~~Confidential~~

Helsinki, 23 May 2024

Addressees
Registrants of PHBA consortium as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
16 December 2021

Registered substance subject to this decision ("the Substance")
Substance name: 4-hydroxybenzoic acid
EC/List number: 202-804-9

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***30 August 2027***.

Requested information must be generated using the Substance unless otherwise specified.

Information required from all the Registrants subject to Annex VIII of REACH

1. *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: EU B.17./OECD TG 476 or EU B.67./OECD TG 490).

Information required from all the Registrants subject to Annex IX of REACH

2. Sub-chronic toxicity study (90 days), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats.

3. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit).

Information required from all the Registrants subject to Annex X of REACH

4. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rabbit or rat).

The reasons for the requests are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

You are only required to share the costs of information that you must submit to fulfil your

information requirements.

How to comply with your information requirements

To comply with your information requirements, you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also **update the chemical safety report, where** relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general requirements for testing and reporting new tests under REACH, see Appendix 4.

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the request(s)
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons for the request(s)

Contents

Reasons common to several requests

0.1. Read-across adaptation rejected

1 You have adapted the following standard information requirements by using grouping and read-across approach under Annex XI, Section 1.5.:

- Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study, one species (Annex IX, Section 8.7.2.)
- Pre-natal developmental toxicity study, second species (Annex X, Section 8.7.2.)

2 ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following sections.

3 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

4 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

0.1.1. Scope of the grouping of substances

5 You provide a read-across justification document in IUCLID Section 13.

6 You predict the properties of the Substance from information obtained from the following source substance(s):

- Methyl 4-hydroxybenzoate, EC 202-785-7, (source substance 1);
- Ethyl 4-hydroxybenzoate, EC 204-399-4, (source substance 2);

7 You provide the following reasoning for the prediction of toxicological properties: "*substances that are both structurally related to the target substance, as well as higher-molecular weight substances, which may in turn metabolize to these substances*".

8 ECHA understands that your read-across hypothesis is based on the formation of common (bio)transformation products. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

0.1.2. Predictions of toxicological properties

0.1.2.1. Incomplete characterisation of the group members

9 Annex XI, Section 1.5. provides that "*substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as group*."

10 Therefore, qualitative and quantitative information on the compositions of the Substance and of the source substances must be provided to allow assessing

whether the attempted predictions are compromised by the composition and/or impurities.

11 In your read-across justification, you do not inform on the composition and the presence of impurities for any of the source substances (1 and 2).

12 Regarding the source substances, you state "[...] *it is reasonable to assume also a high purity of the two test articles, Methyl- and Ethylparaben, even when the studies were performed as early as 1933*." However, you do not specify what "*high purity*" of the source substances entails qualitatively or quantitatively.

13 Without this information, no qualitative or quantitative comparative assessment of the compositions of the Substance and of the source substances can be completed. Therefore, it is not possible to assess whether the attempted predictions are compromised by the composition of the source substances.

0.1.2.2. Missing supporting information on the impact of non-common compound(s)

14 Annex XI, Section 1.5. requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6., Section R.6.2.2.1.f.).

15 Supporting information must include bridging studies to compare properties of the Substance and the selected source substances, adequate toxicokinetic information to support fast hydrolysis *in vivo*, and information on the impact of exposure to the parent compounds on the predictions.

16 As indicated above, your read-across hypothesis is based on the (bio)transformation of the Substance and of the source substance(s) to a common compound(s). In this context, exposure to the Substance and of the source substance(s) may also lead to exposure to other compounds than the common compound of interest. The impact of exposure to these non-common compounds on the prediction of properties of the target needs to be assessed to ensure that a reliable prediction can be made.

17 In your read-across justification, you state that the source substances are all metabolised to the Substance. In your read across justification document, you provide a table (Appendix B), in which you list studies which address to a limited extent the toxicokinetic properties of the source substances. Therein, you make a number of statements on the rate and extent of metabolisation, distribution and excretion, such as;

18 On source substance 1:

- "*After the oral administration of Methyl paraben to dogs 89% of the dosage were recovered in the urine, 21.3% as free 4-HBA, 35.1% as glucoronide acid conjugate*";
- "*50% of the administered dose was recovered from the urine after 12 hours as "Total" material of which 11% of the administered dose were excreted with the urine as 4-HBA within 12 hours*";

- "*Appreciable Methylparaben is only found in the brain and spleen. High "total" concentrations are found in the liver and kidney and high concentrations of free p-Hydroxybenzoic acid are detected in the kidney. Other than these instances, levels in the various organs are below plasma levels*".

