ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 28 May 2019

Addressee: [redacted]

Decision number: CCH-D-2114471566-40-01/F
Substance name: Reaction products of 3,4,5,6-tetrabromobenzene-1,2-dicarboxylate with 2,2'-oxy-diethanol and 2-epoxypropane
EC number: 616-436-5
CAS number: 77098-07-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 26 June 2018
Registered tonnage band: 100-1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **Vapour pressure (Annex VII, Section 7.5.; test method: EU A.4./OECD TG 104) of the registered substance;**

2. **Surface tension (Annex VII, Section 7.6.; test method: EU A.5./OECD TG 115) of the registered substance;**

3. **Water solubility (Annex VII, Section 7.7.; test method: EU A.6./OECD TG 105) of the registered substance;**

4. **Partition coefficient n-octanol/water (Annex VII, Section 7.8.; using an appropriate test method) of the registered substance;**

5. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) with the registered substance;**

6. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487) with the registered substance;**

7. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance provided that both studies requested under 5. and 6. have negative results;**

8. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421/422) in rats, oral route with the registered substance;**

9. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats with the registered substance;**

10. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

11. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: Alga, growth inhibition test, EU C.3./OECD TG 201) with the registered substance;**

12. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) with the registered substance;**

13. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance;**

14. **Soil simulation testing (Annex IX, Section 9.2.1.3.; test method: Aerobic and anaerobic transformation in soil, EU C.23./OECD TG 307) at a temperature of 12 °C with the registered substance. The biodegradation of each relevant constituent present in concentration at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable shall be assessed. This can be done simultaneously during the same study;**

15. **Identification of degradation products (Annex IX, 9.2.3.) using an appropriate test method with the registered substance.**

You have to submit the requested information in an updated registration dossier by ***06 June 2022***. You shall also update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Ofelia Bercaru, Head of Unit, Hazard Assessment.

[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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation.

1. Vapour pressure (Annex VII, Section 7.5.)

Vapour pressure is a standard information requirement in Annex VII to the REACH Regulation.

You sought to adapt this information requirement by means of providing results from a quantitative structure-activity relationship model ((Q)SAR). You have predicted the vapour pressure for a single constituent of a UVCB substance.

In the technical dossier under this endpoint you have provided the following information:

- Key study (QSAR, reliability 2): MPBPBP, 2.37 $\times 10^{-14}$mmHg.

Regarding the requirements set by Annex XI, Section 1.3 of the REACH Regulation, ECHA generally notes the following:

a) General considerations regarding adaptations according to Annex XI, Section 1.3

ECHA has assessed your adaptation arguments in line with the conditions specified in Annex XI, Section 1.3 of the REACH Regulation, which stipulates that results obtained from valid (Q)SAR models may be used instead of testing when the following conditions are met[2]:

- results are derived from a (Q)SAR model whose scientific validity has been established,
- the substance falls within the applicability domain of the (Q)SAR model,
- results are adequate for the purpose of classification and labelling and/or risk assessment, and
- adequate and reliable documentation of the applied method is provided.

ECHA notes that in your IUCLID dossier section 1.2 you define your registered substance as a Substance of Unknown or Variable Composition, Complex reaction products and Biological materials (UVCB substance) that is a complex mixture of products with different combinations resulting from a reaction of three reagents; TetraBromoPhthalic Anhydride (TBPA), Di-ethylene Glycol (DEG) and Propylene Oxide (PO). In this context ECHA notes that your QSAR predictions reported in your dossier are based on the substance 2-(2-hydroxyethoxy)ethyl 2-hydroxypropyl 3,4,5,6-tetrabromophthalate (CAS 20566-35-2, EC 243-885-0). ECHA understands from the composition reported in Section 1.2 of the technical dossier that the substance used in your QSAR predictions is a constituent of the registered substance present in concentrations ranging from [redacted] You provided the following justification for the selection of the structure used in the QSAR analysis:

"The nature of the reagents involves the formation of a complex mixture of products with different combinations of these 3 reagents. Current, QSAR models cannot test UVCB

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

substances. Therefore, the QSAR has been performed on the major product which is also the structure with the lowest molecular weight (1 unit of region of TBPA, 1 DEG and 1 PO). In terms of predicted toxicology, it can reasonably be assumed that the structure having the lowest molecular weight should be the most bioavailable. Based on this toxicity principle, QSAR analyses were performed using the SMILE structure of the smallest molecular weight structure which is also the major product of the mixture (identified at 26% area by HPLC)."

b) General notes on the structure used for the QSAR predictions

ECHA agrees with your statement above that "*Current, QSAR models cannot test UVCB substances*". Yet, in the registration dossier for your UVCB substance, you have provided information solely based on QSAR predictions for several REACH standard information requirement endpoints. For the prediction of the physical-chemical and environmental fate/ecotoxicological properties of your UVCB substance, you have used the above mentioned smallest molecural weight structure. However, you have not adequately justified why the structure used for the prediction would represent the registered UVCB substance as a whole. In fact, your registered UVCB substance contains several identified and unidentified constituents and therefore, its physical-chemical and environmental fate/ecotoxicological properties cannot be properly estimated with QSAR predictions with a single structure.

Furthermore, you have not justified why the constituent with the lowest molecular weight would be the most bioavailable one. Low molecular weight as such does not necessarily mean the highest bioavailability in case there are structures with higher molecular weight that are still below the threshold where molecular size starts to decrease bioaccumulation. Even if the prediction from the single structure would be used as a surrogate for predicting the properties of the whole UVCB substance, in some endpoints the structure with the lowest molecular weight might provide the best case rather than the representative worst case scenario (e.g. biodegradation of the larger molecular size structures may be slower due to assumed lower bioavailability).

c) General conclusion

For the reasons described above, ECHA considers that the provided QSAR predictions do not inform on the properties of the registered substance. ECHA therefore concludes that the QSAR predictions in the dossier are not adequate for the purpose of classification and labelling and/or risk assessment of the registered UVCB substance. The endpoints where QSAR predictions were provided are addressed separately in the decision.

Regarding the requirements set by Annex XI, Section 1.3 of the REACH Regulation, ECHA notes the following specifically for the vapour pressure endpoint:

1. You have not provided any documentation that the scientific validity of the (Q)SAR model is established;
2. You have not explained why the registered substance would fall within the applicability domain of the applied model;
3. You have not documented the reliability of the applied model (a QSAR Model Reporting Format, QMRF) or of the individual model prediction (a QSAR Prediction Reporting Format, QPRF);
4. You have not explained why the reported results can be considered to be adequate for the purpose of classification and labelling and/or risk assessment. Your substance is identified as a UVCB, and you have not justified why the structure(s) used for the

prediction would represent the registered UVCB substance as a whole. In fact, the registered substance contains several identified and unidentified constituents and therefore its physical-chemical properties cannot be properly estimated with QSAR predictions with a single structure.

Therefore your proposed adaptation based on Annex XI, Section 1.3 of the REACH Regulation is rejected. ECHA concludes that there is an information gap and that it is necessary to provide information for the endpoints in order to bring the registration dossier into compliance with relevant information requirements.

In your comments to the draft decision, you agreed that adequate documentation of the provided prediction was missing. You also explained further why a single structure was used to represent the whole substance for this specific endpoint, and why the selected structure is the most bioavailable one. ECHA-S finds these explanations plausible, however noting that the substance still contains unidentified constituents. In addition, further proof for the highest vapour pressure and highest bioavailability would be needed for ECHA to consider the information requirement fulfilled. In any case, the documentation for the prediction, together with justifications for highest vapour pressure and highest bioavailability are currently not provided in the dossier.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Vapour pressure (test method: EU A.4./OECD TG 104).

2. Surface tension (Annex VII, Section 7.6.)

Surface tension is a standard information requirement in Annex VII to the REACH Regulation.

You sought to adapt this information requirement with the following justification: *"Surface tension measurement is only required for substances where surface activity is expected or a desired property (REACH Guidance, Chapter R.7A). The substance is neither."*

ECHA notes, that the adaptation according to Annex VII, Section 7.6, Column 2, states, that the study need only be conducted if 1) based on structure, surface activity is expected or can be predicted, or 2) surface activity is a desired property of the material. In addition, if the water solubility is below 1 mg/l at 20 °C the test does not need to be conducted.

The general structural formula reported under Section 1.2 of the IUCLID dossier shows hydrophilic ethylene or propylene glycol chains attached to a hydrophobic brominated phenyl ring. Therefore, based on structure, it can be expected that the substance has surface active properties. In addition, the water solubility value reported by you (0.05697 mg/l at 25 °C) was not found to be acceptable by ECHA (see the statement of reasons for requesting information on water solubility under point 3 below), and therefore this endpoint cannot be adapted based on that value.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Surface tension (test method EU A.5) or surface tension of aqueous solutions (test method: OECD TG 115).

3. Water solubility (Annex VII, Section 7.7.)

Water solubility is a standard information requirement in Annex VII to the REACH Regulation.

You sought to adapt this information requirement by means of providing results from a quantitative structure-activity relationship model ((Q)SAR). You have predicted the water solubility value for three structures present in the registered substance. You reported the predicted value of the structure having the lowest molecular weight and indicating it to be the most bioavailable due to its lowest molecular weight.

