ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 24 July 2019

Addressee: [redacted]

Decision number: CCH-D-2114478450-48-01/F
Substance name: 6'-(dibutylamino)-3'-methyl-2'-(phenylamino)spiro[isobenzofuran-1(3H),9-(9H)-xanthen]-3-one
EC number: 403-830-5
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 09/12/2015
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. **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;**

2. **Soil simulation testing (Annex IX, Section 9.2.1.3.; test method: Aerobic and anaerobic transformation in soil, EU C.23./OECD TG 307) with the registered substance;**

3. **Sediment simulation testing (Annex IX, Section 9.2.1.4.; test method: Aerobic and anaerobic transformation in aquatic sediment systems, EU C.24./OECD TG 308) with the registered substance;**

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

5. **Bioaccumulation in aquatic species (Annex IX, Section 9.3.2.; test method: Bioaccumulation in fish: aqueous and dietary exposure, OECD TG 305, aqueous exposure or dietary exposure) with the registered substance;**

6. **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.**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by ***31 January 2023***. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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

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

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. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "pre-natal developmental toxicity study" (test method OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have provided the following information in IUCLID section 7.8.2:

- End point study record 1: "*In accordance with ECHA guidance Chapter R7a, if a generation study is available, a prenatal developmental toxicity study (EU B.31, OECD TG 414) in the rat may not provide any additional information that would have an influence on the classification decision or risk assessment, and therefore the conduct of this study in the rat may not always be necessary. In the one-generation reproduction toxicity study (NOAEL: parental: 1000 mg/kg bw/day; F1 generation: 1000 mg/kg bw/day), there are no adverse effects on the growth and reproductive capacity of male and female rats or the development of their offspring. With a longer exposure time, the negative results of the subchronic one generation study indicate that the substance has no potential for reproductive or developmental toxicity, which is sufficient for classification and risk assessment. Therefore, the prenatal developmental toxicity study is not necessary both from the scientific view and animal welfare.*"

- End point study record 2:- supporting study: "*developmental toxicity*", rat, oral (OECD TG 415; GLP) with registered substance, [redacted] 2013, reliability 2. This study is the one referred to under end point study record 1.

The one-generation reproductive toxicity study is not the study mandated by Annex IX, Section 8.7.2 of the REACH Regulation. So, ECHA understands that while you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.1.2 (existing data).

ECHA has evaluated the existing information on the one-generation reproductive toxicity study with the registered substance and whether it meets the requirements for the use of existing data according to the provision of REACH Annex, Section 1.1.2. However, this study does not provide the information required by Annex IX, Section 8.7.2 or Annex XI, Section 1.1.2., because it does not adequately and reliably cover key parameters of a pre-natal developmental toxicity study, such as examinations of implantations and examinations of foetuses for skeletal and visceral alterations.

Therefore, your adaptation of the information requirement is rejected.

In addition, you have stated in your justification for adaptation that "*In accordance with ECHA guidance Chapter R7a, if a generation study is available, a prenatal developmental toxicity study (EU B.31, OECD TG 414) in the rat may not provide any additional information that would have an influence on the classification decision or risk assessment, and therefore the conduct of this study in the rat may not always be necessary".*

However, ECHA does not agree with your claim because it contradicts with what is stated in the ECHA Guidance. More specifically, ECHA Guidance on information requirements and chemical safety assessment (version 6.0, July 2017) Chapter R.7a, Section R.7.6.4.2.2 states that "*It is to be noted that screening studies (OECD TGs 421 or 422) or the extended one-generation reproductive toxicity study do not provide equivalent information on prenatal developmental toxicity to that from the prenatal developmental toxicity study.*" In addition, in the Appendix R.7.6-3, section 2.2 of this guidance, it is stated that "*It is, however, to be noted that the extended one-generation reproductive toxicity study does not provide equivalent information to the prenatal developmental toxicity study and thus cannot replace a prenatal development toxicity study*".

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.

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 solid, ECHA concludes that testing should be performed by the oral route.

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.

