~~Confidential~~

Helsinki, 06 June 2023

Addressees
Registrants of 110-95-2_JS as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
02/03/2015

Registered substance subject to this decision ("the Substance")
Substance name: N,N,N',N'-tetramethyltrimethylenediamine
EC number/List number: 203-818-8

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

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

2. *In vitro* micronucleus study (Annex VIII, Section 8.4.2., test method: OECD TG 487). The aneugenic potential of the Substance must be assessed with an additional control group for aneugenicity on top of the control group for clastogenicity, if the Substance induces an increase in the frequency of micronuclei

3. Justification for an adaptation of the short-term repeated dose toxicity study (28 days) (Annex VIII, Section 8.6.1., Column 2) based on the request 5 below.

4. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats. Due to reasons explained in Section 4 of Appendix 1, 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.

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

5. Sub-chronic toxicity (90 days), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats
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). Due to reasons explained in Section 6 of Appendix 1, 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.

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 request(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.

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.

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 request(s)
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 request(s)

Contents

Reasons common to several requests

0.1. Read-across adaptation rejected

1 You have adapted the following standard information requirements by using grouping and read-across approach under Annex XI, Section 1.5.:

- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

2 ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following sections.

3 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

4 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

0.1.1. Predictions for toxicological properties

5 You provide a read-across justification document in IUCLID Section 13.2.

6 You predict the properties of the Substance from information obtained from the following source substance(s):

- DMAPA; N,N-dimethylpropane-1,3-diamine, EC 203-680-9 (source substance 1);
- DEAPA; N,N-diethylpropane-1,3-diamine, EC 203-236-4 (source substance 2).

7 You provide the following reasoning for the prediction of toxicological properties:

- "*This read-across is based on the hypothesis that source and target substances have similar chemical structure (low molecular weight tertiary alkyl amines), similar physicochemical properties and similar toxicological profiles*"
- "*A structure that contains only aliphatic organic substituents*"
- "*Two functional amine groups those are primary and/or tertiary in nature*"
- "*Elemental compositions of only carbon, hydrogen and nitrogen*"
- "*A incremental change between DMAPA and TMPDA/DEAPA consisting of increasing number of carbon atoms*"
- "*Molecular weights of < 200 Daltons*"
- "*There is a commonality in the metabolism of these tertiary amines. N-oxide formation and excretion of both free base and N-oxide forms, with a small quantity undergoing dealkylation, appears to be the major route of excretion for the lower molecular weight tertiary amines*"

8 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

9 We have identified the following issue(s) with the prediction(s) of toxicological properties:

0.1.1.1. Missing supporting information to compare properties of the substances(s)

10 Annex XI, Section 1.5. requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6., Section R.6.2.2.1.f.).

11 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substance(s) cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the substance(s) is necessary to confirm that the substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

12 For the source substance 1 (DMAPA), you provide the 28-d repeated dose toxicity study (OECD TG 407) and reproduction/developmental toxicity screening test (OECD TG 421) used in the prediction in the registration dossier. Apart from these studies, your read-across justification or the registration dossier does not include any robust study summaries or descriptions of data for the Substance or for the source substance 2 that would confirm that these substances (the Substance and source substances 1 and 2) cause the same type of effects in repeated dose toxicity and reproductive and developmental toxicity studies.

13 In the absence of such information, you have not established that the Substance and the source substance(s) are likely to have similar properties. Therefore you have not provided sufficient supporting information to scientifically justify the read-across for the information requirements listed above.

0.1.1.2. Inadequate or unreliable study on the source substance(s)

14 According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must:

- be adequate for the purpose of classification and labelling and/or risk assessment;
- have adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement.

15 Specific reasons why the study on the source substance do not meet these criteria are explained further below under the applicable information requirement section 4. Therefore, no reliable predictions can be made for this information requirement.

16 In addition, you have not provided any studies on the source substance(s) for the following information requirements:

- Sub-chronic toxicity study (90 days), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

0.1.2. Conclusion on the read-across approach

17 Based on the above, you have not established that relevant properties of the Substance can be predicted from data on the source substance(s). Your read-across approach under Annex XI, Section 1.5. is rejected.