In the technical dossier under this endpoint you have provided the following information:

- Key study (QSAR, reliability 2): WSKOW v.4.1, 0.05697 mg/L (pH not specified).

Regarding the requirements set by Annex XI, Section 1.3 of the REACH Regulation, ECHA notes the following:

1. You have not explained why the registered substance would fall within the applicability domain of the applied model;
2. You have not documented the reliability of the model prediction (a QSAR Prediction Reporting Format, QPRF);
3. You have not explained why the reported results can be considered to be adequate for the purpose of classification and labelling and/or risk assessment. Your substance is identified as a UVCB, and you have not justified why the structure(s) used for the prediction would represent the registered UVCB substance as a whole. In fact, the registered substance contains several identified and unidentified constituents and therefore its physical-chemical properties cannot be properly estimated with QSAR predictions with a single structure. Furthermore, bioavailability that you used for the selection of structure for the prediction is not a factor when assessing the water solubility of a substance.

Therefore your proposed adaptation based on Annex XI, Section 1.3 of the REACH Regulation is rejected. ECHA concludes that there is an information gap and that it is necessary to provide information for the endpoints in order to bring the registration dossier into compliance with relevant information requirements.

In your comments to the draft decision, you indicated that you had provided a predicted water solubility value for three structures. ECHA has modified the draft decision accordingly.

In addition, you indicated that you had explained why the predicted structures would fall within the applicability domain of the used model and that you also have provided a QPRF in your dossier.

ECHA notes that you have provided a QMRF explaining e.g. the scientific validity and the applicability domain of the model used, but you have not provided any explanation how the

predicted structures would fall within the applicability domain described in the provided QMRF document. An adaptation according to Annex XI, Section 1.3. requires both documents, as explained in Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008).

Finally, you explained that for the UVCB substance in question, structures containing dimers, trimers and oligomers are likely to have much lower water solubility values compared to the strutures used in the predictions. ECHA agrees to this and concludes that although your explanations seem plausible to fulfil the information requirement, but the necessary documentation is missing in your dossier.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Water solubility (test method: EU A.6./OECD TG 105)

4. Partition coefficient n-octanol/water (Annex VII, Section 7.8.)

Partition coefficient n-octanol/water is a standard information requirement in Annex VII to the REACH Regulation.

You sought to adapt this information requirement by means of providing results from a quantitative structure-activity relationship model ((Q)SAR). You have predicted the partition coefficient value for seven structures with increasing number of TBPA groups and corresponding increasing partition coefficient values.

In the technical dossier under this endpoint you have provided the following information:

- Key study (QSAR, reliability 2): KOWWIN v.1.68, LogKow 3.8256 based on a fragment constant methodology.

Regarding the requirements set by Annex XI, Section 1.3 of the REACH Regulation, ECHA notes the following:

1. You have not documented the reliability of the model prediction (a QSAR Prediction Reporting Format, QPRF);
2. You have not explained why the reported results can be considered to be adequate for the purpose of classification and labelling and/or risk assessment. Your substance is identified as a UVCB, and you have not justified why the structure(s) used for the prediction would represent the registered UVCB substance as a whole. In fact, the registered substance contains several identified and unidentified constituents and therefore, its physical-chemical properties cannot be properly estimated with QSAR predictions with a single structure. Furthermore, you have not justified why the constituent with the lowest molecular weight would be the most bioavailable one as low molecular weight does not necessarily mean the highest bioavailability.

Therefore your proposed adaptation based on Annex XI, Section 1.3 of the REACH Regulation is rejected. ECHA concludes that there is an information gap and that it is necessary to provide information for the endpoints in order to bring the registration dossier into compliance with relevant information requirements.

In your comments to the draft decision, you indicated that you had provided a predicted partition coefficient value for seven structures. ECHA has modified the draft decision accordingly.

In addition, you indicated that you had explained why the predicted structures would fall within the applicability domain of the used model and that you also have provided a QPRF in your dossier.

ECHA notes that indeed you did include an explanation of the applicability of the model used for the predicted structures. ECHA has modified the draft decision accordingly. However, you have not provided a QPRF, contrary to what you indicate in your comments. ECHA notes that you have provided a QMRF explaining e.g. the scientific validity and the applicability domain of the model used, but you have not provided sufficient documentation for the prediction itself. An adaptation according to Annex XI, Section 1.3. requires both documents (QMRF and QPRF), as explained in Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008).

In your comments you indicated that ECHA has not evaluated the latest submission for your registration.

ECHA has evaluated the latest submission, [redacted], dated 26 June 2018, as indicated on the first page of this decision.

Finally, you indicated that ECHA should give further advice on the appropriate method to be used for an experimental test for partition coefficient of the registered substance.

ECHA notes that the selection of the test method is your responsibility. However, ECHA acknowledges the possible difficulties in experimental testing for the registered substance, and concludes that an adaptation according to Annex XI, Section 1.3. seems a plausible option, provided that all the requirements of that section are fulfilled.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Partition coefficient n-octanol/water. Guidance for determining appropriate test methods for the partition coefficient n octanol/water is available in the ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.1.8 (version 6.0, July 2017).

5. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

An "*In vitro* gene mutation study in bacteria" is a standard information requirement in Annex VII, Section 8.4.1. to the REACH Regulation.

In the technical dossier you have provided two study records for a bacterial reverse mutation tests ([redacted] 1985 and [redacted] 1977). These studies have been conducted with the substance 2-(2-hydroxyethoxy)ethyl 2-hydroxypropyl 3,4,5,6-tetrabromophthalate (EC 243-885-0; CAS 20566-35-2). ECHA understands from the composition reported in section 1.2 of the technical dossier that the test material used to perform the two bacterial reverse mutation tests is a constituent of the registered substance present in concentrations ranging from [redacted]

However, the registered substance is defined as a UVCB substance. By definition, the composition of such substances is complex, the number of constituents is relatively large, the composition is, to a significant part, unknown, and/or the variability of composition is relatively large. The toxicological properties of the registered substance are determined by the combined exposure to each of these constituents and, as a general rule, are identified by conducting toxicological studies using the registered substance as test material.

Whilst these studies inform on the gene mutation properties in bacteria of this constituent, you have not provided information on such properties for the other constituents of the registered substance. You did not elaborate on the impact of co-exposure to all of these constituents on the properties of the registered substance for the endpoint under consideration and you have not explained why these properties of the registered substance can be predicted solely from information obtained on this specific constituent. In the absence of this information and justification, ECHA considers that the information provided does not inform on the properties of the registered substance.

In addition, ECHA highlights the following deficiencies in the design of these two studies:

- According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: S. typhimurium TA1535; TA1537 or TA97a or TA97; TA98; TA100; S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). This includes four strains of S. typhimurium (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four S. typhimurium strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by E.coli WP2 strains or S. typhimurium TA102 which have an AT base pair at the primary reversion site.

  You have provided a study from the year 1985 [redacted] according to the method described by Ames et al. (1975) (Mutation Research 31:347-364) with an assigned reliability score of 1 and a study from the year 1977 [redacted] with no reference to any test guideline and assigned a reliability score of 2. The study by [redacted] used four different strains of S. typhimurium TA 1535, TA 1537, TA 98 and TA 100. The study by [redacted] used five different strains of S. typhimurium TA 1535, TA 1537, TA 1538, TA 98 and TA 100. None of these studies included tests with strains S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). However, from the time when the test was conducted significant changes have been made to the OECD TG 471 so that additionally testing with S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is now required. Therefore, the provided study does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

- The robust study summary included in the technical dossier for the study conducted by [redacted] (1977) provides very little details on the study design and does not report on the test doses used and does not inform on the inclusion and results obtained from positive controls. In the absence of this information, ECHA considers that the negative results obtained from this study are unreliable and cannot be used to fulfil information requirements of the REACH Regulation.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471).

6. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

An "*In vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement in Annex VIII, Section 8.4.2. to the REACH Regulation.

You have not provided any study record of an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study in the dossier that would meet the information requirement of Annex VIII, Section 8.4.2.

Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and the *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

In your comments to the draft decision, you indicated that the viscosity of the registered substance and the very low solubility of some constituents of the registered substance make it particularly difficult to conduct in vitro genotoxicity studies. You also stressed anticipated challenges in the characterisation of the test material requiring additional time.

ECHA acknowledges the challenges in the characterisation of the test material arising from the UVCB nature of the registered substance. However it is essential that information on the test material used to conduct the test confirms that is representative of the registered substance as described in the registration dossier, taking into account the inherent variability and unknown dimension of a UVCB substance.

With regard to the viscosity of the registered substance and the poor solubility of constituents of the substance, ECHA draws your attention to the recommendations on solvent selection and identification of the test concentration for poorly soluble substances included in the OECD test guidelines 473 and 487.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian chromosome aberration test (test method: OECD

TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

7. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

An "*In vitro* gene mutation study in mammalian cells" is an information requirement in Annex VIII, Section 8.4.3. to the REACH Regulation, if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained.

Adequate information *on in vitro* gene mutation in mammalian cells will however need to be present in the technical dossier for the registered substance to meet this information requirement provided that both studies requested under 5 and 6 have negative results. ECHA set the deadline for provision of the information to allow for sequential testing.

