~~Confidential~~

Helsinki, 25 April 2022

Addressees
Registrant(s) of JS_269-665-4_DMATO as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
13/12/2016

Registered substance subject to this decision ("the Substance")
Substance name: Amides, tall-oil fatty, N,N-di-Me
EC number: 269-665-4

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***2 November 2023***.

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

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

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

2. Long-term toxicity testing on aquatic invertebrates also requested below (triggered by Annex VII, Section 9.1.1., column 2)

3. Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: EU C.4. C/D/E/F/OECD TG 301B/C/D/F or EU C.29./OECD TG 310)

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

4. Long-term toxicity testing on fish also requested below (triggered by Annex VIII, Section 9.1.3., column 2)

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

5. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats. The study must include the following to investigate the kidney function after administration of the Substance:
   i. urinalysis (for specifications see OECD TG 422, paragraph 57); and
   ii. histopathological examination of the kidneys of all animals in all dose groups with an additional immunohistochemical staining for alpha-2µ globulin.

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

7. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211)

8. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: EU C.47./OECD TG 210)

The reasons for the decision(s) are explained in Appendix 1.

Information required depends on your tonnage band

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

In the requests above, the same study has been requested under different Annexes. This is because some information requirements may be triggered at lower tonnage band(s). In such cases, only the reasons why the information requirement is triggered are provided for the lower tonnage band(s). For the highest tonnage band, the reasons why the standard information requirement is not met and the specification of the study design are provided. Only one study is to be conducted; all registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the others under Article 53 of REACH.

How to comply with your information requirements

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

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

Appeal

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

Failure to comply

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

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

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

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

Appendix 1: Reasons for the decision

Contents

Reasons related to the information under Annex VII of REACH

1. Growth inhibition study aquatic plants

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

1.1. Information provided

2 You have provided:

i. a study according to OECD TG 201 on the Substance (2013)

ii. a study according to OECD TG 201 on a formulation containing the substance (2005)

1.2. Assessment of the information provided

3 We have assessed this information and identified the following issues:

1.2.1. The identity of the test material used in study ii. is unclear

4 To comply with this information requirement, the test material in a study must be representative for the Substance (Article 10 and Recital 19 of REACH; ECHA Guidance R.4.1).

5 For study ii. above, you have identified the test material as "Busperse 2422". You specify that this formulation contains the Substance at approximately [redacted]%. However, you provide no further information, including compositional information on the remaining [redacted]%.

6 In the absence of composition information on the test material, the identity of the test material and its impurities cannot be assessed and you have not demonstrated that the test material is representative for the Substance.

7 Therefore, the information provided is rejected.

8 In the comments to the draft decision, you indicate that the composition information on the test material "Busperse 2422" is not available. You therefore propose to remove study ii. from the dossier.

1.2.2. The studies i. and ii. above do not meet the information requirement

9 To fulfil the information requirement, a study must comply with OECD TG 201 and the requirements of OECD GD 23 if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

10 Additional requirements applicable to difficult to test substances

a) if the test material is poorly water soluble, the maximum dissolved concentration that can be achieved in the specific test solution under the test conditions is determined;

b) if the test material is tested at the saturation concentration, evidence must be provided that all reasonable efforts have been taken to achieve a saturation concentration, which include:

- an analytical method validation report demonstrating that the analytical method is appropriate, and

- the results of a preliminary experiment demonstrating that the test solution preparation method is adequate to maximize the concentration of the test material in solution.

11 Reporting of the methodology and results

c) the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form.

12 Your registration dossier provides an OECD TG 201 showing the following:

13 Requirements applicable to difficult to test substances

a) in the provided OECD TG 105 (2013), the saturation concentration of the Substance in water was determined to be below the limit of detection of the analytical method (*i.e.* LOD = 2.1 mg/L based on TOC analysis). Therefore, the Substance is considered to be poorly water soluble. However, you have not provided an estimate of the maximum dissolved concentration that can be achieved in the specific test solution under the test conditions in neither studies i. or ii.;

b) the highest loading rate used to prepare the test solutions was 32 mg/L in study i. and 10 mg/L (corresponding to 1.5 mg Substance/L) in study ii., which in both cases above the water solubility as determined in the OECD TG 105 study. Therefore, ECHA concludes that the test material was tested at saturation. However, you have not provided an analytical method validation report and the results of a preliminary experiment described above in neither studies i. or ii.;