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

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. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Soil simulation testing" is a standard information requirement as laid down in Annex IX, Section 9.2.1.3. of the REACH Regulation for substances with a high potential for adsorption to soil. The registered substance has low water solubility; 20 µg/L according to experimental data, but QSAR calculations performed by ECHA (WSKOW v1.41 and WATERNT v 1.01) suggest that the water solubility may be even lower, high partition coefficient (log Kow >4.66) and high adsorption coefficient (experimental log Koc in soil ranging from 2.4 to 3.61), all indicating that the registered substance has a high potential for adsorption.

Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to column 2 of Annex IX, of the REACH Regulation. You provided the following justification for the adaptation: "*In accordance with column 2 of REACH annex IX, further degradation testing does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation*".

Column 2 of Annex IX, Section 9.2 of the REACH Regulation specifies that simulation studies need to be conducted if the chemical safety assessment (CSA) according to Annex I of the REACH Regulation indicates the need to investigate further the degradation of the substance and its degradation products. Column 2 of Section 9.2.1.3. of Annex IX of the REACH Regulation further indicates that a simulation study in soil does not need to be conducted if the substance is readily biodegradable or if direct and indirect exposure of soil is unlikely.

ECHA notes that only negligible degradation of the substance was observed in the ready biodegradability test presented in the registration dossier (only 5% biodegradation of the substance observed after 28d in a ready biodegradability test conducted according to OECD 301D (Closed Bottle Test)). Therefore, the substance is not readily biodegradable.

ECHA further notes that exposure of soil is expected to occur and to be significant. The exposure estimations that you have provided in your Chemical Safety Report (CSR) indicate that there is exposure to soil in several of your exposure scenarios. For instance, in exposure scenario 3 ('Consumer use of receipts, tickets and labels printed on thermal-sensitive paper'), you have calculated for agricultural soil a local predicted environmental concentration (PEC) of [redacted], leading to a risk characterisation ratio (RCR) of [redacted]. ECHA therefore considers that you have not demonstrated that exposure of soil is unlikely.

Finally, ECHA considers that your CSA does not demonstrate the absence of concerns for potential PBT/vPvB properties of the registered substance. Only negligible biodegradation of the substance was observed in the ready biodegradability test, therefore it is potentially P and vP. The substance has a high potential for bioaccumulation and high levels of bioaccumulation were observed in fish (see section 5 of the present draft decision). It is therefore potentially B and vB. As for toxicity, information is currently incomplete in your registration dossier (see sections 6 and 1 of the present draft decision). Therefore, it is not possible to rule out that the registered substance could meet the T criteria. Consequently ECHA considers that your CSA does indicate the need to investigate further the degradation of the substance and its degradation products for the assessment of its potential PBT/vPvB properties.

Therefore, ECHA concludes that your adaptation does not meet the specific rules for adaptation of column 2 of Annex IX, Section 9.2 and Section 9.2.1.3. of the REACH Regulation, and your adaptation is not 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. Therefore, the test results, and in particular the degradation rates and the substance half-life, shall correspond to the temperature of 12°C (285K).

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 for obtaining a quantitative measure of NER.

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).

Notes for your consideration

Before conducting the requested tests you are advised to consult the ECHA Guidance on information requirements and chemical safety assessment, Chapter R7b, Sections R.7.9.4 and R.7.9.6 (version 4.0, June 2017) and Chapter R.11, Section R.11.4.1.1 (version 3.0, June 2017) on PBT assessment to determine the sequence in which the simulation tests are to be conducted and the necessity to conduct all of them. The order in which the simulation biodegradation tests are performed needs to take into account the intrinsic properties of the registered substance and the identified use and release patterns which could significantly influence the environmental fate of the registered substance.

In accordance with Annex I, Section 4, of the REACH Regulation you should revise the PBT assessment when the results of the tests requested in this decision are available.

3. Sediment simulation testing (Annex IX, Section 9.2.1.4.)

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. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Sediment simulation testing" is a standard information requirement as laid down in Annex IX, section 9.2.1.4. of the REACH Regulation for substances with a high potential for adsorption to sediment. The registered substance has low water solubility; 20 µg/L according to experimental data, but QSAR calculations performed by ECHA (WSKOW v1.41 and WATERNT v 1.01) suggest that the water solubility may be even lower, high partition coefficient (log Kow >4.66) and high adsorption coefficient (experimental log Koc in soil ranging from 2.4 to 3.61), all indicating that the registered substance has a high potential for adsorption. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to column 2 of Annex IX, of the REACH Regulation. You provided the following justification for the adaptation: "*In accordance with column 2 of REACH annex IX, further degradation testing does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation*".