19 On source substance 2:

- "*5 h after the intravenous administration of the test substance, the excretion of the test substance and its metabolites via urine almost ceased. At this time point, a total amount of 91.34% of the dose was excreted. Identified metabolites in urine and bile were p-hydroxybenzoic acid, p-hydroxyhippuric acid, p-hydroxybenzoyl glucuronide and p-carboxyphenyl sulfate. The main route of excretion was via urine. The unmetabolised test substance was only found in urine in marginal amounts of 0.03%*";
- "*70% of the test substance were recovered within 48 h in urine*";
- "*66% of the test substance was recovered within 48 h in urine. [...] After oral uptake, 0.034% of the test substance as such was found in urine. The major part of the recovered test substance was found as free p-hydroxybenzoic acid (12.3%) and as conjugate with glucuronic acid (32.5%)*".

20 You have also discussed the metabolic reactions that are expected to predominately drive the metabolization of the source substances (1 and 2) to the Substance, and you provide OECD QSAR toolbox results to inform on the expected metabolites.

21 Although these data suggest that overall, source substances 1 and 2 are extensively metabolised to the Substance, exposure to the parent compound for a considerable period of time after administration still cannot be excluded. More specifically, you do not provide conclusive experimental evidence that metabolisation of the parent compounds to the Substance may be considered effectively instant and complete following exposure. Furthermore, within a timeframe of hours, a considerable amount of the parent compound may not have been excreted yet. As such, the impact of exposure to non-common parent compounds or metabolites on your prediction may not be negligible.

22 In your comments to the draft decision, you state that "*Methylparaben as well as Ethylparaben are synthesized by starting with 4-HBA and Methanol or Ethanol. In the presence of sulfuric acid the partners react to the esters*." In turn, you speculate that "[...] *this reaction of the synthesis is reversed in acid of the stomach so that oral administration of Methyl- or Ethylparaben leads to an exposure with 4-HBA and Methanol or Ethanol.*" For source substances 1 and 2, you claim " [...] *~100% hydrolysis after systemic absorption* [...]". However, you do not provide any experimental evidence to support this hypothesis, nor do you inform on the rate at which such a reversed reaction may take place.

23 Regarding bridging studies to compare properties of the category members, you have provided incomplete bridging data (repeated dose toxicity studies). More specifically, none of the studies with source substances 1 and 2 inform on blood chemistry and none of the studies (with the Substance, source substance 1 and 2) inform on behaviour. Furthermore, for the reasons explained under 4.2, none of these studies can be considered as reliable. Similarly, you have provided bridging data for reproductive and developmental toxicity (Substance and all source substances), but none of these studies can be considered reliable for the reasons explained under 5.2. As such, there are no reliable bridging data in your dossier, which inform on systemic toxicological effects, that would support your predictions.

24 ECHA understands that in the context of bridging studies, in your comments to the draft decision you refer to three uterotrophic assays with the Substance (2000b, 2000, 2000), which you claim do not indicate an endocrine disrupting effect. In addition, you refer to a repeated dose reproduction and developmental toxicity study (1997) with the Substance, where "*reproductive organs in male and female rats (testes, epididymis, ovaries and uterus) as well as functional aspects on fertility (spermatogenesis, copulation index, fertility index, estrus cycles), which are assumed to be possibly affected by estrogens, were investigated*." In this study, you state that "*no significant differences*" were observed. Regarding data on the source substances (1 and 2), you refer to "*studies* [...] *on fertility in rats revealing a lack of spermatotoxic effects (Oishi, 2004)*". You conclude your discourse by stating "*From these results and evaluations (by the Registrants as well as by SCCS) it can be concluded that there is no concern on reproductive toxicity which could be possibly linked with endocrine disrupting modes (i.e. estrogenic activity). Thus, there is no rational basis for this draft decision of the ECHA stating that there is no information on endocrine disruption and behaviour*." In addition to these studies, you refer to "*5 studies*", where you claim "*No effects were observed", with mouse, rat, rabbit and hamster, on developmental toxicity with methylparaben and ethylparaben, precursors of 4-HBA* [...]". In table 1 of the document '*4-HBA: Comments to the draft decision of ECHA, Helsinki 25. April 2023*' provided as part of your comments to the draft decision, you also refer to two uterotrophic assays (both 1998) with source substances 1 and 2. ECHA understands that this uterotrophic data may help support in part your read-across prediction, specifically in the context of endocrine disruption via estrogenic activity. However, bridging studies informing only on the estrogenic aspect of endocrine disruption do not suffice to support your conclusion, as there are various other aspects to endocrine disruption and behaviour. In addition, there are various other systemic parameters that may operate independently of endocrine disruption, thus affecting your toxicological prediction.