In your comments to the draft decision, you state that, for study i., the study report mentions a "*validation test to determine the mixing period for WAF preparation*". You explain at "*nominal loading rates of 10 and 100 mg/L,* […] *measured concentrations of 0.0641 and 0.0962 mg/L* [were determined]*, respectively*". You state that "*Microscopic examination of the WAFs showed there to be no micro-dispersions of test item present." This would suggest that the test material WAFs were not tested at saturation*". Finally you explain that "*The analytical method used in the study report was shown to be valid, with the LOQ determined to be 0.0041 mg/L. At 0 hours, the nominal loading rates of the test item of 0.32, 1.0, 3.2, 10 and 32 mg/L corresponded to measured concentrations of 0.0319, 0.0315, 0.0116, 0.0633, and 0.0542 mg/L respectively*".

ECHA notes that you have not provided further information on study ii. and that, on study i., you have only provided a statement referring to a preliminary study to investigate solubility at two loading rates (i.e. 10 and 100 mg/L) but no detailed information on the methodology (mixing regime, separation method) or of the results. In the absence of this information, the relevance of this information cannot be assessed. On the analytical method in study i., ECHA notes that the LOQ cannot be considered on its own as a basis to conclude on the validity of the analytical method and appropriate justification should include other parameters such as specificity, precision, repeatability and recovery. Finally, ECHA notes that the measured concentration at 0 hours at the highest loading rate (i.e. 32 mg/L) was about half the concentration determined in the prelimary experiment at 100 mg/L loading rate. Therefore, this indicates that the test medium preparation did not allow maximizing the exposure to the Substance.

In your comments to the draft decision, you also state that the studies predate the publication of the 2nd edition of the OECD GD 23 for difficult to test substances

(which was released in 2019). You consider that this study was compliant with the version of the OECD GD 23 applicable at the time (i.e., 1st version from 2000). You therefore consider that repeated the study is not warranted.

However, ECHA notes that the specifications mentioned above were already specified in the first version of the OECD GD 23. Therefore, your comment is not relevant to address the above issue.

This comment and ECHA's reply equally apply to requests 2 and 7.

14 Reporting of the methodology and results

c) tabulated data on the algal biomass determined daily for each treatment group and control are not reported in neither studies i. or ii.

In your comments to the draft decision, you state that you will provide the table for the daily measured alga biomass in a IUCLID dossier update. The information in your comments is not sufficient for ECHA to make an assessment. Please note that this decision does not consider updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation).

15 Based on the above,

i. the Substance is difficult to test as it is highly adsorptive and there are critical methodological deficiencies resulting in the rejection of the study results from studies i. and ii. First, you have not provided an estimate of the limit of solubility of the test material in the test medium used to conduct these studies. Then, you have not provide adequate supporting information to demonstrate that exposure to the Substance was maximized in study i. Therefore, you have not demonstrated that exposure was satisfactory during this test in neither study i. or ii.

In your comments to the draft decision and as already explained above, propose to remove study ii. from the dossier.

ii. the reporting of studies i. and ii is not sufficient to conduct an independent assessment of their reliability. In particular, you have not provided adequate reporting of algal biomass determinations for any of the study. In the absence of this information, ECHA conduct an independent assessment of whether the validity criteria of the test guideline were met and of the interpretation of the results of these studies.

16 Therefore, the requirements of OECD TG 201 are not met for any of the studies.

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

1.3. Study design and test specifications

18 The Substance is difficult to test due to the low water solubility (< LOD of 2.1 mg/L based on TOC analysis) and adsorptive properties (log kow mainly > 6). OECD TG 201 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure

concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 201. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

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

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

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

2. Long-term toxicity testing on aquatic invertebrates

21 Short-term toxicity testing on aquatic invertebrates is an information requirement under Column 1 of Annex VII to REACH (Section 9.1.1.). However, long-term toxicity testing on aquatic invertebrates must be considered (Section 9.1.1., Column 2) if the substance is poorly water soluble.

2.1. Information provided

22 You have provided an OECD TG 211 study on the Substance (2013).

2.2. Assessment of the information provided

23 We have assessed this information and identified the following issue:

24 Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests does not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (Guidance on IRs and CSA, Section R.7.8.5).

25 In the provided OECD TG 105 (2013), the saturation concentration of the Substance in water was below the limit of detection of the analytical method (i.e. LOD = 2.1 mg/L based on TOC analysis).

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

27 The examination of the information provided, as well as the selection of the requested test and the test design are addressed under Request 7.

