~~Confidential~~

Helsinki, 06 November 2023

**Addressees**
Registrants of EO_JS_201305-16-0 as listed in Appendix 3 of this decision

**Date of submission of the dossier subject to this decision**
15 March 2017

**Registered substance subject to this decision ("the Substance")**
Substance name: Benzoic acid, 4-hydroxy- ester with alcohols C18-22-alkyl (even numbered)
EC/List number: 606-441-0

**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 ***11 November 2027***.

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

**Information required from all the Registrants subject to Annex VII of REACH**

1. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201)

2. Long-term toxicity testing on aquatic invertebrates (triggered by Annex VII, Section 9.1.1., column 2; test method: EU C.20./OECD TG 211)

3. Skin sensitisation (Annex VII, Section 8.3.)
   a) *in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (OECD TG 442E) (Annex VII, Section 8.3.1.); and
   b) only if the *in vitro/in chemico* test methods specified under point a) above are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment, *in vivo* skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429).

4. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, OECD TG 471 (2020)).

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

5. *In vitro* micronucleus study (Annex VIII, Section 8.4.2., test method: OECD TG 487). The aneugenic potential of the Substance must be assessed with an additional control group for aneugenicity on top of the control group for clastogenicity, if the Substance induces an increase in the frequency of micronuclei.

6. Only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained, *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).

7. Short-term repeated dose toxicity (28 days) (Annex VIII, Section 8.6.1.) by oral route, in rats, to be combined with the screening for reproductive/developmental toxicity requested below.

8. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.64/OECD TG 422) by oral route, in rats.

9. Long-term toxicity testing on fish (triggered by Annex VIII, Section 9.1.3., column 2; test method: EU C.47./OECD TG 210).

10. Soil simulation testing (triggered by Annex VIII, Section 9.2.; test method: EU C.23./OECD TG 307) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.

11. Sediment simulation testing (triggered by Annex VIII, Section 9.2.; test method: EU C.24/OECD TG 308) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.

12. Identification of degradation products (triggered by Annex VIII, Section 9.2; test method: EU C.23/OECD TG 307 and EU C.24/OECD TG 308).

13. Bioaccumulation in aquatic species (triggered by Annex VIII, Section 9.3., Column 2.; test method: EU C.13/OECD TG 305), aqueous or dietary exposure.

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.

In addition, the studies relating to biodegradation and bioaccumulation are necessary for the PBT assessment. However, to determine the testing needed to reach the conclusion

on the persistency and bioaccumulation of the Substance you should consider the sequence in which these tests are performed and other conditions described in this Appendix.

**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.:

- Skin sensitisation (Annex VII, Section 8.3.)
- *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- *In vitro* micronucleus study (Annex VIII, Section 8.4.2.)
- Short-term repeated dose toxicity (28 day) (Annex VIII, Section 8.6.1.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.64/OECD TG 422)

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 substances:

- Methyl 4-hydroxybenzoate, EC 202-785-7 (source substance 1);
- Ethyl 4-hydroxybenzoate, EC 204-399-4 (source substance 2);
- Propyl 4-hydroxybenzoate, EC 202-307-7 (source substance 3);
- Butyl 4-hydroxybenzoate, EC 202-318-7, (source substance 4);
- Benzoic acid, C12-15-alkyl esters, EC 270-112-4 (source substance 5).

7 You provide the following reasoning for the prediction of toxicological properties: "*The toxicological properties show that the target and source substances have similar toxicokinetic behaviour due to the common metabolic fate. Due to the structural similarities and consistent trend in physico-chemical, toxicological and toxicokinetic behaviour, the selected source substances are considered suitable and human health effects can be directly read-across to Benzoic acid, 4-hydroxy-, C18-22-alkyl esters in accordance with Regulation (EC) No 1907/2006, Annex XI, 1.5* [...] *The target substance and the source substances result from the esterification reaction of the alcohol with the respective aromatic carboxylic acid. Esterification is, in principle, a reversible reaction (hydrolysis). Thus, the alcohol and acid moieties are simultaneously precursors and breakdown products of the target and*

*source substance. The hydrolysis represents the first chemical step in the absorption, distribution, metabolism and excretion (ADME) pathways likely to be similarly followed by all carboxylic acid alkyl esters.* [...] *The available information indicate that the hydrolysis product 4-hydroxybenzoic acid is readily distributed via blood circulation, rapidly metabolised and excreted mainly in the urine without evidence for accumulation even after chronic exposure*".

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 the extent that this is measurable, to allow assessing whether the attempted predictions are compromised by the composition and/or impurities (Guidance on IRs and CSA, Section R.6.2.5.5.).

11 In addition, the Test Methods Regulation (EU) 440/2008, as amended by Regulation (EU) 2016/266, requires that "*if the test method is used for the testing of a MCS, UVCB or mixture, sufficient information on its composition should be made available, as far as possible, e.g. by the chemical identity of its constituents, their quantitative occurrence, and relevant properties of the constituents*". Such information includes the distribution of alkyl chain length and information on the branching of alkyl side carbon chain (i.e., isomeric composition) depending on the type of UVCB substance.

12 You claim to provide information on "*all known components of the* [source] *substances (monoconstituents and UVCBs)* [...] *No impurities have been identified that would lead to classification*."

13 For source substances 1 to 4 (which ECHA understands are mono-constituents) you have provided the following information on purity in table 2 in your read-across justification:

- EC 202-785-7, (source substance 1): >[redacted]%
- EC 204-399-4, (source substance 2): >[redacted]%
- EC 202-307-7, (source substance 3): >[redacted]%
- EC 202-318-7, (source substance 4): >[redacted]%

14 However, you do not inform on the contents of the remaining <[redacted]% of each of these source substances. No other information has been provided on composition.

15 For source substance 5 (which ECHA understands is a UVCB) you state that the composition is "*Not specified*". No other information has been provided on composition, carbon chain length, and any potential branching and isomerisation.

16 Without qualitative and quantitative information on the compositions of the Substance and of the source substances, 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 compounds*

17 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.).

18 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.

19 As indicated above, your read-across hypothesis is based on the (bio)transformation of the Substance and the 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.

20 In your read-across justification you state that the Substance and the source substances are all metabolised to the common metabolite 4-hydroxybenzoic acid. You claim that "*4-hydroxybenzoic acid is readily distributed via blood circulation, rapidly metabolised and excreted mainly in the urine without evidence for accumulation even after chronic exposure*". You also state that the "*monoesters are hydrolysed by enzymes in the gastrointestinal tract to the corresponding acid and the free alcohol. The rate varies depending on the acid and alcohol chain length* [...]".

21 ECHA understands that your read-across hypothesis implies that the Substance and selected source substances would be hydrolysed to form 4-hydroxybenzoic acid and alcohols of varying carbon chain length.

22 However, your justification does not provide supporting evidence to assess the rate and the extent at which the parent compounds are metabolised *in vivo*. In the absence of this information you fail to demonstrate similar toxicokinetic of the Substance and selected source substances and that impact to the parent compounds is unlikely to impact the predictions.

23 Furthermore, your justification lacks supporting evidence to demonstrate similar rate and extent of distribution and excretion of the non-common compounds. In particular, you provide no justification as to why differences in alcohol chain length of the Substance and source substances is not expected to affect the predictions.

24 Finally, for source substance 5, you do not provide any evidence to support that the absence of the 4-hydroxy group would not impact the predictions.

25 ECHA further notes that your justification does not include any bridging studies to support similar properties between the Substance and the selected source substances.

26 In the absence of the information listed above, 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*

27 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.

28 Specific reasons why the studies on the source substances do not meet these criteria are explained further below under the applicable information requirement sections 1, 2, 5, 7 and 8. Therefore, no reliable predictions can be made for these information requirements.

*0.1.3. Conclusion*

29 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.

**Reasons related to the information under Annex VII of REACH**

## 1. Skin sensitisation

30 Skin sensitisation is an information requirement under Annex VII, Section 8.3. Under Section 8.3., Column 1, the registrants must submit information allowing (1) a conclusion whether the substance is a skin sensitiser and (2) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

### *1.1. Information provided*

31 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) an OECD TG 406 Buehler study (1979) with the source substance EC 270-112-4;

(ii) an OECD TG 406 GPMT study (1995) with the source substance EC 202-307-7;

(iii) a HRIPT study (1994) with the source substance EC 270-112-4 provided in Section 7.10.4 of IUCLID.

### *1.2. Assessment of the information provided*

#### *1.2.1. Assessment whether the Substance causes skin sensitisation*

##### *1.2.1.1. Read-across adaptation rejected*

32 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 has identified the following endpoint specific deficiency:

*1.2.1.1.1. Incomplete information on the identity of the test material in study (i and iii)*

33 Under Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must be adequate for the purpose of classification and labelling and/or risk assessment.