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the*Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

In your comments to the draft decision, you indicated that the viscosity of the registered substance and the very low solubility of some constituents of the registered substance make it particularly difficult to conduct in vitro genotoxicity studies. You also stressed anticipated challenges in the characterisation of the test material requiring additional time.

ECHA acknowledges the challenges in the characterisation of the test material arising from the UVCB nature of the registered substance. However it is essential that information on the test material used to conduct the test confirms that is representative of the registered substance as described in the registration dossier, taking into account the inherent variability and unknown dimension of a UVCB substance.

With regard to the viscosity of the registered substance and the poor solubility of constituents of the substance, ECHA draws your attention to the recommendations on solvent selection and identification of the test concentration for poorly soluble substances included in the OECD test guidelines 476 and 490.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that both studies requested under 5. and 6. have negative results.

8. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement in Annex VIII, Section 8.7.1. to the REACH Regulation, if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier.

According to the specific rules for adaptation of Annex VIII, Section 8.7.1., column 2, the "screening for reproductive/developmental toxicity" study does not need to be conducted if a pre-natal developmental toxicity study is available. You have sought to adapt the information requirement of Annex VIII, 8.7.1 according to this specific rule. Your justification states: "*the study does not need to be conducted because a pre-natal developmental toxicity study is available*".

ECHA notes that a pre-natal developmental study conducted with the registered substance is not available in the dossier. In section 7.8.2 of the IUCLID dossier, you have submitted results obtained in a pre-natal developmental toxicity study (Tice, 1999) conducted in rats using the analogue substance tetrabromophthalic anhydride (EC 211-185-4; CAS 632-79-1). However, for the reasons presented in section 10 of this decision, it does not meet the requirements for an adaptation under Annex XI, Section 1.5 of the REACH Regulation.

Consequently, the information from that study cannot be used to fulfil the specific rule for adaptation of Annex VIII, Section 8.7.1., column 2. Therefore, your adaptation of the information requirement is rejected, there is an information gap and it is necessary to provide information for this endpoint.

According to the test methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision you indicated anticipated difficulties in identifying a suitable vehicle to conduct the study and flagged particular analytical challenges in the determination of the homogeneity of the dosing solutions. You reported that 6 months would be required to overcome these difficulties and therefore requested an extension of the deadline to provide the requested information of 6 months. This request for an extension of the deadling to provide the requested information is addressed in the section on "*Deadline to submit the requested information in this decision"* in Appendix 1 of this decision.

You expressed your intentions to conduct a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) as a dose range finding study for the requested sub-chronic toxicity study. You inquired in your comments on the possibility to have an interim exchange with ECHA once the results from this OECD TG 422 are available in order to "*determine the feasibility of further vertebrate animal studies*". You also highlighted that the data from the OECD TG 422 study "*could be used to support and improve the read across which could avoid to sacrifice further vertebrate animals*" and indicated that the outcome of this OECD TG 422 study would be taken into account to "*allow an informed decision on the further testing and/or evaluation strategy*".

ECHA cannot provide advice or comments on any alternative strategies or approaches that the registrant considers to use to fulfil the request in the decision. Therefore, ECHA declined

your request for a discussion on the use of the data generated in an OECD TG 422 with the objective to comply with the compliance check decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision:
- Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.5 and 7.6 (version 6.0, July 2017).

You should also carefully consider the order of testing of the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure that unnecessary animal testing is avoided, paying particular attention to the endpoint specific guidance (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf) Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017.

9. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX, Section 8.6.2. to the REACH Regulation.

You have sought to adapt this information requirement according to Annex XI, Section 1.5.

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. 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 (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[3]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical

[3] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[4]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the adequacy and reliability of the studies which are to be read-across.

a) Information provided

You have provided information from studies conducted with the following analogue substances:

- tetrabromophthalic anhydride (CAS 632-79-1):
  - [redacted] 1975e: 3-week repeated-dose toxicity study conducted in rats via the inhalation route;
  - [redacted] 1975d: 4-week repeated-dose toxicity study in rabbits via the dermal route;
  - Tice, 1999: pre-natal developmental toxicity study conducted in rats via the oral route;
- phthalic anhydride (CAS 85-44-9):
  - [redacted]: 7-week repeated-dose toxicity study conducted in rats and in mice via the oral route (diet)
  - [redacted]: 103-week repeated-dose toxicity study conducted in rats and in mice via the oral route (diet)
- diallyl phthalate (CAS 131-17-9):
  - [redacted], 1985: 2-week repeated-dose toxicity study conducted in rats and mice via the oral route (gavage);
  - [redacted], 1985: 13-week repeated-dose toxicity study

[4] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

conducted in rats and mice via the oral route (gavage);
  - [redacted], 1985: 103-week repeated-dose toxicity study conducted in rats and mice via the oral route (gavage);
- di(2-ethylhexyl)-3,4,5,6-tetrabromophthalate (DEHTBP) (CAS 26040-51-7) :
  - unspecified author and year : 4-week repeated-dose toxicity study conducted in rats via the oral route (diet).

You have provided information to support your adaptation in an attachment to the technical dossier (in section 7.12 of the IUCLID file) [redacted]. In that document you have summarised the information obtained from each of the above-mentioned studies conducted with the structural analogues. You indicated that information from tetrabromophthalic anhydride (CAS 632-79-1) is particularly relevant for this adaptation "*because the UVCB product consists of a mixture of esterified tetrabromophthalic anhydrides, which in the diol ester form is susceptible to hydrolytic cleavage to tetrabromophthalic acid*". You stated that phthalic anhydride (CAS 85-44-9) "*is structurally related to the hydrolysed form of the reference substance, excluding the bromine atoms, and provides a useful surrogate of toxicological effects given that phthalic acid is readily absorbed following ingestion*". When addressing the relevance of information obtained from diallyl phthalate (CAS 131-17-9) you reported on a conclusion drawn by the [redacted] according to which the findings from a chronic study on diallyl phthalate "*support that the ester-linked moiety to phthalic acid are released and require consideration when evaluating the toxicity of a phthalate ester*". Eventually, you considered that "*DEHTBP (CAS 26040-51-7) provides a worse case scenario of the potential for an esterified form of 3,4,5,6-tetrabromophthalic acid to induce reproductive toxicity. These findings are important for a structure activity comparison to the reference substance and the UVCB product because they demonstrate that bromination of a chemical shown to cause reproductive toxicity in rodents (i.e. di(2-ethylhexylphthalate) prevents that outcome*".

ECHA understands from the documentation of your adaptation that the quotes reported above constitute the sole justification for your read-across hypothesis whereby you consider that the constituents of the registered substance and the source substance tetrabromophthalic anhydride may be hydrolysed to form the common biotransformation product tetrabromophthalic acid.

b) ECHA's evaluation of the information provided

i) Missing grouping and read-across hypothesis for the analogue substances phthalic anhydride, diallyl phthalate and di(2-ethylhexyl)-3,4,5,6-tetrabromophthalate (DEHTBP)

Your proposed adaptation argument is that the structural similarity between the source substances phthalic anhydride, diallyl phthalate and di(2-ethylhexyl)-3,4,5,6-tetrabromophthalate (DEHTBP) and the registered substance is a sufficient basis for predicting the properties of the registered substance.

The registered substance is defined as a Substance of Unknown or Variable Composition, Complex reaction products and Biological materials (UVCB substance). If an adaptation based on Annex XI, Section 1.5 is proposed for UVCB substances with a complex composition, specific aspects need to be considered, as described in the document Read-

Across Assessment Framework – Considerations on multi-constituent substances and UVCBs[5]. These considerations apply to the grouping justification and address the presence of several or many constituents in the target substance with in their concentration ranges, but also to the prediction of properties on aspects such as impact of combined exposure to several constituents and variations in the concentrations of constituents.

The registered substance is described as a pool of monomers with a tetrabromo phthalic acid backbone [redacted] This pool consists of mixed esters [redacted]. The di-alcohol units may be present as repetitive units. IUCLID Section 1.2 contains this note for the monomers: "*Major components of this fraction have been identified by HPLC/MS with regard to the number of diethyleneglycol (DEG) units and propylene glycol (PG) units as depicted in table 1. Because of the complexity of the mixture and the different isomers possible for each molecular weight, the exact structure of each component was not determined.*" Additional tetrabromo phthalic acid moities may be attached to free alcohol functions forming dimers [redacted] and and trimers [redacted], also with differing esters and repetitive units. The resulting constituent pattern is complex and variable. ECHA notes that you did not provide details on the composition of the source substances informing on their constituents and purity profiles.

In view of the composition complexity of the registered substance ECHA points out that you did not explain and justify the nature and the extent of the structural similarity between the source and registered substances.

Structural similarity is a prerequisite for applying the grouping and read-across approach. ECHA cannot confirm that you have established structural similarity between the source and registered substances.

Moreover, structural similarity does not necessarily lead to predictable or similar human health properties. You have not established why a prediction for a human health property is reliable. Thus structural similarity per se is not sufficient to enable the prediction of human health properties of a substance.

On that basis, the requirement of Annex XI, Section 1.5., that human health effects may be predicted from data for reference substance(s) within the group, has not been met.