Reasons related to the information under Annex VII of REACH

1. Growth inhibition study aquatic plants

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

1.1. Information provided

19 You have provided a growth inhibition study on aquatic plants/algae (2003) with the Substance.

1.2. Assessment of the information provided

1.2.1. The provided study does not meet the specifications of the test guideline(s)

20 To fulfil the information requirement, a study must comply with OECD TG 201 (Article 13(3) of REACH). Therefore, the following specifications must be met:

Reporting of the methodology and results

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

21 In the provided study:

Reporting of the methodology and results

a) tabulated data on the algal biomass determined daily for each treatment group and control are not reported.

22 Based on the above, the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, in the absence of tabulated data on the algal biomass, ECHA cannot assess whether the validity criteria of the test guideline were met and verify the interpretation of the results.

23 On this basis, the specifications of OECD TG 201 are not met.

24 In your comments on the draft decision, you provided the missing information listed under a) above. ECHA acknowledges that based on this additional information in your comments the study meets the information requirement. However, as the information is currently not available in your registration dossier, the issue in the dossier content remains. You should therefore submit this information in an updated registration dossier by the deadline set in the decision.

25 Therefore, the information requirement is currently not fulfilled.

Reasons related to the information under Annex VIII of REACH

2. *In vitro* micronucleus study

26 An in vitro mammalian chromosomal aberration study or an in vitro mammalian micronucleus study is an information requirement under Annex VIII, Section 8.4.2.

2.1. Information provided

27 You have provided an in vitro cytogenicity study in mammalian cells (2000) with the Substance.

2.2. Assessment of the information provided

2.2.1. The provided study does not meet the specifications of the test guideline(s)

28 To fulfil the information requirement, the study has to be an in vitro chromosomal aberration test or an in vitro micronucleus test conducted in mammalian cells. The study must comply with the OECD TG 473 or the OECD TG 487, respectively (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) the positive controls induce responses compatible with those generated in the historical positive control database;

b) the positive controls produce statistically significant increase compared with the negative control;

c) the negative control data is ideally within the 95% control limits of the distribution of the laboratory's historical negative control database;

d) data on the cytotoxicity and the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures is reported.

29 In the provided study:

a) not shown that the positive control data is compatible with those generated in the historical positive control database;

b) not shown that the positive control produced a statistically significant increase in the induced response when compared with the concurrent negative control;

c) not shown that the negative control showed a response within the historical control range of the laboratory;

d) data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures were not reported.

30 In your comments on the draft decision, you provided the missing information listed under a) to d) above. This information allows to conclude that the study is adequate and reliable. However, as the information is currently not available in your registration dossier, the issue in the dossier content remains. You should thereofore submit this information in an updated registration dossier by the deadline set in the decision.

31 Therefore, the information requirement is currently not fulfilled.

2.3. Specification of the study design

32 According to the Guidance on IR & CSA, Section R.7.7.6.3., either the in vitro mammalian chromosomal aberration ("CA") test (test method OECD TG 473) or the in vitro mammalian cell micronucleus ("MN") test (test method OECD TG 487) can be used to investigate chromosomal aberrations in vitro. However, while the MN test detects both structural chromosomal aberrations (clastogenicity) and numerical chromosomal aberrations (aneuploidy), the CA test detects only clastogenicity, as OECD TG 473 is not designed to measure aneuploidy (see OECD TG 473, paragraph 2).Therefore, you must perform the MN test (test method OECD TG 487), as it enables a more comprehensive investigation of the chromosome damaging potential in vitro. Moreover, in order to demonstrate the ability of the study to identify clastogens and aneugens, you must include two concurrent positive controls, one known clastogen and one known aneugen [1] (OECD TG 487, paragraphs 33 to 35).

2.3.1. Assessment of aneugenicity potential

33 If the result of the MN test is positive, i.e. your Substance induces an increase in the frequency of micronuclei, you must assess the aneugenic potential of the Substance.

34 In line with the OECD TG 487 (paragraph 4), you should use one of the centromere labelling or hybridisation procedures to determine whether the increase in the number of micronuclei is the result of clastogenic events (i.e. micronuclei contain chromosome fragment(s)) and/or aneugenic events (i.e. micronuclei contain whole chromosome(s)).

[1] According to the TG 487 (2016) "At the present time, no aneugens are known that require metabolic activation for their genotoxic activity" (paragraph 34).

3. Short-term repeated dose toxicity (28 days)

35 A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII, Section 8.6.1. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 or a general adaptation rule under Annex XI.

