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Helsinki, 24 November 2022

Addressees
Registrant of JS-UVCB-268-215-4-13485 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
27/05/2016

Registered substance subject to this decision ("the Substance")
Substance name: Amines, C16-22-alkyl
EC/List number: 268-215-4

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 ***1 June 2026***.

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

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

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

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

3. Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: EU C.4. B/C/D/F/OECD TG 301C/D/E/F) on relevant constituent(s)/fraction(s) of the Substance, as described under the corresponding appendix on reasons for the request.

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. Extended one-generation reproductive toxicity study (triggered by Annex IX, Section 8.7.3., column 1; test method: OECD TG 443) by oral route, in rats, specified as follows:

- Ten weeks premating exposure duration for the parental (P0) generation;
- The highest dose level in P0 animals must be determined based on clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals as specified further in Appendix 1, or follow the limit dose concept. The reporting of the study must provide the justification for the setting of the dose levels;
- Cohort 1A and 1B (Reproductive toxicity); and

- Cohort 3 (Developmental immunotoxicity).

  You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified. Due to reasons explained in Section 7, the test sample must be chosen to minimise gastrointestinal irritation and to allow investigation of intrinsic properties at adequate dose levels. This could be achieved by testing a neutral salt of the Substance.

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

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

The reasons for the requests are explained in Appendix 1.

Information required depends on your tonnage band

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

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.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

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

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

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.

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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. Long-term toxicity testing on aquatic invertebrates

1 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.

1.1. *Triggering of the information requirement*

2 Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term test 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).

3 In the provided OECD TG 123 (2013), the saturation concentration of the Substance in water was determined to be 394 µg/L.

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

1.2. *Information provided*

5 You have provided the following justification for omitting the information on long-term toxicity on aquatic invertebrates for the Substance: "*The study is waived as there is limited exposure of the aquatic compartment since the waste water from the manufacturing site is incinerated*". ECHA understands that you intended to adapt this information requirement on the basis of Annex XI, Section 3.

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

2. Growth inhibition study aquatic plants

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

2.1. *Information provided*

8 You have provided an OECD 201 (2012) with the Substance

2.2. *Assessment of the information provided*

2.2.1. The provided study does not meet the specifications of the applicable test guideline

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 Technical specifications impacting the sensitivity/reliability of the test

a) one of the two alternative growth medium (*i.e.,* the OECD or the AAP medium) is used. Any deviations from recommended test media must be described and justified;

11 Additional requirements applicable to difficult to test substances

b) for adsorbing test chemical, dissolved total organic carbon concentrations (other than that due to the test chemical) must be maintained in all test solutions at or below 2 mg/L;
c) where loses due to e.g. adsorption potential are anticipated samples for analysis should normally be taken at the beginning of the test, and 24-hour intervals throughout the test in order to obtain the mean measured concentrations;

12 Reporting of the methodology and results

d) the method for determination of biomass and evidence of correlation between the measured parameter and dry weight are reported. Algal biomass is normally determined based on dry weight per volume, or alternatively as cell counts or biovolume using microscopy or an electric particle counter. If an alternative method is used (*e.g.,* flow cytometry, *in vitro* or *in vivo* fluorescence, or optical density), a satisfactory correlation with biomass must be demonstrated over the range of biomass occurring in the test.

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

14 Technical specifications impacting the sensitivity/reliability of the test

a) you specify that "[t]*he test was carried out in natural river water with a NPOC of mg/L*". You have not reported any information on the source of the dilution water and on key physico-chemical parameters such as its DOC content. To justify this deviation, you state: "*Using natural river water which contains particulate as well as dissolved organic carbon to which the test item can sorb partially reduces the difficulties encountered in tests with synthetic water (e.g., preventing that the test item settles onto surfaces).* […] *This so called Bulk Approach is described by ECETOC (2003)*";

