake new tests on the BP to be authorised. GB BPR describes a sequential test strategy for the assessment of eye irritation / damage, in which *in vitro* / *ex vivo* tests are conducted before any tests are undertaken on live animals.
37. In 2017, the OECD published an 'IATA' for serious eye damage and irritation (Guidance document 263)<sup>3</sup> applicable to both individual substances and mixtures. This describes the use of existing test data, physico-chemical properties and non-test methods (such as bridging and additivity) in a weight-of-evidence approach to decide upon the predicted irritative effects on human eye and the need for new tests. The OECD *in vitro* test methods that were included in the IATA testing strategy at that time were only able to differentiate between chemicals that cause serious eye damage (CLP Category 1 as it applies in GB) and those that do not cause eye irritation (not classified under CLP as it applies in GB) – (e). However, they could not identify eye irritants that would be classified in CLP Category 2 (as it applies in GB).
38. In June 2022, the OECD published the first *in vitro* test method (OECD test guideline 492B) recommended as a full replacement to the *in vivo* eye irritation test (OECD test guideline 405). Test guideline 492B (SkinEthic™ Human Corneal Epithelium (HCE) Time-to-Toxicity (TTT) test) is able to correctly identify and discriminate chemicals (both substances and mixtures) into the 3 CLP classification categories for eye irritation / damage as it applies in GB. Within the test guideline, it is also

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<sup>3</sup> [OECD \(2017\). Guidance document 263 on an integrated approach on testing and assessment \(IATA\) for serious eye damage and eye irritation.](#)

highlighted that the Guidance Document No. 263 on the IATA should be consulted for further testing with other adequate *in vitro* tests, if deemed necessary.

39. Therefore, in GB *in vitro* eye irritation / damage tests can now be used to fully replace tests on experimental animals, provided the test material is within the scope and applicability domain of the methods used and there are no chemical-specific limitations to those methods (for example, the testing of gases and aerosols is not possible) – (e).
40. Another approach to meeting the information requirement is to use the results of an existing eye irritation study on the BP in experimental animals – (f). See the principles described in paragraphs 24 – 26 for the conditions that apply to the use of results from tests on experimental animals. Of particular importance in justifying the use of results from a study on animals is the lack of availability of *in vitro* alternatives at the time the test was conducted or uncertainties in the outcome of the calculation method of the CLP Regulation, as it applies in GB. Thus, applicants should **not have** proceeded directly to a test in animals without having first undertaken a weight-of-evidence assessment (including the calculation method) and appropriate *in vitro* tests; the results of *in vivo* eye irritation tests conducted since 2017 (date of publication of the IATA) in isolation (i.e. without reference to a tiered, weight-of-evidence approach) will not be considered by HSE as fulfilling the information requirements for eye irritation / damage in BP authorisations.
41. If the approach taken is to use the results of an eye irritation study on the BP in experimental animals and a justification for this approach has not been provided, or is considered by HSE to be insufficient, the application will be rejected at the sift stage. HSE will also consider investigating whether there has been a contravention of Article 62(1) of GB BPR.
42. As the implementation date for the BPR was 1 September 2013, a justification to the use of a test on vertebrate animals that was commissioned after that date is required – regardless of the purpose for which the study was originally undertaken.
43. So, although information on the eye irritation / damage potential relating to a BP for which authorisation is sought is required, this should not be generated by experimental animal testing on BPs if available alternatives are appropriate. Whilst the data requirement in GB BPR mentions the use of information from eye irritation studies on experimental animals, the science has progressed and there are now OECD test guidelines for *in vitro* tests that can fully replace *in vivo* eye irritation tests. Therefore, we would now expect there to be few, if any, instances when new *in vivo* eye irritation tests on BPs are necessary or justifiable. For *in vivo* studies commissioned after December 2022 (6 months after the publication of OECD test guideline 492B), HSE will consider only **previously accepted** studies submitted for other applications, unless a valid scientific justification is provided (e.g. formulation

outside the applicability domain of available *in vitro* tests and uncertain outcome of the calculation method).