Column 2 of Annex IX, Section 9.2 of the REACH Regulation specifies that simulation studies need to be conducted if the chemical safety assessment (CSA) according to Annex I of the REACH Regulation indicates the need to investigate further the degradation of the substance and its degradation products. Column 2 of Section 9.2.1.4. of Annex IX of the REACH Regulation further indicates that a simulation study in sediment does not need to be conducted if the substance is readily biodegradable or if direct and indirect exposure of sediment is unlikely.

ECHA notes that only negligible degradation of the substance was observed in the ready biodegradability test presented in the registration dossier (only 5% biodegradation of the substance observed after 28d in a ready biodegradability test conducted according to OECD 301D (Closed Bottle Test)). Therefore, the substance is not readily biodegradable.

ECHA further notes that exposure of sediment is expected to occur and to be significant. The exposure estimations that you have provided in your Chemical Safety Report (CSR) indicate that there is exposure to sediment in several of your exposure scenarios. For instance, in exposure scenario 1 ('Formulation of preparations') and exposure scenario 2 ('Industrial use resulting in inclusion into or onto a matrix'), you have calculated for freshwater sediment a local predicted environmental concentration (PEC) of [redacted], leading to a risk characterisation ratio (RCR) of [redacted]. ECHA therefore considers that you have not demonstrated that exposure of sediment is unlikely.

Finally, ECHA considers that your CSA does not demonstrate the absence of concerns for potential PBT/vPvB properties of the registered substance. Only negligible biodegradation of the substance was observed in the ready biodegradability test, therefore it is potentially P and vP. The substance has a high potential for bioaccumulation and high levels of bioaccumulation were observed in fish (see section 5 of the present draft decision).

It is therefore potentially B and vB. As for toxicity, information is currently incomplete in your registration dossier (see sections 6, and 1 of the present draft decision). Therefore, it is not possible to rule out that the registered substance could meet the T criteria. Consequently ECHA considers that your CSA does indicate the need to investigate further the degradation of the substance and its degradation products for the assessment of its potential PBT/vPvB properties.

Therefore, ECHA concludes that your adaptation does not meet the specific rules for adaptation of column 2 of Annex IX, Section 9.2 and Section 9.2.1.4. of the REACH Regulation, and your adaptation is not 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 aquatic sediment systems (test method EU C.24. / OECD TG 308) is the preferred test to cover the standard information requirement of Annex IX, Section 9.2.1.4.

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. Therefore, the test results, and in particular the degradation rates and the substance half-life, shall correspond to the temperature of 12°C (285K).

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 NERs in your test results you should explain and scientifically justify the extraction procedure and solvent used for obtaining a quantitative measure of NERs.

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 aquatic sediment systems (test method: EU C.24./OECD TG 308).

Notes for your consideration

Before conducting the requested tests you are advised to consult the ECHA Guidance on information requirements and chemical safety assessment, Chapter R7b, Sections R.7.9.4 and R.7.9.6 (version 4.0, June 2017) and Chapter R.11, Section R.11.4.1.1 (version 3.0, June 2017) on PBT assessment to determine the sequence in which the simulation tests are to be conducted and the necessity to conduct all of them. The order in which the simulation biodegradation tests are performed needs to take into account the intrinsic properties of the registered substance and the identified use and release patterns which could significantly influence the environmental fate of the registered substance.

In accordance with Annex I, Section 4, of the REACH Regulation you should revise the PBT assessment when the results of the tests requested in this decision are available.

4. Identification of degradation products (Annex IX, 9.2.3.)

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. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

The identification of the degradation products is a standard information requirement according to column 1, Section 9.2.3. of Annex IX of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

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 column 2 of Annex IX, Section 9.2. of the REACH Regulation, degradation products need to be identified if the chemical safety assessment (CSA) according to Annex I of the REACH Regulation indicates the need to investigate further the degradation of the substance and its degradation products. Column 2 of Annex IX, Section 9.2.3. of the REACH Regulation further specifies that the identification of degradation products does not need to be provided if the substance is readily biodegradable.