25 In addition, you state: "*Regarding the acute toxicity, the LD50(rat) values are higher than 2000 mg/kg/bw for all 3 substances. None is regarded as skin irritant. 4-HBA is considered irritating to the eyes in vivo, whereas the esters are not classified as irritating to eyes, even though they caused slight irritation in the eyes of rabbits (due to full reversibility within the observation period)*."However, a single parameters such as acute mortality and an exclusively local effect (i.e. irritation and/or sensitisation) is not sufficient to support a read-across prediction for systemic toxicity. More specifically, mortality as a whole does not support the prediction of all potential adverse outcomes that may be observed under the information requirements you have adapted with a read-across. In addition, data on exclusively local effects does not account for the plethora of ADME considerations that are to be made for the sub-chronic and pre-natal developmental toxicity (in a 1st and 2nd species) information requirements.

26 Besides the comments addressed above, you do not provide any other relevant new information that addresses the issues listed above.

27 In the absence of such information, you have not established that a reliable prediction of the property under consideration of the Substance can be derived on the basis of your read-across hypothesis. Therefore, you have not provided sufficient supporting information to scientifically justify for the read-across.

0.1.2.3. Inadequate or unreliable studies on the source substances

28 According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must:

(1) be adequate for the purpose of classification and labelling and/or risk assessment;

(2) have adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement;

(3) cover an exposure duration comparable to or longer than the corresponding study that shall normally be performed for a particular information requirement if exposure duration is a relevant parameter.

29 Specific reasons why the studies on the source substances do not meet these criteria are explained further below under the applicable information requirement sections 2, 3 and 4. Therefore, no reliable predictions can be made for these information requirements.

0.1.3. Conclusion

30 Based on the above, you have not established that relevant properties of the Substance can be predicted from data on the source substance(s). Your read-across approach under Annex XI, Section 1.5. is rejected.

0.2. Weight of evidence adaptation rejected

31 ECHA understands that you have adapted the following standard information requirements by using Annex XI, Section 1.2. (weight of evidence):

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.)

32 Annex XI, Section 1.2. states that there may be sufficient weight of evidence from several independent sources of information enabling, through a reasoned justification, a conclusion on the information requirement, while the information from each single source alone is insufficient to fulfil the information requirement.

33 The justification must have regard to the information that would otherwise be obtained from the study that must normally be performed for this information requirement.

34 According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude on the corresponding information requirement.

0.2.1. Lack of documentation justifying the weight of evidence adaptation

35 Annex XI, Section 1.2. requires that adequate and reliable documentation is provided to describe a weight of evidence approach. This documentation must include robust study summaries of the studies used as sources of information and a justification explaining why the sources of information together provide a conclusion on the information requirement.

36 In your dossier, you have not included a justification for your weight of evidence adaptation for each of the relevant information requirement, which would include

an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude on the information requirements under consideration.

37 In your comments to the draft decision, specifically in the context of requests 2, 3, and 4 in this decision, you acknowledge that "[...] *there appear to be gaps in data regarding the target substance (4-HBA)* [...]". However, in contrast you also claim that "[...] *there is sufficient information to fulfil the information requirements using a Weight of Evidence approach".* You refer to the read-across justification document in your dossier, which you claim contains a justification for the weight of evidence adaptation. However, therein, you simply state "*There is sufficient information* [...]", and in various sections of the document you simply list various studies and again claim that they together in a weight of evidence approach can fulfil the information requirements. This does not explain why the sources of information together provide a conclusion on the information requirement, and as such does not provide a justification of how the evidences must be weighed.

38 Beside this critical deficiency common to all information requirements under consideration, your weight of evidence approach has additional deficiencies.

39 Additional deficiencies that are specific for each of the information requirements individually are addressed under requests 2, 3, and 4.

40 Besides the comments addressed above and under the endpoints, you did not provide any new information that addressed all identified issues.

41 In your comment to the draft decision you also state in support of your adaptation "*When, for certain endpoints, it is proposed not to provide information for other reasons than those mentioned in column 2 of this Annex or in Annex XI, this fact and the reasons shall also be clearly stated." (cited from Annex VII, VIII, IX, X, REACh)*." However, this quotation is irrelevant in your case, as your adaptations are explicitly made under the Annex XI sections on read-across and weight of evidence.