34 In order to predict the properties of the Substance, the test material used in the study on the source substance must be representative for the source substance (Article 10 and Recital 19 of REACH; Guidance on IRs and CSA, Section R.4.1.). Therefore, the unambiguous characterisation of the composition of the test material used to generate the source data is required to assess whether the test material is representative for the source substance. The Test Methods Regulation (EU) 440/2008, as amended by Regulation (EU) 2016/266, requires that "*if the test method is used for the testing of a [...] UVCB [...] sufficient information on its composition should be made available, as far as possible, e.g. by the chemical identity of its constituents, their quantitative occurrence, and relevant properties of the constituents*". Such information includes purity, composition, carbon chain length, saturation, branching, depending on the type of UVCB substance.

35 You have identified the test material in studies (i) and (iii) as EC 270-112-4, without further information on purity, composition, carbon chain length, and branching.

36 In the absence of the information on the composition of the test material, you have not demonstrated that the test material is representative for the source substance. Therefore,

the study is not adequate for the purpose of classification and labelling and/or risk assessment.

*1.2.1.1.2. The provided study (i) does not meet the specifications of the test guideline (Buehler test)*

37 To fulfil the information requirement, and to enable concluding whether the Substance causes skin sensitisation, a study must comply with the EU Method B.6/OECD TG 406 (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) a dose level selection rationale is provided;

b) the induction concentration is the highest causing mild irritation to the skin;

c) the challenge dose is the highest non-irritation concentration;

d) the appropriate number of animals is included in the study: 20 in test and 10 in control group;

e) positive and negative controls are included to establish the sensitivity and reliability of the experimental technique.

38 In study (i):

a) no dose level selection rationale was provided;

b) it was not reported whether the concentration used for induction caused mild irritation;

c) it was not reported whether the challenge concentration was the highest non-irritating concentration;

d) only 12 animals were used, while the result was negative;

e) no information on positive and negative control groups was provided.

39 The information provided does not cover the specifications required by the EU Method B.6/OECD TG 406.

*1.2.1.1.3. The provided study (ii) does not meet the specifications of the test guideline (GPMT)*

40 To fulfil the information requirement, and to enable concluding whether the Substance causes skin sensitisation, a study must comply with the EU Method B.6/OECD TG 406 (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) the induction concentration is the highest causing mild-to-moderate irritation to the skin;

b) the challenge dose is the highest non-irritation concentration;

c) the appropriate number of animals is included in the study: minimum 10 in test group and 5 in control, if negative results 20 in test group and 10 in control group is highly recommended.

41 In study (ii):

d) it was not reported whether the concentrations used for induction caused mild-to-moderate irritation;

e) it was not reported that the challenge dose was the highest non-irritating concentration;

f) only 5 animals were used, while the result was negative.

42 The information provided does not cover the specifications required by the EU Method B.6/OECD TG 406.

*1.2.1.1.4. Adequacy of the provided study (iii) for hazard identification*

43 A study must be adequate for the corresponding information requirement. According to the Guidance on IRs and CSA, Section R.4. (page 1), "*The evaluation of data quality includes assessment of adequacy of the information for hazard/risk assessment and C&L purposes". The Guidance on IRs and CSA, Section R.4. (page 1) defines adequacy as "the usefulness of data for hazard/risk assessment purposes*". As a consequence, a study must be relevant for hazard assessment and for classification and labelling purposes.

44 You have provided a study according to the Human Repeat Insult Patch Test (HRIPT) (study iii), and you consider that the Substance is not a skin sensitiser.

45 The study (iii) appears to have been designed to establish safe levels for specific intended uses, considering the notably low exposure concentration (10%), rather than to investigate the intrinsic properties of the Substance as required for the purpose of hazard identification. In particular, the dose levels used in this study is far lower (i.e. 10%) than the doses expected to be used for hazard assessment purposes, as HRIPT is intended to confirm the absence of irritation and sensitisation potential.

46 Therefore, the study (iii) is not relevant for hazard assessment and classification purposes.

47 On this basis, the read-across adaptation you provided does not contribute to the assessment whether the Substance causes skin sensitisation.

*1.2.2. No assessment of potency*

48 To be considered compliant and enable a conclusion in cases where the substance is considered to cause skin sensitisation, the information provided must also allow a conclusion whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

49 As the currently available data does not allow to conclude whether the Substance causes skin sensitisation (see section 1.2.1 above), this condition cannot be assessed.

50 Therefore, the information requirement is not fulfilled.

*1.3. Study design*

51 To fulfil the information requirement for the Substance, information on molecular interaction with skin proteins and inflammatory response in keratinocytes and activation of dendritic cells (OECD TG 442C and OECD TG 442D and OECD TG 442E) must be provided. Furthermore an appropriate risk assessment is required if a classification of the Substance as a skin sensitiser (Cat 1A or 1B) is warranted.

52 In case no conclusion on the skin sensitisation potency can be made for the Substance based on the existing data or newly generated data, in vivo skin sensitisation study must be performed and the murine local lymph node assay (EU Method B.42/OECD TG 429) is considered as the appropriate study for the potency estimation.

## 2. *In vitro* gene mutation study in bacteria

53 An in vitro gene mutation study in bacteria is an information requirement under Annex VII, Section 8.4.1.

### *2.1. Information provided*

54 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) an *in vitro* gene mutation study in bacteria (2005) with the source substance EC 270-112-4;

(ii) an *in vitro* gene mutation study in bacteria (1994) with the source substance EC 270-112-4.

### *2.2. Assessment of the information provided*

#### *2.2.1. Read-across adaptation rejected*

55 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 has identified the following endpoint specific deficiency:

##### *2.2.1.1. Incomplete information on the identity of the test material*

56 Under Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must be adequate for the purpose of classification and labelling and/or risk assessment.

57 In order to predict the properties of the Substance, the test material used in the study on the source substance must be representative for the source substance (Article 10 and Recital 19 of REACH; Guidance on IRs and CSA, Section R.4.1.). Therefore, the unambiguous characterisation of the composition of the test material used to generate the source data is required to assess whether the test material is representative for the source substance. The Test Methods Regulation (EU) 440/2008, as amended by Regulation (EU) 2016/266, requires that "*if the test method is used for the testing of a [...] UVCB [...] sufficient information on its composition should be made available, as far as possible, e.g. by the chemical identity of its constituents, their quantitative occurrence, and relevant properties of the constituents*". Such information includes purity, composition, carbon chain length, saturation, branching, depending on the type of UVCB substance.

58 You have identified the test material in studies (i) and (iii) as EC 270-112-4, without further information on purity (study (ii) only), composition, carbon chain length, and branching.

59 In the absence of the information on the composition of the test material, you have not demonstrated that the test material is representative for the source substance. Therefore, the study is not adequate for the purpose of classification and labelling and/or risk assessment.

60 Therefore, the information requirement is not fulfilled.

### *2.3. Study design*

61 To fulfil the information requirement for the Substance, the in vitro gene mutation study in bacteria (OECD TG 471) is considered suitable.

## 3. Long-term toxicity testing on aquatic invertebrates

62 Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII, Column 1, Section 9.1.1. However, under Column 2, long-term toxicity testing on aquatic invertebrates may be required by the Agency if the substance is poorly water soluble, i.e. solubility below 1 mg/L.

### *3.1. Triggering of the information requirement*

63 In the provided EU Method A.6 Guideline (2011), the saturation concentration of the Substance in water was determined to be < 0.05 mg/L.

64 Therefore, the Substance is poorly water soluble and information on long-term toxicity on aquatic invertebrates must be provided.

### *3.2. Information provided*

65 You have provided a short-term toxicity study on aquatic invertebrates but no information on long-term toxicity on aquatic invertebrates for the Substance.

66 Instead, you have adapted the information requirement on long-term toxicity on aquatic invertebrates and provided the following justification: "*According to Regulation (EC) No. 1907/2006, Annex IX, Column 2, 9.1.6, long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicate the need to investigate further effects on aquatic organisms. As the test substance is highly insoluble in water (< 0.05 mg/L) and exhibits a log Koc > 5, if at all, only very small amounts of the test substance are expected to be released from STP facilities in water (adsorption to sewage sludge is expected). Furthermore, no effects were observed to daphnia in the range of water solubility (< 0.05 mg/L) in the short-term test*".

### *3.3. Assessment of the information provided*

#### *3.3.1. Your justification to omit the study has no legal basis*

67 A registrant may only adapt this information requirement based on the general rules set out in Annex XI.

68 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH and the legal basis you are relying on for your intended adaptation is not apparent to ECHA.