As described above, further elements are needed to establish a reliable prediction for a toxicological property, based on recognition of the structural similarities and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties.

ii) Missing supporting information for the grouping and read-across from tetrabromophthalic anhydride

Moreover, Annex XI, Section 1.5 of the REACH Regulation states that "*adequate and reliable documentation of the applied method shall be provided*". The ECHA Guidance on information

[5] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.6, Section R.6.2.2.1.f indicates that "*it is important to provide supporting information to strengthen the rationale for the read-across*" as part of the documentation of a read-across approach. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the registered substance can be predicted from the data on the source substance tetrabromophthalic anhydride (CAS 632-79-1). ECHA notes that supporting information in relation to important elements of your read-across hypothesis is missing, as explained below.

Information on the formation of the common hydrolysis product

Information characterising the rate and extent of the hydrolysis of the constituents of the target substance and of the source substance tetrabromophthalic anhydride is necessary to confirm the formation of the proposed common hydrolysis product tetrabromophthalic acid and to assess the impact of the exposure to the parent compounds. You have not provided any experimental data or other adequate and reliable information, neither about the hydrolysis of the registered substance nor about the hydrolysis of the source substance tetrabromophthalic anhydride. In the absence of this information, ECHA considers that you have not demonstrated that the proposed common hydrolysis product is formed as assumed in your read-across hypothesis.

Information on exposure to non-common hydrolysis products

ECHA observes that the constituent of the registered substance which is a precursor of the proposed common hydrolysis product is a diester. The formation of the common hydrolysis product requires hydrolysis of both of these esters. Information characterising the hydrolysis of each of the ester groups is necessary to assess the potential exposure to intermediate hydrolysis products, i.e. mono esters, and its impact on the toxicological properties of the target substance. However no such information is provided in your dossier.

As explained under i), the registered substance is defined as UVCB substance. The potential hydrolysis of the constituents of the registered substance will lead to the formation of a variety of non-common hydrolysis products, such as monoesters and alcohols derived from the monomers, but also complex hydrolysis products derived from the dimers and trimers. Further metabolic conversions of potential intermediate hydrolysis products may be expected. The contribution of exposure to these hydrolysis products to the toxicological properties of the registered substance cannot be predicted from information on the proposed common hydrolysis product, tetrabromophthalic acid, and therefore require specific considerations. In your read-across justification you stress this yourself by referring to a conclusion from the [redacted] according to which the findings from a chronic study on diallyl phthalate "*support that the ester-linked moiety to phthalic acid are released and require consideration when evaluating the toxicity of a phthalate ester*". No further information on the intrinsic toxicological properties of these non-common hydrolysis products and on their impact on the properties of the registered substance is however provided.

Conclusion

For the reasons presented above, ECHA considers that you have not established that exposure to the constituents of the registered substance and to the non-common hydrolysis

products formed from these constituents do not impact the toxicological properties of the registered substance. Consequently ECHA concludes that you failed to establish that the properties of the registered substance can be predicted from information derived from the source substance tetrabromophthalic anhydride.

iii) Adequacy and reliability of source studies

Finally, Annex XI, Section 1.5 of the REACH Regulation requires that adequate and reliable documentation of read-across adaptations is provided. Pursuant to Article 10(a)(vii) of the REACH Regulation, the information set out in Annex VII to XI must be provided in the form of a robust study summary. Under Article 3(28) of the REACH Regulation, a robust study summary "*means 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 minimising the need to consult the full study report*".

In the read-across justification document and in the technical dossier, you have described the studies conducted with the analogue substances.

However, ECHA observes that, contrary to Article 3(28) of the REACH Regulation, these study descriptions do not allow for an independent assessment of the sources of information. In this regard, ECHA notes that the study summaries do not include critical information required by the OECD test guideline 408, as also decribed in ECHA's Practical Guide 3 "*How to report robust study summaries*". This critical information concerns in particular information on the test animals (number of animals per sex per dose; age and weight at the study initiation), information on the study design (method of administration, scope of the clinical observations, clinical biochemistry, haematology, pathology and histopathology) and detailed reporting of the findings of the study.

This information is missing for each of the source substances.

Furthermore, the test material for these studies is not described in terms of constituents and purity, a prerequisite to use the study results in grouping and read-across approaches.

In the absence of this critical information, ECHA considers that no independent assessment of the reliability of the information obtained from these studies can be conducted. Therefore, ECHA concludes that the requirements of Annex XI, Section 1.5 of the REACH Regulation for adequate and reliable documentation of read-across adaptations is not met.

Furthermore, ECHA emphasises that the route of administration used to conduct a study is an important parameter to consider when assessing the adequacy of information aimed at deriving systemic toxicity of a substance. It is important to determine whether and to which extent the test substance reaches its biological targets, i.e. to characterise the systemic bioavailability of the test substance. ECHA points out that two studies on tetrabromophthalic anhydride (CAS 632-79-1) ([redacted] 1975d; [redacted] 1975e), and described in the attachment to the technical dossier "*Structural analog data: mammalian repeated dose toxicity*", have been conducted via the dermal and inhalation routes, respectively. However no information on the systemic bioavailability of tetrabromophthalic anhydride after dermal and inhalation exposure is provided in the technical dossier. The possibility that the systemic toxicity of tetrabromophthalic anhydride derived from these studies may be underestimated as a result of reduced systemic

bioavailability cannot be dismissed.

ECHA notes that the exposure duration of some of the source studies that you have used in your read-across approach on tetrabromophthalic anhydride ([redacted] 1975e and 1975d; Tice, 1999), on phthalic anhydride (US NCI), on diallyl phthalate ([redacted]) and on di(2-ethylhexyl)-3,4,5,6-tetrabromophthalate (unknown author) range from 2 to 7 weeks. These study durations are shorter than the exposure duration required from a sub-chronic toxicity study (90 days) performed according to the OECD TG 408. Therefore, ECHA considers that these source studies do not fulfil the requirement of Annex XI, Section 1.5. of the REACH Regulation for an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3).

Based on the information provided in the technical dossier, the study by Tice et al (1999) conducted with the source substance tetrabromophthalic anhydride corresponds to a pre-natal developmental toxicity study performed according to the OECD test guideline 414. ECHA higlights that a study conducted according to the OECD test guideline 414 does not provide the same level of information as that expected from a sub-chronic (90-day) toxicity study conducted according to the OECD test guideline 407. Therefore ECHA is of the opinion that this study by Tice et al (1999) does not constitute relevant information and cannot be used as a source study in the context of a read-across approach aimed at predicting the properties of the registered substance after sub-chronic administration.

c) Conclusion

As presented above, there is not sufficient support for your proposal that the toxicological properties of the registered substance relate to the hydrolysis product tetrabromophthalic acid. Furthermore, you have not established why and how the properties of the registered substance can be predicted from information on phthalic anhydride, diallyl phthalate and di(2-ethylhexyl)-3,4,5,6-tetrabromophthalate (DEHTBP). The limited information provided on the source studies prevents an independent assessment of their adequacy and reliability. For these reasons, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 5.0, December 2016) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure and no uses with spray application are reported that could potentially lead to aerosols of inhalable size. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

In your comments to the draft decision you indicated anticipated difficulties in identifying a suitable vehicle to conduct the study and flagged particular analytical challenges in the determination of the homogeneity of the dosing solutions. You reported that 6 months would be required to overcome these difficulties and therefore requested an extension of the deadline to provide the requested information of 6 months. This request for an extension of the deadling to provide the requested information is addressed in the section on *"Deadline to submit the requested information in this decision"* in Appendix 1 of this decision.

You expressed your intentions to conduct a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) as a dose range finding study for the requested sub-chronic toxicity study. You inquired in your comments on the possibility to have an interim exchange with ECHA once the results from this OECD TG 422 are available in order to *"determine the feasibility of further vertebrate animal studies"*. You also highlighted that the data from the OECD TG 422 study *"could be used to support and improve the read across which could avoid to sacrifice further vertebrate animals"* and indicated that the outcome of this OECD TG 422 study would be taken into account to *"allow an informed decision on the further testing and/or evaluation strategy"*.

ECHA cannot provide advice or comments on any alternative strategies or approaches that the registrant considers to use to fulfil the request in the decision. Therefore, ECHA declined your request for a discussion on the use of the data generated in an OECD TG 422 with the objective to comply with the compliance check decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: OECD TG 408) in rats.

10. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

A Pre-natal developmental toxicity study (test method OECD TG 414) with a first species is a standard information requirement in Annex IX, Section 8.7.2. to the REACH Regulation.

You have sought to adapt this information requirement according to Annex XI, Section 1.5.

The generic considerations on adaptations according to Annex XI, Section 1.5 are provided in section 9. And they are applicable also to the current section. Also the description of the composition of the registered substance as explained in 9. b) i) is applicable.

a) Information provided

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a pre-natal developmental toxicity study (test guideline equivalent to the OECD test guideline 414) with the analogue substance tetrabromophthalic anhydride (EC 211-185-4; CAS 632-79-1 – thereafter referred to as "the source substance").

Based on the information provided in the technical dossier, ECHA considers that your read-across hypothesis is based upon the formation of a common hydrolysis product, i.e. tetrabromophthalic acid. This hydrolysis product is supposed to be formed from the constituents of the registered substance with the lowest molecular weight, i.e. with only one unit of [redacted], and also from the proposed source substance tetrabromophthalic anhydride.

