ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 23 July 2019

Addressee: [redacted]

Decision number: CCH-D-2114476180-53-01/F
Substance name: N,N',N'',N'''-tetrakis(4,6-bis(butyl-(n-methyl-2,2,6,6-tetramethylpiperidin-4-yl)amino)triazin-2-yl)-4,7-diazadecane-1,10-diamine
EC number: 401-990-0
CAS number: 106990-43-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 17/11/2014
Registered tonnage band: Over 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. **Water solubility (Annex VII, Section 7.7.; test method: EU A.6./OECD TG 105) with the registered substance;**

2. **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;**

3. **Robust study summary for key study [redacted] in vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3. in conjunction with Annex I, Section 1.1.4.);**

4. **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;**

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

6. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**

- **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and**
- **Cohort 3 (Developmental immunotoxicity).**

7. **Robust study summary for key study [redacted] Growth inhibition study aquatic plants (Annex VII, Section 9.1.2. in conjunction with Annex I, Section 3.1.5);**

   or

   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;

8. **Robust study summary for key study [redacted] Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5. in conjunction with Annex I, Section 3.1.5);**

   or

   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;

9. **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;**

10. **Identification of degradation products (Annex IX, 9.2.3.) using an appropriate test method with the registered substance including each relevant constituent present in concentrations at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable.**

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 ***01 August 2022***. 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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met".

In the registration, you have adapted the standard information requirements for

- Pre-natal developmental toxicity study (*Annex IX, Section 8.7.2.)* in a first species;
- Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.) and

by applying a read-across adaptation following REACH Annex XI, Section 1.5.

The proposed read across in respect to carcinogenicity is not addressed in this Decision as the conditions requiring provision of this information as set out in Annex X, Section 8.9.1 column 2 are currently not met.

According to Annex XI, section 1.5. there needs to be structural similarity among the substances within a group or category and furthermore, it is required that the relevant properties of a substance within the group can be predicted from the data for the reference substance(s), and the data should be adequate for the purpose of classification and labelling and/or risk assessment. The REACH Regulation aims at promoting wherever possible the use of alternative means, where equivalent results to the prescribed test are provided on health and environmental hazards. In accordance with these objectives and the objectives of the Compliance Check process, ECHA shall assess whether a prediction of the relevant properties of the substance subject to this decision by using the results of the proposed read-across is acceptable based on the information currently available.

ECHA based its decision on the evaluation of your registration dossier with the submission number [redacted] that contains adaptation arguments in form of a grouping and read-across approach under Annex XI, 1.5. of the REACH Regulation, for certain toxicological endpoints which are addressed in the current decision. ECHA has assessed first the scientific and regulatory validity of your read-across approach in general in section (section 0) of this decision. The corresponding sections 4 and 6 refer back to this section.

0.1 Description of the grouping and read-across approach proposed by you

You have proposed read-across between the substance subject to this decision, N,N',N'',N'''-TETRAKIS(4,6-BIS(BUTYL-(N-METHYL-2,2,6,6-TETRAMETHYLPIPERIDIN-4-YL)AMINO)TRIAZIN-2-YL)-4,7-DIAZADECANE-1,10-DIAMINE [EC 401-990-0, CAS 106990-43-6, hereafter referred to as CB 20-119] as target substance and the substance N,N'-bis(2,2,6,6-tetramethylpiperidin-4-yl)hexane-1,6-diamine; 2,4,6-trichloro-1,3,5-triazine; 2,4,4-trimethylpentan-2-amine [EC 615-678-9, CAS 71878-19-8, hereafter referred to as Chimassorb 944] as the source substance.

Your dossier contains read-across documentation as a separate attachment titled "Read across justification" in IUCLID, Section 13.

In summary, you use the following arguments to support the prediction of properties of the target substance from data of the source substance:

- Similar functional groups and structural similarities:
  "Both chemicals have the same functional groups. Both compounds consist of several [redacted] *CB 20-119 has* [redacted] *attached to the molecule, whereas Chimassorb 944 has* [redacted]

- Similar physico-chemical properties and molecular size:
  "The physico-chemical properties of the read-across candidate are in good correlation with the data for the substance under evaluation. Specifically, the water solubility was found to be in a comparable (low) range as is the partition coefficient. In addition, both compounds are rather large molecules. This relationship gives rise to an expected comparable degree of bioavailability and toxicological profile. On this basis, it is expected that any toxicological effects shown by the reference substances should encompass the full range of potential toxicological properties".

- Similar toxicological properties:
  "Both chemicals share very similar toxicological properties in all endpoints tested such as acute toxicity, irritation and genetic toxicity. Furthermore, the assessment of the available repeated dose toxicity studies for both substances revealed the same target organs with very similar effects caused by exposure to the chemicals. The derived NOAELs in these studies were also of similar magnitude".

- Metabolic similarities:
  "Both chemicals are not absorbed through the intestinal cells and excreted rapidly via the faeces, as demonstrated by TK studies. However, small amounts of both substances are taken up through the mesenterical lymph nodes, which also reflect the primary target organ.

  Further distribution throughout the body is observed at higher doses by foam cells, reflecting macrophages with liquid or xenobiotic material. Chimassorb 944 shows a higher tendency to accumulate in different organs, as shown by the experimental data. This substance therefore serves as a worst case scenario and read across from Chimassorb 944 to CB 20-119 is justified".

- Similar mode of action: *"Cell proliferation in the mesenteric lymph nodes is the first effect observed in several repeated dose toxicity studies, indicating that the Peyer's patches are target organs and the likely route of uptake... Following uptake through macrophages both substances are then distributed throughout the body and can accumulate in other organs".*

You propose that due to structural similarity, same functional groups, physico-chemical properties and mode of action, the source and target substances have similar toxicity profiles for all toxicological properties. ECHA considers this as the hypothesis under which you make predictions for the properties of pre-natal developmental toxicity and extended one-generation reproductive toxicity.

0.1 ECHA analysis of the grouping and read-across approach in light of the requirements of Annex XI, 1.5.

With regard to the justification for read-across, ECHA has the following observations:

A. Substance characterisation of source and target substance

The substance characterisation of the source substance needs to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In the ECHA's Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4) (version 2.0, July 2016), it is indicated that a read-across should include satisfactory substance identification of all the source and target substances, including constituents, and purity/impurity profiles. It is also recommended to follow the ECHA *Guidance for identification and naming of substances under REACH and CLP* (version 2.1, May 2017) also for the source substances. This ensures that the identity of the source substance and its impurity profile allows an assessment of the suitability of the substances for read-across purposes. In particular, this guidance recommends that "Impurities present in a concentration >1% should be specified by at least one of the following identifiers: chemical name (IUPAC and/or CAS name), CAS-number and EC-number and/or molecular formula. Impurities that are relevant for the classification and/or PBT assessment shall always be specified by the same identifiers, independently from their concentration."

ECHA notes that you have provided only the name and CAS Number of the source substance Chimassorb 944 and no purity/impurity profile or any other identification of the substance. In addition, purity/impurity information has not been provided for the test material under endpoint study records. Further, you have not addressed the impact of impurities on the toxicity profiles of the target and source substances.

Hence, these data cannot be assessed using the information provided in the registration dossier and the suitability of the substance for predictions based on read-across purposes cannot be verified.

B. Reliability and adequacy of the source studies

ECHA notes that you have submitted study records in the registration dossier of a two generation reproductive toxicity study in rats, a PNDT study in rats and a carcinogenicity study in rats conducted with the source substance. No study records have been submitted for the toxicokinetic, acute toxicity, irritation, sensitisation, genotoxicity and sub-chronic toxicity studies with the source substance. These studies are only referenced in your "read across justification" document and their results are presented either in tabulated form (acute toxicity, irritation, sensitisation and genotoxicity studies) or described briefly in text (toxicokinetic study and sub-chronic toxicity studies). In the absence of adequate and reliable information, an independent assessment of the source studies and whether they support your read-across is not possible. ECHA has evaluated under this reservation the information included in your read-across justification document.