ECHA notes that based on the information provided in your technical dossier, the registered substance is not readily biodegradable as also discussed in section 2 and section 3 above.

Furthermore, ECHA considers that your CSA indicates the need to investigate further the degradation products. Pursuant to Annex XIII of the REACH Regulation "*the identification* [of PBT and vPvB substances] *shall also take account of the PBT/vPvB-properties of relevant constituents of a substance and relevant transformation and/or degradation products*". However, your CSA does not contain any justification for omitting to provide information on the degradation products and does not demonstrate the absence of concerns for their potential PBT/vPvB properties. Information on degradation products shall also be taken into account for the exposure assessment (Annex I, Section 5.2.4. of the REACH Regulation), when applicable, and for the hazard assessment (e.g. column 2 of Annex X, Section 9.4 and Annex X, Section 9.5.1 of the REACH Regulation). Finally, information on degradation

products is required for the preparation of Section 12 of the safety datasheet (Annex II of the REACH Regulation), when applicable.

As explained above, 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, 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 degradation studies also requested in this decision (section 2 and section 3 above), 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.

5. Bioaccumulation in aquatic species (Annex IX, Section 9.3.2.)

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. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Bioaccumulation in aquatic species, preferably fish" is a standard information requirement as laid down in Annex IX, Section 9.3.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier, you have provided study records for a QSAR prediction from model BCFBAF v3.01 (a module of the EPISuite program) and for an experimental result with rainbow trout ([redacted], 1993)[2]. From the QSAR model, a bioconcentration factor (BCF) of 551.7 was predicted. From the experimental study, a BCF of 4800 was reported. For your chemical safety assessment (CSA) you have assumed a BCF value of 551.7, i.e. the value predicted from the QSAR model, and you have disregarded the result from the experimental study.

[2] [redacted]; Bioaccumulation in Rainbow Trout. [redacted].

As explained below, ECHA disagrees with your assessment for bioaccumulation.

The QSAR prediction for BCF is uncertain and not sufficient to meet the standard information requirement

The QSAR model you have used for your assessment predicts a log BCF value from log Kow. It is based on 3 distinct linear regression equations, depending on whether Log Kow is < 1.0, between 1.0 and 7.0, or > 7.0. ECHA notes that you have used a log Kow value of 4.66 as input to the model. However, the value reported in the log Kow study is in fact *above* 4.66 (>4.66). ECHA considers that the actual log Kow value may potentially be much higher than 4.66. In particular, ECHA notes that the log Kow predicted by QSAR model KOWWIN v1.68, also a module of the EPISuite program, is 9.28.

Assuming that only lipophilicity governs the bioaccumulation or the bioconcentration of the substance and that lipophilicity and hydrophilicity are inversely proportional, it is generally assumed that the bioconcentration or bioaccumulation of a substance is correlated to its log Kow value. However, the linear relationship between log Kow and the bioconcentration factor (BCF) seems not to apply to highly hydrophobic substances. It is apparent in the documentation of the BCFBAF v3.01 model that the goodness of fit for chemicals with log Kow > 7 is very poor. Therefore, the model's predictions for substance with very high log Kow are regarded as uncertain.

As explained above, ECHA concludes that the QSAR prediction you have used for the assessment of bioaccumulation is uncertain as the log Kow value to be used as input parameter to the model is itself uncertain but is likely to be very high. Therefore, the QSAR prediction is not adequate to conclude on the bioaccumulation potential of the substance.

Available screening information indicates potential B properties for the substance

Annex XIII of the REACH Regulation makes the distinction between 'screening information' and 'assessment information'.

Section 2.1. of this Annex specifies that "*no additional information needs to be generated for the assessment of PBT/vPvB properties if there is no indication of P or B properties following the result from the screening test or other information*". Therefore, as long as one piece of screening information indicates that the substance could potentially be bioaccumulative (B) or very bioaccumulative (vB), then further information will need to be generated.

