~~Confidential~~

Helsinki, 04 October 2021

Addressees
Registrants of JS_203-183-7 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
09/10/2020

Registered substance subject to this decision ("the Substance")
Substance name: N,N,4-trimethylpiperazine-1-ethylamine
EC number: 203-183-7
CAS number: 104-19-8

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 the deadline of ***10 April 2024***.

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

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

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

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

1. In vivo mammalian erythrocyte micronucleus test (Annex VIII, Section 8.4., column 2; test method: OECD TG 474) in mice or rats, oral route; OR In vivo mammalian bone marrow chromosomal aberration test (Annex VIII, Section 8.4., column 2; test method: OECD TG 475) in mice or rats, oral route; OR In vivo mammalian alkaline comet assay (Annex VIII, Section 8.4., column 2; test method: OECD TG 489) in rats, oral route, on the following tissues: liver, oral: glandular stomach and duodenum.

2. Simulation testing on ultimate degradation in surface water (triggered by Annex VIII, Section 9.2.; test method: EU C.25./OECD TG 309) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.

3. Identification of degradation products (triggered by Annex VIII, Section 9.2; test method: using an appropriate test method or test method OECD TG 309)

4. Bioaccumulation in aquatic species (triggered by Annex I, sections 0.6.1. and 4.; Annex XIII, Section 2.1.; test method: OECD TG 305, aqueous exposure)

5. Adsorption/ desorption screening (Annex VIII, Section 9.3.1.; test method: OECD TG 106)

Reasons for the request(s) are explained in the appendices entitled "Reasons to request information required under Annexes VII to VIII of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa),
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa.

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 testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

The studies relating to biodegradation and bioaccumulation are necessary for the PBT assessment. However, to determine the testing needed to reach the conclusion on the persistency and bioaccumulation of the Substance you should consider the sequence in which these tests are performed and other conditions described in Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes".

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 Christel Schilliger-Musset, Director of Hazard Assessment

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

Appendix A: Reasons to request information required under Annex VII of REACH

1. Growth inhibition study aquatic plants

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

You have provided the following information:
1. an OECD TG 201 study with the Substance ([redacted], 2018);
2. an OECD TG 201 study with the Substance ([redacted], 2001).

We have assessed this information and identified the following issue:

To fulfil the information requirement, a study must comply with OECD TG 201 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

Validity criteria
- a. exponential growth in the control cultures is observed over the entire duration of the test;
- b. the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures is ≤ 35%;

Characterisation of exposure
- c. the test media prepared specifically for analysis of exposure concentrations during the test is treated identically to those used for testing (*i.e.* inoculated with algae and incubated under identical conditions);
- d. for some substances (*e.g.* adsorbing substances), the results may only be expressed based on nominal concentrations if the decrease in measured concentrations of the test substance during the test is not accompanied by a decrease in growth inhibition. If a reduction in growth inhibition is observed, a suitable model describing the decline of the concentration of the test material must be used;

Reporting of the methodology and results
- e. the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form;
- f. detailed information on the methodology and analytical verification of the exposure concentrations.

Your registration dossier provides two robust study summaries on OECD TG 201 studies showing the following:

- With regard to study 1 above, tabulated data on the algal biomass determined daily for each treatment group and mean coefficient of variation are not reported (point b and e) and control are not reported for studies 1 and 2 (point a, b and e above). In the absence of this information, it is not possible to make an independent assessment of whether or not the validity criteria of OECD TG 201 were met;

  In your comments on the draft decision, you provided the missing information specified under point e. and you specify that you will update your dossier with the missing information. ECHA has assessed this information and concluded that the study 1 meets the validity criteria of OECD TG 201 (point a and b). However until this information is provided in a dosser update this incompliance remains.

- for study 1, you did not report clearly how the exposure concentrations were determined (points c and d above). For instance, you have not specified if the exposure concentrations were determined with or without presence of algae (point f above). Then, it is unclear what the values in bracket correspond to in table 1 of your robust study summary.

  In your comments on the draft decision, you provided further information on the determination of the exposure concentrations (with measurements of the test concentrations in the range finding test and definitive test). However from that new information it remains unclear whether or not the reported measurements were conducted with or without presence of algae.

- for study 2, as you have not provided tabulated data on the algal biomass (point e above), it is not possible to verify if effect values can reliably be expressed based on nominal concentrations.

  In your comment on the draft decision you have not provided the missing information.

Therefore, none of these studies currently meet the requirements of OECD TG 201.

On this basis, the information requirement is not fulfilled.

Study design

The Substance is difficult to test due to the potential adsorptive properties of the Substance since it is ionised at environmentally relevant pHs. 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.