Reasons related to the information under Annex VIII of REACH

1. *In vitro* gene mutation study in mammalian cells

42 An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII, Section 8.4.3., in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

1.1. Triggering of the information requirement

43 Your dossier contains (I) a negative result for *in vitro* gene mutation study in bacteria, and (II) negative result for *in vitro* cytogenicity study in mammalian cells.

44 Consequently, you are required to provide information for this information requirement.

1.2. Information provided

45 You have not submitted any information for this requirement in your dossier.

46 In your comments to the draft decision, you state that "*The results of the presented studies demonstrate that 4-HBA is neither mutagen, nor reprotoxic, nor a carcinogen nor is it an endocrine disrupting chemical*." In turn, you conclude that the study requested in this section "*will not give additional information*.".

1.3. Assessment of the information provided in your comments to the draft decision

1.3.1. Your statement has no legal basis

47 A registrant may only adapt this information requirement based on the general rules set out in Annex XI or the specific rules set out in Annex VIII, Section 8.4.3., column 2.

48 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH or Annex VIII, Section 8.4.3., Column 2 and the legal basis you are relying on for your intended adaptation is not apparent to ECHA.

49 Therefore, you have not demonstrated that this information can be omitted.

50 Therefore, the information requirement is not fulfilled.

1.4. Study design

51 To fulfil the information requirement for the Substance, either the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable.

Reasons related to the information under Annex IX of REACH

2. Sub-chronic toxicity study (90 days)

52 A sub-chronic toxicity study (90 days) is an information requirement under Annex IX, Section 8.6.2.

2.1. Information provided

53 ECHA understands that in your dossier you have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence) based on the following sources of information:

(i) an OECD TG 422 study (1997) with the Substance;

(ii) a five-day oral toxicity study on humans (1933) with the Substance;

(iii) a 12-day inhalation toxicity study on rats (1981) with the Substance;

(iv) a subcutaneous dose-setting study (2000) with the Substance;

(v) a 96-week oral toxicity study in rats (1956) with the source substance EC 202-785-7;

(vi) a 422-day oral toxicity study in dogs (1956) with the source substance EC 202-785-7;

(vii) a 120-day oral toxicity study in guinea pigs (1935) with the source substance EC 202-785-7;

(viii) a 120-day oral toxicity study in rabbits (1935) with the source substance EC 202-785-7;

(ix) a 120-day oral toxicity study in rats (1935) with the source substance EC 202-785-7;

(x) an 8-week oral toxicity study in rats (2004) with the source substance EC 202-785-7;

(xi) a 12-week oral toxicity study in rats (1956) with the source substance EC 204-399-4;

(xii) a 25-week oral toxicity study in rats (1973 and 1984) with the source substance EC 204-399-4;

(xiii) an 8-week oral toxicity study in rats (2004) with the source substance EC 204-399-4.

54 In your comments to the draft decision, you state that "*The results of the presented studies demonstrate that 4-HBA is neither mutagen, nor reprotoxic,nor a carcinogen nor is it an endocrine disrupting chemical*". In turn, you conclude that the study requested in this section "*will not give additional information*".

2.2. Assessment of the information provided

55 In addition to the deficiencies identified in Section 0.2., ECHA identified endpoint specific issues addressed below.

56 Information that can be used to support weight of evidence adaptation for the information requirement of Annex IX, Section 8.6.2 includes similar information that is produced by the OECD TG 408. OECD TG 408 requires the study to investigate the following key parameters:

(1) In-life observations
(2) Blood chemistry
(3) Organ and tissue toxicity

2.2.1. In-life observations

57 In-life observations must include information on survival, body weight development, clinical signs, functional observations, food/water consumption and other potential aspects of in life observations on the relevant physiological systems (circulatory, digestive/excretory, integumentary, musculoskeletal, nervous, renal/urinary, and respiratory).

58 The sources of information may provide limited information on survival (sources of information i to xi and xiii), body weight development (sources of information i and iii to xiii), clinical signs (sources of information i to xiii), and food/water consumption (sources of information i, v, vii, viii, x to xiii).

59 None of the sources of information provide information on functional observations.

2.2.2. Blood chemistry

60 Information on blood chemistry must include haematological (full-scale) and clinical chemistry analysis (full-scale), and other potential aspects related to blood chemistry to address relevant physiological systems (circulatory digestive/excretory, endocrine, immune, musculoskeletal, and renal/urinary).

61 The sources of information may provide limited information on haematological (full-scale) (sources of information i, iii, vi, vii, ix, and xii) and clinical chemistry analysis (full-scale) (sources of information i, iii, and xii), and other potential aspects related to blood chemistry to address relevant physiological systems (endocrine (sources of information x and xiii), and renal/urinary (sources of information ii and vi)).