Section 3.1.2. of Annex XIII of the REACH Regulation indicates that the log Kow of the substance can constitute screening information for the assessment of B and vB properties. Chapter R.11 of the ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, June 2017), specifies that the threshold value for screening for B and vB properties is log Kow greater than 4.5.

ECHA notes that you have reported for the registered substance an experimental log Kow value which is above 4.66, although ECHA understands that the actual log Kow may be higher (see above). Therefore, ECHA concludes that the screening criterion of log Kow >4.5 is positively met for the substance. Consequently, there is indication of B properties from the available screening information.

A QSAR prediction cannot be regarded as assessment information

Section 3.2. of Annex XIII of the REACH Regulation presents 'assessment information' that could be used to conclude on the PBT/vPvB status of a substance. However, ECHA notes that QSAR predictions are not mentioned as possible assessment information. Therefore, ECHA considers that the BCF value of 551.7 predicted by the BCFBAF v3.01 model cannot be regarded as assessment information that would supersede the screening information represented by the log Kow of >4.66.

Section 3.2. of Annex XIII of the REACH Regulation further specifies that available assessment information shall be considered using a weight-of-evidence approach. ECHA notes that several pieces of information available in the dossier tend to indicate potential B/vB properties of the substance: log Kow is above 4.5 and the BCF calculated from the experimental study you have disregarded ([redacted] 1993) is 4800 (see next paragraph below). These contradict the prediction of the BCFBAF v3.01 model. Therefore, even if the QSAR prediction were to be considered for the assessment, it would not constitute enough evidence to conclude on the B/vB status of the substance.

The results from the experimental study are unreliable but provide evidence of high bioaccumulation potential

Your dossier report an experimental result with rainbow trout ([redacted] 1993), but which you have disregarded for your assessment with the justification that it has some "*major methodological deficiencies*".

Two different test concentrations were used: 0.5 µg/L and 5.0 µg/L (nominal concentrations). The depuration period was 14 days.

During exposure to 0.5 µg/L (measured: 0.55 µg/L), mean concentrations in fish increased to 530 µg/kg after 3 days and to 2500 µg/kg after 28 days. After the 14 days depuration period, the mean concentrations in fish had decreased slowly to 1300 µg/kg. The corresponding bioconcentration factor is reported to be 4300.

During exposure to a nominal 5 µg/L (measured: 3.53 µg/L), mean concentrations in fish increased to 4300 µg/kg after 3 days and to 15000 – 16000 µg/kg after 21 - 28 days. During the 14 days depuration period, the mean concentrations in fish had decreased slowly to 9300 µg/kg. The corresponding bioconcentration factor is reported to be 4800.

ECHA agrees that the two BCF values calculated from this study are unreliable as it is indeed clear from the information available on this study that the steady state concentration in fish was not reached after 28 days. This may underestimate the true level of bioaccumulation.

Besides, ECHA notes that important pieces of information are missing for this study:

- It is not clear whether BCF values were calculated from nominal or measured aqueous concentrations
- It is not clear whether reported values include metabolites or not. It is not specified whether parent compound analyses were performed.

- It is not specified whether data were normalised to 5% lipid content.
- It is specified that fish weight showed a steady increase during the study, but it is not clear whether the growth dilution was taken into account to calculate the reported BCF values. The fish weight data are not reported therefore it is not possible to assess the growth dilution correction.

However, ECHA considers that this study does provide information useful for the B/vB assessment of the substance. From this information, depuration rates and kinetic BCF can be calculated.

Assuming first-order kinetics, the uptake of the substance by the fish can be described as follows:

$dC_f/dt = k1\ C_w - k2\ C_f$

and therefore:

$C_f = k1/k2\ .\ [C_w\ (1-e^{-k2.t})]$,

where C_f is the concentration in fish, C_w the concentration in water (assumed to be constant), k1 the first order rate constant for uptake into fish, k2 the first order rate constant for depuration from fish.

As for the depuration rate, it can be calculated as follows, still assuming first-order kinetics:

$dC_f/dt = - k2\ C_f$

therefore:

$C_f = C_{f0}\ e^{-k2.t}$

k2 can be estimated from experimental data as follows:

$k2 = (\ln C_{f1} - \ln C_{f2})/t$

where C_{f1} is the concentration in fish at the beginning of the depuration period, C_{f2} the concentration in fish at the end of the depuration period, and t the duration of the depuration period (i.e. 14 days).