15 Additional requirements applicable to difficult to test substances

b) You have not provided adequate information to demonstrate that dissolved total organic carbon concentrations (other than that due to the test chemical) was at or below 2 mg/L;
c) you report that analytical exposure of exposure concentration was conducted at in new medium (0h) and old medium (72h) only. The percentage recovery at t=0h of the fractions C18 and C22 of C16-22-(even numbered)-alkylamines were determined to be in the range of 91 to 116 % and 93 to 137 % of the nominal values, respectively. The recoveries in the old media (72 hours) of the fractions C18 and C22 of C16-22-(even numbered)-alkylamines decreased to values in the range between 19 to 53 % and 27 to 107 % of the nominal values, respectively.

16 Reporting of the methodology and results

d) the method used to determine algal biomass is not reported / you report that algal biomass was determined using chlorophyll-a- fluorescence. However, you have not reported evidence of correlation between the measured parameter and dry weight or cell numbers over the range of biomass occurring in the test.

17 Based on the above, there are critical methodological deficiencies resulting in the rejection of the study results. More specifically,

- the study was conducted with river water with an unknown organic carbon content.
- you justify the use of natural water by referring to the bulk approach. However, we note that in its RAC Opinions on Primary Alkyl Amines (i.e., EC No. 204-015-5, EC No. 204-695-3, EC No. 262-977-1, EC No. 263-125-1, EC No. 262-976-6), RAC concluded that, for studies conducted with a dilution water containing a high level of suspended matter and humic acid, nominal concentrations do not represent truly dissolved concentrations and that such study has limited usefulness for the purposes of classification. The Guidance on Application of CLP Criteria, Section 1.1.3., also clarifies that classification must be based on intrinsic hazards, i.e. the basic properties of a substance as determined in standard tests or by other means designed to identify hazards. As the CLP Regulation is hazard-based, the data on intrinsic properties must not take exposure into consideration. Therefore, the bulk approach which aims at mimicking exposure under "*more environmentally realistic*" conditions must not be used for classification and labelling. As already explained above, this conclusion was confirmed by RAC, among other cases, for primary alkyl amines. Similar considerations apply for the PBT assessment. As per Annex XIII of REACH, the PBT assessment should be based on data generated under 'relevant conditions', i.e. those conditions that allow for an objective assessment of the PBT/vPvB properties of a substance and not the PBT/vPvB properties of a substance in particular environmental conditions. This has been also confirmed by the Board of Appeal in its Decision of 7 December 2016 in case A-013-2014.
- you have not provided any supporting information to demonstrate that *in vivo* fluorescence provides an adequate determination of algal biomass, therefore it is not possible to verify that the study is reliable. The physiological status of algal cells is known to impact the efficiency of the non-photochemical quenching (NPQ) of fluorescence and differences in physiological status between treatments may bias the relationship between re-emitted fluorescence and biomass. Further, river water does contain natural algal populations and you have not justified that it did not affect the sensitivity of the test.
- the sampling frequency for the determination of exposure concentration was too low to adequately characterise losses of the test substance from the exposure medium.

18 Therefore, the requirements of OECD TG 201 are not met.

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

20 In your comments on the draft decision, you state that "[a]*lthough, we believe that the use of the bulk approach for the aquatic studies is still valid, we intent to fulfill the data requirements by following the water accommodated fraction approach according to the requirements of OECD GD 23 by using a recommended test medium and a sufficient sampling frequency*".

2.3. *Study design and test specifications*

21 The Substance is difficult to test due to the low water solubility (394 µg/L). 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.

22 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).

23 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.