## Respiratory Tract Irritation

44. This is an additional data set (ADS) requirement. Testing on the product/mixture for respiratory tract irritation does not need to be conducted if:
- a. there are valid data available on each of the components in the mixture to allow classification of the mixture according to the rules laid down in Regulation (EC) No 1272/2008 (CLP) as it applies in GB, and synergistic effects between any of the components are not expected.
45. See the principles described in paragraph 16 for other conditions that apply to the use of this approach.

## Skin sensitisation

46. Sufficiently reliable information is required to establish the skin sensitisation potential of the BP and enable the applicant to propose a classification, if appropriate. There are multiple ways in which this requirement might be satisfied, with important conditions associated with each approach:

- a. if the active substance(s) or any co-formulant is known to have sensitising properties and is present at a level greater than or equal to the relevant concentration limit of the CLP Regulation (as it applies in GB), no further information is needed;

If no component triggers classification of the product, then the following approaches should be considered in a sequential manner:

- b. prediction of the skin sensitisation potential of the BP from the skin sensitisation test data of its individual components;
- c. use of a pre-existing (commissioned before December 2021 – 6-month implementation period after the date of publication of OECD Guideline 497) *in vivo* skin sensitisation study on the BP of interest, if available;
- d. “bridging” – prediction of the skin sensitisation potential of the BP by reading across from a pre-existing (commissioned before December 2021) *in vivo* study available on another product of similar composition;
- e. application to the BP of one of the defined approaches within the recently adopted and published (June 2021) OECD DASS (Defined Approaches for Skin Sensitisation) 497 guideline<sup>4</sup>;
- f. via the results of a new skin sensitisation test on the BP in experimental animals.

47. Further details on the appropriate conditions for each approach are given below.

48. If any component of the BP to be authorised, whether it be an active substance or a co-formulant, is known to have sensitising properties and is present at a level greater than or equal to the relevant concentration threshold, no further information is needed – (a). For components that meet the criteria of Category 1 / 1B of the CLP Regulation (as it applies in GB), the relevant generic concentration threshold is 1%;

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<sup>4</sup> [Guideline No. 497: Guideline on Defined Approaches for Skin Sensitisation \(oecd-ilibrary.org\)](https://www.oecd-ilibrary.org/govt/oes/guideline-no-497-guideline-on-defined-approaches-for-skin-sensitisation_95891201)

for Category 1A, it is 0.1%. Some chemicals have a specific concentration limit (SCL), which takes precedence over the generic limits. If any known sensitising component is present at a level greater than or equal to the relevant concentration threshold, it is presumed that the BP will be a skin sensitiser, and no further information needs to be provided.

49. If no component triggers classification of the product, the next option is to consider the skin sensitisation potential of **all relevant** components of the BP – (b). Co-formulants that are presumed not to be skin sensitisers (for example some polymers, chemicals with high log  $P_{ow}$  unlikely to cross the skin or food grade components) would be considered not relevant. Specifically in relation to polymers, if an applicant can show that a specific component meets the REACH (as it applies in GB) definition of a polymer and can provide a declaration that none of its monomers, reactants and starting materials are known skin sensitisers, then such a component could be dismissed as not relevant. For skin sensitisation HSE requires actual experimental or human experience data (as described in section 11 of the SDS or the associated REACH registration dossier where available or publicly-available information) on all **relevant** co-formulants present  $\geq 1\%$  for products for which a negative classification has been proposed by the applicant when applying the calculation method (no data / unknown is **not** acceptable). The reasons for a different approach for this endpoint compared to the other acute endpoints are multiple: skin sensitisation is a serious, insidious and delayed effect; it has a very low GCL (generic concentration limit for mixtures) of 1% under the CLP Regulation; it is not an additive endpoint; and it has a significant impact on the risk assessment/management of the product. If no component is a known skin sensitiser, or if known skin sensitisers are present at a level lower than the relevant concentration limits, it can be presumed that the BP will not be a skin sensitiser.
50. If skin sensitisation information is not available on all relevant components, another option is to use a pre-existing (commissioned before December 2021) *in vivo* skin sensitisation study generated on the BP of interest – (c).
51. If such pre-existing *in vivo* skin sensitisation study on the BP is not available, another option is the bridging approach, in which an applicant will rely upon skin sensitisation data generated in a pre-existing (commissioned before December 2021) study on vertebrate animals conducted with another closely-related formulation – (d). To be considered acceptable by HSE, the *in vivo* study on a related formulation needs to have been commissioned before December 2021 (6 months after the publication of the OECD DASS Guideline 497 in June 2021) (see paragraph 52 below). For *in vivo* studies commissioned after December 2021, HSE will consider only **previously accepted** studies submitted for other applications unless a valid scientific justification is provided (see paragraph 53 below).
52. If bridging is not possible, the *hazard identification module* (“2 out of 3”) or one of the