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

70 In the comments to the draft decision, you agree to perform the requested study.

### *3.4. Study design*

71 The Substance is difficult to test due to the low water solubility (< 0.05 mg/L) and adsorptive properties (Log $K_{ow}$ > 4.5 and log Koc > 4). OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as

described in OECD TG 211. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

72 For multi-constituents/UVCBs, the analytical method must be adequate to monitor qualitative and quantitative changes in exposure to the dissolved fraction of the test material during the test (e.g. by comparing mass spectral full-scan GC or HPLC chromatogram peak areas or by using targeted measures of key constituents or groups of constituents).

73 If you decide to use the Water Accommodated Fraction (WAF) approach, in addition to the above, you must:

- use loading rates that are sufficiently low to be in the solubility range of most constituents (or that are consistent with the PEC value). This condition is mandatory to provide relevant information for the hazard and risk assessment (Guidance on IRs and CSA, Appendix R.7.8.1-1, Table R.7.8-3);
- provide a full description of the method used to prepare the WAF (including, among others, loading rates, details on the mixing procedure, method to separate any remaining non-dissolved test material including a justification for the separation technique);
- prepare WAFs separately for each dose level (i.e. loading rate) and in a consistent manner.

## 4. Growth inhibition study aquatic plants

74 Growth inhibition study on aquatic plants is an information requirement under Annex VII to REACH (Section 9.1.2.).

### *4.1. Information provided*

75 You have adapted this information requirement by using Column 2 of Annex VII, Section 9.1.2. To support the adaptation, you have provided following statement:

(i) *"According to Regulation (EC) No. 1907/2006, Annex VII, 9.1.2, toxicity testing on algae species does not need to be conducted if there are mitigating factors indicating that aquatic toxicity is unlikely to occur, for instance if the substance is highly insoluble in water. Benzoic acid, 4-hydroxy-, C18-22-alkyl esters is poorly soluble in water (water solubility < 0.05 mg/L). Significant concentrations in the water phase are thus not expected to be reached, and the substance is not expected to be bioavailable for algae.";*

76 In addition, you have provided the following statement:

(ii) "*The low water solubility and high adsorption potential (log Kow > 10) may critically hinder the technical feasibility of the study. Highly hydrophobic and adsorptive substances tend to adsorb to the walls of the test vessels and to the surface of algae cells, often causing effects on biomass and growth by direct physical interaction with the algae (e.g. hindering the access to light and nutrients, whereas dissolved concentrations in the test medium are actually close to zero.*"

77 ECHA understands that you provided this statement in an attempt to adapt this information requirement under Annex XI, Section 2.

### *4.2. Assessment of the information provided*

*4.2.1. The provided adaptation does not meet the criteria of Annex VII, Section 9.1.2., Column 2*

78 Under Annex VII, Section 9.1.2., Column 2, first indent, the study may be omitted if aquatic toxicity is unlikely, for instance if the Substance is highly insoluble in water. Guidance on IRs and CSA, Section R.7.8.5 explains that there is no scientific basis to define a cut off limit for solubility below which toxicity is unlikely. Therefore, the justification must demonstrate very low water solubility and low likelihood to cross biological membranes. For the latter, the indicators used for low likelihood of a high bioaccumulation potential (Guidance on IRs and CSA, Figure R.11-4) must be considered, including:

- physico-chemical indicators of hindered uptake due to large molecular size (*e.g.* $D_{max}$ > 17.4 Å and MW > 1100 or MML > 4.3 nm) or high octanol-water partition coefficient (Log $K_{ow}$ > 10) or low potential for mass storage (octanol solubility (mg/L) < 0.002 x MW), and
- supporting experimental evidence of hindered uptake (no chronic toxicity for mammals and birds, no chronic ecotoxicity, no uptake in mammalian toxicokinetic studies, very low uptake after chronic exposure).

79 Unless it can reliably be demonstrated that aquatic toxicity is unlikely to occur, the Substance must be considered as poorly water soluble.

80 Your registration dossier provides:

- information on the solubility of the Substance in water (<0.05) mg/L. Based on this you indicate that "*significant concentrations in the water phase are thus not expected to be reached, and the Substance is not expected to be bioavailable for algae*";

81 Even though the reported water solubility estimate for the Substance is low, ECHA notes the following with regard your justification:

- the provided log Kow estimate (i.e., > 10) is based on QSAR prediction for the C18 and C22 constituents of the Substance. While it suggest high lipophilicity for those constituents, ECHA notes that the Substance may include up to 5% of Benzoic acid,4-hydroxy-, tetradecyl ester (i.e., C14) whish is expected to show a significantly lower log Kow.
- as specified above, the justification on low likelihood to cross biological membranes must be supported by physico-chemical indicators of hindered uptake and supporting experimental evidence of hindered uptake. However, your registration dossier does not include any reliable chronic ecotoxicity studies (see requests 2 and 5) and/or repeated-dose toxicity studies (see request 12 and 13) to support your conclusion of hindered uptake.

82 Therefore, you have not demonstrated that toxicity is unlikely to occur and your adaptation is rejected and the Substance must be considered as poorly water soluble.

*4.2.2. The provided adaptation does not meet the criteria of Annex XI, Section 2*

83 Under Annex XI, Section 2, a study may be omitted if it is technically not feasible to conduct because of the properties of the substance.

84 You claim that the study was difficult to conduct based on the low water solubility and high adsorption potential (log Kow > 10) . However you do not provide evidence to demonstrate that it was technically not feasible to conduct it. ECHA highlights that OECD TG 23 and OECD TG 201 provide recommendations on how to test poorly soluble substances.

85 Therefore, your adaptation under Annex XI, Section 2 is rejected

86 On this basis, the information requirement is not fulfilled.

87 In the comments to the draft decision, you agree to perform the requested study.

*4.3. Study design*

88 OECD TG 201 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in "Study design" under request 2 for long term toxicity testing on aquatic invertebrates.

**Reasons related to the information under Annex VIII of REACH**

## 5. *In vitro* micronucleus study

89 An in vitro cytogenicity study in mammalian cells or an in vitro micronucleus study is an information requirement under Annex VIII, Section 8.4.2.

### *5.1. Information provided*

90 ECHA understands that you have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) an *in vitro* chromosome aberration study in mammalian cells (1979) with the source substance EC 202-785-7;

(ii) an *in vitro* chromosome aberration study in mammalian cells (1978) with the source substance EC 202-785-7;

(iii) an *in vivo* mammalian bone marrow chromosome aberration test (1974) with the source substance EC 202-785-7;

(iv) an *in vivo* rodent dominant lethal test (1974) with the source substance EC 202-785-7.

### *5.2. Assessment of the information provided*

#### *5.2.1. Read-across adaptation rejected*

91 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.

##### *5.2.1.1. Inadequate or unreliable studies (i) and (ii) on the source substance (in vitro chromosome aberration)*

92 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 473. Therefore, the following specifications must be met:

a) two separate test conditions are assessed: in absence of metabolic activation and in presence of metabolic activation;

b) the maximum concentration tested induces 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration corresponds to 10 mM, 2 mg/mL or 2 µL/mL, whichever is the lowest;

c) at least 3 concentrations are evaluated, in absence and in presence of metabolic activation;

d) at least 300 well-spread metaphases are scored per concentration;

e) one positive control is included in the study;

f) the positive controls induce responses compatible with those generated in the historical positive control database;

g) the negative control data is ideally within the 95% control limits of the distribution of the laboratory's historical negative control database;

h) data on the cytotoxicity and the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures is reported;

i) to conclude on a negative outcome, a negative response is obtained in all three experimental conditions described in paragraph 28 of OECD TG 473, using a short-term treatment with and without metabolic activation and long-term treatment without metabolic activation.

93 In studies (i) and (ii):

a) the test was performed only in absence of metabolic activation (ii);

b) it is not transparently reported that the maximum tested concentration did not induce 55+5% of cytotoxicity compared to the negative control, and it did not induce the precipitation of the tested substance, and it was less than 10 mM, 2 mg/mL or 2 µL/mL (i and ii);

c) the number of concentrations which were evaluated in absence and in presence of metabolic activation is not transparently reported (ii);

d) the reporting suggests that only 100 metaphases (i.e., less than 300 metaphases) were scored per concentration (i and ii);

e) no positive control was included in the study (ii);

f) there is no indication of a historical positive control range (i and ii);

g) there is no indication of a historical negative control range (i and ii);

h) data on the cytotoxicity and the frequency of cells with structural chromosomal aberration(s) for all treated and control cultures were not reported (i and ii);

i) experimental conditions described in paragraph 28 of OECD TG 473 (i.e. a short-term treatment with metabolic activation (ii), a short-term treatment without metabolic activation (ii), and a long-term treatment without metabolic activation (i)) are missing to conclude on a negative outcome.