3. Ready biodegradability

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

3.1. *Information provided*

25 You have provided an OECD 301 D study (2013) with the Substance

3.2. *Assessment of information provided*

3.2.1. Ready biodegradation tests are normally intended for pure substances

26 The revised introduction to the OECD Guidelines For Testing Of Chemicals, Section 3 Part I states that ready biodegradability tests are intended for pure substances but may also be relevant, on a case-by-case basis, to mixtures of structurally similar chemicals (i.e., which are composed of constituents expected to show similar degradation kinetics). However, such tests are not generally applicable for complex mixtures or substances (i.e., UVCB or multi-constituent substances) containing different types of constituents. For complex substances, a single ready biodegradability test does not allow to conclude on the ready biodegradability of all constituents and therefore, does not fulfil the information requirement.

27 You have provided a study conducted on a test material claimed to be representative of the Substance as a whole. In Section 1.1. of your dossier you describe the Substance as UVCB. In Section 1.2, you describe the substance as a mixture of alkylamines ranging from C12 to C24.

28 The Substance is a complex substance and contains constituents with significant structural differences described above. Therefore, the provided study does not provide unequivocal conclusion that all constituents can safely be regarded as readily biodegradable.

3.2.2. The provided study does not meet the specifications of the applicable test guideline

29 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:

30 Technical specifications impacting the sensitivity/reliability of the test

a) test solutions are prepared using an appropriate nutrient medium, which includes ammonium chloride;
b) the concentration of the test material is in the range of 2-10 mg/L, corresponding to 5 to 10 mg ThOD/L;

31 Reporting of the methodology and results

c) the inoculum concentration in the test vessel is reported as cells/L in the test vessel and as volume of added inoculum (for OECD TG 301D, the concentration of the inoculum is set to reach a bacterial cell density of 10^4 to 10^6 cells/L in the test vessel. The concentration of added inoculum is ≤ 5 mL);
d) the results of measurements at each sampling point in each replicate is reported in a tabular form;
e) the calculation of the ThOD is described and justified;
f) 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).

32 Your registration dossier provides a study claimed to be conducted according to OECD TG 301D showing the following:

33 Technical specifications impacting the sensitivity/reliability of the test

a) you report that "*Ammonium chloride was omitted from medium to prevent nitrification*". You justify the deviation by stating that "*the omission does not result in nitrogen limitation as shown by the biodegradation of the reference compound*";
b) the concentration of the test material was 1 mg/L.

34 Reporting of the methodology and results

c) you have not reported inoculum concentration in the test vessel in cells/L nor the volume of added inoculum;
d) you have not reported the results of measurements at each sampling point in each replicate;
e) you have not described and justified the ThOD calculation;
f) you have not reported whether a correction for nitrification was applied on the theoretical oxygen demand.

35 Based on the above,

- there are critical methodological deficiencies impacting the overall reliability of the study results. More specifically,
  - you have not used a standard test medium as you report that Ammonium chloride was omitted from the test medium. This deviation is no considered acceptable as it may artificially reduce oxygen consumption and lead to underestimating respiration in the inoculum blank (i.e., one of the validity

criteria of OECD TG 301D). The lack of nitrogen limitation in the positive control does not address the above issue.

- the test item concentration was too low which may have led to unprecise determination of oxygen consumption.

In your comments on the draft decision, you agree that low test material concentration may have led to less accurate quantification of oxygen consumption.

- the reporting of the study is not sufficient to fully assess its reliability. More specifically:
  - as you have not reported inoculum concentration in the test vessel in cells/L and as added volume, it is not possible to verify if the conditions are consistent with the specifications of OECD TG 301D;
  - as you have not provided an adequate reporting of the study results, it is not possible to verify if validity criteria consistent with the specifications of OECD TG 301D were met;
  - you have not specified of ThOD was estimated and, as the test material is a nitrogen-containing substance, that the calculated ThOD takes into account oxygen consumption through nitrification (or alternatively supporting information that nitrification did not occur)

In your comments on the draft decision, you explain that the robust study summary will be updated to include the missing information. You have updated your registration dossier on 23 June 2022. However, your registration dossier still do no include the missing information listed under points c) to f) above. Furthermore, you have specified that information on inoculum concentration is not available for this study.