*hazard potency modules* (ITSv1 and ITSv2) within the recently adopted and published OECD DASS 497 guideline should be applied to the BP – (e). In June 2021, the OECD has published guideline 497 for Defined Approaches to Skin Sensitisation (DASS). The DASS include three approaches: a hazard identification module based on validated *in vitro/in chemico* tests (OECD TG 442C, 442D, 442E) and two hazard characterisation/potency modules (ITSv1 and ITSv2) based on a combination of *in vitro/in chemico* tests and QSAR predictions. Although QSAR models cannot be applied to mixtures (i.e. mixtures are out of domain), in some instances, conclusive potency scores can still be obtained from the two *in vitro/in chemico* tests of ITSv1 and ITSv2 through a data interpretation procedure specified in the guideline. It is noted that a fully quantitative skin sensitisation risk assessment could not be performed even when applying the potency modules of the DASS, as the potency scores obtained are arbitrary numbers of no biological value.

53. If the DASS cannot be applied to the BP to be authorised (e.g. BP is out of domain of the *in vitro/in chemico* tests), produce inconclusive results or a quantitative or semi-quantitative risk assessment is required to refine the evaluation, another approach is to use the results of a “new” (post-December 2021) skin sensitisation study on the BP in experimental animals - (f). Overall, a “new” *in vivo* skin sensitisation study (preferably a Local Lymph Node Assay - LLNA) commissioned post-December 2021 will only be accepted by HSE when 1) no component triggers classification of the product; and 2) skin sensitisation information is not available on all co-formulants; 3) a pre-existing (pre-December 2021) *in vivo* skin sensitisation study is not available; 4) bridging is not possible; 5) the DASS is either not feasible or produces inconclusive results; or 6) a quantitative or semi-quantitative risk assessment is required to refine the evaluation.
54. New or pre-existing *in vivo* skin sensitisation studies on BPs providing positive results and leading to classification of the product (especially where other approaches appear to indicate no skin sensitisation potential) will also be accepted by HSE as they constitute “adverse” data under Article 47 of GB BPR
55. A combination of different alternative approaches (as described at step (b), (c) and (d)) will also be accepted by HSE using a weight-of-evidence analysis.
56. As with any guidance, scientifically justified exceptions to the sequence of approaches described above will be carefully and thoroughly considered by HSE, on a case-by-case basis.

## Respiratory Sensitisation

57. This is an additional data set (ADS) requirement. Under section 8.4 of Annex III of GB BPR testing on the product/mixture for respiratory sensitisation does not need to be conducted if:

- a. there are valid data available on each of the components in the mixture to allow classification of the mixture according to the rules laid down in Regulation (EC) No 1272/2008 (CLP) (as it applies in GB), and synergistic effects between any of the components are not expected.