C. Similar functional groups and structural similarities

Structural similarity is a prerequisite for applying the grouping and read-across approach, and therefore, it has to be justified why prediction of similar human health properties is possible in view of the identified structural differences. Hence, you have to address any stuctural differences between the source and the target substances and explain why those

differences would not lead to differences in the toxicity profile of target and source substances for the properties of pre-natal developmental toxicity and extended one-generation reproductive toxicity for which you make predictions.

ECHA acknowledges that the target and the source substances have triazine and methylated piperidine groups in their structure. Nevertheless, ECHA observes that the target and source substances display significant structural differences:

- the target substance CB 20-119 is a monomer with [redacted]
- the source substance Chimassorb 944 is a oligomer/polymer [redacted] In addition to variability in size, there are variations in the repeating structures, e.g. the source substance contains additional [redacted] when compared with the target substance.

You have not explained whether or how the differences in the repeating structures and in the number of functional groups between the source and the target substances will impact their toxicity profiles. Moreover, the source substance appears to be a mixture of polymers of different size and you have not explained either whether this has an impact on its toxicity.

ECHA concludes that you have not addressed the stuctural differences between the source and the target substances and you did not sufficiently explain why those differences would not lead to differences in the toxicity profile of target and source substances for the properties of pre-natal developmental toxicity and extended one-generation reproductive toxicity for which you make predictions. Therefore, your hypothesis cannot be considered as valid to establish a scientific credible link between the structural similarity and the prediction.

D. Similar physicochemical properties and molecular size:

ECHA agrees that the physicochemical properties of the source and the target substance are within the same range due to similar functionalities and due to the high molecular weight.

E. Similar toxicological properties

Annex XI, Section 1.5. provides that "*substances whose physicochemical properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances*". One prerequisite for a prediction based on read-across, therefore, is that the substances involved are structurally similar and are likely to have similar properties. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern. In addition, 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 endopint under consideration.

To substantiate the similarity in the toxicological properties of the source and target substances, you have submitted the data on source substance presented in point B. For the target substance you have submitted study records in the registration dossier of studies on

acute oral and dermal toxicity, skin and eye irritation and skin sensitisation, 28-day oral toxicity, 90-day oral toxicity, *in vitro* and *in vivo* genotoxicity.

As indicated in point D, the available data do not enable the independent evaluation of the toxicological properties of the source substance. Nevertheless, ECHA has evaluated under this reservation, the information included in your read-across justification document and has the following observations based on your reporting:

i. Both substances appear to have similar acute toxicity and eye and dermal irritation properties, but the target substance CB 20-119 is a skin sensitizer whereas the source substance Chimassorb 944 is not. Since the target substance induces skin sensitisation it may have also potential to penetrate the skin. On the contrary, ECHA notes there is no indication that Chimassorb 944 can be dermally absorbed.
ii. In the repeated dose toxicity (RDT) studies, ECHA observes that the data matrix supports a similar pattern in sub-chronic toxicity induced by the source and the target substances. ECHA notes that similar effects in the sub-chronic toxicity are also supported by the observations in the carcinogenicity study with the source substance, submitted in the registration dossier of the target substance ([redacted] 1987).
iii. From the comparison of the NOAEL/LOAEL values and the effects observed in sub-chronic and chronic toxicity studies, ECHA notes that your argument that the source substance is a worst-case scenario compared to the target substance cannot be verified, since the induced effects are similar and the lowest NOAEL value for both substances is at 5mg/kg/bw. Hence, the source substance does not appear to induce more severe effects and/or effects at lower levels than the target substance.

F. Metabolic similarities

Although the available data do not enable the independent evaluation of the toxicokinetic properties of the source substance, ECHA has evaluated under this reservation, the information included in your read-across justification document and has the following observations based on your reporting:

iv. The available ADME studies indicate that the oral absorption of both the target substance CB 20-119 and source substance Chimassorb 944 is very low.
v. You have not provided any information on the metabolism of the target and source substances.
vi. Regarding your suggestion that the source substance represents a worst case scenario, ECHA understands that you imply that since Chimassorb 944 seems to be of greater accumulation potential, then its toxicity potential would be greater as well. ECHA notes that this assumption is not verified by the results of the repeated dose toxicity studies, as described above in point (iii).
vii. Regarding the pattern of uptake and distribution, ECHA agrees that the findings of the RDT studies indicate a similar likely pattern of uptake via phagocytic cells and further distribution in various organs for the target and source substances.

G. Read-across justification based on similar mode of action (MoA)

Although the available data do not enable the independent evaluation of the proposed mode of action of the source substance, ECHA has evaluated under this reservation, the information included in your read-across justification document and has the following observations based on your reporting:

viii. ECHA understands that your proposed MoA refers to a proposal on the uptake and distribution of the source and target substances as presented in point vii. Hence, ECHA

considers that your proposal is relevant to the disposition of the target and source substances and acknowledges that the available data support your claim.

H. Endpoint specific considerations

ECHA has the following observations on the read across properties of developmental and reproductive toxicity:

ix. No data are available for the target substance. For the source substance, you provided study records in the registration dossier of a two generation reproductive toxicity study in rats and a PNDT study in rats. No biologically relevant embryotoxic / teratogenic effects were detected in the PNDT study. In the two generation reproductive toxicity study, no treatment related adverse effects were observed on the offspring and on the mating performance and fertility of parental animals.

ECHA notes you have provided no specific information, argument or data on its reproductive and developmental toxicity properties of the target substance (such as a screening study according to OECD 422 or 421) that would allow the comparison of these properties between the target and the source substance.

Hence, although the source substance Chimassorb 944 is not a reproductive toxicant, you have not explained why the structurally different target substance would not be a reproductive toxicant itself.

x. Further, you have provided data that indicate likely similar uptake and sub-chronic toxicity profile, but you have not explained either how the developmental and reproductive toxicity of the target substance can be predicted by the similarities in the toxicokinetic properties and sub-chronic toxicity with the source substance. Two substances may have similar toxicokinetic properties and even similar toxicity for specific endpoints such as sub-chronic toxicity, but their structural dissimilarity may cause different toxicodynamic properties, which may induce different effects relevant to other toxicological properties such as developmental or reproductive toxicity.

In the absence of such explanations and/or data for the target substance, ECHA cannot compare the properties of source and target substances and establish whether indeed they are similar or follow a regular pattern of toxicity for pre-natal developmental effects or reproductive toxicity. Therefore, ECHA considers that there is no adequate basis for predicting these properties of the target substance from the source substance.

0.3 Conclusion on the read-across approach

The adaptation of the standard information requirements *Pre-natal developmental toxicity study* (Annex IX, Section 8.7.2) and *Extended one-generation reproductive toxicity study* (Annex X, Section 8.7.3.) in the technical dossier is based on the proposed read-across approach examined above. For all the reasons explained above, ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the target substance for the reasons set out above. Thus, the adaptation does not comply with the rules of adaptation as set out in Annex XI, 1.5. Therefore, ECHA rejects the above adaptations that are based on Annex XI, 1.5.

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

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

"Water solubility" is a standard information requirement as laid down in Annex VII, Section 7.7 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 endpoint summary for water solubility (ws), you indicate a value < 0.002 g/L at 20°C, with additional information: "The water solubility was determined by photometric method and the detection limit of the method is 1mg/L."

You have provided two endpoint study records:

[1] Key study with the result ws < 0.002 g/L at 20°, pH value not reported, EU Method A.6 (Water Solubility), not in compliance with GLP.

You have indicated as the analytical method: photometric determination with detection limit: 1mg/liter. You have performed the test with the registered substance with [redacted] purity. Name of test material was (as cited in study report): [redacted] Lot/batch No.: EN 315143.12.