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

37 In your comments on the draft decision, you state that "*if the endogenous respiration would use more oxygen there is less oxygen available to assess the biodegradation of the test substance resulting in a less accurate biodegradation assessment*". Furthermore, you state that "*by adding the ammonium chloride to the medium there is a high chance of failing the endogenous respiration validity criteria. This means the test validity criterion might be failed because of the oxygen consumption by the nitrification of the ammonium added to the test medium. Not passing the endogenous validity criteria as a result of adding the ammonium chloride to the test medium might be used by ECHA as an indication of a too high bacterial density*".

38 ECHA notes that the validity criteria of the OECD TG 301D were set based on the use of a test medium that do contain ammonium chloride and that the method was validated through ring testing. Furthermore, while ECHA agrees that low respiration in the inoculum blank ensures that suffcient oxygen remains available in the test system for biodegradation assessment, this parameter also provides some information about inoculum activity (and not only bacterial density). Respiration in the inoculum blank depends on the bacterial density of the inoculum as well as from the concentration of exogenous compounds that are introduced with the inoculum. High inoculum blank respiration (i.e. above the validity criteria of OECD TG 301D) could indicate that the inoculum density and/or the inorganic matter introduced with the inoculum was too high. This could indicate that the conditions of the test were too favourable. By omitting ammonium chloride a direct comparison with the OECD TG 301D limit value for inoculum blank respiration is no longer possible.

39 In your comments, you consider that that tests with omission of ammonium chloride from the test medium should be accepted. You claim that this conclusion was supported in a previous compliance check decision (e.g. CCH-D-2114522376-51-01/F, page 14).

40 ECHA considers that there were case specific considerations which explain why this deviation was considered of secondary importance in the earlier compliance check decision that you are referring to. In particular, the respiration in the inoculum blank after 28 days was well below the cut-off value value of 1.5 mg O2/L in the corresponding studies (i.e., 0.5 mg O_2/L) and it can be reasonably assumed that it would have still remained under that value in the presence of ammonium chloride. However, in the provided study, the respiration in the inoculum blank after 28 days was already close to the cut-off value (i.e. 1.3 mg O_2/L) in the absence of ammonium chloride. As stated by you "*assuming 100% nitrification this will result in an additional 0.6 mg/L additional oxygen consumption*". Therefore, higher uncertainty exists as to whether it would have remained below 1.5 mg/L if a standard test medium had been used.

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

42 In your comments on the draft decision, you agree to conduct further ready biodegradability studies on the Substance. In this context, you agree that "*a single ready biodegradability test result of the substance as a whole does not allow to conclude on ready biodegradability of all constituents*". You propose to perform ready biodegradation screening tests with the Substance as a whole and with some individual constituents (having short and longer alkyl chain length). You state that you will provide a "*justification for the reasonable worst-case selection of testing the constituent with a high biocidal effect (high bioavailability) and with a low bioavailability (less toxic but with a hampered biodegradation rate due to low bioavailability)*".

3.3. *Study design and test specification*

43 The Substance is a complex substance and contains constituents with significant structural differences described above.

44 For the reasons provided above, testing on the Substance as a whole does not fulfil the information requirement. For the generation of information on ready biodegradability, you must consider the level of information required for the purposes of classification and labelling and, if applicable to your registration, the PBT/vPvB assessment and the exposure assessment/risk characterisation. In order to conclude on which of constituents of the Substance are and which are not readily biodegradable, you may have to consider conducting more than one study using selected individual constituents and/or fractions. If you choose to test one (or more) fraction(s) of the Substance, you must provide a justification that their constituents within chosen fraction(s) are similar enough so that similar degradation kinetics can be assumed. If you decide to conduct a single study in order to prove that all constituents of the Substance are readily biodegradable, you must provide a justification that the selected constituent/fraction can be considered a reasonable worst-case for the Substance as a whole in terms of degradation kinetics.