58. See the principles of paragraph 16 for other conditions that apply to the use of this approach.

## Acute oral toxicity

59. Sufficiently reliable information to establish the acute oral toxicity of the BP and enable the applicant to propose a classification, if appropriate, is required. There are three sequential ways in which this requirement might be satisfied, with important conditions applying to each approach:

- a. by the “calculation method” – prediction of the acute oral toxicity of the BP from the acute oral toxicity data of its individual components;
- b. by “bridging” – prediction of the acute oral toxicity of the BP by reading across from such data available on another product of similar composition;
- c. via the results of an acute oral toxicity study on the BP in experimental animals. The study might be a pre-existing one (perhaps originally conducted for a different purpose), or one undertaken specifically for the BP authorisation application.

60. Further details on the appropriate conditions for each approach are given below. [Note that at present there are no internationally-recognised *in vitro* tests for assessing acute oral toxicity.]

61. In relation to the requirement for information on acute oral toxicity, there are options for the applicant to use an alternative approach to acute oral toxicity assessment that are recognised under the CLP Regulation (1272/2008) as it applies in GB; i.e., without undertaking an acute oral toxicity test on the BP for which authorisation is being sought. Applicants should first consider if one of these alternative approaches is appropriate.

62. One such approach is the calculation method of the CLP Regulation as it applies in GB – (c). If this approach is used, section 8.1 of Annex III of GB BPR states that the applicant shall justify that it is appropriate and shall provide information on the acute oral toxicity of all relevant components of the BP. See the principles described in paragraph 16 for other conditions that apply to the use of this approach. As lack of classification is interpreted as lack of hazard, the additivity formula with no unknowns described in paragraph 3.1.3.6.1 of Annex I of the CLP Regulation (as it applies in GB) should be used. Note that if all components have an LD50 > 2000 mg/kg bw or are not classified, the calculation method does not need to be applied, but it can be presumed that the BP will also have an LD50 > 2000 mg/kg bw.

63. Another alternative approach under Annex 1 to the CLP Regulation is bridging, in which an applicant will rely upon acute oral toxicity data generated in an existing study on vertebrate animals conducted with another closely-related formulation. The principles and conditions for the use of this approach are outlined in paragraph 18.

64. If neither of the above approaches is feasible for the BP concerned (e.g. no suitable bridging or no SDSs provided for some co-formulants or uncertain outcome of the calculation method), another approach is to use the results of an acute oral toxicity study on the BP in experimental animals. However, if such an approach is considered, it is crucial to keep in mind the stipulations of Article 62(1) of GB BPR and the guidance on HSE's website ([Vertebrate testing - Biocides - HSE](#)). The use of this approach should be considered only in situations where it is judged that no other methods are available by which to adequately assess the acute oral toxicity of the BP; and an explanation of why it was not possible to avoid animal testing should be provided.
65. As the implementation date for GB BPR was 1 September 2013, a justification for the use of a test on vertebrate animals that was commissioned after that date is required – regardless of the purpose for which the study was originally undertaken.
66. If the approach taken is to use the results of an acute oral toxicity study on the BP in experimental animals and a justification for this approach has not been provided, or is considered by HSE to be insufficient, the application will be rejected at the sift stage. HSE will also consider investigating whether there has been a contravention of Article 62(1) of GB BPR.
67. So, although acute oral toxicity information relating to a BP for which authorisation is sought is required, this should not be generated by experimental animal testing where an alternative approach can be justified. There are criteria to be satisfied for each of the possible approaches. A particular issue is the desirability of minimising the use of experimental animals in satisfying this information requirement and the need to justify its use.
68. Note that if an experimental animal study has already been done and the result indicates a degree of toxicity (acute oral in this case) substantially greater than anticipated, then such data (meeting the definition of “adverse data” under Article 47 of GB BPR will be used in HSE's evaluation.