In order to justify this hypothesis, you explain that constituents with only one unit of [redacted] are responsible for potential systemic toxicity of the registered substance. You assume that this toxicity is mediated through the rapid hydrolysis of such constituents of the registered substance to form the toxicologically relevant metabolite tetrabromophthalic acid. ECHA understands that this is your hypothesis based on which you consider that the toxicity of the registered substance in a pre-natal developmental toxicity study can be predicted based on the results obtained with tetrabromophthalic anhydride.

b) ECHA's evaluation and conclusion of the information provided

i) Missing supporting information

Annex XI, Section 1.5 of the REACH Regulation states that "*adequate and reliable documentation of the applied method shall be provided*". The ECHA Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.6, Section R.6.2.2.1.f indicates that "*it is important to provide supporting information to strengthen the rationale for the read-across*" as part of the documentation of a read-across approach. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the registered substance can be predicted from the data on the source substance. ECHA notes that supporting information in relation to important elements of your read-across hypothesis is missing, as explained below.

Information on the formation of the common hydrolysis product

Information characterising the rate and extent of the hydrolysis of the constituents of the registered substance and of the source substance is necessary to confirm the formation of the common hydrolysis product and to assess the impact of the exposure to the parent compounds. You have not provided any experimental data or other adequate and reliable information, neither about the hydrolysis of the registered substance nor about the hydrolysis of the source substance. In the absence of this information, ECHA considers that you have not demonstrated that the common hydrolysis product is formed as assumed in your read-across hypothesis.

Information on exposure to non-common hydrolysis products

ECHA observes that the constituent of the registered substance which is a precursor of the common hydrolysis product is a diester. The formation of the proposed common hydrolysis product requires hydrolysis of both of these esters. Information characterising the hydrolysis of each of the ester groups is necessary to assess the potential exposure to intermediate hydrolysis products, i.e. mono esters, and its impact on the toxicological properties of the target substance. However no such information is provided in your dossier.

Besides the assumed formation of the proposed common hydrolysis product, the hydrolysis of the constituent of the registered substance that you consider as toxicologically relevant will lead to the formation of non-common hydrolysis products, such as monoesters and alcohols. The contribution of exposure to these alcohols to the toxicological properties of the registered substance cannot be predicted from information on the proposed common hydrolysis product and therefore require specific considerations. In your read-across justification you address this by indicating that *"the other hydrolysis products are supposed to be rapidly excreted and metabolised via physiological pathways"*.

However, no further information on the intrinsic toxicological properties of these non-common hydrolysis products is provided. Also your claim of rapid excretion of these hydrolysis products is not supported by data and the potential impact of exposure to these non-common hydrolysis products on the properties of the registered substance is not discussed. ECHA also stresses that metabolism via physiological pathways does not constitute evidence of absence of toxicity.

Information on exposure to other constituents of the target substance

As explained under 9. b) i) the registered substance is defined as a UVCB substance. You have considered the complex composition of the registered substance and concluded that "*due to the high molecular weight of the components with multiple rings and their volume it is anticipated that the constituents with molecular weights higher than 1000 have a limited absoprtion. The relevant species for absorption and potential systemic effects are the mono-aromatic ring constituents*". On that basis you have identified one mono-aromatic ring constituent in the composition of the registered substance and developed a read-across hypothesis based on the hydrolysis of that specific constituent.

ECHA observes that whilst you refer to limited absorption of other constituents of the registered substance as a result of their molecular weight or volume you have not provided information supporting this assumption on the toxicokinetic behaviour of these constituents. Furthermore, hydrolysis of the ester functions of the mono-aromatic ring constituents is a core element of your read-across hypothesis. However the hydrolytic fate of the other constituents of the registered substance is not elaborated upon in your read-across justification. The possibility that the ester functions of the constituents with multiple aromatic rings may be hydrolysed prior to systemic absorption and generate smaller hydrolysis products with a potential for systemic absorption is not discussed and their potential impact on the toxicological properties of the registered substance is not assessed.

Conclusion on missing supporting information

For the reasons presented above, ECHA considers that you have not established that exposure to the parent compounds and to non-common hydrolysis products formed from the constituent of the registered substance do not impact the toxicological properties of the registered substance. Furthermore, in the absence of information on the absorption, hydrolytic fate and potential toxicity of the different constituents of the registered substance or their hydrolysis products, ECHA considers that your assumption that mono-aromatic ring constituents are the ony constituents of toxicological relevance is not substantiated. Consequently ECHA concludes that you failed to establish that the properties of the

registered substance can be predicted from information derived from the source substance tetrabromophthalic anhydride.

ii. Adequacy and reliability of the source study

Annex XI, Section 1.5 of the REACH Regulation requires that the results of a read-across approach "*have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3)*" of the REACH Regulation. The information requirement of Annex IX, 8.7.2, column 1 of the REACH Regulation for a pre-natal developmental toxicity study specifically refers to the test method "*B.31 as referred to the Commission Regulation on test method as specified in article 13(3) or OECD 414*". The requirements from these test guidelines indicate that "*each test and control group should contain a sufficient number of females to result in approximately 20 female animals with implantation sites at necropsy*".

Based on the information provided in the robust study summary of the source study included in your dossier, it appears that only 5 females were used in each test group. The number of animals per dose group is significantly lower than that required by the test method EU B.31 and OECD 414. This affects the sensitivity of the study and the reliability of its results.

Therefore, ECHA considers that this source study does not fulfil the requirement of Annex XI, Section 1.5. of the REACH Regulation for an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

c) Conclusion

For the reasons presented above, there is not sufficient support for your proposal that the toxicological properties of the registered substance relate to the hydrolysis product tetrabromophthalic acid. Furthermore, limitations in the design of the source study have been identified, affecting the adequacy and reliability of the source data. For these reasons, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

You provided comments to the draft decision on this request. However, no comments specifically relating to the endpoint pre-natal developmental toxicity have been submitted.

The comments provided under this endpoint are identical to those provided for the endpoint sub-chronic toxicity study (90-day). The responses to your comments on the request for a sub-chronic toxicity study (90-day) presented above under Appendix 1- Section 9 also apply to these comments.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: OECD TG 414) in a first species (rat or rabbit) by the oral route.

11. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

Growth inhibition study aquatic plants is a standard information requirement in Annex VII, Section 9.1.2. to the REACH Regulation.

You sought to adapt this information requirement by means of providing results from a quantitative structure-activity relationship model (QSAR). You have predicted the growth inhibition in green algae for the structure having the lowest molecular weight and indicating it to be the most bioavailable due to its lowest molecular weight.

In the technical dossier under this endpoint you have provided the following information:

- Key study (QSAR, reliability 2): ECOSAR v1.00, 96-h EC50 4.391 mg/L (ECOSAR class ESTERS), 96-h EC50 9.052 mg/L (ECOSAR class Neutral Organic SAR)

Regarding the requirements of Annex XI, Section 1.3 of the REACH Regulation, ECHA notes the following:

1. You have not explained why the registered UVCB substance would fall within the applicability domain of the applied model. While the reported log Kow and molecular weight are in the applicability domain range, the registered substance contains brominated phenyl groups that are not included in the substances used in the training set of the QSAR model. Therefore, ECHA considers that the condition of the substance falling within the applicability domain of the QSAR model is not met;
2. You have not explained why the reported results can be considered to be adequate for the purpose of classification and labelling and/or risk assessment. Your substance is identified as a UVCB, and you have not justified why the structure(s) used for the prediction would represent the registered UVCB substance as a whole. In fact, the registered substance contains several identified and unidentified constituents and therefore, its ecotoxicological properties cannot be properly estimated with QSAR predictions with a single structure. Furthermore, you have not justified why the constituent with the lowest molecular weight would be the most bioavailable and hence potentially most toxic as low molecular weight does not necessarily mean the highest bioavailability. Therefore, ECHA considers that the reported QSAR prediction cannot be regarded as reliable for the purpose of classification and labelling and/or risk assessment of your registered UVCB substance.

Therefore your proposed adaptation based on Annex XI, Section 1.3 of the REACH Regulation is rejected. ECHA concludes that there is an information gap and that it is

necessary to provide information for the endpoints in order to bring the registration dossier into compliance with relevant information requirements.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) Algae growth inhibition test (test method EU C.3. / OECD TG 201) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.2.

In your comments to the draft decision you indicated your concern whether ECHA has evaluated the latest submission with the attached QMRF and you expressed your opinion that insoluble components are unlikely to contribute to aquatic toxicity. Regarding all the requests for aquatic toxicity testing in the draft decision you also indicated that testing may not be technically feasible or give any reliable results. You, however, suggested to start with a dissolution testing in the test media trying to identify any dissolved components. You also anticipated that a water accommodated fraction (WAF) testing method could be feasible but requiring pre-studies and development of analytical methods that could take up to two years.

ECHA firstly notes that the latest submission, [redacted] dated 26 June 2018, as indicated on the first page of this decision has been assessed and the QMRF was found attached in your dossier. However, you have not provided a QPRF (QSAR Prediction Reporting Format) providing the information about the prediction itself and the substance for which the prediction was made. An adaptation according to Annex XI, Section 1.3. requires both documents, as explained in Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008).