45 Justification for selection of relevant constituent and/or fractions for the testing, must consider degradation kinetics of constituents of the Substance based, as minimum, on the similarity/differences of the chemical structures and the physico-chemical properties of constituents of the Substance. For that purpose, tools and approaches mentioned in Guidance on IRs and CSA, Sections R.7b and R.11 should be considered.

Reasons related to the information under Annex VIII of REACH

4. Long-term toxicity testing on fish

46 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. *Triggering of the information requirement*

47 As already explained in Request 2, the Substance is poorly water soluble and information on long-term toxicity on aquatic invertebrates must therefore be provided.

4.2. *Information provided*

48 You have provided the following justification for omitting the information on long-term toxicity on aquatic invertebrates for the Substance: "*The study is waived as there is limited exposure of the aquatic compartment since the waste water from the manufacturing site is incinerated*". ECHA understands that you intended to adapt this information requirement on the basis of Annex XI, Section 3.

4.3. *Assessment of the information provided*

49 The examination of the information provided, as well as the selection of the requested test and the test design are addressed under section 9.

Reasons related to the information under Annex IX of REACH

5. Extended one-generation reproductive toxicity study

50 An extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is an information requirement under Annex IX, Section 8.7.3., if the available repeated dose toxicity studies indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. Furthermore column 2 defines the conditions under which the study design needs to be expanded.

5.1. *Triggering of the information requirement*

51 You claim that: "*All available data from both the OECD 414 study and the OECD 421 study, involving the evaluation of reproduction and developmental parameters, have not shown any indication of reproductive or developmental effects*".

52 Therefore, you consider that there are no concerns.

53 However, your dossier contains two studies which indicate adverse effects on the testes and the prostate in males and on the thyroid/parathyroid and the ovaries in females:

(i) 28-day study (2013), including a 28-day recovering period

(ii) 28-day study (2013), including a 14-day recovering period

(iii) screening study (2013).

54 The study (i) indicates a statistically significant increase in absolute testes weights observed in HDR group (Recovery High Dose – 30 mg/kg bw/day) when compared to the controls at the end of the recovery period. Similarly, in females, a statistically significant decrease in absolute thyroid/parathyroid weight was observed in HDR group when compared to the controls. The study (ii) shows a statistically significant decrease in absolute prostate (including coagulating glands) weight observed in males at HD group at the end of the treatment period and the recovery period. In females, at the end of treatment period, statistically significant decrease in absolute ovaries weights were observed in HD group when compared with controls. The study (iii)[2] indicates adverse effects on the prostate in males. A statistically significant decrease in absolute prostate weight (with seminal vesicles and coagulating glands) was observed in the HD group (high Dose – 180 mg/kg bw/day) when compared with control. A decreased secretory content of the prostate gland was also observed in a dose-related manner in the MD group (mid-dose – 60 mg/kg bw/day) and high dose. A reduction in copulation index and fertility index in HD group was also reported. In addition, adverse effects are reported in the litter. A statistically significant decrease in group mean litter weight on PND 4 in HD, total litter weight on PND 0 and 4 in MD and HD, male litter weight on PND 4 in HD, female litter weight on PND 4 in MD and HD group. The survival of the pups was also affected. A statistically significant decrease in total number of pups born, total number of live pups on PND 0 and total number of female pups and live pups on PND 4 in HD group were observed when compared with controls. A degeneration of the testicular seminiferous epithelium is also reported and can be considered treatment related.

55 Based on the above, the information available in the dossier reveals concerns regarding reproductive toxicity. Therefore, the information requirement is triggered.

[2] This study was incorrectly referred to as "study (ii)" in the draft decision notified to you.