94 Based on the above, the study submitted in your adaptation, as currently reported in your dossier, does not provide an adequate and reliable coverage of the key parameter(s) of the corresponding OECD TG.

95 Therefore, the information requirement is not fulfilled.

*5.2.1.2. Inadequate or unreliable study (iii) on the source substance (in vivo mammalian bone marrow chromosome aberration)*

96 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 475. Therefore, the following specifications must be met:

a) the mitotic index is determined as a measure of cytotoxicity in at least 1000 cells per animal for all treated animals (including positive controls), and negative control animals;
b) at least 200 metaphases are analysed for each animal for structural chromosomal

aberrations including and excluding gaps;
c) the mitotic index and the mean number of cells with aberrations per group are reported for each group of animals;
d) a clear negative outcome is concluded when the data available shows that bone marrow exposure to the Substance, or its metabolite(s), occurred;
e) the negative control data is ideally within the 95% control limits of the distribution of the laboratory's historical negative control database;

97 In study (iii):

a) the mitotic index was determined in 500 cells (i.e. less than 1000 cells) for each treated animals (including positive controls), untreated or negative control animals;
b) an unspecified number of metaphases (i.e. not clear if less than 200 metaphases) were analysed for each animal for structural chromosomal aberrations including and excluding gaps;
c) the mitotic index and the mean number of cells with aberrations per group were not reported for each group of animals;
d) you did not demonstrate that bone marrow exposure to the Substance, or its metabolite(s), occurred;
e) there is no indication that the negative control showed a response within the historical control range of the laboratory, and there is no indication that there is a historical negative control range;

*5.2.1.3. The provided adaptation does not meet the criteria of Annex VIII, Section 8.4.2., Column 2 (study iv)*

98 Under Annex VIII, Section 8.4.2., Column 2, the study usually does not need to be conducted "*if adequate data from an in vivo cytogenicity test are available*". The Guidance on IRs and CSA, Section R.7.7.6.3 and Table R.7.7–3 clarifies that the in vivo somatic cell cytogenicity test must be either a micronucleus test or a chromosomal aberration test, performed according to the OECD TG 474 or 475, respectively.

The study (iv) is described as equivalent or similar to OECD TG 478 (Rodent Dominant Lethal Test).

99 The dominant lethal mutations detected by the OECD TG 478 are generally the result of structural and/or numerical chromosomal aberrations. This study is an in vivo cytogenicity test, however it is performed on germ cells. Therefore, the results of such test cannot be used for the first level of classification as germ cell mutagen, i.e. category 2. Indeed in vivo data obtained on somatic cells is necessary for this purpose.

100 Moreover, for the data to be considered adequate, the in vivo cytogenicity test you submitted has to meet the requirements of the OECD TG 478, and the specifications/conditions of this test guideline include:

a) the number of males in each group should be sufficient to provide between 30 and 50 pregnant females per mating interval;
b) data on the the number of live and dead implants per female, and the calculated post-implantation loss, for the treated and control groups is reported.

101 The reported data for the in vivo study you submitted did not include:

a) onformation on the number of pregnant females per mating interval
b) tabulated data on the the number of live and dead implants per female, and the calculated post-implantation loss, for the treated and control groups

102 The information provided does not cover the specification(s) required by the OECD TG 478.

103 Based on the above, your adaptation is rejected.

*5.3. Study design*

104 According to the Guidance on IR & CSA, Section R.7.7.6.3., either the in vitro mammalian chromosomal aberration ("CA") test (test method OECD TG 473) or the in vitro mammalian cell micronucleus ("MN") test (test method OECD TG 487) can be used to investigate chromosomal aberrations in vitro. However, while the MN test detects both structural chromosomal aberrations (clastogenicity) and numerical chromosomal aberrations (aneuploidy), the CA test detects only clastogenicity, as OECD TG 473 is not designed to measure aneuploidy (see OECD TG 473, paragraph 2).Therefore, you must perform the MN test (test method OECD TG 487), as it enables a more comprehensive investigation of the chromosome damaging potential in vitro. Moreover, in order to demonstrate the ability of the study to identify clastogens and aneugens, you must include two concurrent positive controls, one known clastogen and one known aneugen [1] (OECD TG 487, paragraphs 33 to 35).

*5.3.1. Assessment of aneugenicity potential*

105 If the result of the MN test is positive, i.e. your Substance induces an increase in the frequency of micronuclei, you must assess the aneugenic potential of the Substance.

106 In line with the OECD TG 487 (paragraph 4), you should use one of the centromere labelling or hybridisation procedures to determine whether the increase in the number of micronuclei is the result of clastogenic events (i.e. micronuclei contain chromosome fragment(s)) and/or aneugenic events (i.e. micronuclei contain whole chromosome(s)).

[1] According to the TG 487 (2016) "At the present time, no aneugens are known that require metabolic activation for their genotoxic activity" (paragraph 34).

## 6. *In vitro* gene mutation study in mammalian cells

107 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.

*6.1. Triggering of the information requirement*

108 Your dossier contains data for an in vitro gene mutation study in bacteria, and data for an in vitro cytogenicity study in mammalian cells or in vitro micronucleus study.

109 The information for the in vitro gene mutation study in bacteria and for the *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study provided in the dossier are rejected for the reasons provided in requests 2 and 5.

110 The result of the requests for an *in vitro* gene mutation study in bacteria and for an *in vitro* cytogenicity study in mammalian cells will determine whether the present requirement for an in vitro mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3. is triggered.

111 Consequently, you are required to provide information for this information requirement, if the *in vitro* gene mutation study in bacteria and the *in vitro* micronucleus study provides a negative result.

*6.2. Information provided*

112 You have not submitted any information for this requirement.

113 Therefore, the information requirement is not fulfilled.

*6.3. Study design*

114 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.

## 7. Short-term repeated dose toxicity (28 days)

115 A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII, Section 8.6.1.

*7.1. Information provided*

116 ECHA understands that you have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) a 96-week study on rats (1956) with the source substance EC 202-785-7;

(ii) a 422-day study on dogs (1956) with the source substance EC 202-785-7;

(iii) a 12-week study on rats (1956) with the source substance EC 204-399-4;

(iv) a 25-week study on rats (1973) with the source substance EC 204-399-4;

(v) a 96-week study on rats (1956) with the source substance EC 202-307-7;

(vi) a 394-day study on dogs (1956) with the source substance EC 202-307-7;

(vii) a 12-week study on rats (1956) with the source substance EC 202-318-7.

*7.2. Assessment of the information provided*

*7.2.1. Read-across adaptation rejected*

117 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.

*7.2.1.1. Source studies not adequate for the information requirement*

118 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 407. Therefore, the following specifications must be met:

a) at least 5 male and 5 female animals are used for each concentration and control group;
b) clinical signs (nature, severity, and duration) are observed daily and functional observations (i.e. sensory activity, grip strength and motor activity ) are made during the fourth exposure week;
c) haematological and clinical biochemistry tests are performed as specified in OECD TG 407;
d) terminal organ and body weights are measured;
e) full histopathology, including incidence and severity, is performed as specified in

OECD TG 407.

119 In studies (i) to (vii):

a) only 2-3 (study ii) and 1-3 (not stated if this includes both males and females) (study vi) animals were included in each test and control group;
b) the following clinical signs and functional aspects were not assessed: functional observations (studies i to vii) and clinical signs (nature, severity, and duration) (studies iii and v);
c) haematology and clinical biochemistry were not performed (studies i to iii, v to vii). In studies (ii) and (vi) haematology is claimed to be investigated, but no details are provided on which parameters were measured;
d) terminal organ weights and organ/body weight ratios were not recorded (studies i to iii, v to vii);
e) histopathology appeared limited to kidney, liver, heart, lung, spleen (studies i to vii), and pancreas (studies i to iii, v to vii).

120 The information provided does not cover the specifications required by the OECD TG 407.

121 Based on the above, the studies (i) to (vii) do not provide an adequate and reliable coverage of the key parameters specified in OECD TG 407. Therefore, these studies are not an adequate basis for your read-across predictions.