Appendix B: Reasons to request information required under Annex VIII of REACH

1. ***In vivo mammalian erythrocyte micronucleus test***
   OR
   In vivo mammalian bone marrow chromosomal aberration test
   OR
   In vivo mammalian alkaline comet assay

Under Annex VIII, Section 8.4, column 2 of REACH, the performance of an appropriate *in vivo* somatic cell genotoxicity study must be considered if there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII.

Your dossier contains positive results for the *in vitro* cytogenicity tests which raise the concern for chromosomal aberration.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5 using the following study:

- Leung 1993, with Aminoethylpiperazine (CAS 140-31-8).

You have also provided a read-across justification document in IUCLID Section 13.

You predict the properties of the Substance from the structurally similar substance: 2-piperazin-1-ylethylamine or Aminoethylpiperazine (AEP), CAS No. 140-31-8 i.e. the source substance).

The source study that you have used in your read-across approach, Leung 1993, corresponds to an in vivo micronucleus non-guideline study.

You have provided the following reasoning for the prediction of toxicological properties:

Hypothesis: "*the two chemicals are hypothesized to have the same type of effect(s) – Scenario 2 of the RAAF guidance*."
and
"*The similarity in their structures and physical-chemical properties serves as the foundation for this read-across and justify prediction of the target substance's toxicological properties for 1 endpoint from the source substance. The structural differences between the source and the target substance are such that it is expected that the source substance is more toxic than the target compound based on the information presented in the data matrix. Given this difference, using the source substance as the analogue for the target substance is presumed to be a health-protective choice*."

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted based on a based on a worst-case approach.

We have assessed this information and identified the following issue:

Read-across hypothesis contradicted by existing data

Annex XI, Section 1.5. provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances. The ECHA

Guidance[2] indicates that "*it is important to provide supporting information to strengthen the rationale for the read-across*". The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance. The observation of differences in the toxicological properties between the source substance(s) and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substances. An explanation why such differences do not affect the read-across hypothesis needs to be provided and supported by scientific evidence.

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar target and source substances cause the same type of effect(s).

The results of the information on mutagenicity obtained with the source substance vary. Specifically, positive results are observed in the *in vitro* chromosomal aberration study conducted with the Substance (N,N,4-trimethylpiperazine-1-ethylamine) while negative results are reported for similar studies conducted for the source substance (Aminoethylpiperazine).

The available set of data on the target and source substances indicates differences in the toxicological properties of the substances. This contradicts your read-across hypothesis whereby the structurally similar target and source substances cause the same type of effect(s). Therefore you have not demonstrated and justified that the properties of the source substance(s) and of the Substance are likely to be similar despite the observation of these differences.

Therefore, the information requirement is not fulfilled.

In your comments you acknowledged that the information requirement is not fulfilled by the available information and agreed to perform an appropriate in vivo follow up mutagenicity study with the substance: "*in vivo mammalian erythrocyte micronucleus test (OECD TG 474) in mice or rats, oral route; or in vivo mammalian bone marrow chromosomal aberration test (OECD TG 475) in mice or rats, oral route; or in vivo mammalian alkaline comet assay (OECD TG 489) in rats, oral route (on the following tissues: liver, oral: glandular stomach and duodenum).*"

ECHA considers that an appropriate *in vivo* follow up mutagenicity study is necessary to address the concern identified *in vitro*.

According to the ECHA Guidance Chapter R.7a, Section R.7.7.6.3, the mammalian erythrocyte micronucleus test ("MN test", OECD TG 474) or the mammalian bone marrow chromosomal aberration test ("CA test", OECD TG 475) are suitable to follow up a positive *in vitro* result on chromosomal aberration if the Substance or its metabolite(s) will reach the target tissue. Alternatively, the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) is a suitable test to be performed. Therefore, the MN test, the CA test and the comet assay are suitable tests to follow up the chromosomal aberration concern identified for the Substance.

In case you decide to perform a MN or CA assay, according to the test method OECD TG 474 / OECD TG 475, the test must be performed in mice or rats. Having considered the anticipated routes of human exposure and the need for adequate exposure of the target tissue(s) performance of the test by the oral route is appropriate.

[2] Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.6, Section R.6.2.2.1.f

Regarding the exposure of the target tissue, the applicable test guideline (OECD TG 474 / OECD TG 475) states "If there is evidence that the test substance(s), or its metabolite(s), will not reach the target tissue, it may not be appropriate to use this test". Additionally, a negative test result can be considered reliable if "Bone marrow exposure to the test substance(s) occurred". Accordingly, if the Substance is negative in this test, but it is not possible to demonstrate that bone marrow exposure to the Substance occurred, then ECHA will consider any remaining uncertainty concerning the mutagenic potential of the Substance and whether to request any further information.