3.1. Information provided

36 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) a 28-day repeated dose toxicity study (1996) with the source substance N,N-dimethylpropane-1,3-diamine, EC 203-680-9 / DMAPA.

3.2. Assessment of the information provided

3.2.1. Read-across adaptation rejected

37 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

38 Therefore, the information requirement is not fulfilled.

3.3. Justification for an adaptation of the short-term repeated dose toxicity study (Annex VIII, Section 8.6.1., Column 2)

39 The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see request 5).

40 According to Annex VIII, Section 8.6.1., Column 2 and to prevent unnecessary animal testing, a short-term toxicity study (28 days) does not need to be conducted. Therefore, to comply with the information requirement in Annex VIII, Section 8.6.1., you are requested to provide a justification for adaptation, as provided in Annex VIII, Section 8.6.1., Column 2.

4. Screening study for reproductive/developmental toxicity

41 A screening study for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII, Section 8.7.1.

4.1. Information provided

42 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) a reproduction/developmental toxicity screening test (1999) with the source substance N,N-dimethylpropane-1,3-diamine, EC 203-680-9 / DMAPA.

4.2. Assessment of the information provided

4.2.1. Read-across adaptation rejected

43 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint specific issue(s) addressed below.

4.2.1.1. Inadequate or unreliable study (i) on the source substance

44 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case EU B.63/OECD TG 421 or EU B.64/OECD TG 422. Therefore, the following specifications must be met:

a) at least 10 male and 12-13 female animals are included for each dose and control group;

b) offspring parameters such as number and sex of pups, stillbirths and live births, and litter weight are reported.

45 In study (i):

a) 5 males/females (i.e., less than 10 male animals/12-13 female animals) were included in each dose and control group;

b) data on number and sex of pups, stillbirths and live births, and litter weight are missing.

46 Therefore, the study submitted in your adaptation, as currently reported in your dossier, does not provide an adequate and reliable coverage of the key parameter(s) of the corresponding OECD TG.

47 Therefore, the information requirement is not fulfilled.

4.3. Specification of the study design

48 A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats.

49 The Substance is a corrosive liquid and you apply a self-classification as Skin Corr. 1B (H314). Therefore, the study must be conducted with oral administration of the Substance (Annex VIII, Section 8.7.1, Column 1, and Guidance on IRs and CSA, Section R.7.6.2.3.2.). 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.

50 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.

51 In your comments on the draft decision, you agree to perform the requested study by the oral route. But you state that:

- *"[…] testing of the neutral salt is considered inappropriate, since it masks the most important intrinsic property with regard to hazard identification and risk assessment."* and
- the Substance "*is corrosive, and local effects are expected to be the leading health hazard.*"

52 Therefore, you propose "*to conduct the animal studies with the registered substance and use the local irritation as dose limiting factor to avoid in vivo testing causing corrosivity […]*." In addition, you also argue that you are facing technical issues when neutralising the Substance.

53 ECHA takes note of your comments but stresses that testing a neutralized salt is only mentioned as an option to mitigate corrosivity and subsequent gastrointestinal irritation. You remain responsible to select an appropriate test material to conduct the test.

54 As already stated above, ECHA considers that investigating intrinsic properties related to reproductive toxicity at adequate dose levels may require testing a neutralised salt of the Substance. Otherwise, the already known corrosivity of the Substance may not allow investigation of reproductive toxicity in relation to systemic toxicity. Also, the irritation of the Substance may affect the behaviour of the animals confounding the interpretation of reproductive toxicity-related parameters and induce also unnecessary stress to the animals with consequences to the outcome of the study.

Reasons related to the information under Annex IX of REACH

5. Sub-chronic toxicity study (90 days)

55 A sub-chronic toxicity study (90 days) is an information requirement under Annex IX, Section 8.6.2.

5.1. Information provided

56 ECHA understands that you have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on the following justification:

(i) "*A sub-chronic toxicity study (90 days) (oral) in rats according to the OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) was proposed for the analogue substance 3-aminopropyldiethylamine (CAS no. 104-78-9). Therefore, it is proposed to waive the 90-day study for N, N, N', N'-tetramethyltrimethylenediamine (TMPDA).*"

5.2. Assessment of the information provided

5.2.1. Read-across adaptation rejected

57 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint specific issue(s) addressed below.