2.2.3. Organ and tissue toxicity

62 Organ and tissue toxicity must include information on terminal observations on organ weights, gross pathology and histopathology (full-scale and other potential aspects related to organ and tissue toxicity to address relevant physiological systems (circulatory, digestive/excretory, endocrine, immune, integumentary, musculoskeletal, nervous, renal/urinary system, reproductive, and respiratory).

63 The sources of information may provide limited information on terminal observations on organ weights (sources of information i, iii, x, and xiii), gross pathology (sources of information i, iii, v, vi, x to xii) and histopathology (sources of information i, iii, v, vi, x to xiii) (full-scale) and other potential aspects related to organ and tissue toxicity to address relevant physiological systems (reproductive (sources of information x and xiii)).

64 However, the reliability of these sources of information is affected by the following deficiencies:

2.2.4. Read-across adaptation rejected (sources of information v – xiii)

65 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint-specific issue(s) addressed below.

2.2.5. Study not conducted by the most appropriate route (sources of information iii and iv)

66 According to the 'Guidance on IRs and CSA, Section R.7.5.4.3.2.', the default route is oral. However, the dermal or the inhalation route may be appropriate, depending on the physico-chemical properties of the Substance, the most relevant route of human exposure, and other toxicological considerations.

67 Under Annex IX, Section 8.6.2., Column 2, Paragraph 2, the appropriate route shall be chosen on the following basis:

68 Testing by the dermal route is appropriate if:

- skin contact in production and/or use is likely; and
- the physicochemical properties suggest a significant rate of absorption through the skin; and
- one of the following conditions is met:
  - toxicity is observed in the acute dermal toxicity test at lower doses than in the oral toxicity test, or
  - systemic effects or other evidence of absorption is observed in skin and/or eye irritation studies, or
  - *in vitro* tests indicate significant dermal absorption, or
  - significant dermal toxicity or dermal penetration is recognised for structurally-related substances.

69 Testing by the inhalation route is appropriate if:

- exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size.

70 Dosing was performed in source of information (iii) via the inhalation and subcutaneous route in source of information (iv).

71 However, you do not provide any justification for these selected routes.

72 Based on the above, the provided study is not performed according to the appropriate route. Therefore, the information requirement is not fulfilled.

2.2.6. Reliability of the contribution of the sources of information (ii to iv, and vi to xiii) to your to the weight of evidence adaptation

73 To fulfil the information requirement, normally the sub-chronic toxicity study (90 days) has to meet the requirements of the OECD TG 408, which specifies that:

a) testing is performed with at least three dose levels (unless conducted at the limit dose) and with concurrent controls;

b) the highest dose level should aim to induce toxicity or reach the limit dose;

c) at least 10 male and 10 female animals are used for each concentration and control group;

d) dosing of the Substance is performed daily for a minimum of 90 days;

74 The reported data for the studies you have provided included:

a) only one (in sources of informations ii and viii) dose levels and no concurrent controls (in sources of information ii and iv) were described. The number of doses is not specified in source of information (ix);

b) no justification for the dose setting, while the highest dose level tested was 3 g total per day (ii), 100 mg/kg bw/day (iv, vii), 2.5 mg/kg bw/day (viii), 5 mg/kg

bw/day (ix), which is below the limit dose of OECD TG 408, and no adverse effects were observed;

c) there are only 5 males (source of information iii and xii), 2-3 males (source of information vi), 6 males (source of information vii), 8 males (sources of information x and xiii), , and 1 female (source of information ii), 5 females (sources of information iii and xii), 2 females (source of information iv), 2-3 females (source of information vi), 6 females (source of information vii)in each test and control group. Source of information (viii) used only 6 animals/dose in test 1, and an unspecified number of animals/dose in test 2. Sources of information (ii) and (iv) did not include males, and sources of information (x) and (xiii) did not include females;

d) an exposure duration limited to 42 days (source of information i), 5 days (source of information ii), 10 days (source of information iii), 3 days (source of information iv), 80 days (source of information ix) days, 8 weeks (sources of information x and xiii), and 12 weeks (source of information xi).

75 Therefore, the provided studies do not cover all elements of in-life observations, and even for the elements covered, none of the sources of information could reliably contribute to the conclusion on any of the key parameters investigated by the required study. More specifically, the lack of sufficient dose levels and controls makes it impossible to correctly interpret the toxicological profile of the test substance. A top dose that is set too low and a dosing duration that is too short may make it impossible to detect an adverse effect. Furthermore, an insufficient sample size may reduce the statistical power to negligible levels.