In case you decide to perform the comet assay according to the test method OECD TG 489, the test must be performed in rats. Having considered the anticipated routes of human exposure and the need for adequate exposure of the target tissue(s) performance of the test by the oral route is appropriate.

In line with the test method OECD TG 489, the test must be performed by analysing tissues from liver as primary site of xenobiotic metabolism, glandular stomach and duodenum as sites of contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

Germ cells
In case you decide to perform the comet assay, you may consider to collect the male gonadal cells collected from the seminiferous tubules in addition to the other aforementioned tissues in the comet assay, as it would optimise the use of animals. You can prepare the slides for male gonadal cells and store them for up to 2 months, at room temperature, in dry conditions and protected from light. Following the generation and analysis of data on somatic cells in the comet assay, you should consider analysing the slides prepared with gonadal cells. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

2. Simulation testing on ultimate degradation in surface water

Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

This information requirement is triggered in case the chemical safety assessment (CSA) indicates the need for further degradation investigation (Annex I, Section 4; Annex XIII, Section 2.1), such as if the substance is a potential PBT/vPvB substance (ECHA Guidance R.11.4.). This is the case if the Substance itself or any of its constituent or impurity present in concentration ≥ 0.1% (w/w) or relevant transformation/degradation product meets the following criteria :

- it is potentially persistent or very persistent (P/vP) as:
  - it is not readily biodegradable (*i.e.* <60/70% degradation in an OECD 301B);
- it is potentially bioaccumulative or very bioaccumulative (B/vB) as:
  - for some groups of substances (*e.g.* organometals, ionisable substances, surfactants) other partitioning mechanisms may drive bioaccumulation (e.g. binding to protein/cell membranes) and high potential for bioaccumulation cannot be excluded solely based on its potential to partition to lipid.
- it meets the T criteria set in Annex XIII: NOEC or EC_{10} < 0.01 mg/L or classification as carc. 1A or 1B, muta. 1A or 1B, repro. 1A, 1B or 2, or STOT RE 1 or 2.

However, your registration dossier provides the following:

- The Substance is not readily biodegradable (0% degradation after 28 days in an OECD TG 301B);

Furthermore, the information in your dossier is currently incomplete and therefore:

- it is not possible to conclude on the bioaccumulation potential of the Substance (see Appendix B.4. of this decision), and
- it is not possible to conclude on the toxicity of the Substance (see Appendices A.1. and B.1. of this decision).

The information above indicates that the Substance is a potential PBT/vPvB substance.

In your comments on the draft decision, you disagreed that the Substance is potentially PBT/vPvB as you consider that the Substance is not B/vB. The information you have provided in your comments would address the incompliance identified in this decision for the information requirement on bioaccumulation in aquatic species and hence on PBT trigger as indicated in issue B.4. However, as the information is currently not available in your registration dossier, the data gap remains.

Furthermore you propose to predict potential degradation products of your Substance using EAWAG BBD pathway prediction system and to conduct a PBT/vPvB assessment of the estimated degradation products.

However as this information is currently not in your dossier the incompliance remains.

Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

Study design

Simulation degradation studies must include two types of investigations (ECHA Guidance R.7.9.4.1.):

1) a degradation pathway study where transformation/degradation products are quantified and, if relevant, are identified, and
2) a kinetic study where the degradation rate constants (and degradation half-lives) of the parent substance and of relevant transformation/degradation products are experimentally determined.

You must perform the test, by following the pelagic test option with natural surface water containing approximately 15 mg dw/L of suspended solids (acceptable concentration between 10 and 20 mg dw/L) (ECHA Guidance R.11.4.1.1.3.).

The required test temperature is 12°C, which corresponds to the average environmental temperature for the EU (ECHA Guidance R.16, Table R.16-8) and is in line with the applicable test conditions of the OECD TG 309.

As specified in ECHA Guidance R.7.9.4.1., the organic carbon (OC) concentration in surface water simulation tests is typically 2 to 3 orders of magnitude higher than the test substance concentration and the formation of non-extractable residues (NERs) may be significant in surface water tests. Therefore, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents. By default, total NER is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NER may be differentiated

and quantified as irreversibly bound or as degraded to biogenic NER, such fractions could be regarded as removed when calculating the degradation half-life(s) (ECHA Guidance R.11.4.1.1.3.). Further recommendations may be found in the background note on options to address non-extractable residues in regulatory persistence assessment available on the ECHA website.

Relevant transformation/degradation products are at least those detected at ≥ 10% of the applied dose at any sampling time or those that are continuously increasing during the study even if their concentrations do not exceed 10% of the applied dose, as this may indicate persistence (OECD TG 309; ECHA Guidance R.11.4.1.).