56 In your comments, you acknowledge that the information provided in your dossier raised reproductive and developmental concerns. However, you also request ECHA to take into account the general toxicity that can explain the reproductive and developmental toxicity. ECHA acknowledges that the effects in the testes weights observed in HDR group (Recovery High Dose – 30 mg/kg bw/day) are only reported in the study (i) and that the effects on the ovaries are only reported in the study (ii).

57 ECHA also notes that the effects on the pups reported in the study (iii) are occurring at the same time as the poor conditions of the dams reported, although no individual data are provided.

58 However, effects on the prostate including seminal vesicle and coagulating gland are observed in the studes (ii) and (iii) and can be considered as treatment related.

59 In addition, reduced copulation index is observed in Control, Low Dose (LD) and High Dose (HD) groups. Reduced fertility index is observed in Control and HD (80 and 40 % respectively) dose group as compared to LD and MD groups (100 %). Those effects are reported together with a minimally decreased secretory content of the prostate gland observed in a dose-related manner at 60 and 180 mg/kg/day.

60 Those effects (protated/copulation/fertility index) are considered to be treatment related effect.

61 Therefore, there is a concern on the male fertility which is a trigger for the request of the EOGRTs at Annex IX.

62 You also indicate that the LOAEL used to determine the DNEL is sufficiently lower: "*For Amines, C16-22-alkyl LOAEL that is used to determine DNELs is sufficiently lower than that of reproductive and developmental attributed NOAELs of the 28-day study (OECD 407, 2013), including a 28-day recovering period, 28-day study (OECD 407, 2013), including a 14-day recovering period, Screening for reproductive and developmental toxicity study (OECD 421, 2013), and Developmental toxicity study (OECD 414, 2013)*."

63 The EOGRT study has a longer duration exposure and higher statistical power (more animals) compared to the *the 28-day study (OECD 407), screening for reproductive (OECD 421), and Developmental toxicity study (OECD 414)* studies. This study also assesses additional parameters (like the post-natal pup development) which are not part of any of the mentioned studies.

Therefore, the EOGRTS may lead to lower LOAEL values.

5.2. *Information provided*

64 You have not provided any source of information to fulfil the information requirement.

65 Therefore, the information requirement is not fulfilled.

5.3. *Specification of the study design*

5.3.1. Species and route selection

66 A study according to the test method OECD TG 443 must be performed in rats with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

5.3.2. Pre-mating exposure duration

67 The length of pre-mating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

68 Ten weeks pre-mating exposure duration is required to obtain results adequate for classification and labelling and/or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration (Guidance on IRs and CSA, Section R.7.6.).

69 In this specific case, ten weeks exposure duration is supported by the lipophilicity of the Substance (Log K_{ow} = >4.5) to ensure that the steady state in parental animals has been reached before mating.

70 Therefore, the requested pre-mating exposure duration is ten weeks.

5.3.3. Dose-level setting

71 The aim of the requested test must be to demonstrate whether the classification criteria of the most severe hazard category for sexual function and fertility (Repr. 1B; H360F) and developmental toxicity (Repr. 1B; H360D) under the CLP Regulation apply for the Substance (OECD TG 443, paragraph 22; OECD GD 151, paragraph 28; Annex I Section 1.0.1. of REACH and Recital 7, Regulation 2015/282), and whether the Substance meets the criteria for a Substance of very high concern regarding endocrine disruption according to Art.57(f) of REACH as well as supporting the identification of appropriate risk management measures in the chemical safety assessment.

72 To investigate the properties of the Substance for these purposes, the highest dose level must be set on the basis of clear evidence of an adverse effect on sexual function and fertility, but no deaths (i.e., no more than 10% mortality; Section 3.7.2.4.4 of Annex I to the CLP Regulation) or severe suffering such as persistent pain and distress (OECD GD 19, paragraph 18) in the P0 animals.

73 In case there are no clear evidence of an adverse effect on sexual function and fertility, the limit dose of at least 1000 mg/kg bw/day or the highest possible dose level not causing severe suffering or deaths in P0 must be used as the highest dose level. A descending sequence of dose levels should be selected to demonstrate any dose-related effect and aiming to establish the lowest dose level as a NOAEL.