Subsequently, k1 can be estimated as follows:

$k1 = (C_f.k2) / [C_w\ (1-e^{-k2t})]$

BCF can be calculated as C_f/C_w only if steady state concentration has been reached (static BCF). Alternatively, BCF can be calculated as k1/k2 (kinetic BCF), if uptake and depuration follow first-order kinetics.

Assuming first-order kinetics, and using measured concentrations in water instead of nominal, the corresponding kinetic BCF values can therefore be calculated:

- For the test concentration of 0.55 µg/L (measured):

  k2 is estimated as 0.0467 day^{-1},

  k1 is estimated as 291 $L.kg^{-1}.day^{-1}$,

  and the kinetic BCF as 6230.

- For the test concentration of 3.53 µg/L (measured):

  k2 is estimated as 0.0387 day^{-1},

  k1 is estimated as 265.3 $L.kg^{-1}.day^{-1}$,

  and the kinetic BCF as 6845.

The large differences between the static BCF values reported in your study summary, and the kinetic BCF values calculated by ECHA can be explained by the fact that the steady state concentrations in fish were not reached after 28 days.

ECHA notes that the calculated kinetic constants k1 and k2 and the kinetic BCFs are consistent for the two concentrations tested. ECHA further notes that the very low values of the depuration rates (k2) and the very high values for the corresponding kinetic BCFs suggest a very high bioaccumulation potential of the substance.

ECHA notes that the BCF values might even be higher if lipid normalisation or growth dilution correction had been taken into account. Furthermore, according to QSAR predictions (e.g. WSKOW v1.41 and WATERNT v 1.01), the water solubility of the substance may actually be much lower than the one reported in the dossier and much lower than the concentrations used in the bioaccumulation study. This would too imply that the actual BCF values might be higher.

Therefore, ECHA agrees that the BCF values reported in the study of [redacted] (1993) are insufficient to definitively conclude on the B/vB status as it can be shown that the steady state concentration in fish was not reached after 28 days and as some important elements of the study are not documented. However, ECHA considers that this study still provides some evidence that the substance could be bioaccumulative (B) and even very bioaccumulative (vB). In particular, ECHA notes that the static BCF values reported from this study are well above the threshold of 2000 for the B criterion and close to the threshold level of 5000 for the vB criterion. The fact that the steady state concentration in fish was not reached after 28 days may actually underestimate the true level of bioaccumulation. This is supported by the kinetic BCF values calculated by ECHA. The very low depuration constants (k2) and the very high kinetic BCFs suggest that the substance could exceed the thresholds for the B and vB criteria.

Outcome

As explained above, ECHA disagrees with your conclusion that the registered substance is not (very) bioaccumulative and considers that available information indicates potential B and even vB properties. Pursuant to Sections 2 and 3 of Annex XIII of the REACH Regulation, assessment information shall then be generated. Bioconcentration or bioaccumulation studies in aquatic species (Annex IX, Section 9.3.2. of the REACH Regulation) constitute adequate assessment information for the B and vB properties.

According to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017) bioaccumulation in fish: aqueous and dietary exposure (test method EU C.13. / OECD TG 305) is the preferred test to cover the standard information requirement of Annex IX, Section 9.3.2. of the REACH Regulation.

For the selection of the appropriate exposure route for the test, you are advised to consult OECD Test Guideline 305 (version of 2 October 2012) and the ECHA Guidance on information requirements and chemical safety assessment (version 3.0, June 2017), Chapter R7c, Section R.7.10.3 and Chapter R.11, Section R.11.4.1.2.

According to OECD Test Guideline 305 (OECD TG 305), the aqueous exposure test is most appropriately applied to stable organic chemicals with log Kow values between 1.5 and 6.0 but may still be applied to strongly hydrophobic substances (having log Kow > 6.0), if a stable and fully dissolved concentration of the test substance in water can be demonstrated.