2.2.7. Conclusion on the weight of evidence adaptation

76 In summary, there is no information provided on in-life functional parameters. While you have provided limited information on in-life observations, blood chemistry, and organ and tissue toxicity, the corresponding sources of information have deficiencies affecting their reliability. As in this case these deficiencies significantly affect the read-across predictiveness, species relevance, number of doses, dose range and statistical power, of these sources of information, it prevents drawing the conclusion on in-life observations, blood chemistry, and organ and tissue toxicity.

77 Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for sub-chronic toxicity study (90 days).

78 Based on the above, your adaptation is rejected.

2.3. Assessment of the information provided in your comments to the draft decision

2.3.1. Your statement has no legal basis

79 A registrant may only adapt this information requirement based on the general rules set out in Annex XI or the specific rules set out in Annex IX, Section 8.6.2., column 2.

80 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH or Annex VIII, Section 8.6.2., Column 2 and the legal basis you are relying on for your intended adaptation is not apparent to ECHA.

81 Therefore, you have not demonstrated that this information can be omitted and the information requirement is not fulfilled.

2.4. Study design

82 Following the criteria provided in Annex IX, Section 8.6.2., Column 2, and considering the Guidance on IRs and CSA, Section R.7.5.6.3.2., the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance, because not all criteria to conclude that the dermal or inhalation route is appropriate, as listed in Annex IX, Section 8.6.2., Column 2, Paragraph 2, are met. More specifically, there are no clear uses reported where inhalation or skin contact is likely. Furthermore, significant absorption through the skin appears unlikely, as you state "*4-HBA is not resorbed through the intact skin in relevant amounts*".

83 According to the OECD TG 408, the rat is the preferred species.

84 Therefore, the study must be performed in rats according to the OECD TG 408 with oral administration of the Substance.

3. Pre-natal developmental toxicity study in one species

85 A pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is an information requirement under Annex IX, Section 8.7.2.

3.1. Information provided

86 ECHA understands that, in your dossier, you have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence) based on the following:

(i) An OECD TG 422 study in rats (1997) with the Substance;

(ii) a pre-natal developmental toxicity study in mice (1972) with the source substance EC 202-785-7.

(iii) a pre-natal developmental toxicity study in rats (1972) with the source substance EC 202-785-7.

(iv) a pre-natal developmental toxicity study in hamster (1972) with the source substance EC 202-785-7.

(v) a pre-natal developmental toxicity study in rats (1975) with the source substance EC 204-399-4.

(vi) a pre-natal developmental toxicity study in rats (1990) with the Substance.

(vii) a pre-natal developmental toxicity study in rabbits (1973) with the source substance EC 202-785-7.

87 ECHA understands, based on your comments to the draft decision, that you also intend to include the following studies in your weight of evidence adaptation:

(viii) Mouse uterotrophic assay (2000b) with the Substance.

(ix) Mouse uterotrophic assay (2000) with the Substance.

(x) Rat uterotrophic assay (2000) with the Substance.

(xi) Study on fertility in rat (2004) with the source substance EC 202-785-7.

(xii) Uterotrophic Assay (1998) with the source substance EC 202-785-7.

(xiii) Study on fertility in rat (2004) with the source substance EC 204-399-4.

(xiv) Uterotrophic Assay (1998) with the source substance EC 204-399-4.

88 In your comments to the draft decision, you also state that "*The results of the presented studies demonstrate that 4-HBA is neither mutagen, nor reprotoxic,nor a carcinogen nor is it an endocrine disrupting chemical*". In turn, you conclude that the study requested in this section "*will not give additional information*".

3.2. Assessment of the information provided in your dossier

89 In addition to the deficiencies identified in Section 0.2., ECHA identified the specific issues addressed below.

90 Information that can be used to support weight of evidence adaptation for the information requirement of Annex IX, Section 8.7.2 includes similar information that is produced by the OECD TG 414.

91 The following aspects are covered: 1) prenatal developmental toxicity, 2) maternal toxicity, and 3) maintenance of pregnancy.

3.2.1. Pre-natal developmental toxicity

92 Pre-natal developmental toxicity includes information after pre-natal exposure on embryonic/foetal survivial (number of live foetuses; number of resorptions and dead foetuses, postimplantation loss), growth (body weights and size) and structural malformations and variations (external, visceral and skeletal).

93 Study i may provide limited information on all these elements, except embryonic/foetal survivial, and skeletal malformations and variations. Study vi may potentially provide limited information on all these elements, except skeletal malformations and variations. Sources of information ii, iii, iv, v, and vii may potentially provide limited information on all these elements.