[2] Key study with the result ws <0.01 g/L at 20°, pH >= 5.2 <=5.8 i.e. as a cconclusion ws <0.01 g/L at 20°C at ca. pH 5.5, EU Method A.6 (Water Solubility), in compliance with GLP.

You have provided the following results ws: <0.004 / <0.004 / <0.006 g/L with pH values : 5.4 / 5.2 / 5.8 and the average for the different flasks: <0.005 g/L. Test temperature was 20°C . You have performed the test with the registered substance. Name of test material was (as cited in study report): [redacted] Lot/batch No.: Op Ba 17/18/19.

You have provided a remark that "the water solubility of the test substance is very low (approx. detection limit of method). Therefore the result is given as being inferior to 0.01 g/L."

You also indicated that the flask method was used instead of the column method because a change in crystal structure might occur when the test substance is deposited on the support material.

The concentration in the water solution was determined by diluting with tetrahydrofurane in a 1:1 ratio and analysing by liquid chromatography, using an external standard for calibration.

ECHA notes that for the key study 1 you have not indicated the study type. Only one test has been performed by treating the sample 24 h at 30°C and 24 h at 20°C. This would indicate a study following Flask method protocol. According to the guideline, when performing Flask method study, three studies are required with durations of 24 h at 30°C plus 1 days, 2 days and 3 days of re-equilibration. The pH of each sample should also be recorded. You have not provided purity or composition of the sample. Therefore EU Method A.6 (Water Solubility) guideline or reporting has not been followed. Detection limit 1 mg/L of the photometric method cannot be evaluated by ECHA. ECHA understands that under

normal circumstances detection limits below 1 mg/L can be achieved with aromatic compounds with UV/light absorbance properties.

For the key study 2, there are no further details on which type of change in crystalline form might occur with the substance if column elution method were used. Based on information in the dossier it is not apparent that this change occurs or that it could impact a column elution study. For low water solubility substances, column elution method is recommended in the Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a: Endpoint specific guidance (Version 6.0, July 2017, p. 68).

For the key study 2 you gave informed detection limit of 1 mg/L for the liquid chromatographic method. This limit cannot be evaluated by ECHA as no further information has been provided. ECHA understands that under normal circumstances detection limits below 1 mg/L can be achieved with aromatic compounds with UV/light absorbance properties.

For the key study 2 you have not reported any timelines followed in the study. Therefore it cannot be verified if you have followed appropriate timelines for the test according to EU Method A.6 (Water Solubility).

ECHA would also like to note that for risk assessment purposes, unbound results on physicochemical properties should not be reported. This is true especially when the properties are close to a threshold limit, in this case 1 mg/L which may impact other studies. You justify the unbound result by stating that the water solubility of the test substance is very low (approx. the detection limit of method). Therefore the result is given as being less than 0.01 g/L. According to ECHA guidance (Chapter R.7a: Endpoint specific guidance Version 6.0 – July 2017, p. 72) when following Flask method, you should report individual analytical determinations and the average of the values for different flasks and as a result water solubility in mg/l at temperature (°C). Also any deviation from the guideline method used or any other special consideration should be reported.

According to EU Method A.6 (Water Solubility), precise specification of the substance (identity and impurities) should be reported. In this case composition/purity of the sample is relevant when considering the reported property. You have reported the analytical purities as [redacted] for key study 1 and [redacted] for the key study 2 but no further information on the composition. In the absence of a precise specification of the test material, ECHA cannot verify whether it is representative of the registered substance.

ECHA also notes that according to ECHA guidance (Chapter R.7a: Endpoint specific guidance Version 6.0, July 2017), for ionising substances the pH -dependence of the water solubility should be known. At least the pH of the test water needs to be identified. In the context of marine risk assessment, when the pKa is close to 8 it may be necessary to obtain realistic measurements using seawater. ECHA notes that the registered substance has ionising properties that may impact water solubility in different pH values.

As a conclusion, you have provided 2 key studies. However there are deficiencies in both. ECHA considers that those studies do not cover the information requirement for water solubility.

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: Water solubility (test method: EU A.6./OECD TG 105 using an appropriate test method).

Guidance for determining appropriate test methods for the water solubility is available in the ECHA Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.7a, Section R.7.1.7.

In your comments to the draft decision you expressed your agreement to provide the requested information.

2. *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 as laid down in Annex VIII, Section 8.4.2. 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 a study record for an *in vivo* Chinese Hamster micronucleus test [redacted] 1986 [similar to OECD TG 474, reliability 2, Key study, under GLP like quality control]. However, this study does not provide the information required by Annex VIII, Section 8.4.2. Specifically, in the study the test material was administered by gavage and the sampling times were 16, 24 and 48 hours after single treatment. As a limitation of the study design, ECHA notes that only 1000 polychromatic erythrocytes per animal were scored for the incidence of micronuclei (instead of 2000 and 4000 recommended by OECD TG474 1997 and OECD TG474 2016, respectively). In the results of the study, no statistically significant change in the ratio of polychromatic to normochromatic erythrocytes was observed. Therefore, there is no clear indication from the study results that the test substance reached the bone marrow. ECHA observes that information on the bioavailability of the registered substance can be derived from the results of the ADME study in rats ([redacted] 1999; Basic toxicokinetics *in vivo*), which demonstrate that CB 20-119 is very poorly absorbed by the oral route.

Hence, ECHA considers that there is strong evidence that the registered substance does not reach the bone marrow after single oral administration. OECD TG 474 indicates: "*If there is evidence that the test substance, or a reactive metabolite, will not reach the target tissue, it is not appropriate to use this test*". Consequently, ECHA concludes that the conducted *in vivo* micronucleus test OECD 474 ([redacted] 1986c) is not valid to demonstrate the absence of genotoxic potential of the registered substance.

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 *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.

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).

In your comments to the draft decision you expressed your agreement to provide the requested information.

3. Robust study summary for key study [redacted] in vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3. in conjunction with Annex I, Section 1.1.4.);

Pursuant to Article 10(a)(vii) of the REACH Regulation, the information set out in Annexes VII to XI must be provided in the form of a robust study summary, if required under Annex I. Article 3(28) of the REACH Regulation defines a robust study summary as 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. Guidance on the preparation of the robust study summaries is provided in ECHA's Practical Guide 3 "*How to report robust study summaries*" (version 2.0, November 2012).

An *in vitro* gene mutation study in mammalian cells is a standard information requirement if a negative result in Annex VII, Section 8.4.1 and Annex VIII Section 8.4.2 as laid down in Annex VIII, Section 8.4.3. 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. Robust summaries will be required of all key data used in the hazard assessment.

You have provided a study record for a mammalian cell gene mutation assay with the registered substance [[redacted]1995; key study; reliability 1; OECD 476; GLP] to meet the standard information requirement of Annex VIII, Section 8.4.3.

However, ECHA notes that, contrary to Article 3(28) of the REACH Regulation, the documentation of this study is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment. In particular, the growth inhibition values are not reported in tabulated form. More specifically, in the endpoint study record, you have provided the following information regarding these values:

Mutagenicity test with metabolic activation
Original experiment: "*... The mean growth inhibiting values found at the next lower concentration after treatment and expression were 98.9% and 57.4% respectively ...*".
Confirmatory experiment: "*The mean growth inhibitory effect after the expression period was 65.5%*".

Mutagenicity test without metabolic activation
Original experiment: "*The mean growth inhibition values found at the highest concentration after treatment and expression were 95.0%* and 31.9%* respectively*".
Confirmatory experiment: "*The highest concentration proved toxic. The next lower concentration revealed a mean acute growth inhibitory effect of 70.5%. The mean growth inhibition after the expression period was 11.6%*".