## Acute dermal toxicity

69. Sufficiently reliable information to establish the acute dermal toxicity of the BP and enable the applicant to propose a classification, if appropriate, is required on a case-by-case basis (for example, it might be possible to justify non-submission of information if there is evidence that none of the components of the BP is likely to be absorbed through the skin to any significant extent). One consideration in deciding how to meet this information requirement is that, in general, the acute dermal toxicity of an individual chemical or a product is unlikely to be higher than its acute oral toxicity, because the speed and extent of absorption into the systemic circulation is usually greater in the latter case.
70. Therefore, there are several sequential ways in which this requirement might be satisfied, with important conditions associated with each approach:
- a. by the “calculation method” – prediction of the acute dermal toxicity of the BP from the acute dermal toxicity data of its individual components;
  - b. by extrapolation from the results of an acute oral toxicity study on the BP in experimental animals. The study might be a pre-existing one, or one undertaken specifically for the BP authorisation application;
  - c. by “bridging” – prediction of the acute dermal toxicity of the BP by reading across from such data (dermal or oral) available on another product of similar composition;
  - d. via the results of an acute dermal toxicity study on the BP in experimental animals. The study might be a pre-existing one, or one undertaken
  - e. specifically for the BP authorisation application.
71. Further details on the appropriate conditions for each approach are given below. [Note that at present there are no internationally-recognised in vitro tests for assessing acute dermal toxicity.]
72. In relation to the requirement for information on acute dermal toxicity, there are options for the applicant to use an alternative approach to the acute dermal toxicity assessment that are recognised under the CLP Regulation (1272/2008) as it applies in GB; i.e., without undertaking an acute dermal toxicity test on the BP for which authorisation is being sought. Applicants should first consider if one of these alternative approaches is appropriate.
73. One such alternative approach is the calculation method (additivity) of the CLP Regulation as it applies in GB. If this approach is used, section 8.5 of Annex III of

GB BPR states that the applicant shall justify that it is appropriate and shall provide information on the acute dermal (or oral) toxicity of all relevant components of the BP. See the principles described in paragraphs 16 and 62 for other conditions that apply to the use of this approach.

74. Another approach is to use the results of an acute oral toxicity study on the BP to predict its dermal toxicity (route-to-route extrapolation). The principles and conditions outlined in paragraphs 24 – 26 would also apply to the use of the results from an acute oral toxicity study on experimental animals in this scenario.
75. Another alternative is the bridging approach, in which an applicant will rely upon acute dermal (or oral) toxicity data generated in an existing study on vertebrate animals conducted with another closely-related formulation. The principles and conditions for the use of this approach are outlined in paragraph 18.
76. Only if none of the above approaches can be used (e.g. no suitable bridging or route-route extrapolation, no SDSs provided for some co-formulants or uncertain outcome of the calculation method) and it has been determined that information is needed, the final approach is to use the results of an acute dermal toxicity study on the BP in experimental animals. See the principles described in paragraphs 24 – 26 for the conditions that apply to the use of results from tests on experimental animals.
77. So, although acute dermal toxicity information relating to a BP for which authorisation is sought might be required, this needs not be generated by experimental animal testing. There are criteria to be satisfied for each of the possible approaches. A particular issue is the desirability of minimising the use of experimental animals in satisfying this information requirement and the need to justify its use.

## Acute inhalation toxicity

78. Sufficiently reliable information to establish the acute inhalation toxicity of the BP and enable the applicant to propose a classification, if appropriate, is required. There are three sequential ways in which the information requirements might be satisfied, with important conditions applying to each approach:
- by the “calculation method” – prediction of the acute inhalation toxicity of the BP from the acute inhalation toxicity data of its individual components;
  - by “bridging” – prediction of the acute inhalation toxicity of the BP by reading across from such data available on another product of similar composition;
  - via the results of an acute inhalation toxicity study on the BP in experimental animals. The study might be a pre-existing one, or one undertaken specifically for the BP authorisation application.
79. Further details on the appropriate conditions for each approach are given below. [Note that at present there are no internationally-recognised *in vitro* tests for assessing acute inhalation toxicity.]
80. In relation to the requirement for information on acute inhalation toxicity, there are options for the applicant to take, using an alternative approach to acute inhalation toxicity assessment that are recognised under the CLP Regulation (1272/2008) as it applies in GB; i.e., without undertaking an acute inhalation test on the BP for which authorisation is being sought. Applicants should first consider if one of these alternative approaches is appropriate.
81. One such approach is the calculation method (additivity) of the CLP Regulation as it applies in GB. If this approach is used, section 8.5 of Annex III of GB BPR states that the applicant shall justify that it is appropriate and shall provide information on the acute inhalation toxicity of all relevant components of the BP. See the principles described in paragraphs 16 and 62 for other conditions that apply to the use of this approach.
82. Another approach is the bridging approach, in which an applicant will rely upon acute inhalation toxicity data generated in an existing study on vertebrate animals conducted with another closely-related formulation. The principles and conditions for the use of this approach are outlined in paragraph 18.
83. If neither of the above approaches is feasible (e.g. no suitable bridging or no SDSs provided for some co-formulants or uncertain outcome of the calculation method) for the BP to be authorised, another approach is to use the results of an acute inhalation toxicity study on the BP in experimental animals (normally by head/nose-only