28 In your comments to the draft decision, you disagree with the request. Your comments are addressed under request 7.

3. Ready biodegradability

29 Ready biodegradability is an information requirement in Annex VII to REACH (Section 9.2.1.1.).

3.1. Information provided

You have provided an OECD TG 301F study on the Substance (2005)

3.2. Assessment of information provided

30 We have assessed this information and identified the following issues:

3.2.1. The provided study does not meet the information requirement

31 To fulfil the information requirement, a study must comply with the OECD TG 301 or 310 (Article 13(3) of REACH). Therefore, for a study according to OECD TG 301, the following requirements must be met:

32 Reporting of the methodology and results

a) The concentration of the inoculum in the test is adequately described;

b) The test temperature is reported;

c) The calculation of the ThOD is described and justified;

d) For nitrogen-containing test materials, correction for nitrification is applied on the theoretical oxygen demand (*i.e.* $ThOD_{NO3}$) unless it can be demonstrated that nitrification did not occur (*e.g.* by monitoring changes in concentrations in nitrite and nitrate);

e) The results of measurements at each sampling point in each replicate is reported in a tabular form.

33 Your registration dossier provides an OECD TG 301F showing the following:

34 Reporting of the methodology and results

a) You have reported the inoculum density as 30 mg SS/L. However, you have not provided information on cell density;

b) The test temperature is not reported;

c) The calculation of the ThOD is not described;

d) you have not specified whether a correction for nitrification was applied and you have provided no justification that nitrification did not occur during the test;

e) The results of measurements at each sampling point in each replicate is not reported.

35 Based on the above, the reporting of the study is not sufficient to conduct an independent assessment of its reliability. In particular:

- you have not provided adequate reporting of the inoculum density and therefore it

is not possible to verify whether the specification of the OECD TG 301F were met (i.e., bacterial cell density of 10^7 to 10^8 cells/L in the test vessel). Further, the test temperature is not described.

- you have not provided adequate reporting of the study results and therefore, it is not possible to verify that all validity criteria of the test guideline were met (for instance, the oxygen uptake of the inoculum blank at the end of the test).
- you have not described how the calculation of the ThOD and you have not specified whether a correction for nitrification was applied. Therefore, it is not possible to verify whether the interpretation of the study results is correct.

36 Therefore, the requirements of OECD 301 F are not met.

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

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

Reasons related to the information under Annex VIII of REACH

4. Long-term toxicity testing on fish

39 Short-term toxicity testing on fish is an information requirement under Column 1 of Annex VIII to REACH (Section 9.1.3.). However, long-term toxicity testing on fish must be considered (Section 9.1.3., Column 2) if the substance is poorly water soluble.

4.1. Information provided

40 You have provided an OECD TG 203 study with the Substance but no information on long-term toxicity on fish for the Substance.

4.2. Assessment of the information provided

41 We have assessed this information and identified the following issue:

42 As already explained under Request 1, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

43 The examination of the information provided, as well as the selection of the requested test and the test design are addressed under Request 8.

44 In your comments to the draft decision, you disagree with the request. Your comments are addressed under request 8.

Reasons related to the information under Annex IX of REACH

5. Sub-chronic toxicity study (90-day)

45 A sub-chronic toxicity study (90 day) is an information requirement under Annex IX to REACH (Section 8.6.2.).

5.1. Information provided

46 You have provided:

(i) The following statement: *"Waiving of the conduct of a 90-day study is proposed, based on the absence of toxicologically significant effects in the OECD 422 reproductive/developmental toxicity screening study. Following repeated subacute oral administration over at least 42 days (Study I), no effects were apparent in the offspring and no fertility effects were apparent at the highest dose for males, 1000 mg/kg bw/day. The females showed some effects on reproductive performance at 1000 mg/kg bw/d and the NOAEL was determined to be 300 mg/kg bw/day, the same dose was the systemic NOAEL for males, with species and sex specific rena effects apparent in the high dose males - increased hyaline droplets in renal tubules indicative of alpha-2μ - globulin deposition which is not relevant to the human risk assessment. Hepatocellular hypertrophy was evident in the high dose group males and females, and although this was likely to have arisen due to adaptive changes following increased liver metabolism, the effect was used to determine an overall NOAEL of 300 mg/kg bw/d in the repeated administration study. Based on the observation of reliable no effect levels in parents and offspring , and the establishment of a short term NOAEL in the screening study, conducting a further subchronic exposure study is not considered scientifically justifiable on animal use and welfare grounds"*

(ii) A Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test in the Wistar Rat with the Substance (2014).