94 Studies (viii) – (xiv) do not inform on pre-natal developmental toxicity.

3.2.2. Maternal toxicity

95 Maternal toxicity includes information after gestational exposure on maternal survival, body weight and clinical signs and other potential aspects of maternal toxicity in dams.

96 Sources of information i to vii may provide limited information on all elements. Study vi may provide limited information on survival and body weight.

97 Studies (viii) – (xiv) do not inform on maternal toxicity.

3.2.3. Maintenance of pregnancy

98 Maintenance of pregnancy includes information on abortions and/or early delivery as a consequence of gestational exposure and other potential aspects of maintenance of pregnancy.

99 The source of information i to vii may provide limited information on these elements.

100 Studies (viii) – (xiv) do not inform on maintenance of pregnancy.

101 However, the reliability of the sources of information that may provide relevant information is affected by the following deficiencies:

3.2.4. Read-across adaptation rejected (sources of information ii – vii)

102 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified the specific issues addressed below.

3.2.5. Reliability of the contribution of the sources of information (i to vii) to the weight of evidence adaptation

103 To fulfil the information requirement, normally the pre-natal developmental toxicity study has to meet the requirements of the OECD TG 414, which specifies that:

a) the highest dose level aims to induce toxicity or aims to reach the limit dose;

b) at least 20 female animals with implantation sites for each test and control group are included;

c) the exposure duration is at least from implantation until one day prior to scheduled caesarean section;

d) the study is conducted in rats or rabbits.

104 The reported data for the studies you have provided included:

a) the highest dose levels tested was 550 mg/kg bw/day (sources of information ii, iii, iv) and 300 mg/kg bw/day (source of information vii), which is below the limit dose of the test guideline. No adverse effects were observed and no justification for the dose setting is provided;

b) in source of information (i) only 13 females are reported, of which it is not stated that all had implantation sites, in each test and control group. In source of information (v) there were only 5 pregnant rats in the control group, and 8-12 pregnant rats in each test group. In source of information (vi) there were only 16 animals per test group. In source of information (vii) there were only 9-11 females, of which it not stated that all had implantation sites, in each test group;

c) the exposure duration was only a single day in source of information vi and was limited to day 6 - 18 of gestation, while caesarian section was performed on gestation day 29 in source of information vii;

d) the study was conducted in mice in source of information ii and hamster in source of information iv without justification.

105 Therefore, even if all studies taken together address all the elements, they have significant reliability issues and cannot be considered as reliable sources of information that could contribute to the conclusion on prenatal developmental toxicity, maternal toxicity, and maintenance of pregnancy, which are investigated by the required study. More specifically, a top dose that is set too low and a dosing duration that is too short may make it impossible to detect an adverse effect. Furthermore, an insufficient sample size may reduce the statistical power to negligible levels, and the unjustified use of a non-TG species may affect the relevance of the data.

3.2.6. Conclusion on the weight of evidence adaptation

106 In summary, while you have provided limited information on prenatal developmental toxicity, maternal toxicity, and maintenance of pregnancy, the corresponding sources of information have deficiencies affecting their reliability. As in this case these deficiencies significantly affect the read-across predictiveness, species relevance, dose range, and statistical power of these sources of information, it prevents drawing a conclusion on prenatal developmental toxicity, maternal toxicity, and maintenance of pregnancy.

107 Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for Pre-natal developmental toxicity study in one species.

108 Based on the above, your adaptation is rejected.

3.3. Assessment of the information provided in your comments to the draft decision

3.3.1. Your statement has no legal basis

109 A registrant may only adapt this information requirement based on the general rules set out in Annex XI or the specific rules set out in Annex IX, Section 8.7.2., column 2.

110 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH or Annex IX, Section 8.7.2., Column 2 and the legal basis you are relying on for your intended adaptation is not apparent to ECHA.

111 Therefore, you have not demonstrated that this information can be omitted and the information requirement is not fulfilled.

3.4. Study design

112 A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species.

113 As the Substance is a solid, the study must be conducted with oral administration of the Substance (Annex IX, Section 8.7.2., Column 1).

114 Therefore, the study must be conducted in rats or rabbits with oral administration of the Substance.

Reasons related to the information under Annex X of REACH

4. Pre-natal developmental toxicity study in a second species

115 Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is an information requirement under Annex X, Section 8.7.2.

4.1. Information provided

116 You state that "...*the substance evaluation for the endpoint developmental toxicity is considered as a "sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion" that "the substance has" … "not a particular dangerous property" (fulfilling REACH, Annex XI, 1.2, first paragraph)*". However, you do not specify whether this adaptation is supposed to cover the standard information requirement under Annex IX, Section 8.7.2., Column 1 and/or Annex X, Section 8.7.2.