exposure). See the principles described in paragraphs 24 – 26 for the conditions that apply to the use of results from tests on experimental animals.

84. So, although acute inhalation toxicity information relating to a BP for which authorisation is sought might be required, this needs not be generated by experimental animal testing. There are criteria to be satisfied for each of the possible approaches. A particular issue is the desirability of minimising the use of experimental animals in satisfying this information requirement and the need to justify its use.

## Dermal absorption

85. A study on dermal absorption of the BP to be authorised shall be conducted when dermal exposure is a significant exposure route, and the use of default absorption values does not show that the risk is acceptable.
86. If a test is required, data from dermal absorption studies, **preferably on human skin in an *in vitro* test system**, shall be reported. Studies should be performed on representative BPs at both in-use dilutions (if applicable) and concentrates with consideration to product-type specific guidance for dermal absorption where available<sup>5</sup>.
87. Therefore, a tiered approach should be taken to meet the data requirement for dermal absorption. The following strategy, in order of refinement, is recommended in EFSA's Guidance on Dermal Absorption for plant protection products (2017)<sup>6</sup> which has been adopted for application to BPs, as appropriate:
- a. an initial exposure assessment can be undertaken with default values or data on closely-related products;
  - b. *in vitro* studies on human skin;
  - c. data on rats (or other experimental animals), including the triple pack approach in which *in vivo* data in animals (usually rats) are corrected for the ratio of absorption between rats and human *in vitro*.
88. The default values to be applied to different formulation categories in the absence of experimental data are given in section 6.1 of the EFSA 2017 guidance.
89. When the applicant for authorisation of a BP wishes to rely on data from a closely-related formulation, the conditions outlined in section 6.2 of the EFSA 2017 guidance should be met with consideration to product-type specific guidance for dermal absorption where available<sup>7</sup>.
90. In the context of 'information on experimental animals', HSE will accept such *in vivo* dermal absorption studies only for applications submitted before 6 March 2020 (implementation date of the EFSA 2017 guidance for biocides) which have been

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<sup>5</sup> [https://echa.europa.eu/documents/10162/763823/dermal\\_absorption\\_pt21\\_en.pdf](https://echa.europa.eu/documents/10162/763823/dermal_absorption_pt21_en.pdf)

<sup>6</sup> Buist *et al.* (2017). Guidance on dermal absorption. EFSA Journal 15(6): 4873.

<sup>7</sup> [Dermal absorption values for anticoagulant rodenticides-Agreed at Human Health Working Group meeting WG-I-2021](#)

performed in line with the EFSA 2012 guidance<sup>8</sup>. This is because the older EFSA dermal absorption guidance permits the conduct of *in vivo* studies, using a tiered approach. However, for applications submitted after 6 March 2020, HSE will accept only existing (i.e. performed before March 2020) *in vivo* studies, but not new animal assays. If the use of the *in vitro* dermal absorption study leads to unacceptable risks and no authorisation, then, on a case-by-case basis, HSE will explore with the applicant other possible refinement options, including the conduct of an *in vivo* study if necessary and justified. It is anticipated that this would be a rare occurrence.