Furthermore, ECHA notes that statistically significant positive effects have been observed in the study specifically:

- With metabolic activation in highest concentrations of the original and confirmatory experiments with p values of $0.001<p<0.002$ and $0.02<p<0.05$ respectively.
- Without metabolic activation in highest concentration of the original experiment with $p<0.001$.

ECHA observes that the cytotoxicity levels at which the positive effects were observed is not clearly indicated/documented in the report. In order to assess the biological significance of the observed effects these values have to be reported. Further, it is unclear whether the different wording used for the description of the results ("after treatment and expression" and "after the expression period") describes observations made at comparable points in time. It is not clear from the reporting of the growth inhibition values whether the recommendations of OECD TG 476 regarding cytotoxicity and number of analysable concentrations are met, since the reporting of two separate values obtained after treatment and expression is confusing. ECHA notes that the present study is reported to be in accordance with OECD TG 476 (1984) which indicates that "*Cytotoxicity is determined by measuring the colony-forming ability or growth rate of the cultures after the treatment period*".

Hence, 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: Robust study summary for the mammalian cell gene mutation assay, ([redacted] 1995) including:

- growth inhibition values as a separate column in the Tables of the study (original and confirmatory experiments, with and without metabolic activation);
- the method used for calculating the growth inhibition values.

In your comments to the draft decision you expressed your agreement to provide the requested information.

4. 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) 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 sought to adapt the information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a Prenatal developmental toxicity study in rats (OECD TG 414, [redacted], 1984) with the source substance Chimassorb 944 (EC 615-678-9, CAS 71878-19-8). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

As the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement, 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) R.7a, chapter R.7.2. 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.

In your comments to the draft decision, you agreed with ECHA's conclusion that insufficient information exists on the developmental toxicity of the registered substance. You expressed your intention to perform an OECD 421 with the registered substance in order to strengthen the read-across justification. In case the results from this OECD 421 study do not justify the read-across, the requested PNDT study in the 1st species with the registered substance would be performed.

Data from an OECD 421 study conducted with the registered substance may strengthen the read across justification provided that, for example, there is consistency of effects induced by the registered and the source substances. However since such information is currently not available, the read-across adaptation cannot be accepted and the data gap remains. The information provided in an updated dossier will be assessed in the Dossier Evaluation Follow-Up Process and ECHA will come to a conclusion on whether the information provided adequately fulfils the information requirement of Annex IX, Section 8.7.2.

ECHA notes that this OECD 414 study has been requested in a draft decision to other registrants of the same substance in order to fulfil this information requirement. In this context, ECHA reminds you of the obligation imposed by Articles 11 and Title III of the REACH Regulation on all the registrants of the same substance to submit registrations for the same substance jointly and to share the cost of required studies.

5. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Pre-natal developmental toxicity studies (test method OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the source substance Chimassorb 944 (EC 615-678-9, CAS 71878-19-8) as test material. As explained in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

Moreover, there is no information provided for a pre-natal developmental toxicity study in a second species.

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 consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

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) R.7a, chapter R.7. 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 second species (rabbit or rat) by the oral route.

In your comments to the draft decision you expressed your agreement to provide the requested information.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species with other available information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

6. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

The basic test design of an extended one-generation reproductive toxicity study (test method OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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

a) The 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 two generation reproductive toxicity study [[redacted] 1991; key study; reliability 2; OECD TG 416, GLP] with the analogue substance Chimassorb 944 (CAS no

71878-19-8).

However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

Hence, 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. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the study design

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). Ten weeks exposure duration is supported also by the lipophilicity of the substance (Log Kow 4.5 at pH 7.0) to ensure that the steady state in parental animals has been reached before mating.

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of 8.7.3., Annex X.

ECHA notes that existing information on the registered substance itself and on the structurally analogous substance Chimassorb 944 (CAS 71878-19-8), derived from *in vivo* studies indicated below show evidence of immunotoxicity:

- Sub-chronic toxicity studies conducted with both the registered substance CB 20-119 and the analogue substance Chimassorb 944 (presented in Section 0 of this Appendix) identified mesenteric lymph nodes and spleen as target organs with histopathologic findings such as inflammatory and necrotic changes at dose levels starting from ~50 mg/kg/bw. In addition, in the sub-chronic toxicity study ([redacted]

[redacted] 1991) conducted with the analogue substance, atrophy in thymus was observed.

- As supportive information, ECHA notes that:
  - in the non-guideline screening immunotoxicity study with the registered substance [Key [redacted] 1993 [redacted] reliability 2; no OECD GL; non GLP], the results suggest that macrophage function was affected by the treatment regimen.
  - the registered substance CB 20-110 is a strong skin sensitizer.

The afore-mentioned findings indicate a particular concern which justifies inclusion of the developmental immunotoxicity cohort.

Hence, ECHA concludes that the developmental immunotoxicity Cohort 3 needs to be conducted because there is a particular concern on (developmental) immunotoxicity based on the results from the above-identified *in vivo* studies on the registered substance itself and a substance structurally analogous to the registered substance.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.
Species and route selection

According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in 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.7.2 Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision you agreed with ECHA's conclusion that insufficient information exists on the reproductive toxicity of the registered substance. You expressed your intention to perform an OECD 421 with the registered substance in order to strengthen the read-across justification. In case the results from this OECD 421 study do not justify the read-across, the requested Extended one-generation reproductive toxicity study (test method OECD TG 443), with the registered substance would be performed.

Data from an OECD 421 study conducted with the registered substance may strengthen the read across justification provided that, for example, there is consistency of effects induced by the registered and the source substances. However since such information is currently not available, the read-across adaptation cannot be accepted and the data gap remains. Furthermore a concern for developmental immunotoxicity has been identified for the registered substance, as indicated in the draft decision. This concern cannot be addressed from neither information from the OECD 416 conducted with the source substance nor from a potentially upcoming OECD 421 study performed with the registered substance. The information provided in an updated dossier will be assessed in the Dossier Evaluation Follow-Up Process and ECHA will come to a conclusion on whether the information provided adequately fulfils the information requirement of Annex X, Section 8.7.3.

c) Outcome

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: Extended one-generation reproductive toxicity study (test method OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and
- Cohort 3 (Developmental immunotoxicity).

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B and/or Cohort Cohorts 2A if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

7. Robust study summary for key study [redacted] Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.);

OR

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Pursuant to Article 10(a)(vii) of the REACH Regulation, the information set out in Annexes VII to XI must be provided in the form of a robust study summary, if required under Annex I. Article 3(28) of the REACH Regulation defines a robust study summary as 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. Guidance on the preparation of the robust study summaries is provided in the ECHA Practical Guide 3 "*How to report robust study summaries*".

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. 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. Furthermore, pursuant to Article 10 (a)(vii) and Annex I, Section 3.1.5. of the REACH Regulation if there are several studies addressing the same effect, then, the study or studies giving rise to the highest concern shall be used to draw the conclusion and a robust study summary shall be prepared for that study or studies and included as part of the technical dossier. Robust study summaries will be required of all key data used in the hazard assessment.

In the technical dossier you have provided a study record for a Growth inhibition study aquatic plants: [redacted] according to test guideline ISO 8692 (Water Quality - Fresh Water Algal Growth Inhibition Test with Scenedesmus subspicatus and Selenastrum capricornutum) (equivalent or similar to OECD 201/EU method C.3), GLP compliant, reliable with restrictions (Klimisch 2) with the registered substance, to meet the standard information requirement of Annex VII, Section 9.1.2.