47 Although it is not mentioned, ECHA understands that you have adapted the information requirement based on the section 8.6.2, column 2, fourth indent of Annex IX to REACH.

48 You have adapted the sub-chronic toxicity study (90 day) based the absence of toxicologically significant effects in the OECD 422 reproductive/developmental toxicity screening study.

5.2. Assessment of the information provided

49 We have assessed this information and identified the following issue(s):

5.2.1. Column 2 criteria not met

50 Under Section 8.6.2, Column 2, fourth indent, of Annex IX to REACH, the study may be omitted if if the following cumulative conditions are met:

(1) no evidence of toxicity in a 28-day 'limit test'

51 Your registration dossier provides a study (ii) on the basis of which you state that there is no evidence of toxicity. The following findings are reported :

- slightly fewer females were pregnant in the 300 and 1000 mg/kg bw/day groups and the number of females with live pups was lower in the treated dose groups showing a dose related reduction,
- increased liver weight, hepatocyte hypertrophy and a significant increase in serum cholesterol are observed at 300 mg/kg bw/day in males and at 1000 mg/kg bw/day in females,
- lower implantation sites, lower corpora lutea numbers and smaller litter size at 300 and 1000 mg/kg bw/day are reported.

52 Contrary to your statement, the findings observed in the study (ii) indicate pathological effects in both sexes as well as reproductive performance effects in females at doses below 1000 mg/kg bw/day. Your conclusion on the absence of toxicologically significant effects in the OECD 422 reproductive/developmental toxicity screening study are not supported.

53 Therefore, your adaptation is rejected.

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

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

5.3. Specification of the study design

56 Following the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance (Guidance on IRs and CSA, Section R.7.5.6.3.2).

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

58 In addition, the study I with the Substance shows adverse effects in the kidneys of male rats. This indicates that the kidney is a target organ of the Substance.

59 Alpha-2µ-globulin-mediated nephropathy may occur in male rats. Since this mode of action is not considered relevant to humans, the involvement of alpha-2µ-globulin in the kidney effects is a key parameter for establishing the relevance of the kidney effects for human risk assessment.

60 Therefore, the study must be performed in rats according to the OECD TG 408, in rats and with oral administration of the Substance. The study must include the following to investigate the kidney function after administration of the Substance:

a. urinalysis (for specifications see OECD TG 408, paragraph 37); and

b. histopathological examination of the kidneys of all animals in all dose groups with an additional immunohistochemical staining for alpha-2µ globulin.

6. Pre-natal developmental toxicity study in one species

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

6.1. Information provided

62 You have adapted this information requirement by using Column 2 of Annex IX, Section 8.7. To support the adaptation, you have provided following information:

(i) "*The waiver is proposed in line with Column 2 of Annex IX of the REACH Regulation; in the absence of any concern from the reproductive/developmental toxicity screening study. No reproductive/fertility effects were apparent in male*

rats dosed at up to 1000 mg/kg bw/day. No developmental effects were apparent in offspring exposed to 1000 mg/kg bw/day. Based on lower implantation sites and lower corpora lutea numbers, 300 mg/kg bw/day was the LOAEL for fertility and mating performance in females. Since clear endpoints could be determined in the screening test, it is not considered scientifically justifiable to conduct further determinations of developmental effects."

(ii) Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test in the Wistar Rat with the Substance (2014)

6.2. Assessment of the information provided

63 Under Section 8.7., column 2 of Annex IX to REACH, the study does not need to be conducted if the substance is of low toxicological activity. This needs to be demonstrated with three concomitant criteria, one of them being:

- that it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure.

64 Your registration does not provide toxicokinetic data.

65 In addition, the study (ii) shows the following effects:

- increased liver weight, hepatocyte hypertrophy and a significant increase in serum cholesterol at 300 mg/kg bw/day observed in males,
- minimal to moderate follicular cell hypertrophy in the thyroid was observed in males and females,
- lower implantation sites, lower corpora lutea numbers and smaller litter size at 300 and 1000 mg/kg bw/day.

66 You have not provided toxicokinetic data to show that there is no systemic absorption. In addition, several findings are reported: clinical and histopathological effects in both sexes as well as reproductive perfromance effects in females. Those effects indicate that the substance is absorbed.