122 Therefore, the information requirement is not fulfilled.

*7.3. Study design*

123 When there is no information available neither for the 28-day repeated dose toxicity (EU B.7, OECD TG 407), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

124 The study design is addressed in request 8.

## 8. Screening study for reproductive/developmental toxicity

125 A screening for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII, Section 8.7.1.

*8.1. Information provided*

126 You have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence) based on the following:

(i) a PNDT study (1973) with the analogue substance EC 202-785-7;

(ii) a brief statement on the outcome of an in vitro hydrolysis study "*evaluated according to the method described in EFSA Note for Guidance for Food Contact Materials*"

(iii) a brief statement on the outcome of a "*56 day dietary study in Methylparaben*" (2004)

(iv) a brief statement on the outcome of a "*uterotrophic assay with Methylparaben up to 800 mg/kg bw/d*" (1998).

(v) a brief statement on the outcome of a "*non-rodent subchronic study [...] with 500 mg/kg bw Methylparaben for more than 300 days*" (1956)

(vi) a brief statement on the outcome of "*developmental studies in rabbits, rats, hamsters and guinea pigs with 4-hydroxy benzoic acid esters*" (1973 and 1972)

(vii) a list of references in IUCLID section 13.2

### *8.2. Assessment of the information provided*

127 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.

128 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.

129 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.

#### *8.2.1. Lack of documentation justifying the weight of evidence adaptation*

130 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.

131 To justify your weight of evidence adaptation, you provide the following statement: "*in accordance with Section 1.2 of REACH Annex XI, there is sufficient weight of evidence from several independent sources of information leading to the conclusion that Benzoic acid, 4-hydroxy-, C18-22-alkyl esters (CAS 201305-16-0) does not cause toxicity to reproduction and thus does not have to be classified, because based on an analogue approach.*" To support this statement, you provide the studies and statement listed under 8.1. However, this justification for your weight of evidence adaptation does not 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.

##### *8.2.1.1. Missing robust study summaries*

132 Annex XI, Section 1.2. requires that whenever weight of evidence is used adequate and reliable documentation of the applied method must be provided. Such documentation must include a robust study summary for each source of information used in the adaptations.

133 A robust study summary must provide a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study (Article 3(28)).

134 In addition, for weight of evidence adaptations, the robust study summary must clearly indicate which key parameters of the study normally required for the information requirement are investigated in the study.

For the following sources of information:

(ii) a brief statement on the outcome of an in vitro hydrolysis study "*evaluated according to the method described in EFSA Note for Guidance for Food Contact Materials*";

(iii) a brief statement on the outcome of a "*56 day dietary study in Methylparaben*" (2004);

(iv) a brief statement on the outcome of a "*uterotrophic assay with Methylparaben up to 800 mg/kg bw/d*" (1998);

(v) a brief statement on the outcome of a "*non-rodent subchronic study [...] with 500 mg/kg bw Methylparaben for more than 300 days*" (1956);

(vi) a brief statement on the outcome of "*developmental studies in rabbits, rats, hamsters and guinea pigs with 4-hydroxy benzoic acid esters*" (1973 and 1972);

(vii) a list of references in IUCLID section 13.2.

135 You have provided only the name of the studies, the authors and a high-level conclusion, but you have not provided detailed information on the methods, results and conclusions, allowing for an independent assessment of each source of information and contributing to the overall weight of evidence for the information requirement under consideration.

136 In the absence of robust study summaries, the coverage of reproductive/developmental toxicity by these sources of information and the reliability of their contribution to your weight of evidence adaptations cannot be evaluated.

137 ECHA concludes that you have failed to provide a robust study summary for each source study/some of the source studies used in the adaptation as required by Annex XI, Section 1.2.

138 Consequently, sources of information that are lacking robust study summaries cannot be considered as contributing to the overall weight of evidence for the information requirement under consideration.

139 Beside these critical deficiencies, ECHA has also assessed the other aspects of your adaptation.

140 Information that can be used to support weight of evidence adaptation for the information requirement of Annex VIII, Section 8.7.3 includes similar information that is produced by the EU B.63/OECD TG 421 or EU B.64/OECD TG 422, which requires the study to investigate the following key parameters:

(1) Sexual function and fertility
(2) Toxicity to offspring
(3) Systemic toxicity

### *8.2.2. Sexual function and fertility*

141 Sexual function and fertility on both sexes must include information on mating, fertility, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, organ weights and histopathology of reproductive organs and tissues, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

142 The source of information (i) may provide limited information on gestation (length), maintenance of pregnancy (abortions, total resorptions), organ weights and histopathology of reproductive organs and tissues (maternal only), and litter sizes.

143 Studies (iii) and (iv) may provide limited information on organ weights and histopathology of reproductive organs and tissues, and studies (v) and (vi) may provide limited information

on some aspects of sexual function and fertility, but ECHA cannot confirm this for the reasons set out in 8.2.1.1.

144 None of the sources of information provide information on mating, fertility, parturition, lactation, and nursing performance.

#### *8.2.3. Toxicity to offspring*

145 Information on pre- and perinatal developmental toxicity reflected by litter sizes, postimplantation loss (resorptions and dead foetuses), stillborns, and external malformations, postnatal developmental toxicity reflected by survival, clinical signs and body weights of the pups (or litters), and other potential aspects related to pre-, peri- and postnatal developmental toxicity observed up to postnatal day 13.

146 The source of information (i) may provide limited information on litter sizes, postimplantation loss (resorptions and dead foetuses), stillborns, and external malformations.

147 Study (vi) may provide limited information on some aspects related to offspring toxicity, but ECHA cannot confirm this for the reasons set out in 8.2.1.1.

148 None of the sources of information provide information on survival, clinical signs and body weights of the pups (or litters), and other potential aspects related to pre-, peri- and postnatal developmental toxicity observed up to postnatal day 13.

#### *8.2.4. Systemic toxicity*

149 Information on systemic toxicity include information on clinical signs with specific observations, survival, body weights, food consumption, haematology, clinical biochemistry, organ weights and histopathology of non-reproductive organs and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

150 The source of information (i) provides information on clinical signs with specific observations, survival, body weights, and food consumption.

151 Study (vi) may provide limited information on some aspects related to maternal systemic toxicity, but ECHA cannot confirm this for the reasons set out in 8.2.1.1.

152 None of the sources of information provide information on haematology, clinical biochemistry, organ weights and histopathology of non-reproductive organs and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

153 Therefore, the provided sources information only provides a partial coverage of the information provided for by the study that should normally be performed. Furthermore, the reliability of these sources of information is affected by the deficiencies described below.

#### *8.2.5. Read-across adaptation rejected*

154 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.

##### *8.2.5.1. The provided source of information (i) is not reliable due to technical deficiencies*

155 To fulfil the information requirement, normally a study according to EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be provided. A pre-natal developmental toxicity study (OECD TG 414) referred to in Annex IX, point 8.7.2 may also inform on the information

requirement 'Screening study for reproductive/developmental toxicity'. OECD TG 414 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;

156 The reported data for the studies you have provided did not include:

a) the highest dose levels tested was 300 mg/kg bw/day, which is below the limit dose of the test guideline, and no adverse effects were observed, and no justification for the dose setting;
b) only 9-10 females were included in each test and control group.

157 In summary, the source of information (i) has significant reliability issues (too low dosing may make it impossible to detect an adverse effect, and too small sample sizes reduce the statistical sensitivity to unacceptable levels) and cannot therefore contribute to the conclusion on screening for reproductive/developmental toxicity for the Substance.

#### *8.2.6. Conclusion on the weight of evidence adaptation*

158 In summary, you provide information on some elements of sexual function and fertility (gestation (length), maintenance of pregnancy (abortions, total resorptions), organ weights and histopathology of reproductive organs and tissues (maternal only), and litter sizes), toxicity to offspring (litter sizes, postimplantation loss (resorptions and dead foetuses), stillborns, and external malformations), and systemic toxicity (clinical signs with specific observations, survival, body weights, and food consumption). The source of information (i) has deficiencies affecting its reliability. In particular, the statistical power of this source of information is low, which prevents drawing the conclusion on the parameters investiguated in this study. Furthermore, as explained in Section 8.2.1.1., you have not provided detailed information on the methodology, results and conclusions of the sources of information (ii) to (vii), they cannot support your weight-of-evidence adaptation. Finally, the information you provided covers, at best, only some of the parameters normally investiguated by this information requirement. In particular, no information is provided on the following elements:

- Mating, fertility, parturition, lactation, and nursing performance.
- Survival, clinical signs and body weights of the pups (or litters), and other potential aspects related to pre-, peri- and postnatal developmental toxicity observed up to postnatal day 13.
- Haematology, clinical biochemistry, organ weights and histopathology of non-reproductive organs and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

159 Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for 'Screening study for reproductive/developmental toxicity'.