However, ECHA notes that you have not provided sufficient information in the technical dossier to allow the assessment of the reliability of the study. In particular, the following elements are missing:

- Details on test material. According to paragraph 61 of OECD TG 201, the test report must include chemical identification data (e.g. CAS number), including purity (impurities), of the test substance. Furthermore, according to Practical Guide 3 "*How to report robust study summaries*", any deviations of the test material from the registered substance should be listed (e.g. amount of impurities) and all possible effects of the deviation from the registered substance to the obtained test results should be analysed and reported in the RSS. However, ECHA notes that for this study the test material is only described as [redacted] and information on the purity and composition of the test material is not provided. In addition, you have not discussed whether possible deviation from the registered substance might have influenced the results. Given the large molecular weight and size of the main constituent, it is not clear whether the main constituent or its potential (bio)transformation product(s) or an impurity is causing the observed (eco)toxicological effects. Therefore, in this specific case, information on the composition of the test material (including impurities) is of particular importance. In the absence of details on test material (including impurities), ECHA cannot verify whether the test material is representative of the registered substance.

- Information to assess the validity of the study. In the RSS you do not report information on biomass and on growth rates in the control cultures during the test. Thus, it is not possible to verify whether the validity criteria of OECD TGD 201, paragraph 11, was met:
  - The biomass in the control cultures should have increased exponentially by a factor of at least 16 (corresponds to a specific growth rate of 0.92/day) within the 72-hour test period;
  - The mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures must not exceed 35%;
  - The coefficient of variation of average specific growth rates during the whole test period in replicate control cultures must not exceed 7% in tests with *Pseudokirchneriella subcapitata*.

  ECHA notes that you have neither populated the "Validity criteria fulfilled" in the relevant IUCLID fields under this endpoint study record. Considering the above

mentioned deficiencies in reporting, ECHA cannot verify whether the validity criteria have been fulfilled for the key study.

Furthermore, ECHA notes the following regarding the reporting of the study results. You have expressed the effect values from this study based on nominal concentrations, since you have reported an EC50 of 16 mg/L (biomass) and a NOEC of 10 mg/L (growth rate) to be used for the CSA. In the algae study submitted, Water Accommodated Fractions (WAFs) were used with the following nominal loadings: 0.3, 1, 3, 10, 30 and 100 mg/L. ECHA notes that analytical monitoring of test substance concentrations took place and you provided the following average measured concentrations: 0.141, 0.0562, 0.0579, 0.416, 3.11 and 4.39 mg/L. According to paragraph 39 of OECD TG 201, if the deviation from the nominal or measured initial concentration is not within the range of ± 20 %, analysis of the results should be based on geometric mean concentration during exposure. Based on the average measured concentrations provided in the RSS, ECHA notes that the difference with nominal concentrations is above 20% at all loadings. Therefore, ECHA considers it not adequate to report the effect values based on nominal loading levels.

Further, ECHA notes that in the course of the algae test the pH range was 7.9 - 9.3. This shift in pH during the test from 7.9 to 9.3 is within the range allowed in OECD TG 201. However, ECHA notes that the registered substance has "*pKa1= ca 9.4 (*[redacted]*) pKa2= <3 (*[redacted]*) (*calculated*)*", as reported in IUCLID section 4.21 of the the technical dossier. Regarding aquatic testing of ionisable substances, OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6, indicates that relatively small changes in pH can significantly alter the balance between the dissociated and non-dissociated forms of some organic acids and bases. Altered dissociation equilibrium affects the water solubility, bioavailability and measured toxicity of the test substance. Hence, when testing compounds like the registered substance that partly ionise at an environmentally relevant pH, it may be necessary to limit the pH drift to obtain reproducible and well defined results, as indicated in par. 30 of OECD TG 201. However, ECHA notes that neither the technical dossier nor the RSS of the algae study contain a discussion/statement on the change of bioavailability and toxicity of the registered substance with the pH. For the algae study you have also not discussed the extent of dissociation of the test substance in the test solutions based on the pH conditions and whether the pH drift affected the results. In the absence of such discussion, it is not possible for ECHA to assess the reliability of the study.

In your comments to the draft decision you expressed your agreement to provide more information on this algae growth inhibition study and to update the robust study summary. You further provided the full study report (Annex A), as well as the statistical evaluation and the assessment of the validity criteria (Annex B).

Based on the information on the validity of the test (as well as on biomass and growth rates in the control cultures) provided in Annex B of your comments to the draft decision, ECHA acknowledges that the validity criteria of OECD TG 201 have been fulfilled for this study. ECHA notes that this information should be included in the technical dossier and reflected in the RSS.

In your comments to the draft decision, you provided information on the composition of the test material and on the effect of the pH on the results, which ECHA has assessed in the following.

Based on the details on the composition of the test material provided in your comments, ECHA notes the following deviations of the test material from the composition of the registered substance:

- The test material has a purity of [redacted] whereas the concentration range of the registered substance is [redacted] (typical concentration [redacted]) as reported in the technical dossier.
- The test material contains an impurity [redacted] with MW [redacted] (identified only by name and SMILES notation in your comments, but not reported in the full study report) and "*about ten further unidentified components (incl. impurities) at relative amounts of* [redacted]", whereas the registered substance contains only two impurities (at typical concentrations of [redacted]) as reported in the technical dossier.

ECHA considers that from the data you provided in your comments, it is not possible to determine to which extent the two impurities of the registered substances are present in the test material. Furthermore, ECHA notes that in your comments you did not analyse the possible effects of the deviations of the test material from the registered substance to the obtained test results, in particular regarding the unidentified impurities. As a consequence, ECHA cannot currently conclude that the test material is representative of the registered substance.

Regarding the observed increase in pH, you consider that it does not affect the outcome of the study. You indicated that increase in pH normally takes place in algae study where significant growth of the algal cell is observed and consequently CO_2 decreases. ECHA agrees that the observed increase in pH in the controls is within the range of 1.5 units given in the OECD TG 201, as already stated above. However, ECHA reiterates that for ionisable substances such as the registered substance a shift in pH might affect the results. ECHA notes that in your comments you have not discussed the issues listed above, i.e. the extent of dissociation of the ionisable registered substance based on the pH conditions and how the shift in pH might have changed the bioavailability and toxicity of the ionisable registered substance. Therefore, ECHA considers that you have currently not demonstrated that the increase in pH did not affect the results of this study.

Due to above, with regards to the test material composition and to the effect of the pH on the results, ECHA considers that the information provided in the comments and in the draft decision does not currently allow the assessment of the reliability of the study. However, ECHA acknowledes your intention to assess the test material composition and the dissociation in the future update of the technical dossier. ECHA further acknowledges your intention to consider the results of the water solubility study (request 1) for the assessment of the available data on aquatic toxicity. While for the purpose of this decision making, ECHA does not take into account any dossier updates after the notification of this draft decision under Article 50(1) of the REACH Regulation, ECHA notes that dossier updates and any new information therein will be evaluated by ECHA at the follow up stage.

Finally, regarding the reporting of the study results, in your comments to the draft decision you maintain that the effect concentrations can be based on the nominal loading rates and that the WAF approach was appropriate for this algae growth inhibition study. You indicated that the impurities are likely more soluble than the main constituent. Hence, at nominal test concentrations above the water solubility limit, the composition of the test material in the test solutions can differ markedly from the original composition. Since the impurities were not quantified in the test solutions, you consider that the nominal loading rate would best reflect the aquatic toxicity of the whole substance. ECHA notes that if the substance

contains constituents with a large range in water solubilities, the results of chronic tests (such as algae and long-term aquatic invertebrates studies) obtained with WAFs will reflect the toxicity of the less soluble constituents, as indicated in Table R.7.8-3 of ECHA Guidance Chapter R.7b (version 4.0, June 2017). Since as indicated by you the main constituent is less soluble than the impurities, ECHA considers that the results of this study should be expressed based on the measured concentration of the main constituent.

ECHA notes that, contrary to Article 3(28) of the REACH Regulation the documentation of the study is insufficient and does not allow an independent assessment of the adequacy of the study, their results and use for hazard assessment. In particular, in addition to the above, the following elements, needed to verify the reliability of the results, are not reported in the RSS submitted:

a. observations in the controls and treated cultures;
b. determination of growth rates in the controls and treated cultures;
c. determination of the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control;
d. determination of the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures;
e. other effects (frond and root size and appearance, necrosis, chlorosis, gibbosity, loss of buoyancy, etc.);
f. EC50, EC10 or NOEC and LOEC at the different reporting timings, dose-response relationships, description of statistical analysis performed.