67 Therefore, your adaptation is rejected.

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

6.3. Specification of the study design

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

70 The study must be performed with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

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

7. Long-term toxicity testing on aquatic invertebrates

72 Long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

7.1. Information provided

73 You have provided a study according to OECD TG 211 on the Substance (2013)

7.2. Assessment of the information provided

74 We have assessed this information and identified the following issue:

7.2.1. The provided study does not meet the information requirement

75 To fulfil the information requirement, a study must comply with the OECD TG 211 [and the requirements of OECD GD 23 if the substance is difficult to test] (Article 13(3) of REACH). Therefore, the following specifications must be met:

76 Technical specifications impacting the sensitivity/reliability of the test

a) the number of animals used for semi-static tests are ≥ 10 animals at each test concentration and in the control series. Test animals are individually held;

77 Additional requirements applicable to difficult to test substances

b) if the test material is poorly water soluble, the maximum dissolved concentration that can be achieved in the specific test solution under the test conditions is determined;

c) if the test material is tested at the saturation concentration, evidence must be provided that all reasonable efforts have been taken to achieve a saturation concentration, which include:

- an analytical method validation report demonstrating that the analytical method is appropriate, and
- the results of a preliminary experiment demonstrating that the test solution preparation method is adequate to maximize the concentration of the test material in solution.

78 Reporting of the methodology and results

d) adequate information on the analytical method (including performance parameters of the method);

e) the results of all analyses to determine the concentration of the test substance in the test vessels are reported;

f) the full record of the daily production of living offspring during the test by each parent animal is provided;

g) the coefficient of variation for control reproductive output is reported;

79 Your registration dossier provides an OECD TG 211 showing the following:

80 Requirements applicable to difficult to test substances

a) in the provided OECD TG 105 (2013), the saturation concentration of the Substance in water was determined to be below the limit of detection of the analytical method (i.e. LOD = 2.1 mg/L based on TOC analysis). Therefore, the Substance is considered to be poorly water soluble. However, you have not provided an estimate of the maximum dissolved concentration that can be achieved in the specific test solution under the test conditions;

b) the highest loading rate used to prepare the test solutions was 0.75 mg/L which is potentially under the water solubility as determined in the OECD TG 105 study. Therefore, ECHA cannot conclude if the test material was tested at saturation or

not. However, you have not provided an analytical method validation report and the results of a preliminary experiment described above;

In your comments to the draft decision, you provided the same comment on the applicability of the latest version of the OECD GD 23 as already specified in Request 1. ECHA's reply equally apply to this endpoint.

In your comments to the draft decision, you also state that the study report mentions a "*validation test to determine the mixing period for WAF preparation*". You explain at "*nominal loading rates of 10 and 100 mg/L,* […] *measured concentrations of 0.0641 and 0.0962 mg/L* [were determined]*, respectively*". You state that "*Microscopic examination of the WAFs showed there to be no micro-dispersions of test item present." This would suggest that the test material WAFs were not tested at saturation*". Finally you explain that "*The analytical method used in the study report was shown to be valid, with the LOQ determined to be 0.0080 mg/L*".

ECHA notes that you have only provided a statement referring to a preliminary study to investigate solubility at two loading rates (i.e. 10 and 100 mg/L) but no detailed information on the methodology (mixing regime, separation method) or of the results. In the absence of this information, the relevance of this information cannot be assessed. Furthermore, ECHA notes that the results you refer to (i.e. measured concentration of 0.0641 and 0.0962 mg/L at 10 and 100 mg/L loading rates are the same as those obtained in the algae study. ECHA notes that such preliminary study must be conducted on the test medium used to conduct the test. In this context, it is unlikely that the very same value would be obtained. On the analytical method, ECHA notes that the LOQ cannot be considered on its own as a basis to conclude on the validity of the analytical method and appropriate justification should includes other parameters such as specificity, precision, repeatability and recovery.

81 Reporting of the methodology and results

c) the analytical method used to determine exposure concentrations is not described;

d) the results of all analyses to determine the concentration of the test substance in the test vessels are not reported;

e) the full record of the daily production of living offspring during the test by each parent animal is not provided;

f) the coefficient of variation for control reproductive output is not reported;

In your comments to the draft decision, you explain that the missing information from point c) to f) above can be provided through a dossier update. However, you have not provided this information as part of your comments on the draft decision. Therefore, no independent assessment can be conducted. Please note that this decision does not consider updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation").