5.2.1.1. Missing robust study summary for study (i)

58 Annex XI, Section 1.5. requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must include robust study summary for each source study used in the adaptation.

59 You have not provided a sub-chronic toxicity study (90 days) according to the OECD TG 408 nor a testing proposal in accordance with Article 10(a)(ix) and the format set under Article 111 of REACH in you registration dossier. You only refer to a proposed 90-day study on the analogue substance.

60 You have not provided detailed information on the methods, results and conclusions, allowing for an independent assessment of the study (i). Therefore, you have failed to provide a robust study summary for each source study used in the adaptation as required by Annex XI, Section 1.5.

61 Therefore, the information requirement is not fulfilled.

5.3. Specification of the study design

62 Following the criteria provided in Annex IX, Section 8.6.2., Column 2, and considering the Guidance on IRs and CSA, Section R.7.5.6.3.2., the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance, because the Substance is a liquid with low vapour pressure and no uses with spray application are reported that could potentially lead to aerosols of inhalable size.

63 In your comments on the draft decision, you consider that the most relevant human exposure route for the Substance "*would be via inhalation in terms of the vapor pressure*

(8,4 hPa at 25°C) and the predominant intrinsic property of corrosiveness and causing irritations in the respiratory tract after inhalation."

64 However, despite the corrosivity of the Substance, ECHA notes that the low vapour pressure of 8.4 hPa (i.e. 0.84 kPa) and the use profile do not support the inhalation route as the most appropriate route of administration in a repeated dose toxicity study. ECHA also understands from your general comments to the draft decision that you agree with performing the test by the oral route.

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

66 Therefore, the study must be performed in rats according to the OECD TG 408 with oral administration of the Substance.

6. Pre-natal developmental toxicity study in one species

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

6.1. Information provided

68 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) a reproduction/developmental toxicity screening test (1999) with the source substance N,N-dimethylpropane-1,3-diamine, EC 203-680-9 / DMAPA.

(ii) *"A Developmental toxicity / teratogenicity (oral: gavage) in rats according to the OECD Guideline 414 (Prenatal Developmental Toxicity Study) was proposed for the analogue substance 3-aminopropyldiethylamine (CAS no. 104-78-9). Therefore, it is proposed to waive the developmental toxicity study for N, N, N', N'-tetramethyltrimethylenediamine (TMPDA)."*

6.2. Assessment of the information provided

6.2.1. Read-across adaptation rejected

69 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint specific issue(s) addressed below.

6.2.1.1. Inadequate or unreliable study (i) on the source substance(s)

70 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall be normally performed for a particular information requirement, in this case OECD TG 414. Therefore, the following specifications must be met:

a) at least 20 female animals with implantation sites for each test and control group are included;

b) the foetuses are examined for body weight, number and percent of live and dead foetuses and resorptions, sex ratio, external, skeletal and soft tissue

alterations (variations and malformations), measurement of anogenital distance in all live rodent foetuses.

71 In study (i):

a) only 10 females were included in each test and control group, and therefore the statistical power is not equivalent to OECD TG 414;

b) data on the examination of the foetuses, including incidence and severity, are missing; In particular, the following investigations are missing: external, skeletal and soft tissue alterations (variations and malformations).

72 Therefore, the study submitted in your adaptation, as currently reported in your dossier, does not provide an adequate and reliable coverage of the key parameter(s) of the corresponding OECD TG.

6.2.1.2. Missing robust study summary for study (ii)

73 Annex XI, Section 1.5. requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must include robust study summary for each source study used in the adaptation.

74 You have not provided a pre-natal developmental toxicity (PNDT) study according to OECD TG 414 nor a testing proposal in accordance with Article 10(a)(ix) and the format set under Article 111 of REACH in you registration dossier. You only refer to a proposed PNDT study on the analogue substance.

75 You have not provided detailed information on the methods, results and conclusions, allowing for an independent assessment of the study (ii). Therefore, you have failed to provide a robust study summary for each source study used in the adaptation as required by Annex XI, Section 1.5.

76 Therefore, the information requirement is not fulfilled.

6.3. Specification of the study design

77 A PNDT study according to the test method OECD TG 414 should be performed in rats or rabbits as preferred species.

78 The Substance is a corrosive liquid and you apply a self-classification as Skin Corr. 1B (H314). Therefore, the study must be conducted with oral administration of the Substance (Annex IX, Section 8.7.2., Column 1, and Guidance on IRs and CSA, Section R.7.6.2.3.2.). 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.