160 Based on the above, your adaptation is rejected.

161 Therefore, the information requirement is not fulfilled.

### *8.3. Study design*

162 When there is no information available neither for the 28-day repeated dose toxicity study (EU B.7, OECD TG 407), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure

that unnecessary animal testing is avoided (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

163 The information requirement for the 28-day repeated dose toxicity study is not fulfilled for the reasons explained under request 7.

164 Therefore, a study according to the test method EU B.64/OECD TG 422 must be performed in rats.

165 As the Substance is a solid, the study must be conducted with oral administration of the Substance (Annex VIII, Section 8.7.1., Column 1).

166 Therefore, the study must be conducted in rats with oral administration of the Substance.

## 9. Long-term toxicity testing on fish

167 Short-term toxicity testing on fish is an information requirement under Annex VIII, Column 1, Section 9.1.3. However, long-term toxicity testing on fish may be required by the Agency (Section 9.1.3., Column 2) if the substance is poorly water soluble, i.e. solubility below 1 mg/L.

### *9.1. Triggering of the information requirement*

168 As already explained in request 2 for long-term toxicity testing on aquatic invertebrates, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

169 Therefore, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

### *9.2. Information provided*

170 You have adapted the information requirement for short term toxicity on fish based on a justification you consider in line with Annex VIII, 9.1.3, column 2.

171 Furthermore, you have adapted the information requirement on long term fish toxicity and provided the following justification: *"According to Regulation (EC) No. 1907/2006, Annex IX, Column 2, 9.1.6, long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicate the need to investigate further effects on aquatic organisms. As the test substance is highly insoluble in water (< 0.05 mg/L) and exhibits a log Koc > 5, if at all, only very small amounts of the test substance are expected to be released from STP facilities in water (adsorption to sewage sludge is expected). If released into the environment, the main target compartments of environmental distribution will be sediment and soil. Therefore, the fraction available to fish species via water is expected to be low. Furthermore, no effects were observed to daphnia in the range of water solubility (< 0.05 mg/L)."*

### *9.3. Assessment of the information provided*

#### *9.3.1. Your justification to omit the study has no legal basis*

172 A registrant may only adapt this information requirement based on the general rules set out in Annex XI.

173 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH and the legal basis you are relying on for your intended adaptation is not apparent to ECHA.

174 Therefore, you have not demonstrated that this information can be omitted. The information requirement is not fulfilled.

175 In the comments to the draft decision, you agree to perform the requested study.

*9.4. Study design*

176 To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (Guidance on IRs and CSA, Section R.7.8.2.).

177 OECD TG 210 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under request 2 for long term toxicity testing on aquatic invertebrates.

## 10. Soil simulation testing

178 Under Annex VIII, Section 9.2., Column 2, further information on degradation or further testing as described in Annex IX must be generated if the chemical safety assessment (CSA) in accordance with Annex I indicates the need to investigate further the degradation of the substance.

*10.1. Triggering of the information requirement*

179 This information requirement is triggered in case if for example additional information on degradation as set out in Annex XIII, point 3.2.1, is required to assess PBT or vPvB properties of the substance in accordance with subsection 2.1 of that Annex. This is the case if the Substance itself or any of its constituent or impurity present in concentration ≥ 0.1% (w/w) or relevant transformation/degradation product meets the following criteria:

- it is potentially persistent or very persistent (P/vP) as it is not readily biodegradable (e.g.: <60/70% degradation in an ISO 10708 BODIS test);
- it is potentially bioaccumulative or very bioaccumulative (B/vB) as it has a high potential to partition to lipid storage (e.g. Log $K_{ow}$ > 4.5).

180 Your registration dossier provides the following:

- the Substance is not readily biodegradable (34% degradation after 28 days in ISO 10708 BODIS test). Further, in Section 2.3 of the Dossier you conclude that persistency in the environment (P and vP) cannot be excluded;
- the Substance has a high potential to partition to lipid storage (Log $K_{ow}$ > 10 for the C18 and C22 constituents).

181 Furthermore:

- it is not possible to conclude on the bioaccumulation potential of the Substance (see request 13 this decision), and
- it is not possible to conclude on the toxicity of the Substance (see requests 1 to 9 of this decision).

182 Under section 2.3 of your IUCLID dossier and section 8 of your CSR ('PBT assessment'), you conclude that the Substance is not B/vB and T.

183 You base your conclusion on the following additional information:

- For substances with a log Kow value > 10 it is unlikely that they reach the pass level of being bioaccumulative according to the PBT assessment criteria (BCF > 2000 L/kg),
- QSAR calculations using BCFBAF v3.01 performed for benzoic acid, 4-hydroxy-, C18-22-alkyl esters, result in BCF/BAF values of 0.98-1.38 L/kg and 16.2-27.1 L/kG,
- The L(E)50 values reported in the test conducted with aquatic invertebrates is higher than 0.01 mg/L, and the substance is not classified as carcinogenic, mutagenic or toxic for reproduction nor is there any evidence of chronic toxicity according to the 2nd ATP of Regulation (EC) No. 1272/2008 (CLP) and Directive 67/548/EEC.

184 However:

- For the reasons explained under Request 13, the information you provided on bioaccumulation in aquatic species does not meet the information requirement. Therefore, no conclusion on B/vB can currently be reached.
- Similarly, as already indicated above, no conclusion on T can currently be reached.

185 Based on the above, the available information on the Substance indicates that it is a potential PBT/vPvB substance and the additional information from your PBT assessment is not adequate to conclude on the PBT/vPvB properties of the Substance.

186 Further, the Substance has low water solubility (< 0.05 mg/L), high partition coefficient (Log $K_{ow}$ > 4.5) and high adsorption coefficient (Log $K_{oc}$ > 4) , indicating high potential to adsorb to soil.

187 Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation. Based on the adsorptive properties of the Substance, soil represents a relevant environmental compartment.

*10.2. Information provided*

188 Your registration dossier does not include any information on soil simulation testing.

189 Therefore, the information requirement is not fulfilled.

190 In your comments to the draft decision, you propose a stepwise approach to assess the PBT/vPvB potential of the Substance. In your comments, you describe the following steps:

(1) "*repeat the biodegradation test extending the test duration up to 60 days*"

(2) "*commission the bioaccumulation test (OECD TG 305), the short-term toxicity study on aquatic plants (OECD TG 201) as well as the long-term toxicity studies on fish and daphnia (OECD TG 210 and 211 respectively)*"

(3) "*Then, depending on the results of all these aforementioned new studies, we might be able in a last step to refute the presumption that the Substance has a PBT/vPvB potential. In that case, no further investigation of the degradation of the substance shall be needed (triggered by Annex VIII, Section 9.2)*"

191 As this strategy relies on a an approach that has not yet been fully described and justified, as well as on data which is yet to be generated, no conclusion on the compliance of the proposed approach can be made.

192 In your comments to the draft decision, you also provide a generic description of the manufacture and use of the Substance. You indicate that "*during production and distribution*

*of the Substance, the exposure into the environment would be only accidentally"* and that "*during processing of the Substance* [redacted]". You consider this information sufficient to support that direct and indirect exposure of the soil and sediment compartments are unlikely.

193 ECHA understands that you refer to the adaptation possibility under Column 2 of Annex IX, Sections 9.2.1.3 and 9.2.1.4. to REACH. ECHA emphasizes that if it is not possible to derive a definitive conclusion n (i) ("The substance does not fulfil the PBT and vPvB criteria") or (ii) ("The substance fulfils the PBT or vPvB criteria") in the PBT/vPvB assessment, using the relevant available information, a registrant must, based on section 2.1 of Annex XIII to REACH, generate the necessary information for deriving one of these conclusions. Alternatively, the substance may be considered and managed "as if it is a PBT or vPvB" (Guidance on IRs and CSA, Section R.7.9.2.). Therefore, if no conclusion can be reached based on currently available information, additional information as set out in Section 3.2 of Annex XIII may only be omitted if the substance meets the conditions specified in Section 3.2(b) or (c) of Annex XI, in which case the Substance is considered to be managed "as if it is a PBT or vPvB".

194 Under Annex XI, Section 3.2(b), it must be demonstrated and documented for all relevant scenarios that throughout the life cycle strictly controlled conditions as set out in Article 18(4)(a) to (f) apply (see further Guidance on Intermediates and Practical Guide 16). Further, Under Annex XI, Section 3(2)(c), it must be demonstrated and documented that the substance is not released during its life cycle, that the likelihood of exposure to workers or the general public or the environment under normal or reasonably foreseeable conditions of use is negligible, and that the substance is handled according to the conditions set out in Article 18(4)(a) to (f) during all manufacturing and production stages including the waste management of the substance during these stages.

195 In your comments, you have provided a general description on the production, distribution and processing of the Substance.