82 Based on the above,

- the Substance is difficult to test as it is highly adsorptive and there are critical methodological deficiencies resulting in the rejection of the study results. First, you have not provided an estimate of the limit of solubility of the test material in the test

medium used to conduct the study. Then, you have not provide adequate supporting information to demonstrate that exposure to the Substance was maximized. Therefore, you have not demonstrated that exposure was satisfactory during this test and that test conditions were fulfilled as per OECD TG 211.

iii. In addition, the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More, specifically, there is no description of the analytical method used and no reporting of the analytical measurements of test concentrations. Therefore, you have not demonstrated that exposure was satisfactorily maintained during the test. Further, you have not provided an adequate reporting of the study results. In the absence of this information, ECHA cannot conduct an independent assessment of whether the validity criteria of the test guideline were met and of the interpretation of the study results.

83 Therefore, the requirements of OECD TG 211 are not met.

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

7.3. Study design and test specifications

85 OECD TG 211 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Request 1.

8. Long-term toxicity testing on fish

86 Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

8.1. Information provided

87 You have provided the following justification to omit the study: "Based on the available data Daphnia appear to be the most sensitive species and fish the least sensitive species, therefore in the interests of animal welfare and to reduce vertebrate testing it is considered inappropriate to conduct a long term chronic fish test".

8.2. Assessment of the information provided

88 We have assessed this information and identified the following issue:

8.2.1. Your justification to omit the study has no legal basis

89 A registrant may only adapt this information requirement based on the general rules set out in Annex XI. It is noted that Column 2 of Annex IX, Section 9.1, does not allow omitting the need to submit information on long-term toxicity to fish under Column 1 (Decision of the Board of Appeal in case A-011-2018).

90 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH. Therefore, you have not demonstrated that this information can be omitted.

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

92 In your comments to the draft decision, you emphaiszes that "*REACH regulation strongly encourages that vertebrate testing be avoided where possible (with Article 25 of the REACH Regulation ((EC) No. 1907/2006)*". You intend to improve the justification to omit this information with the following arguments:

i. "*As stated in Column 2 of Annex IX, "Long-term testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms". Given that fish are shown to be the least sensitive species to DMATO (based on available acute toxicity data) and that acceptable risk is shown in the chemical safety assessment based on currently available data, in the interests of animal welfare and to reduce vertebrate testing it is considered inappropriate to conduct a long-term chronic fish test*".

ii. "*We acknowledge that the guidance states that for poorly water-soluble substances chronic aquatic toxicity studies should be conducted instead of acute tests (due to "difficulties maintaining a high enough and constant concentration of the substance")"*. You consider that the test material WAFs were not tested at saturation.

ECHA has assessed the additonal information from your comments on the draft decision and identified the following issues:

8.2.2. Annex IX, Section 9.1., Column 2 is not a valid basis to omit the study

93 As already explained above, a registrant may only adapt this information requirement based on the general rules set out in Annex XI. Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to fish under Column 1. Minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI.

94 Your justification under point i. above is therefore rejected.

8.2.3. Your justification under point ii. is unclear

95 As explained under Request 4, long-term toxicity testing on fish must be considered (Section 9.1.3., Column 2) if the substance is poorly water soluble. It is unclear why the fact that saturation may or me not have been reached in a specific study would impact this legal obligation.

96 Your justification under point ii. above is therefore rejected.

97 Therefore, the additonal information from your comments on the draft decision do not meet the information requirement.

8.3. Study design and test specifications

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

99 OECD TG 210 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Request 1.

References

The following documents may have been cited in the decision.

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

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

Guidance on data-sharing; ECHA (2017).

All Guidance on REACH is available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

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

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

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

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

Appendix 2: Procedure

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

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

The compliance check was initiated on 2 June 2021.

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

ECHA took into account your comments and amended the requests by removing the request for in vitro gene mutation study in mammalian cells.

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

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

Appendix 3: Addressees of this decision and their corresponding information requirements

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

- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa.

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

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

Appendix 4: Conducting and reporting new tests for REACH purposes

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

1.1. Test methods, GLP requirements and reporting

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

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

(3) Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[2].

1.2. Test material

1. Selection of the Test material(s)

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

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

2. Information on the Test Material needed in the updated dossier

a) You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
b) The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods,

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[3].

[2] https://echa.europa.eu/practical-guides
[3] https://echa.europa.eu/manuals

2. General recommendations for conducting and reporting new tests

2.1. Environmental testing for substances containing multiple constituents

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

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

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

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