While ECHA agrees with you that insoluble components are unlikely to contribute to the aquatic (pelagic) toxicity, ECHA considers that you have not demonstrated in your dossier that all the components of your subtance are insoluble. Potential poorly water soluble components of your substance could cause hazardous chronic effects for aquatic (pelagic) organisms especially after long lasting exposures.

ECHA acknowledges the challenges in relation with conducting the requested aquatic toxicity testing and developing analytical methods to identify dissolved components of your registered UVCB substance. ECHA agrees with you that pre-studies and the development of analytical methods are necessary before testing and eventually the final testing may still need to be conducted using the Water Accommodated Fraction (WAF) method. In this regard ECHA reminds you that you should also report the results of any pre-studies in your dossier update. Regarding the WAF method, ECHA remindes that the OECD guidance document on aqueous-phase aquatic toxicity testing of difficult test chemicals (ENV/JM/MONO(2000)6/REV1 (July 2018) provides general guidance on testing UVCB substances using WAF method. The guidance also underscores the importance of chemical-specific analytical determinations and also mentions some newer techniques (e.g. passive dosing) that may potentially be used to deal with some of the shortcomings of WAFs for poorly soluble UVCBs. However, it is reminded that reliable quantitative information on the actual dissolved concentrations to which the animals have been exposed to in the study is essential in order to reliably identify the potential biological effect values.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Algae growth inhibition test, EU C.3./OECD TG 201).

Notes for your consideration

Due to the assumed low solubility of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

12. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

Long-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex IX, Section 9.1.5. to the REACH Regulation.

You sought to adapt this information requirement according to Annex XI, Section 1.3. by means of providing results from a quantitative structure-activity relationship model (QSAR) and according to Annex IX, Section 9.1.5, Column 2. You have predicted the long-term toxicity on aquatic organisms for a number of structures of the lower molecular weight range and the predicted value of the structure having the lowest molecular weight was indicated to be the most bioavailable worst case structure due to its low molecular weight.

In the technical dossier under this endpoint you have provided the following information:

- Supporting study (QSAR, reliability 2): ECOSAR v1.00, 21-d ChV 4.945 mg/L (ECOSAR class ESTERS), 21-d ChV 1.266 mg/L (ECOSAR class Neutral Organic SAR);
- Data waiver using the following justification: "*The registrant is of the opinion that the chemical safety assessment does not indicate the need for further testing, based on the existing hazard data and the limited uses of the substance with a low potential to enter the aquatic environment. Therefore, the waiver for long-term toxicity testing on aquatic organisms based on the column 2 of annex IX of REACH regulation (No 1907/2006) will be adopted*".

Regarding the requirements of Annex XI, Section 1.3 of the REACH Regulation for the use of results from QSAR, ECHA notes the following:

1. You have not explained why the registered UVCB substance would fall within the applicability domain of the applied model. While the reported log Kow and molecular weight are in the applicability domain range, the registered substance contains brominated phenyl groups that are not included in the substances used in the training set of the QSAR model. Therefore, ECHA considers that the condition of the substance falling within the applicability domain of the QSAR model is not met;
2. You have not explained why the reported results can be considered to be adequate for the purpose of classification and labelling and/or risk assessment. Your substance is identified as a UVCB, and you have not justified why the structure(s) used for the prediction would represent the registered UVCB substance as a whole. In fact, the

registered substance contains several identified and unidentified constituents and therefore, its ecotoxicological properties cannot be properly estimated with QSAR predictions with a single structure. Furthermore, you have not justified why the constituent with the lowest molecular weight would be the most bioavailable and hence potentially most toxic as low molecular weight does not necessarily mean the highest bioavailability. Therefore, ECHA considers that the reported QSAR prediction cannot be regarded as reliable for the purpose of classification and labelling and/or risk assessment of your registered UVCB substance.

Regarding an adaptation based on Annex IX, Section 9.1.5, Column 2, ECHA further notes that no exposure assessment and risk characterisation are reported in your chemical safety assessment. In the absence of all these data the chemical safety assessment cannot be used as a basis for the adaptation of the standard information requirement for long-term toxicity to aquatic invertebrates.

Therefore your proposed adaptations based on Annex XI, Section 1.3 and Annex IX, Section 9.1.5, Column 2 of the REACH Regulation are rejected. ECHA concludes that there is an information gap and that it is necessary to provide information for the endpoints in order to bring the registration dossier into compliance with relevant information requirements.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.

In your comments to the draft decision you indicated that you have done QSAR for a number of structures of the lower molecular weight range and selected the lowest value as worst case. ECHA has modified the draft decision in this respect. You expressed your opinion that components with higher molecular weight are unlikely to contribute to aquatic toxicity. Regarding all the requests for aquatic toxicity testing in the draft decision you also indicated that testing may not be technically feasible or give any reliable results. You, however, suggested to start with a dissolution testing in the test media trying to identify any dissolved components. You also anticipated that a water accommodated fraction (WAF) testing method could be feasible but requiring pre-studies and development of analytical methods that could take up to two years.

In line with point 11 above, ECHA notes that the latest submission has been assessed and the QMRF was found attached in the dossier whereas no QPRF was provided.

ECHA considers that you have not demonstrated in your dossier that the components with higher molecular weight (>1000) and low water solubility do not bioaccumulate and contribute to toxicity. Potential poorly water soluble large components of your substance could still bioaccumulate and cause hazardous chronic effects for aquatic (pelagic) organisms especially after long lasting exposures.

ECHA acknowledges the challenges in relation with conducting the requested aquatic toxicity testing and developing analytical methods to identify dissolved components of your registered UVCB substance. ECHA agrees with you that pre-studies and the development of analytical methods are necessary before testing and eventually the final testing may still need to be conducted using the Water Accommodated Fraction (WAF) method. In this

regard ECHA reminds you that you should also report the results of any pre-studies in your dossier update. Regarding the WAF method, ECHA remindes that the OECD guidance document on aqueous-phase aquatic toxicity testing of difficult test chemicals (ENV/JM/MONO(2000)6/REV1 (July 2018) provides general guidance on testing UVCB substances using WAF method and, as indicated below in "Notes for your consideration", the guidance also underscores the importance of chemical-specific analytical determinations. The guidance also mentions some newer techniques (e.g. passive dosing) that may potentially be used to deal with some of the shortcomings of WAFs for poorly soluble UVCBs. However, it is reminded that reliable quantitative information on the actual dissolved concentrations to which the animals have been exposed to in the study is essential in order to reliably identify the potential biological effect values.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *Daphnia magna* reproduction test (test method: EU C.20./OECD TG 211).

Notes for your consideration

Once results of the test on long-term toxicity to aquatic invertebrates are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation.

Due to the expected low solubility of the constituents of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

In addition, if you decide to use the Water Accommodated Fraction (WAF) approach, please note that the WAF approach may not be adequate when used with a test substance containing several constituents, as in the case of the registered substance. In general, it is critical that a robust chemical analysis is carried out to identify those constituents present in the water to which the test organisms are exposed. Additionally, chemical analysis to demonstrate attainment of equilibrium in WAF preparation and stability during the conduct of the test is required. Methods capable of identifying gross changes in the composition of WAFs with time are required and methods such as ultra-violet spectroscopy or total peak area have been used successfully for this purpose. The method used to prepare the WAF should be fully described in the test report and evidence of its compositional stability over time should be provided. Regarding the expression of the result of the test, the above guidance document recommends that all test results are expressed in terms of measured concentrations as far as possible. In particular, the "loading rate" may be used for expressing exposures of mixtures that neither wholly dissolve nor completely form a stable dispersion or emulsion over the required test range. WAFs may be thus considered analogous to the term "nominal concentration" used for typical test substances, with all the limitations inherent to that term. As indicated in the OECD TG 211 and OECD GD 23, when the measured concentrations do not remain within 80-120% of the nominal concentration, the effect concentrations should be determined and expressed relative to the arithmetic or geometric mean of the measured concentrations (see paragraph 50 of the OECD TG 211 and chapter 5 of the OECD GD 23).

Therefore, it is recommended that you should first consider conducting the preliminary stability test as per above mentioned OECD GD 23. If based on that test you consider that the WAF is the only option to prepare the test solution, you should report the potential effect concentrations from the WAF test based on mean measured concentrations.

13. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

Long-term toxicity testing on fish is a standard information requirement in Annex IX, Section 9.1.6. to the REACH Regulation.

You sought to adapt this information requirement by means of providing results from a quantitative structure-activity relationship model ((Q)SAR). You have predicted the long-term toxicity on fish for a number of structures of the lower molecular weight range and the predicted value of the structure having the lowest molecular weight was indicated to be the most bioavailable worst case structure due to its low molecular weight.