74 In summary: Unless limited by the physical/chemical nature of the Substance, the highest dose level in P0 animals must be as follows:

(1) in case of clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals, the highest dose level in P0 animals must be determined based on such clear evidence, or
(2) in the absence of such clear evidence, the highest dose level in P0 animals must be set to be the highest possible dose not causing severe suffering or death, or
(3) if there is such clear evidence but the highest dose level set on that basis would cause severe suffering or death, the highest dose level in P0 animals must be set to be the highest possible dose not causing severe suffering or death, or
(4) the highest dose level in P0 animals must follow the limit dose concept.

75 You have to provide a justification with your study results demonstrating that the dose level selection meets the conditions described above.

76 Numerical results (i.e. incidences and magnitudes) and description of the severity of effects at all dose levels from the dose range-finding study/ies must be reported to facilitate the assessment of the dose level section and interpretation of the results of the main study.

77 The Substance has a self-classification as Skin Corr. 1B (H314). ECHA Guidance R.7.6.2.3.2. specifies that corrosive or highly irritating substances must be tested preferably via the oral route. However, testing at concentration/dose levels causing corrosivity must be avoided. Testing of neutral salts of alkaline or acidic substances is therefore more appropriate as it allows the investigation of intrinsic properties at adequate dose levels.

78 Therefore, a study according to the test method OECD TG 443 must be performed in rats with oral administration (ECHA Guidance R.7.6.2.3.2). The test sample must be chosen to minimise gastrointestinal irritation and to allow investigation of intrinsic properties at adequate dose levels. This could be achieved by testing a neutralised salt of the Substance.

79 If the extended one-generation reproductive toxicity study submitted in response of this decision does not deliver reliable results because of gastrointestinal irritation, further testing may be considered necessary in order to investigate the intrinsic properties at adequate dose levels. Therefore, if the Member State competent authorities consider that a concern must be clarified in that respect, they may decide to require further testing under Substance Evaluation

7.2.1.1. Cohorts 1A and 1B

80 Cohorts 1A and 1B belong to the basic study design and must be included.

7.2.1.1.1. Histopathological investigations in Cohorts 1A and 1B

81 In addition to histopathological investigations of cohorts 1A, organs and tissues of Cohort 1B animals processed to block stage, including those of identified target organs, must be subjected to histopathological investigations (according to OECD TG 443, paragraph 67 and 72) if

- the results from Cohort 1A are equivocal,
- the test substance is a suspected reproductive toxicant or
- the test substance is a suspected endocrine toxicant.

7.2.1.1.2. Splenic lymphocyte subpopulation analysis

82 Splenic lymphocyte subpopulation analysis must be conducted in Cohort 1A (OECD TG 443, paragraph 66; OECD GD 151, Annex Table 1.3).

7.2.1.1.3. Investigations of sexual maturation

83 To improve the ability to detect rare or low-incidence effects, all F1 animals must be maintained until sexual maturation to ensure that sufficient animals (3/sex/litter/dose) are available for evaluation of balano-preputial separation or vaginal patency (OECD GD 151, paragraph 12 in conjunction with OECD TG 443, paragraph 47). For statistical analyses, data on sexual maturation from all evaluated animals/sex/dose must be combined to maximise the statistical power of the study.

7.2.1.2. Cohort 3

84 The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity.

85 Existing information on the Substance itself derived from the available 28-day study, GLP, OECD TG 407, including 28-day recovering period (2013) and screening study, GLP, OECD TG 421 (2013) show evidence of adverse effects on the immune system:

- A statistically significant decrease of the lymphocytes,
- Histopathological effects seen in the spleen and the mesenteric lymph node that are not reversible,
- Atrophy/degeneration of the lymphoid organs.