117 ECHA understands that you have adapted this information requirement (Annex X, Section 8.7.2) by using Annex XI, Section 1.2. (weight of evidence) based solely on the following source of information:

(i) a pre-natal developmental toxicity study in rabbits (1973) with the source substance EC 202-785-7.

118 We understand that you consider the rat (and other small rodents such as mouse and hamster) as being the first species addressed under section 5 above and the rabbit as being a second species addresses under the present information requirement.

119 In your comments to the draft decision, you state that "*The results of the presented studies demonstrate that 4-HBA is neither mutagen, nor reprotoxic,nor a carcinogen nor is it an endocrine disrupting chemical*." In turn, you conclude that the study requested in this section "*will not give additional information*."

4.2. Assessment of the information provided in your dossier

120 In addition to the deficiencies identified in Sections 0.1 (read across) and 0.2 (weight of evidence), ECHA identified the specific issues addressed below.

4.2.1. Only one source of information provided

121 Annex XI, Section 1.2. states that there may be sufficient weight of evidence from several independent sources of information based on which a conclusion on the information requirement can be drawn.

122 BoA case A-004-2012, Para. 72 states: "*As a preliminary observation, the Board of Appeal notes that the information requirements set out in Column 1 of Annexes VII to X to the REACH Regulation are cumulative*" and 73 states: "*As a result of the cumulative nature of the requirements contained in Column 1 to the testing Annexes, the Board of Appeal considers that, pursuant to Section 8.7.2 of Annex X, registrants are required to perform a developmental toxicity study on a species other than the species used in the performance of the pre-natal developmental toxicity study under Column 1 of Section 8.7.2 of Annex IX, unless one or more of the adaptations in Section 8.7 of Annex X or Annex XI apply*".

123 You have only provided one source of information with the second species (rabbit).

124 Based on the above, your adaptation is rejected.

125 Furthermore, the reliability of this source (vii) of information is affected by the deficiencies listed under 3.2.

126 Based on the above, your adaptation is rejected.

4.3. Assessment of the information provided in your comments to the draft decision

4.3.1. Your statement has no legal basis

127 A registrant may only adapt this information requirement based on the general rules set out in Annex XI or the specific rules set out in Annex X, Section 8.7.2., column 2.

128 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH or Annex X, Section 8.7.2., Column 2 and the legal basis you are relying on for your intended adaptation is not apparent to ECHA.

129 Therefore, you have not demonstrated that this information can be omitted and the information requirement is not fulfilled.

4.4. Study design

130 A PNDT study according to the test method OECD TG 414 should be performed in rabbit or rat as preferred second species, depending on the species tested in the first PNDT study (request 3 in this decision).

131 As the Substance is a solid, the study must be conducted with oral administration of the Substance (Annex X, Section 8.7.2., Column 1).

132 Based on the above, the study must be conducted in rabbits or rats with oral administration of the Substance.

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).
Guidance for monomers and polymers; ECHA (2012).
Guidance on intermediates; ECHA (2010).
All guidance documents are available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF); ECHA (2017).
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs; ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: Procedure

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 07 October 2022.

The information requirement for long-term toxicity testing on fish (Annex IX, Section 9.1.6.) is not addressed in this decision. This is because information that will be generated from the studies requested in the present decision is needed:

- to inform on the potential endocrine disrupting properties of the Substance; and
- to decide on the most appropriate test(s) to meet the information requirement.

This information requirement may be addressed in a separate decision at a later stage.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

ECHA notified you of the draft decision and invited you to provide comments.

You have provided comments during the decision-making phase which were found to address the incompliance(s) identified in the draft decision and you included this information in an update of your registration dossier (submission date: 23 August 2023). Therefore, the original requests for a growth inhibition study on aquatic plants (Annex VII, Section 9.1.2.) and an *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method: OECD TG 487) were removed.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix 3: Addressee(s) of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third-party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1 Test methods, GLP requirements and reporting

(1) Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

(2) Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

(3) Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries (https://echa.europa.eu/practical-guides).

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2 Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

(1) Selection of the Test material(s)

The Test Material used to generate the new data must be selected taking into account the following:

- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- the impact of each constituent/impurity on the test results for the endpoint to be assessed. For example, if a constituent/impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/impurity.

(2) Information on the Test Material needed in the updated dossier

- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include all constituents of each Test Material and their concentration values.

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers (https://echa.europa.eu/manuals).