196 However, you did not provide evidence to support your claim that the Substance is not released during its life-cycle (including during article service life as you report article manufacturing). Furthermore, you have provided no exposure assessment in your CSR and no documentation to support that the substance is used under strictly controlled conditions.

197 In the absence of this information, you have not demonstrated that the conditions set out in Annex XI, Section 3.2(b) or Section 3.2(c) are met.

198 the information provided in your comments does not fulfil the information requirement. You remain responsible for complying with this decision by the set deadline.

*10.3. Study design*

199 Simulation degradation studies must include two types of investigations (Guidance on IRs and CSA, Section R.7.9.4.1):

(4) a degradation pathway study where transformation/degradation products are quantified and, if relevant, are identified, and

(5) a kinetic study where the degradation rate constants (and degradation half-lives) of the parent substance and of relevant transformation/degradation products are experimentally determined.

200 In accordance with the specifications of OECD TG 307, you must perform the test using at least four soils representing a range of relevant soils (i.e. varying in their organic content, pH, clay content and microbial biomass).

201 In accordance with the specifications of OECD TG 307, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents (Guidance on IRs and CSA, Section R.7.9.4.1.). By default, total NER is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NER may be differentiated and quantified as irreversibly bound or as degraded to biogenic NER, such fractions could be regarded as removed when calculating the degradation half-life(s) (Guidance on IRs and CSA, Section R.11.4.1.1.3.). Further recommendations may be found in the background note on options to address non-extractable residues in regulatory persistence assessment available on the ECHA website.

202 Relevant transformation/degradation products are at least those detected at ≥ 10% of the applied dose at any sampling time or those that are continuously increasing during the study even if their concentrations do not exceed 10% of the applied dose, as this may indicate persistence (OECD TG 307; Guidance on IRs and CSA, Section R.11.4.1.).

## 11. Sediment simulation testing

203 Under Annex VIII, Section 9.2., Column 2, further information on degradation or further testing as described in Annex IX must be generated if the chemical safety assessment (CSA) in accordance with Annex I indicates the need to investigate further the degradation of the substance.

### *11.1. Triggering of the information requirement*

204 This information requirement is triggered in case if for example additional information on degradation as set out in Annex XIII, point 3.2.1, is required to assess PBT or vPvB properties of the substance in accordance with subsection 2.1 of that Annex.

205 As already explained in request 10 on soil simulation testing, the Substance is a potential PBT/vPvB substance.

206 Further, the Substance has low water solubility (< 0.05 mg/L), high partition coefficient (Log $K_{ow}$ > 4.5) and high adsorption coefficient (Log $K_{oc}$ > 4), indicating high potential to adsorb to soil.

207 Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation. Based on the adsorptive properties of the Substance, soil represents a relevant environmental compartment.

### *11.2. Information provided*

208 Your registration dossier does not include any information on sediment simulation testing.

209 Therefore, the information requirement is not fulfilled.

210 The examination of your comments on the draft decisison which also apply to this section are addressed in Section 10.

211 On this basis the information requirement is not fulfilled.

### *11.3. Study design*

212 Simulation degradation studies must include two types of investigations (Guidance on IRs and CSA, Section R.7.9.4.1.):

(1) a degradation pathway study where transformation/degradation products are quantified and, if relevant, are identified, and

(2) a kinetic study where the degradation rate constants (and degradation half-lives) of the parent substance and of relevant transformation/degradation products are experimentally determined.

213 In accordance with the specifications of OECD TG 308, you must perform the test using two sediments. One sediment should have a high organic carbon content (2.5-7.5%) and a fine texture, the other sediment should have a low organic carbon content (0.5-2.5%) and a coarse texture. If the Substance may also reach marine waters, at least one of the water-sediment systems should be of marine origin.

214 The required test temperature is 12°C, which corresponds to the average environmental temperature for the EU (Guidance on IRs and CSA, Table R.16-8) and is in line with the applicable test conditions of the OECD TG 308.

215 In accordance with the specifications of OECD TG 308, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents (Guidance on IRs and CSA, Section R.7.9.4.1.). By default, total NER is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NER may be differentiated and quantified as irreversibly bound or as degraded to biogenic NER, such fractions could be regarded as removed when calculating the degradation half-life(s) (Guidance on IRs and CSA, Section R.11.4.1.1.3.). Further recommendations may be found in the background note on options to address non-extractable residues in regulatory persistence assessment available on the ECHA website.

216 Relevant transformation/degradation products are at least those detected at ≥ 10% of the applied dose at any sampling time or those that are continuously increasing during the study even if their concentrations do not exceed 10% of the applied dose, as this may indicate persistence (OECD TG 308; Guidance on IRs and CSA, Section R.11.4.1.).

## 12. Identification of degradation products

217 Under Annex VIII, Section 9.2., Column 2, further information on degradation or further testing as described in Annex IX must be generated if the chemical safety assessment (CSA) in accordance with Annex I indicates the need to investigate further the degradation of the substance.

### *12.1. Triggering of the information requirement*

218 This information requirement is triggered in case if for example additional information on degradation as set out in Annex XIII, point 3.2.1, is required to assess PBT or vPvB properties of the substance in accordance with subsection 2.1 of that Annex.

219 As already explained in request 10 on soil simulation testing, the Substance is a potential PBT/vPvB substance.

220 Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

### *12.2. Information provided*

221 Your registration dossier does not include any information on degradation products identity.

222 Therefore, the information requirement is not fulfilled.

223 The examination of your comments on the draft decisison which also apply to this section are addressed in Section 10.

224 On this basis the information requirement is not fulfilled.

*12.3. Study design*

225 Simulation degradation studies must include two types of investigations (Guidance on IRs and CSA, Section R.7.9.4.1.):

(1) a degradation pathway study where transformation/degradation products are quantified and, if relevant, are identified, and
(2) a kinetic study where the degradation rate constants (and degradation half-lives) of the parent substance and of relevant transformation/degradation products are experimentally determined.

226 Identity, stability, behaviour, and molar quantity of the degradation/transformation products relative to the Substance must be evaluated and reported. In addition, identified transformation/degradation products must be considered in the CSA including PBT assessment.

227 You must obtain this information from the degradation studies requested in requests 10 and 11 on soil simulation data and sediment simulation data.

228 To determine the degradation rate of the Substance, the requested studies according to OECD TG 307 and 308 (requests 10 and 11) must be conducted at 12°C and at test material application rates reflecting realistic assumptions. However, to overcome potential analytical limitations with the identification and quantification of major transformation/degradation products, you may consider running a parallel test at higher temperature (but within the frame provided by the test guideline) and at higher application rate (e.g. 10 times).

## 13. Bioaccumulation in aquatic species

229 Under Annex VIII, Section 9.3., Column 2, further information on bioaccumulation or further testing as described in Annex IX must be generated if the chemical safety assessment (CSA) in accordance with Annex I indicates the need to investigate further the bioaccumulation properties of the substance.

230 Therefore, this information requirement is triggered in case if for example additional information on bioaccumulation as set out in Annex XIII, point 3.2.2, is required to assess PBT or vPvB properties of the substance in accordance with subsection 2.1 of that Annex.

231 As already explained in request 10, the Substance is a potential PBT/vPvB substance.

232 Therefore, the chemical safety assessment (CSA) indicates the need for further investigation on bioaccumulation in aquatic species.

*13.1. Information provided*

233 ECHA understands you have adapted this information requirement by using Column 2 of Annex IX, Section 9.3.2. To support the adaptation, you have provided following statements:

- In relation to the first indent of column 2, on low potential to cross biological membranes:

  (i) *"Substances with log Kow values above 10, which have been calculated for the substance, are considered to have a low bioaccumulation potential. Furthermore, for those substances with a log Kow value > 10 it is unlikely that they reach the pass level of being bioaccumulative according to OECD criteria for the PBT assessment (BCF > 2000 L/kg)";*

(ii) *"If the substance is taken up by ingestion, ingested molecules of the substance is anticipated to undergo ester hydrolysis prior to or following absorption, thus unlikely being available for systemic distribution and accumulation";*

- In relation to the second indent of column 2, on unlikely exposure to aquatic compartment:

(iii) *"Benzoic acid, 4-hydroxy-, C18-22-alkyl esters exhibits a log Koc value of > 5 and is poorly water soluble (< 0.05 mg/L). The Guidance on information requirements and chemical safety assessment, Chapter R7.b (ECHA, 2012) states that once insoluble chemicals enter a standard STP, they will be extensively removed in the primary settling tank and fat trap and thus, only limited amounts will get in contact with activated sludge organisms. Nevertheless, once this contact takes place, these substances are expected to be removed from the water column to a significant degree by adsorption to sewage sludge (Chapter R.7a, (ECHA, 2012)). Thus, discharged concentrations of this substance (if at all) into the aqueous compartment are likely to be low";*

234 In addition, you have adapted this information requirement by using Annex XI, Section 1.3. (Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs). To support the adaptation, you have provided the following information:

(iv) a prediction for the Substance from QSAR BCFBAF v3.01, Estimation Programs Interface Suite™ for Microsoft® Windows v 4.10 (2011) for C18 component of the substance.