In order to allow an independent assessment of the study submitted, pursuant to Article 41(1) and (3) of the REACH Regulation you are requested to provide a complete robust study summary with the above missing elements for the key study.

Alternatively, if you cannot submit the complete RSS or the RSS indicates that the study is not reliable and not adequate to fulfil the information requirement, 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.

8. **Robust study summary for key study [redacted] Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5. in conjunction with Annex I, Section 3.1.5);**

   OR

   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;

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Pursuant to Article 10(a)(vii) of the REACH Regulation, the information set out in Annexes VII to XI must be provided in the form of a robust study summary, if required under Annex I. Article 3(28) of the REACH Regulation defines a robust study summary as 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. Guidance on the preparation of the robust study summaries is provided in the Practical Guide 3 "How to report robust study summaries".

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. 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. Furthermore, pursuant to Article 10 (a)(vii) and Annex I, Section 3.1.5. of the REACH Regulation if there are several studies addressing the same effect, then, the study or studies giving rise to the highest concern shall be used to draw the conclusion and a robust study summary shall be prepared for that study or studies and included as part of the technical dossier. Robust study summaries will be required of all key data used in the hazard assessment.

In the technical dossier you have provided a study record for a *Daphnia magna* reproduction test: [redacted] guideline study (equivalent or similar to OECD 211), GLP compliant, reliable with restrictions (Klimisch 2) with the registered substance, to meet the standard information requirement of Annex VII, Section 9.1.5.

However, ECHA notes that you have not provided sufficient information in the technical dossier to allow the assessment of the reliability of the study. In particular, the following elements are missing:

- Details on test material. According to paragraph 60 of OECD TG 211, the test report should include chemical identification data, including purity, of the test substance. Furthermore, according to Practical Guide 3 "How to report robust study summaries", any deviations of the test material from the registered substance should be listed (e.g. amount of impurities) and all possible effects of the deviation from the registered substance to the obtained test results should be analysed and reported in the RSS.
- However, ECHA notes that the test material is only described as [redacted] but information on the purity and the composition of the test material used in the key study is not provided. In addition, you have not discussed whether possible deviation from the registered substance might have influenced the results. Given the large molecular weight and size of the molecule, it is not clear whether the main constituent (or its potential (bio)transformation product(s)) or an impurity is causing the observed (eco)toxicological effects. Therefore, in this specific case, information on the composition of the test material (including impurities) is of particular importance. In the absence of details on test material (including impurities), ECHA cannot verify whether the test material is representative of the registered substance.

Furthermore, ECHA notes the following regarding the reporting of the study results. You have expressed the effect values from this study based on nominal concentrations, since you have reported a 21d NOEC of 3 mg/L (reproduction) to be used for the CSA. In the key study submitted, Water Accommodated Fractions (WAFs) were used with the following nominal loadings: 0.3, 1, 3, 10, 30 and 100 mg/L. ECHA notes that analytical monitoring of test substance concentrations took place and you provided the following measured concentrations: 0.07, 0.17, 0.37, 0.85, 1.83 and 4.24 mg/L. According to paragraph 50 of OECD TG 211, if the deviation from the nominal or measured initial concentration is not within the range of ± 20 %, analysis of the results should be based on time-weighted mean concentrations. Based on the measured concentrations provided in the RSS, ECHA notes

that the difference with nominal concentrations is above 20% at all loadings. Therefore, ECHA considers it not adequate to report the effect values based on nominal loading levels. In addition, in the RSS you indicate that – despite the efforts to centrifuge and decant during WAF preparation – undissolved test material was observed in the test solutions. Further, you state that in the RSS "*that repeatability of the preparation of the test concentrations was very limited, but that the concentrations measured remained rather stable during the periods between renewals.*" Together with the lack of a clear dose-response this indicates the preparation of the test solutions was inadequate.

Finally, ECHA notes that in the RSS you have not discussed the influence of dissociation on the test results. ECHA notes that the registered substance has "*pKa1= ca 9.4 (*[redacted]*) pKa2= <3 (*[redacted]*) (*calculated*)*", as reported in IUCLID section 4.21 of the the technical dossier. Regarding aquatic testing of ionisable substances, OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6, indicates that relatively small changes in pH can significantly alter the balance between the dissociated and non-dissociated forms of some organic acids and bases. Altered dissociation equilibrium affects the water solubility, bioavailability and measured toxicity of the test substance. ECHA notes that in course of the long-term *Daphnia* test the pH was between 7.0 and 8.6. However, ECHA notes that neither the technical dossier nor the RSS of long-term *Daphnia* study contain a discussion/statement on the change of bioavailability and toxicity of the registered substance with the pH. For the long-term *Daphnia* you have also not discussed the extent of dissociation of the test substance in the test solutions based on the pH conditions and whether the pH drift affected the results. In the absence of such discussion, it is not possible for ECHA to assess the reliability of the study.

In your comments to the draft decision you expressed your agreement to provide more information on this study on long-term toxicity testing on aquatic invertebrates and to update the robust study summary. You further attached to your comments the full study report (Annex C), which includes the elements listed below, i.e. species lifestage, observations and expression of results. ECHA notes that this information should be included in the technical dossier and reflected in the RSS.

In your comments to the draft decision, you provided information on the test material composition for this study, which is the same as for the algae growth inhibition study. Based on this information, which ECHA has fully assessed under point 7 above, ECHA cannot currently conclude that the test material is representative of the registered substance.

In your comments to the draft decision, you further indicated that the change in pH does not affect the outcome of the study, since the variation remained below 0.5 after 10 days in all test solutions. However, as also indicated under point 7 above, in your comments you have not discussed the issues listed above, i.e. the extent of dissociation of the ionisable registered substance based on the pH conditions and how the shift in pH might have changed the bioavailability and toxicity of the ionisable registered substance. Therefore, ECHA considers that you have currently not demonstrated that the increase in pH did not affect the results of this study.

Due to above, with regards to the test material composition and to the effect of the pH on the results, ECHA considers that the information provided in the comments and in the draft decision does not currently allow the assessment of the reliability of the study. However, ECHA acknowledges your intention to assess the test material composition and the dissociation in the future update of the technical dossier. ECHA further acknowledges your

intention to consider the results of the water solubility study (request 1) for the assessment of the available data on aquatic toxicity. While for the purpose of this decision making, ECHA does not take into account any dossier updates after the notification of this draft decision under Article 50(1) of the REACH Regulation, ECHA notes that dossier updates and any new information therein will be evaluated by ECHA at the follow up stage.

Finally, regarding the reporting of the study results, in your comments to the draft decision you maintain that the effect concentrations can be based on the nominal loading rates by providing the same reasons as for the algae growth inhibition. As already explained under point 7 above, if the substance contains constituents with a large range in water solubilities, the results of chronic tests (such as algae and long-term aquatic invertebrates studies) obtained with WAFs will reflect the toxicity of the less soluble constituents. Since as indicated by you the main constituent is less soluble than the impurities, ECHA considers that the results of this study should be expressed based on the measured concentration of the main constituent.

ECHA notes that, contrary to Article 3(28) of the REACH Regulation the documentation of the study is insufficient and does not allow an independent assessment of the adequacy of the study, their results and use for hazard assessment. In particular, in addition to the above, the following elements, needed to verify the reliability of the results, are not reported in the RSS submitted:

a. species lifestage;
b. observations in the controls (number of juveniles per parent, presence of living males, ephippia produced, etc.);
c. observations: number of offspring (daily count), number of dead parents (daily count);
d. expression of results: i.e. total number of living offspring produced per parent animal alive at the end of the test (including control).