Dietary studies were developed to take account of possible uptake via the gut, i.e. from food. For extremely hydrophobic and extremely lipophilic substances, uptake from water, i.e. via the fish gills, is usually limited. Extreme lipophilicity is often correlated with very low water solubility and therefore with very low bioavailability from water. For highly hydrophobic and highly lipophilic substances (high log Kow and low water solubility) exposure via the diet or via ingestion of sediment or suspended matter therefore becomes more significant than exposure via water. The absorption of lipophilic contaminants can occur concomitantly with the absorption of dietary lipids. The gastrointestinal tract includes specialised mechanisms for the absorption of dietary lipids. Lipid digestion in all fishes requires an emulsifier (bile salts or bile alcohols) to solubilise the lipids before being broken down by pancreatic lipases. Gut uptake of lipophilic contaminants is strongly associated with the digestion and assimilation of those dietary lipids. Mechanical mixing, bile salts, and pancreatic lipases, disperse dietary lipids and contribute to the formation of an equilibrium phase consisting of small mixed micelles. Lipophilic contaminants can reside in the interior of these micelles, while the hydrophilic exterior allows the micelles to remain soluble in the aqueous milieu of the luminal contents. Micelles provide a packaging and transport phase that can traverse the water layer of the mucosa. Upon reaching the enterocytes, the micelles are dissociated by the combined action of pH changes and mucosal lipases. In fishes, the lipid-associated contaminants absorbed by the enterocytes are exported as very-low density lipoproteins into the lymph and the systemic circulation. The intestinal absorption efficiency of ingested and digested contaminants differs according to species and chemicals but is also dependent upon the lipid content of the food source. Dissolution from the food source may actually be the rate limiting determinant of the contaminant absorption since desorption half-lives of contaminants from food may be longer than the intestinal transit time.

Results obtained from a test with aqueous exposure can be used directly for comparison with the B and vB criteria of Annex XIII of the REACH Regulation and can be used for hazard classification and risk assessment. On the contrary, comparing the results of a dietary study with the B and vB criteria of Annex XIII is more complex and has higher uncertainty. Therefore, the aqueous route of exposure is by default the preferred route and should be used whenever technically feasible. If you decide to conduct the study using the dietary exposure route, you shall provide scientifically valid justification for your decision. You shall also attempt to estimate the corresponding BCF value from the dietary test data by using the approaches given in Annex 8 of the OECD 305 TG and in OECD Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation, ENV/JM/MONO (2017)16. In any case, you shall report all data derived from the dietary test as listed in the OECD 305 TG.

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: Bioaccumulation in fish: aqueous or dietary bioaccumulation fish test (test method: OECD TG 305)

Notes for your consideration

ECHA informs you that another registrant for this substance has submitted a testing proposal for a bioaccumulation study in aquatic species (test method: OECD TG 305). ECHA expects you and this registrant to coordinate and agree who shall perform the test on behalf of all registrants for the same substance, according to REACH Article 53, to avoid unnecessary testing on vertebrates.

Before conducting the above test you are advised to consult the ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, June 2017), Chapter R.11.4. and Figure R.11-4 on the PBT assessment for further information on the integrated testing strategy for the bioaccumulation assessment of the registered substance. In particular, you are advised to first conclude whether the registered substance may fulfil the REACH Annex XIII criteria of being persistent or very persistent, and then to consult the PBT assessment for Weight-of-Evidence determination and integrated testing strategy for bioaccumulation assessment. You should revise the PBT assessment when information on bioaccumulation is available.

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

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. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.), or Fish, short-term toxicity test on embryo and sac-fry stages (Annex IX, 9.1.6.2.), or Fish, juvenile growth test (Annex IX, 9.1.6.3.) needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex IX, Section 9.1.6., column 2. You provided the following justification for the adaptation: "*In accordance with column 2 of REACH annex IX, long-term toxicity testing does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation*".

You have also provided a study record for a study conducted according to OECD Test Guideline 204 (Fish, Prolonged Toxicity Test: 14-day Study).