(v) A prediction for the Susbtance from QSAR BCFBAF v3.01, Estimation Programs Interface Suite™ for Microsoft® Windows v 4.10 (2011) for C22 component of the substance.

*13.2. Assessment of the information provided*

*13.2.1. The provided adaptation does not meet the first criteria of Annex IX, Section 9.3.2., Column 2*

235 Under Section 9.3.2., Column 2, first indent, Annex IX to REACH, the study may be omitted if the Substance is unlikely to cross biological membranes. Guidance on IRs and CSA, Section R.7.8.5. explains that there is no scientific basis to define molecular characteristics that would render a substance unlikely to cross biological membranes. In this context, the indicators used for low likelihood of a high bioaccumulation potential (Guidance on IRs and CSA, Section R.11., Figure R.11-4.) must be considered, including:

- physico-chemical indicators of hindered uptake due to large molecular size (e.g. $D_{max}$ > 17.4 Å and MW > 1100 or MML > 4.3 nm) or high octanol-water partition coefficient (log $K_{ow}$ > 10) or low potential for mass storage (octanol solubility (mg/L) < 0.002 x MW), and
- supporting experimental evidence of hindered uptake (no chronic toxicity for mammals and birds, no chronic ecotoxicity, no uptake in mammalian toxicokinetic studies, very low uptake after chronic exposure).

236 Your registration dossier provides:

- physico-chemical indicators which you consider supportive of hindered uptake (log kow > 10) followed by an explanation on adsorption, metabolism and excretion.

237 Available information on the Substance do not constitute a valid justification that the Substance is unlikely to cross biological membranes because log kow alone, without experimental indicators of hindrance of uptake, is not enough to prove that a substance is

unlikely to cross biological membranes (see also Section 4.2.1.). In addition, log kow values have not been provided for all the components of the Substance (i.e., C14 constituent which can be present at up to 5%).

238 Therefore your adaptation is rejected.

*13.2.2. The provided adaptation does not meet the second criteria of Annex IX, Section 9.3.2., Column 2*

239 Under Section 9.3.2., Column 2, second indent of Annex IX to REACH, the study may be omitted if direct and indirect exposure of the aquatic compartment is unlikely. Therefore, it must be demonstrated that there is no release to the environment at any stage in the life cycle of the substance (Guidance on IRs and CSA, Section R.7.10.4.5.).

240 In your chemical safety assessment, you report the following uses associated with the following ERCs: 1, 2, 3, 4, 5, 6a, 6b, 6d and 7. Various of these uses have relevant releases to the environment.

241 Therefore, the uses provided in the dossier indicates releases to the environment and contradict your statement of unlikely direct and indirect exposure. Furthermore, no information is provided to demonstrate that no releases to the aquatic environment occurs under the forsees uses of the substance.

Therefore your adaptation is rejected.

*13.2.3. (Q)SAR adaptation rejected*

242 Under Annex XI, Section 1.3., the following conditions must be fulfilled whenever a (Q)SAR approach is used:

(1) the substance must fall within the applicability domain of the model,

(2) results need to be adequate for the purpose of risk assessment or classification and labelling, and

*13.2.3.1. The substance is outside the applicability domain of the model*

243 Under ECHA Guidance R.6.1.5.3., a substance must fall within the applicability domain specified by the model developer.

244 The applicability domain of the model you used is defined as valid for substances with a log Kow in between 0.31-8.70 as indicated in the Dossier.

245 The components of the Substance used as input for the prediction has the following properties related to the estimation of applicability domain: log kow: 10.35 – 11.32.

246 The Substance components used for the prediction are outside the applicability domain of the model as indicated in your Dossier.

247 Therefore, you have not demonstrated that the Substance falls within the applicability domain of the model.

*13.2.3.2. The prediction does not cover all constituents of the Substance*

248 Under ECHA Guidance R.6.1.7.3. a prediction is adequate for the purpose of classification and labelling and/or risk assessment if the following cumulative conditions are met:

- the composition of the substance is clearly defined, and
- different constituents of the same substance are predicted individually.

249 Your registration dossier provides the following information:

- In Section 1.1. of your technical dossier, you define the Substance as a UVCB.
- In Section 1.2., you indicate the following constituents in the composition of your Substance: docosyl 4-hydroxybenzoate, 4-Hydroxybenzoic acid eicosyl ester, octadecyl 4-hydroxybenzoate, docosan-1-ol, Benzoic acid,4-hydroxy-, tetradecyl ester.
- For the assessment, ECHA understand you provided predictions for the following structures: C18 – C22 components of the substance.

250 As you have used only 2 structures for the prediction while the Substance is composed of 5 number of constituents you have not covered all constituents of the Substance. In particular, you have not covered the C14 component which will potentially have a lower log Kow.

251 Therefore, you have not demonstrated that the prediction is adequate for the purpose of classification and labelling and/or risk assessment.

252 Based on the above, your QSAR adaptation under Annex XI, Section 1.3. is rejected.

253 Therefore, the information requirement is not fulfilled.

254 In the comments to the draft decision, you agree to perform the requested study.

*13.3. Study design*

255 Bioaccumulation in fish: aqueous and dietary exposure (Method EU C.13 / OECD TG 305) is the preferred test to investigate bioaccumulation (Guidance on IRs and CSA, Section R.7.10.3.1.). Exposure via the aqueous route (OECD TG 305-I) must be conducted unless it can be demonstrated that:

- a stable and fully dissolved concentration of the test material in water cannot be maintained within ± 20% of the mean measured value, and/or
- the highest achievable concentration is less than an order of magnitude above the limit of quantification (LoQ) of a sensitive analytical method.

256 This test set-up is preferred as it allows for a direct comparison with the B and vB criteria of Annex XIII of REACH.

257 You may only conduct the study using the dietary exposure route (OECD 305-III) if you justify and document that testing through aquatic exposure is not technically possible as indicated above. You must then estimate the corresponding BCF value from the dietary test data according to Annex 8 of the OECD 305 TG and OECD Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation (ENV/JM/MONO(2017)16).

**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.

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

ECHA took into account your comments and did not amend the requests.

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 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] |

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/group of constituents on the test results for the endpoint to be assessed. For example, if a constituent/group of constituents of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/group of constituents.

(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 the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far

as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods.

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).

## 2. General recommendations for conducting and reporting new tests

### 2.1 Strategy for the PBT/vPvB assessment

Under Annex XIII, the information must be based on data obtained under conditions relevant for the PBT/vPvB assessment. You must assess the PBT properties of each relevant constituent of the Substance present in concentrations at or above 0.1% (w/w) and of all relevant transformation/degradation products. Alternatively, you would have to justify why you consider these not relevant for the PBT/vPvB assessment.

You are advised to consult Guidance on IRs & CSA, Sections R.7.9, R.7.10 and R.11 on PBT assessment to determine the sequence of the tests needed to reach the conclusion on PBT/vPvB. The guidance provides advice on 1) integrated testing strategies (ITS) for the P, B and T assessments and 2) the interpretation of results in concluding whether the Substance fulfils the PBT/vPvB criteria of Annex XIII.

In particular, you are advised to first conclude whether the Substance fulfils the Annex XIII criteria for P and vP, and then continue with the assessment for bioaccumulation. When determining the sequence of simulation degradation testing you are advised to consider the intrinsic properties of the Substance, its identified uses and release patterns as these could significantly influence the environmental fate of the Substance. You must revise your PBT assessment when the new information is available.

### 2.2 Environmental testing for substances containing multiple constituents

Your Substance contains multiple constituents and, as indicated in Guidance on IRs & CSA, Section R.11.4.2.2, you are advised to consider the following approaches for persistency, bioaccumulation and aquatic toxicity testing:

- the "known constituents approach" (by assessing specific constituents), or
- the "fraction/block approach", (performed on the basis of fractions/blocks of constituents), or
- the "whole substance approach", or
- various combinations of the approaches described above

Selection of the appropriate approach must take into account the possibility to characterise the Substance (i.e. knowledge of its constituents and/or fractions and any differences in their properties) and the possibility to isolate or synthesize its relevant constituents and/or fractions.

References to Guidance on REACH and other supporting documents can be found under Appendix 1.