79 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.

80 In your comments on the draft decision, you agree to perform the requested study by the oral route. But you state that

- *"[…] testing of the neutral salt is considered inappropriate, since it masks the most important intrinsic property with regard to hazard identification and risk assessment."* and
- the Substance "*is corrosive, and local effects are expected to be the leading health hazard*."

81 Therefore, you propose *"to conduct the animal studies with the registered substance and use the local irritation as dose limiting factor to avoid in vivo testing causing corrosivity […]."* In addition, you also argue that you are facing technical issues when neutralising the Substance.

82 ECHA takes note of your comments but stresses that testing a neutralized salt is only mentioned as an option to mitigate corrosivity and subsequent gastrointestinal irritation. You remain responsible to select an appropriate test material to conduct the test.

83 As already stated above, ECHA considers that investigating intrinsic properties related to reproductive toxicity at adequate dose levels may require testing a neutralised salt of the Substance. Otherwise, the already known corrosivity of the Substance may not allow investigation of reproductive toxicity in relation to systemic toxicity. Also, the irritation of the Substance may affect the behaviour of the animals confounding the interpretation of reproductive toxicity-related parameters and induce also unnecessary stress to the animals with consequences to the outcome of the study.

7. Long-term toxicity testing on fish

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

7.1. Information provided

85 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided following information:

(i) *"Based on the short-term results, fish seems not to be the most sensitive species. Moreover, the exposure levels estimated in all relevant scenarios do not exceed the appropriate PNEC (all risk characterization ratios are under 1.0), and the likelihood and severity of an event occurring due to the physicochemical properties of the substance in the aquatic environment are negligible. Therefore, and for reasons of animal welfare, a chronic test on fish is not provided. In conclusion: In accordance with column 2 of REACH Annex IX, the long term testing on fish does not need to be conducted as the chemical safety assessment according to Annex I has not indicated a need to investigate further the effects on aquatic organisms".*

7.2. Assessment of the information provided

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

86 Annex IX, Section 9.1., Column 2 is not a basis for omitting information on long-term toxicity to fish referred to under Column 1, Section 9.1.6. A registrant may only adapt this information requirement based on the general rules set out in Annex XI.

87 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH. Minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI.

88 Your adaptation is therefore rejected.

89 In your comments to the draft decision you agree that the current waiver for this study is not sufficient according to the REACH regulation. In addition, you have provided a new waiver in an IUCLID extract attached to the comments. ECHA understands that you have

adapted this information requirement according to Annex XI 3.2 (a) by providing the following: "[…] *The exposure levels estimated in all relevant scenarios do not exceed the appropriate PNEC (all risk characterization ratios are under 1.0)*[…]" which is supported by information on identified uses and RCRs in the CSR. ECHA considers that this adaptation meets the information required for adaptation under Annex XI, Section 3. However, as the information is currently not available in your registration dossier, the data gap remains. You should therefore submit this information in an updated registration dossier by the deadline set in the decision.

90 Therefore, the information requirement is not fulfilled.

7.3. Study design and test specifications

91 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.).

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).
Guidance for monomers and polymers; ECHA (2012).
Guidance on intermediates; ECHA (2010).
All guidance documents are 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 14 March 2022.

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

ECHA took into account your comments and did not amend the requests.

In your comments on the draft decision, you require an extension of the deadline by 6 months, i.e. from 36 months to 42 months based on availability of contract research organisations (CROs) and technical issues identified when attempting to neutralise a comparable REACH registered amine substance. ECHA notes that you have not provided documentary evidence as to why CROs' availability would not allow generating the requested information by the set deadline (which, as explained aboved, has already been exceptionally extended by 12 months). Furthermore, while you refers to technical difficulties in preparing a neutralised form of the salt, you have provided no reasoned justification indicating the timeline required to obtain such test material. Therefore, ECHA did not amend the deadline.

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. The editorial change was made to the request 3 to remove the obsolete alternative.

Appendix 3: Addressee(s) 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]
[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

- 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.
- 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.
- 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].
- 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:
  - the variation in compositions reported by all members of the joint submission,
  - the boundary composition(s) of the Substance,
  - 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
  - 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.
  - The reported composition must include all constituents of each Test Material and their concentration values.

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.

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

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).

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