ECHA considers that the study conducted according to OECD Test Guideline 204 is not a proper long-term study and is not adequate to fulfil the information requirement of long-term toxicity to fish (Annex IX, Section 9.1.6. of the REACH Regulation). According to the provisions of Annex IX, Section 9.1.6, information on long-term toxicity to fish as specified in sections 9.1.6.1 Fish, early-life stage (FELS) toxicity test, 9.1.6.2 Fish, short-term toxicity test on embryo and sac-fry stages or 9.1.6.3 Fish, juvenile growth test, shall be provided. Only such studies can be regarded as long-term fish tests, in which sensitive life-stages (juveniles, eggs, larvae) are exposed. For this purpose the most relevant long-term fish tests are OECD test guidelines 210, 212 or 215, OECD TG 210 being the most sensitive and thus accepted/recommended (ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7b (version 3.0, June 2017)). ECHA points out that the study conducted according to the OECD test guideline 204 does not provide an adequate coverage of some key parameters such as observations on the stage of embryonic development, hatching and survival, abnormal appearance/behaviour, weight and length, which are investigated in a study performed according to the OECD test guideline 210. Furthermore, the study duration in OECD TG 204, i.e. 14 days, is shorter than the exposure period expected from a long-term toxicity study on fish performed according to the OECD TG 210. According to OECD TG 210, the test is initiated by placing fertilised eggs in test chambers and is continued for a species-specific time period that is necessary for the control fish to reach a juvenile life-stage (28-60 days post-hatch depending upon the species used). OECD TG 204, in fact is a prolonged acute study with fish mortality as the major endpoint examined. Furthermore, while this test method is an internationally recognised OECD test guideline, it is considered to be obsolete by the OECD and thus was deleted in 2014. Therefore, ECHA concludes that the study according to OECD TG 204 does not fulfil the requirement of Annex IX, Section 9.1.6 of the REACH Regulation for an adequate and reliable coverage of the key parameters addressed and for an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3).

ECHA notes that the registered substance has low water solubility: 20 µg/L according to experimental data, but QSAR calculations performed by ECHA (WSKOW v1.41 and WATERNT v 1.01) suggest that the water solubility may be even lower. Poorly soluble substances require longer time to be significantly taken up by the test organisms and so steady state conditions are likely not to be reached within the duration of a short-term toxicity test. For this reason, short-term tests may not give a true measure of toxicity for poorly soluble substances and toxicity may actually not even occur at the water solubility limit of the substance if the test duration is too short. Still, long-term toxicity cannot be excluded and should be investigated. In particular, Annex VIII 9.1.3. and Annex VII 9.1.1. of the REACH Regulation explicitly recommend that long-term aquatic toxicity tests be considered if the substance is poorly water soluble. ECHA notes that your technical dossier contains information for short-term toxicity to fish but not for long-term toxicity to fish. Therefore, ECHA concludes that the available information in your chemical safety assessment does not rule out long-term effects to aquatic organisms.

According to the Guidance on information requirements and chemical safety assessment (version 3.0, June 2017), Chapter R7b, Section R.7.8.5.3, the Chemical Safety Assessment (CSA) is to be based on all available toxicity information, and that the information used for the derivation of the predicted no effect concentration (PNEC) for water should at least cover species of three trophic levels: algae/aquatic plants, invertebrates (*Daphnia* preferred), and fish, irrespective of the term of the studies (whether short-term or long-term). However, as explained above, ECHA considers that information from short-term tests alone is not adequate to assess the toxicity of poorly soluble substances. Therefore, no adequate information is available for aquatic toxicity to fish and there is not sufficient information available for the PNEC derivation.

Moreover, information on long-term toxicity to fish may be necessary for the PBT assessment. As explained in sections 2 to 5 above, P/vP and B/vB properties of the substance cannot be ruled-out. Therefore, adequate information on toxicity to fish may need to be generated for the PBT assessment.

Finally, information on long-term toxicity to fish shall be considered for classification and labelling of the substance.

As explained above, ECHA considers that your chemical safety assessment does indicate the need to investigate further the long-term effects on fish. ECHA concludes that your adaptation of the information requirement does not meet the specific rules for adaptation of column 2 of Annex IX, Section 9.1.6. of the REACH Regulation and cannot be accepted. 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) 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) are the preferred tests 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 fertilised 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).

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

Due to the 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 and for calculation and expression of the result of the test.

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 1 November 2017.

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 did not receive any comments by the end of the commenting period.

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) 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, or to otherwise fulfil the information requirements with a valid and documented adaptation, 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.