86 For the reasons stated above, the developmental immunotoxicity Cohort 3 must be conducted.

7.2.2. Further expansion of the study design

87 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 Cohorts 2A and 2B if relevant information becomes available from other studies or during conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Annex IX/X, Section 8.7.3., Column 2. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in Guidance on IRs & CSA, Section R.7.6.

6. Long-term toxicity testing on aquatic invertebrates

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

6.1. *Information provided*

89 You have adapted this information requirement by using substance-tailored exposure-driven testing without specifying the legal provision from Annex XI, Section 3. To support the adaptation, you have provided the following justification: "*The study is waived as there is limited exposure of the aquatic compartment since the waste water from the manufacturing site is incinerated*".

90 ECHA understands that you intend to adapt this information requirement under Annex XI, Section 3.2(b) (Substance-tailored exposure-driven testing).

6.2. *Assessment of the information provided*

91 Under Annex XI, Section 3, this information may be omitted based on the exposure scenario(s) developed in the Chemical Safety Report. The justification must be based on a rigorous exposure assessment in accordance with Annex I, Section 5 and must meet the following criterion:

(a) for substances that are not included in articles, it must be demonstrated for all relevant scenarios that strictly controlled conditions as set out in Article 18(4)(a) to (f) apply throughout the life cycle.

92 In section 3.5 of your registration dossier you report uses in manufacturing and in formulations (floating agent). Based on your reported uses the substance is not included in articles. Your registration dossier and specifically your CSR provides an exposure assessment and risk characterisation for the environment. You report Predicted Environmental Concentrations of 0 mg/L for all the compartments. However, you do not provide any detailed and comprehensive documentation to justify strictly controlled conditions.

93 In the absence of detailed and comprehensive documentation to justify strictly controlled conditions, the adaptation cannot be considered to have been based on rigorous exposure assessment in accordance with Annex I, Section 5 and the strictly controlled conditions as set out in Article 18(4)(a) to (f). Therefore, you have not demonstrated the absence or no

significant exposure in all scenarios of the manufacture and all identified uses referred to in Annex VI and that for all exposure scenarios the PECs are well below the PNEC.

94 Therefore, your adaptation is rejected.

95 In your comments to the draft decision, you agree with the above assessment and state that you "*will not use this type of waiving argument in future dossier updates*".

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

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

6.3. *Study design and test specifications*

98 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 and test specifications' under Request 3.

7. Long-term toxicity testing on fish

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

7.1. *Information provided*

100 You have adapted this information requirement by using substance-tailored exposure-driven testing without specifying the legal provision from Annex XI, Section 3. To support the adaptation, you have provided the following justification: "*The long-term toxicity to fish is waived due to a limited exposure situation. This statement is based on the fact that the waste water at the manufacturing site is incinerated*".

101 ECHA understands that you intend to adapt this information requirement under Annex XI, Section 3.2(b) (Substance-tailored exposure-driven testing).

102 As already explained in Request 8, your adaptation is rejected

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

104 In your comments to the draft decision, you propose to "*waiv*[e] *the chronic fish study by weight of evidence and by an interpolating read-across approach with other primary fatty amines*". However, in your comments you have not provided any new scientific information that could address the information requirement/the deficiencies. You remain responsible for complying with this decision by the set deadline.

7.2. *Study design and test specifications*

105 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.).

106 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 and test specifications' under Request 3.

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 06 July 2021.

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

ECHA took into account your comments and amended the requests.

As a result, ECHA has removed the following requests:

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: OECD TG 471, 2020),
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method : OECD TG 476 or TG 490).

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

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

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

Appendix 3: 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 Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

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

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[3].

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

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.

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.
c) The reported composition must also include other parameters relevant for the

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

property to be tested, in this case the distribution of C-chain length and presence of unsaturation.

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers (https://echa.europa.eu/manuals).

2. General recommendations for conducting and reporting new tests

2.1. 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.