In the technical dossier under this endpoint you have provided the following information:

- Key study (QSAR, reliability 2): ECOSAR v1.00, 32-d ChV 0.447 mg/L (ECOSAR class ESTERS), 21-d NOEC 1.258 mg/L (ECOSAR class Neutral Organic SAR)

Regarding the requirements of Annex XI, Section 1.3 of the REACH Regulation, ECHA notes the following:

1. You have not explained why the registered UVCB substance would fall within the applicability domain of the applied model. While the reported log Kow and molecular weight are in the applicability domain range, the registered substance contains brominated phenyl groups that are not included in the substances used in the training set of the QSAR model. Therefore, ECHA considers that the condition of the substance falling within the applicability domain of the QSAR model is not met;
2. You have not explained why the reported results can be considered to be adequate for the purpose of classification and labelling and/or risk assessment. Your substance is identified as a UVCB, and you have not justified why the structure(s) used for the prediction would represent the registered UVCB substance as a whole. In fact, the registered substance contains several identified and unidentified constituents and therefore, its ecotoxicological properties cannot be properly estimated with QSAR predictions with a single structure. Furthermore, you have not justified why the constituent with the lowest molecular weight would be the most bioavailable and hence potentially most toxic as low molecular weight does not necessarily mean the highest bioavailability. Therefore, ECHA considers that the reported QSAR prediction cannot be regarded as reliable for the purpose of classification and labelling and/or risk assessment of your registered UVCB substance.

Therefore your proposed adaptation based on Annex XI, Section 1.3 of the REACH Regulation is rejected. ECHA concludes that there is an information gap and that it is necessary to provide information for the endpoints in order to bring the registration dossier into compliance with relevant information requirements.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) fish early-life stage (FELS) toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215) can be performed to cover the standard information requirement of Annex IX, Section 9.1.6.

However, the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15 / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly fertilized egg, through hatch to early stages of growth (see ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), *Chapter R7b, Section R.7.8.4.1.*

Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects over a longer exposure period, or which require a longer exposure period of time to reach steady state (ECHA *Guidance Chapter R7b,* version 4.0, June 2017).

In your comments to the draft decision you indicated that you have done QSAR for a number of structures of the lower molecular weight range and selected the lowest value as worst case. ECHA has modified the draft decision in this respect. You expressed your opinion that components with higher molecular weight are unlikely to contribute to aquatic toxicity. Regarding all the requests for aquatic toxicity testing in the draft decision you also indicated that testing may not be technically feasible or give any reliable results. You, however, suggested to start with a dissolution testing in the test media trying to identify any dissolved components. You also anticipated that a water accommodated fraction (WAF) testing method could be feasible but requiring pre-studies and development of analytical methods that could take up to two years.

In line with point 11 above, ECHA notes that the latest submission has been assessed and the QMRF was found as attached in the dossier whereas no QPRF was reported.

ECHA considers that you have not demonstrated in your dossier that the components with higher molecular weight (>1000) and low water solubility do not bioaccumulate and contribute to toxicity. Potential poorly water soluble large components of your substance could still bioaccumulate and cause hazardous chronic effects for aquatic (pelagic) organisms especially after long lasting exposures.

ECHA acknowledges the challenges in relation with conducting the requested aquatic toxicity testing and developing analytical methods to identify dissolved components of your registered UVCB substance. ECHA agrees with you that pre-studies and the development of analytical methods are necessary before testing and eventually the final testing may still need to be conducted using the Water Accommodated Fraction (WAF) method. In this regard ECHA reminds you that you should also report the results of any pre-studies in your dossier update. Regarding the WAF method, ECHA remindes that the OECD guidance document on aqueous-phase aquatic toxicity testing of difficult test chemicals (ENV/JM/MONO(2000)6/REV1 (July 2018) provides general guidance on testing UVCB substances using WAF method and, as indicated below in "Notes for your consideration", the guidance also underscores the importance of chemical-specific analytical determinations. The guidance also mentions some newer techniques (e.g. passive dosing) that may

potentially be used to deal with some of the shortcomings of WAFs for poorly soluble UVCBs. However, it is reminded that reliable quantitative information on the actual dissolved concentrations to which the animals have been exposed to in the study is essential in order to reliably identify the potential biological effect values.

Regarding the justifiability of long-term aquatic vertebrate animal testing, ECHA notes that the components of the substance are predicted to be poorly soluble indicating the need for long-term toxicity testing, and there are no reliable data available for the potential sensitivity differences between vertebrates and invertebrates, which indicates that long-term toxicity testing is needed for both vertebrates and invertebrates. You may conduct the long-term toxicity test on invertebrates first along the Integrated Testing Strategy (ITS) and, in case the results indicate low toxicity, consider conducting the fish long-term testing using a limit-test design in order to reduce the amount of fish used in the test.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

Notes for your consideration

Once results of the test on long-term toxicity to fish are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation.

ECHA notes that there are no reliable short-term studies available on aquatic invertebrates and fish for the registered substance. Therefore the Integrated testing strategy (ITS) outlined in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), is not applicable in this case and the long-term studies on both invertebrates and fish are requested to be conducted. As the registered substance has a reported low water solubility, long-term studies are requested.

Due to the expected low solubility of the constituents of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

In addition, if you decide to use the Water Accommodated Fraction (WAF) approach, please note that the WAF approach may not be adequate to determine the toxicity of multi-component substances where its poorly soluble components are of concern, as in the case of the registered substance. In general, it is critical that a robust chemical analysis is carried out to identify those constituents present in the water to which the test organisms are exposed. Additionally, chemical analysis to demonstrate attainment of equilibrium in WAF preparation and stability during the conduct of the test is required. Methods capable of identifying gross changes in the composition of WAFs with time are required and methods such as ultra-violet spectroscopy or total peak area have been used successfully for this purpose. The method used to prepare the WAF should be fully described in the test report and evidence of its compositional stability over time should be provided. Regarding the expression of the result of the test, the above guidance document recommends that all test

results are expressed in terms of measured concentrations as far as possible. In particular, the "loading rate" may be used for expressing exposures of mixtures that neither wholly dissolve nor completely form a stable dispersion or emulsion over the required test range. WAFs may be thus considered analogous to the term "nominal concentration" used for typical test substances, with all the limitations inherent to that term. As indicated in the OECD TG 210 and OECD GD 23, when the measured concentrations do not remain within 80-120% of the nominal concentration, the effect concentrations should be determined and expressed relative to the arithmetic or geometric mean of the measured concentrations (see paragraph 24 of the OECD TG 210 and chapter 5 of the OECD GD 23).

Therefore, it is recommended that you should first consider conducting the preliminary stability test as per above mentioned OECD GD 23. If based on that test you consider that the WAF is the only option to prepare the test solution, you should report the potential effect concentrations from the WAF test based on mean measured concentrations.

14. Soil simulation testing (Annex IX, Section 9.2.1.3.)

Soil simulation testing is a standard information requirement in Annex IX, section 9.2.1.3. to the REACH Regulation for substances with a high potential for adsorption to soil. The registered substance is an UVCB and the water solubility and octanol-water partitioning coefficient values cannot be confirmed, as discussed respectively in sections 3 and 4 above. However, the QSAR predicted values (water solubility of 0.057 mg/L, log partition coefficient of 3.83) reported in the dossier for the selected structure of the registered UVCB substance indicate that the registered substance includes poorly water soluble and hydrophobic constituents. Therefore, despite the low estimated adsorption coeffient of 10, the substance potentially has high adsorptive properties and adequate information on the soil simulation testing endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You sought to adapt this information requirement by providing results from a quantitative structure-activity relationship model ((Q)SAR). You have predicted the biodegradation in soil for the structure having the lowest molecular weight and indicating it to be the most bioavailable due to its lowest molecular weight.

In the technical dossier under this endpoint you have provided the following information:

- Key study (QSAR, reliability 2): BIOWIN v4.10, biodegradation half-life ca. 2880 h.

In your PBT assessment you do not provide an unequivocal conclusion on whether or not the P/vP criteria are met: you say that the substance "*...is not likely to be readily biodegradable*" but you continue that "*...it is equally unlikely to be recalcitrant and will indergo degradation in the environment. However the velocity is hard to predict.*"

Regarding the requirements set by Annex XI, Section 1.3 of the REACH Regulation, ECHA notes the following:

1. You have not explained why the registered UVCB substance would fall within the applicability domain of the applied model. While the reported log Kow and molecular weight are in the applicability domain range, the registered substance contains brominated phenyl groups that are not included in the substances used in the

training set of the QSAR model. Therefore, ECHA considers that the condition of the substance falling within the applicability domain of the QSAR model is not met;

2. You have not explained why the reported results can be considered to be adequate for the purpose of classification and labelling and/or risk assessment. Your substance is identified as a UVCB, and you have not justified why the structure(s) used for the prediction would represent the registered UVCB substance as a whole. In fact, the registered substance contains several identified and unidentified constituents and therefore, its environmental fate properties cannot be properly estimated with QSAR predictions with a single structure. Furthermore, you have not justified why the constituent with the lowest molecular weight would be the most bioavailable as low molecular weight does not necessarily mean the highest bioavailability. On the other hand, you also admit that the assumed lower bioavailability of the other higher molecular weight components of the registered UVCB substance could indicate a slower biodegradation potential and therefore the model prediction for the selected low molecular weight component could over predict the biodegradability of the registered substance. Therefore, ECHA considers that the reported QSAR prediction cannot be regarded as reliable for the purpose of classification and labelling and/or risk assessment (including PBT assessment) of your registered UVCB substance;
3. You have not documented the reliability of the applied model (a QSAR Model Reporting Format, QMRF) or of the individual model prediction (a QSAR Prediction Reporting Format, QPRF) to support the provided BIOWIN v.4.10 model.