91. Taking together the information requirements GB BPR and the EFSA guidance on dermal absorption for plant protection products (2017), a new study on experimental animals to investigate dermal absorption should not normally be conducted. In the exceptional circumstance that a new dermal absorption animal study is considered to be necessary because an *in vitro* assay is not technically feasible, the stipulations of Article 62 (1) of GB BPR and the guidance on HSE's website ([Vertebrate testing - Biocides - HSE](#)) must be borne in mind. A tiered approach, as described in points (a) to (c) above, should always be considered first.

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<sup>8</sup> EFSA (2012). [Microsoft Word - Guidance on Dermal Absorption status 23 4 2012\\_2\\_.doc \(europa.eu\)](#)

## Appendix

### Examples of acceptable and unacceptable justifications for the submission or non-submission of data, including tests on vertebrate animals

Please note that all justifications will be assessed case-by-case.

An example of a justification for the submission of an acute oral toxicity test on vertebrate animals that will not be accepted by HSE is:

***“The test was available, having been done to meet the requirements of another regulatory regime.”***

An example of an acceptable justification for the use of data on the acute oral toxicity of a BP to meet the information requirement for acute dermal toxicity might be:

***“An acute oral toxicity study with the BP is available, with an LD50 > 2000 mg/kg bw. On this basis, and considering the components of the BP, we predict that the acute dermal toxicity of the BP would not be greater than its acute oral toxicity and therefore would also be > 2000 mg/kg bw. Therefore, we propose that the conduct of an acute dermal toxicity study is not justified on animal welfare or scientific grounds.”***

An acceptable justification for doing an acute dermal toxicity study on the full BP could be:

***“The active substance is known to have significant acute dermal toxicity and the BP contains a significant percentage of a co-formulant that is known to facilitate dermal absorption; hence it was considered judicious to examine if the formulation produced an exacerbation of the acute dermal toxicity of the active substance.”***

An example of an unacceptable justification for doing an acute dermal toxicity study could be:

***“The test was done to examine the reliability of the prediction arising from the calculation method.”***

An example of an acceptable justification for the non-submission of data on the acute inhalation toxicity of a BP might be:

***“The product for which authorisation is being sought will not be sprayed as it is supplied. Before being sprayed, the product is intended to be diluted 1 in 200 with water. Therefore, an acute inhalation test on the product as supplied would not be representative of the product as used, and so we consider that the criterion ‘to be applied by spraying’ in the data requirements is not met by the concentrated product. Water is the major component of the dilution (99.5 %); consequently, it can be predicted that the acute inhalation toxicity of the diluted product would be very low. On this basis, we conclude that an acute inhalation toxicity test on either the product as supplied (for which we are seeking authorisation) or the in-use spray dilution is not justified on either scientific or animal-welfare grounds. The product does not meet any of the other criteria listed in section 7.1.3 of Regulation (EC) 284/2013.”***

An example of an acceptable justification for the non-submission of test data on skin sensitisation might be:

***“The active substance in the BP to be authorised has a harmonised classification for skin sensitisation Category 1. The active substance is present in the BP at a concentration of 20%. Therefore, since a known sensitiser is present in the BP at a concentration that is greater than the generic concentration limit of 1% for Category 1 sensitisers, we propose that test data on the BP to be authorised does not need to be provided.”***

Another example of an acceptable justification for the non-submission of test data on skin sensitisation might be:

***“We have not conducted a skin sensitisation test with the BP to be authorised. However, reliable data on the skin sensitisation potential of all the components of the BP was available from tests that were compliant with the relevant OECD test guidelines (LLNA or guinea-pig tests). All the components were negative when tested at high-enough concentrations, as defined in the test guidelines, to give meaningful negative results. On this basis, we conclude that the BP is unlikely to be a skin sensitiser, and we propose that it is not necessary to test the BP itself.”***

## Further information

For information about health and safety, or to report inconsistencies or inaccuracies in this guidance, visit [the HSE website](#).

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