In order to allow an independent assessment of the study submitted, pursuant to Article 41(1) and (3) of the REACH Regulation you are requested to provide a complete robust study summary with the above missing elements for the key study.

Alternatively, if you cannot submit the complete RSS or the RSS indicates that the study is not reliable and not adequate to fulfil the information requirement, 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).

9. 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 more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X 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 Annex IX of Regulation (EC) No 1907/2006, it is laid down that the short-term toxicity testing on fish shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on aquatic organisms. An acute toxicity test on fish did not reveal any adverse effect on mortality. Further long-term studies in fish were not performed due to the fact, that fish are the least sensitive species compared to Daphnia and algae. To properly evaluate the long-term toxicity potential of the substance chronic test was performed using Daphnia magna as test organism due to sensitivity in the acute test. Furthermore according to result of the exposure assessment, all relevant uses of the test substance are considered to be safe with a Risk Characterization Ratio below 1. For these reasons, and for the reason of animal welfare, a long-term toxicity test in fish is not provided."*

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.6., column 2.

ECHA notes that in your adaptation you propose that long-term toxicity to fish is not necessary because based on the short-term studies, fish are the least sensitive species hence the available long-term study on toxicity to *Daphnia* is sufficient to conclude on the long-term toxicity potential of the substance. You propose further that the chemical safety assessment does not indicate the need to investigate further the effects on aquatic organisms because of no risks indicated according to results of the exposure assessment. However, ECHA considers that the information available in your chemical safety assessment and technical dossier does not rule out the possibility of the long-term effects to aquatic organisms and that further investigation is needed, as further explained below.

First, ECHA considers that there are currently no reliable short-term studies available on aquatic plants, aquatic invertebrates and fish.

For aquatic plants, as discussed in section 7 above, with the current information it is not possible for ECHA to verify the validity of the results of the algal growth inhibition study you provided in the technical dossier.

For aquatic invertebrates, the short-term toxicity study you provided in the technical dossier ([redacted], non-GLP study according to OECD TG 202, with analytical monitoring, reliability 4 (not assignable)) has important shortcomings:

- First of all, you indicate that this study has a reliability score of 4 (not assignable) for the following reasons: *"Guideline study with restrictions: - the concentration range is greatly in excess to water solubillity - undissolved particles were observed - highest vehicle concentration 3040 mg/L DMF - the dose-response curve is not consistent resulting in a very high confidence interval (3.8 - 94000 mg/L) - test duration only 24 hours"*
- The composition of the test material is not provided.
- Details on the analytical monitoring are not reported (e.g. whether samples were filtered or not; analytical methods used).
- Tables with results are not reported.
- Information on the validity criteria is not reported.
- The applicant's summary and conclusion section is empty.
- The exposure duration was 24 hours. The standard test duration for a short-term toxicity test on invertebrates according to OECD 202 (2004), *Daphnia sp.* Acute

Immobilisation Test, is 48 hours.

Due to these shortcomings, it is not possible for ECHA to assess whether significant effects occurred at the lowest concentration tested or not. Also, it cannot be assessed what caused the observed effects: undissolved particles, one or more impurities (0-12% impurities can be present in the registered substance), one or more (bio)transformation products and/or the main constituent. Further, although analytical monitoring was performed, it appears from the information you provided in the dossier that the actual dissolved concentrations tested are not known.

Also for fish, the short-term toxicity study you provided in the technical dossier ([redacted] non-GLP study according to OECD TG 203, with analytical monitoring, limit test, reliability 2 (reliable with restrictions)) has important shortcomings:

- You reported as the reasons for assigning reliability 2 to this study: "*Guideline study with restrictions: - the concentration is greatly in excess to water solubility - highest vehicle concentration 954 mg/L - precipitation of test substance during test*". You have also reported that test concentrations were not stable throughout the testing period (119 mg/L at 0 hours and 12 mg/L at 96 hours) and that after 2 hours from the start of the test, a deposit of test material was observed in all loading levels. The OECD TG 203 requires in its validity criteria to maintain constant conditions throughout the test as far as possible. However, testing above the water solubility, the use of vehicle in concentrations 9.5 times higher than recommended by the guideline, the precipitation of the substance and the variable measured concentrations indicate that this validity criteria has not been fulfilled.
- The composition of the test material is not provided.

Therefore, ECHA concludes that this fish study is not reliable.
Furthermore, you report that no mortality occurred in the short-term fish study. ECHA Guidance on information requirements and chemical safety assessment (Version 4.0, June 2017), Chapter R.7b, indicates that absence of toxicity in short-term studies cannot be used to conclude on the toxicity potential of poorly water soluble substances since the time taken for an equilibrium to be reached and toxic effects to be shown for a poorly water soluble substance is too long for an effect to be revealed in an acute study. ECHA notes that, although the water solubility of the registered substance is currently not clear (as described in request 1. above), there are indications that the registered substance is poorly water soluble. For instance, ECHA observes that the test solutions of the algae growth inhibition study (request 7) and of the long-term *Daphnia* study (request 8) were prepared with WAFs indicating that the test substance is difficult to test, considered to be partially soluble in water and may dissociate at environmentally relevant pH. In addition, ECHA notes that the registered substance has a high log Kow (4.5 at pH 7, as reported in the study summary of IUCLID section 4.7). ECHA notes that for difficult to test substances with these properties (i.e. poorly water soluble and with a high log Kow), the Integrated testing strategy (ITS) outlined in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R.7b (Section R.7.8.5 including Figure R.7.8-4), is not applicable.

Therefore, due to the shortcomings of the short-term aquatic toxicity testing described above, ECHA concludes that they cannot be used to determine the sensitivity of the aquatic species.

Even though there are issues with the short-term studies on fish and aquatic invertebrates,

this again confirms that steady state conditions in uptake and effects may only be reached after prolonged exposure. Therefore, long-term aquatic studies are necessary to clarify the toxicity of the substance to aquatic organisms and in order to support a meaningful risk assessment.

Since short-term studies are in any case not recommended for a poorly water soluble substance with a high log Kow and long-term aquatic testing is requested in this decision, short-term aquatic studies are not requested.

Finally, ECHA notes that the aquatic data you have used as basis for PNEC derivation and the current Chemical Safety Assessment (CSA) for environment cannot currently be considered reliable, as described in requests 7-8 regarding the algae growth inhibition study and the long-term study on aquatic invertebrates and as described above regarding the short-term studies on fish and on aquatic invertebrates. Consequently, the CSA including the exposure assessment and risk characterisation sections cannot, with the available information, be used to adapt this information requirement.

In your comments to the draft decision, you did not agree to conduct the requested study. You stated that you will update the robust study summaries of the aquatic toxicity studies in the dossier and that you will revise the aquatic toxicity assessment taking into consideration also the results of the water solubility study (point 1 above). You repeated that fish is not the most sensitive species since no effects have been observed in the short-term fish study up to the highest concentration tested with a [redacted] substance, while effects have been observed in the algae and *Daphnia* study. Nevertheless, as already explained above, due to the substance properties, long-term fish testing is needed for a meaningful risk assessment and absence of toxicity in short-term studies cannot be used to conclude on the toxicity of poorly water soluble substances. Hence, the ITS is not applicable and the long-term studies on both invertebrates and fish are needed.

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 requirement. 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 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 R.7b, Figure R.7.8-4).*

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 R.7b,* 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 for requests 7-9

Before conducting the above test you are advised to consult the ECHA Guidance on information requirements and chemical safety assessment, Chapters R.4 (v.1.1, December 2011), R.5 (v.2.1, December 2011), R.6 (May 2008), R.7b (v 4.0, June 2017) and R.7c (v 3.0, June 2017). If you decide to adapt the testing requested according to the specific rules outlined in Annexes VI to X and/or according to general rules contained in Annex XI of the REACH Regulation, you are referred to the advice provided in practical guides on "How to use alternatives to animal testing to fulfil your information requirements for REACH registration".