Furthermore, QSAR results alone are in most cases not sufficient to conclude on non-persistence but should be supported by additional information. As decribed in ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.11* (version 3.0, June 2017) for the PBT assessment, QSAR predictions can only be used as part of a Weight-of-Evidence approach in persistency assessment.

According to Annex IX, Section 9.2.1.3, column 2 of the REACH Regulation, simulation testing on soil does not need to be conducted if the substance is readily biodegradable or if direct or indirect exposure of soil is unlikely. ECHA notes that based on the information in the technical dossier, you have concluded that the modelled reference substance is "not expected to be readily biodegradable" in BIOWIN v4.10 prediction. Regarding the exposure to soil, ECHA notes that there are no exposure estimations in the Chemical Safety Report (CSR). Furthermore, you report the results of the Level III fugacity distribution model and conclude that soil (with distribution of 89.6%) is the most important compartment with respect to the environmental distribution. ECHA therefore considers that you have not in your CSR demonstrated that indirect and direct soil exposure is unlikely.

ECHA notes also that you have not provided any justification in your chemical safety assessment (CSA) or in the technical dossier for why there is no need to investigate further the degradation of the substance and its degradation products. As explained further below, ECHA considers that the information is needed for the PBT/vPvB assessment and for the identification of the degradation products in relation to the PBT/vPvB assessment.

Based on above, ECHA considers that the you have not demonstrated that an adaptation with general rules of Annex XI or the specific rules for adaptation in accordance with column 2 of Annex IX, Section 9.2.1.3 of the REACH Regulation are met.

Therefore, your adaptation of the information requirement cannot be accepted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) Aerobic and anaerobic transformation in soil (test method EU C.23. / OECD TG 307) is the preferred test to cover the standard information requirement of Annex IX, Section 9.2.1.3.

One of the purposes of the simulation test is to provide the information that must be considered for assessing the P/vP properties of the registered substance in accordance with Annex XIII of REACH Regulation to decide whether it is persistent in the environment. Annex XIII also indicates that "*the information used for the purposes of assessment of the PBT/vPvB properties shall be based on data obtained under relevant conditions*". The Guidance on information requirements and chemical safety assessment R.7b (version 4.0, June 2017) specifies that simulation tests "attempt to simulate degradation in a specific environment by use of indigenous biomass, media, relevant solids [...], and a typical temperature that represents the particular environment". The Guidance on information requirements and chemical safety assessment Chapter R.16 on Environmental Exposure Estimation, Table R.16-8 (version 3.0 February 2016) indicates 12°C (285K) as the average environmental temperature for the EU to be used in the chemical safety assessment. Performing the test at the temperature of 12°C is within the applicable test conditions of the Test Guideline OECD TG 307. Therefore, the test should be performed at the temperature of 12°C.

Simulation tests performed in sediment or in soil possibly imply the formation of non-extractable residues (NER). These residues (of the parent substance and/or transformation products) are bound to the soil or to the sediment particles. NERs may potentially be re-mobilised as parent substance or transformation product unless they are irreversibly bound or incorporated into the biomass. When reporting the non-extractable residues (NER) in your test results you should explain and scientifically justify the extraction procedure and solvent used obtaining a quantitative measure of NER.

In your comments to the draft decision you indicated that it is technically not possible to conduct the requested soil simulation testing or identify the potential degradation products as there is no method to make a representative radiolabelled product of the registered complex UVCB substance. You also included confidential analysis of the analytical possibilities reflecting the need for method development to characterise and quantify the mixture of components.

ECHA acknowledges the technical challenges and need for method development identified in characterising and quantifying the constituents in relation with conducting the requested soil simulation study and identifying the degradation products. However, ECHA reminds you that a reliable information on biodegradation is needed for the PBT/vPvB assessment of your substance.

Regarding the PBT/vPvB assessment, ECHA reminds you about the *ECHA Guidance on information requirements and chemical assessment, Chapter R.11* (version 3.0, June 2017) *for the PBT/vPvB assessment*, where a guidance is provided for the assessment of

substances containing multiple constituents (R.11.4.2.2). Particularly the section on "Fraction profiling" (or "Block profiling") approach is providing advice on assessing cases for which, due to complexity of the substance, it is not feasible to fully identify, assess or isolate single constituents but the substance can be divided into fractions/blocks where the constituents have similar properties. In this regard, you are further reminded that if this approach is applied, the assessment shall include a justification on why you consider the selected "fraction" relevant for the PBT/vPvB assessment.

In case you eventually consider that the requested biodegradation simulation testing is not technically feasible, you must transparently justify the technical infeasibility, report it in the registration dossier and accompany it with adequate supporting data.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Aerobic and anaerobic transformation in soil (test method: EU C.23./OECD TG 307). The biodegradation of each relevant constituent present in concentration at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable shall be assessed. This can be done simultaneously during the same study.

Notes for your consideration

In accordance with Annex I, Section 4, of the REACH Regulation you should revise the PBT assessment when results of the test detailed above is available. You are also advised to consult the ECHA Guidance on information requirements and chemical safety assessment (version 3.0, June 2017), Chapter R.11, Section R.11.4.1.1. and Figure R. 11-3 on PBT assessment for the integrated testing strategy for persistency assessment in particular taking into account the degradation products of the registered substance.

15. Identification of degradation products (Annex IX, Section 9.2.3.)

The identification of the degradation products is a standard information requirement in Annex IX, Section 9.2.3. to the REACH Regulation.

The biodegradation section in the technical dossier does not contain any information in relation to the identification of degradation products, nor an adaptation in accordance with column 2 of Annex IX, Sections 9.2 or 9.2.3. or with the general rules of Annex XI for this standard information requirement.

According to Annex IX, Section 9.2.3., column 2 of the REACH Regulation, identification of degradation products is not needed if the substance is readily biodegradable. ECHA notes that based on the information in the technical dossier, the registered substance is not likely to be readily biodegradable as also discussed in section 14 above.

Furthermore, ECHA notes that you have not provided any justification in your chemical safety assessment (CSA) or in the technical dossier for why there is no need to provide information on the degradation products. ECHA considers that this information is needed in relation to the PBT/vPvB assessment and risk assessment.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Regarding appropriate and suitable test method, the methods will have to be substance-specific. When analytically possible, identification, stability, behaviour, and molar quantity of metabolites relative to the parent compound should be evaluated. In addition, degradation half-life, log Kow and potential toxicity of the metabolite may be investigated. You may obtain this information from the soil simulation study also requested in this decision, or by some other measure. You will need to provide a scientifically valid justification for the chosen method.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision:

Identification of the degradation products (Annex IX, Section 9.2.3.) by using an appropriate and suitable test method, as explained above in this section.

Notes for your consideration

Before providing the above information you are advised to consult the ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R.7b., Sections R.7.9.2.3 and R.7.9.4. This guidance document explains that the data on degradation products is only required if information on the degradation products following primary degradation is required in order to complete the chemical safety assessment. Section R.7.9.4. further states that when substance is not fully degraded or mineralised, degradation products may be determined by chemical analysis.
In accordance with Annex I, Section 4, of the REACH Regulation you should revise the PBT assessment when the information request above is available. You are advised to consult the ECHA Guidance on information requirements and chemical safety assessment (version 3.0, June 2017), Chapter R.11, Section R.11.4. on PBT assessment for relevant constituents, impurities, additives and transformation/degradation products.

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide the requested information was 30 months from the date of adoption of the decision. In your comments on the draft decision, you requested an overall extension of the timeline to the total of 54 months. You sought to justify this request by:

- anticipated difficulties in identifying a suitable vehicle to conduct the study and flagged particular analytical challenges in the determination of the homogeneity of the dosing solutions for conducting *in vivo* toxicological studies. You estimated that 6 months would be required to overcome these difficulties. ECHA considers that this 6-month extension of the deadline is motivated and justified.
- the need to do pre-testing and considerable analytical development before the requested aquatic toxicity tests can be conducted. You anticipated that this could take up to 24 months. ECHA notes that all three requested aquatic toxicity tests can be conducted in parallel and the maximum length of any given aquatic toxicity test is

12 months. With the extension of 6 months granted for the toxicological endpoints, the deadline in the decision would be extended from 30 to 36 months. ECHA considers that this deadline should allow you to conduct the necessary pre-testing and analytical development within 24 months and still provide sufficient time of 12 months for conducting the final aquatic toxicity tests in parallel. Therefore, ECHA considers that the extended deadline is sufficient for aquatic toxicity testing.

- the time required to prepare a dossier update: ECHA points out that the timeline set in the decision already includes time for compiling the new information and updating the relevant sections of the technical dossier, including the chemical safety report. Therefore, ECHA has not granted this extension of the deadline.

Based on the reasons presented above, ECHA has only partially granted the request and set the deadline to 36 months.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 23 July 2018.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

ECHA took into account your comments and amended the deadline.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

ECHA received proposal(s) for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-64 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the requests in this decision will result in a notification to the enforcement authorities of your Member State.

3. In carrying out the tests required by the present decision, it is important to ensure that the particular sample of substance tested is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported. If the registration of the substance covers different grades, the sample used for the new tests must be suitable to assess these.

   Furthermore, there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.