ECHA emphasises that any testing strategy or adaptation is your responsibility. ECHA notes that given its physico-chemical and environmental fate properties (e.g. logKow, ionisability, water solubility), the substance is very likely to fall outside the applicability domain of most commercially available QSAR models predicting ecotoxicity.

As indicated above there are no reliable short-term studies available on aquatic invertebrates and fish, hence it is not possible to determine the sensitivity of species. Additionally the registered substance has low water solubility and high log Kow value. For the substances with these properties, the Integrated testing strategy (ITS) outlined in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R.7b (Section R.7.8.5 including Figure R.7.8-4), is not applicable and the long-term studies on both invertebrates and fish are needed.

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.

Due to high adsorption potential and ionising properties 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 R.7b, 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).

If the test proves to be unfeasible because of the physicochemical properties of the substance you may decide, based on preliminary test results or laboratory assessment, that the test is technically not possible and then stop testing. The information as to why the tests were stopped and the reasons for them not being technically possible should be explicitly included in the registration dossier.

Finally, ECHA notes that you briefly justify the current PNEC freshwater derivation by "*The PNEC aqua (freshwater) is based on a NOEC (Daphnia 21d) of 3 mg/L and an assessment factor of 50.*" According to ECHA *Guidance on information requirements and chemical safety assessment (May 2008), Chapter R10 (Section R.10.3.1.2, including Table R.10-4)* an assessment factor of 50 will normally only be applied when long-term toxicity results (e.g.

EC10 or NOECs) are available from at least two species across two trophic levels (e.g. fish and/or *Daphnia* and/or algae or a non-standard organism instead of a standard organism). As explained above, ECHA can currently not assess the reliability of the algae and Daphnia study. Further, a long-term fish toxicity study is requested. Should you decide to improve the robust study summaries for the algae and *Daphnia* studies (issues 7 and 8) of this decision) and uncertainties would remain (e.g. concerning measured test concentrations, substance particles...) an assessment factor higher than the one recommended under standard conditions in *ECHA Guidance on information requirements and chemical safety assessment (May 2008), Chapter R10 (Section R.10.3.1.2, including Table R.10-4)* would be necessary to cover those uncertainties.

10. 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 more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X 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 on the degradation products, nor an acceptable adaptation for this standard information requirement 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 readily biodegradable in a OECD TG 301B (Readily Biodegradability: CO2 Evolution Test) study (3-6% biodegradation after 28 days). Consequently, the specific rule for adaption presented in column 2 of Annex IX, Section 9.2.3. of the REACH Regulation does not apply.

Column 2 of Section 9.2. of Annex IX of the REACH Regulation specifies that further biotic degradation testing needs to be proposed if the chemical safety assessment according to Annex I of the REACH Regulation indicates the need to investigate further the degradation of the substance and its degradation products and that the choice of the appropriate test(s), which may include simulation degradation tests in appropriate media, depends on the results of the chemical safety assessment. ECHA notes that you have not provided adequate justification in your CSA or in the technical dossier for why there is no need to identify the degradation products, as explained further below.

ECHA notes that no simulation testing was performed for the registered substance and that your chemical safety assessment does not contain any information on the degradation products and their fate, nor on whether they could be PBT/vPvB or not. ECHA notes that information on degradation products is required for the PBT/vPvB assessment as Annex XIII of the REACH Regulation explicitly requires that PBT/vPvB properties of relevant degradation products need to be taken into account. ECHA Guidance on information requirements and chemical safety assessment (version 3.0, June 2017), Chapter R.11.4.1. further specifies that "*constituents, impurities and additives should normally be considered relevant for the*

PBT/vPvB assessment when they are present in concentration of ≥ 0.1% (w/w). This limit of 0.1% (w/w) is set based on a well-established practice rooted in a principle recognised in European Union legislation. […] Similar arguments apply to relevant transformation/degradation products. The PBT/vPvB assessment should normally be carried out for each relevant transformation or degradation product".

In addition, ECHA notes that information on relating PBT endpoints of aquatic toxicity is missing and has been requested in this decision. A bioaccumulation study was requested in the draft decision. Based on your comments to the draft decision, the concern for B/vB has not been clarified for the registered substance. However, ECHA has removed the bioaccumulation request from this decision due to the complexities of clarifying the PBT concern. ECHA may address the Bioaccumulation endpoint at a later stage under further evaluation processes.

ECHA hence considers that due to the data gaps addressed in this decision, the information in the chemical safety assessment (CSA) including the PBT/vPvB assessment is not complete. On this basis, the CSA cannot be used to justify that there is no need to investigate further the degradation products. ECHA considers that this information is needed for the PBT/vPvB assessment (Annex XIII of the REACH Regulation), as well as for the compilation of safety data sheets (Annex II 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 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, 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 will need to provide a scientifically valid justification for the chosen method.

In your comments on the draft decision, you agree to perform this request. You indicate that detailed information on the degradation products is under assessment and could not be completed within the timeframe for commenting the draft decision. While you did not specify how this information will be obtained, ECHA highlights that due to its physico-chemical and environmental fate properties, the substance is very likely to fall outside the applicability domain of most QSARs, as already explained in the Notes for your considerations below.

ECHA notes that any new information should be submitted in a form of a dossier update. While for the purpose of this decision making, ECHA does not take into account any dossier updates after the notification of this draft decision under Article 50(1) of the REACH Regulation, ECHA notes that dossier updates and any new information therein will be evaluated by ECHA at the follow up stage.

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, including each constituent and relevant impurity present in concentrations at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable.

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. These guidance documents explain 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 information request 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.

If you decide to undertake simulation tests in order to fulfil this standard information requirement, the following should be taken into account. 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.

If you decide to adapt the testing requested according to the specific rules outlined in Annexes VI to X and/or according to general rules contained in Annex XI of the REACH Regulation, ECHA emphasises that any testing strategy or adaptation is your responsibility. ECHA also notes that given its physico-chemical and environmental fate properties (e.g. logKow, ionisability, water solubility), the substance is very likely to fall outside the applicability domain of most commercially available QSAR models predicting degradability.

Deadline to submit the requested information in this decision

The timeline indicated in the draft decision to provide the information requested is 36 months from the date of adoption of the decision.

In your comments on the draft decision, you requested an extension of the timeline to 42 months. You justified your request stating that 30 months is not sufficient to perform an OECD 421 study and the requested OECD 443 and OECD 414 studies in case the read-across cannot be justified and all studies will be required. In order to support your request for a 12-month deadline extension you have provided a statement from your laboratory refering to the laboratory's workload, to the need to conduct an extensive range finder and to analytical characterisation of the substance

You have expressed your intention to conduct an OECD 421 study prior to initiating the requested studies with the aim of consolidating your read-across adaptation. The decision to

perform an OECD 421 study is at your discretion and responsibility; the conduct of an OECD 421 study does not require the submission of a Testing Proposal.

Subsequent to a Proposal for Amendment, ECHA grants an extension of the deadline to submit the requested information by 6 months (to 36 months). The reason for extending the deadline is that it is appropriate to do range-finding studies for an OECD 443 study, and you have provided documentation that this will take longer than 24 months. ECHA considers that your suggestion of 42 months is an unreasonable length of time, and provides six months extra which should be appropriate for the conduct of a range-finding study such as an OECD 421 study.

Therefore, ECHA has modified the deadline of the decision.

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 20 February 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 took into account your comments and did not amend the deadline. Based on your comments the concern for B/vB has not been clarified, but ECHA has removed the bioaccumulation request from this decision due to the complexities of clarifying the PBT concern. ECHA may address the Bioaccumulation endpoint at a later stage under further evaluation processes.

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

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendments.

ECHA referred the draft decision to the Member State Committee.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-65 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, 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 relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests 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 by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally 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.