3. Identification of degradation products

Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

This information requirement is triggered in case the chemical safety assessment (CSA) indicates the need for further degradation investigation (Annex I, Section 4; Annex XIII, Section 2.1), such as if the substance is a potential PBT/vPvB substance (ECHA Guidance R.11.4.). As already explained under Section B.2., the Substance is a potential PBT/vPvB substance. Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

You have not provided information on the identity of transformation/degradation products for the Substance.

On this basis, the information requirement is not fulfilled.

In your comments on the draft decision, you explained that you intend to meet the information requirement by providing results from a QSAR model (namely EAWAG BBD pathway prediction system). ECHA notes that you have not provided the results of the QSAR prediction in your comments, therefore ECHA is not in a position to assess the corresponding information.

Study design

Regarding the selection of appropriate and suitable test method(s), the method(s) will have to be substance-specific. Identity, stability, behaviour, and molar quantity of the degradation/transformation products relative to the Substance must be evaluated and reported, when analytically possible. In addition, degradation half-life, log K_{ow} and potential toxicity of the transformation/degradation may need to be investigated. You may obtain this information from the degradation study requested in Appendix B.2. or by some other measure. If any other method is used for the identification of the transformation/degradation products, you must provide a scientifically valid justification for the chosen method.

To determine the degradation rate of the Substance, the requested study according to OECD TG 309 (Appendix B.2) must be conducted at 12°C and at a test concentration < 100 µg/L. However, to overcome potential analytical limitations with the identification and quantification of major transformation/degradation products, you may consider running a parallel test at higher temperature (but within the frame provided by the test guideline, *e.g.* 20°C) and at higher application rate (*i.e.* > 100 µg/L).

4. Bioaccumulation in aquatic species

Bioaccumulation in aquatic species is required for the purpose of PBT/vPvB assessment (Annex I, Sections 0.6.1 and 4 to REACH).

This information requirement is triggered in case the chemical safety assessment (CSA) indicates the need for further degradation investigation (Annex I, Section 4; Annex XIII, Section 2.1), such as if the substance is a potential PBT/vPvB substance (ECHA Guidance R.11.4.). As already explained under Section B.2., the Substance is a potential PBT/vPvB substance. Therefore, the chemical safety assessment (CSA) indicates the need for further investigation on bioaccumulation in aquatic species.

In your comments on the draft decision, while you recognized the rejection of the adaptation of the information requirement, you also specified that you intend to adapt this information requirement under Annex XI, Section 1.2. ('Weight of evidence'). You intend to provide the following justification:

- i. some publications from [redacted] (2013) and [redacted] (2009) on ionisable substances and their hydrophobic potentials (Log Kow and Log Dow),
- ii. a read-across from the similar substance Piperazine (CAS No. 110-85-0) with a reference to an experimental bioaccumulation study on *C.carpio* showing low BCF,
- iii. some estimated BCF values using BCFBAF v3.01 for the Substance and some analogue, including the QMRF and QPRF

We take note of your intention to submit an adaptation. The estimated BCF value from QSAR model you have provided in your comments would address the incompliance identified in this decision for this information requirement. However, as the information is currently not available in your registration dossier, the data gap remains.

Study design

Bioaccumulation in fish: aqueous and dietary exposure (Method EU C.13 / OECD TG 305) is the preferred test to investigate bioaccumulation (ECHA Guidance R.7.10.3.1.). Exposure via the aqueous route (OECD TG 305-I) must be conducted unless it can be demonstrated that:

- a stable and fully dissolved concentration of the test substance in water cannot be maintained within ± 20% of the mean measured value, and/or
- the highest achievable concentration is less than an order of magnitude above the limit of quantification (LoQ) of a sensitive analytical method.

This test set-up is preferred as it allows for a direct comparison with the B and vB criteria of Annex XIII of REACH.

You may only conduct the study using the dietary exposure route (OECD 305-III) if you justify and document that testing through aquatic exposure is not technically possible as indicated above. You must then estimate the corresponding BCF value from the dietary test data according to Annex 8 of the OECD 305 TG and OECD Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation (ENV/JM/MONO(2017)16).

5. Adsorption/ desorption screening

Adsorption/Desorption screening is an information requirement under Annex VIII to REACH (Section 9.3.1.).

You have provided the following information:

1. an adaptation under Annex VIII, Section 9.3.1., column 2 ('low potential for adsorption') with the following justification:
   - *"an assessment of the test item indicated that it would be ionized across the environmentally relevant pH range (pH 5 to 7)";*

- "*Consequently, the true adsorption coefficient of the test item would be significantly higher than a Koc value determined by the Methods C.19 and OECD 121 or via any computer-based Koc estimation software*";
- "*Therefore, based on the expected high cation-exchange ability of the test item, the test item is anticipated to lack mobility in soils*".

2. an adaptation under Annex XI, Section 1.3. ('QSAR') with the following supporting information:
   - predicted Koc values using KOCWIN v2.00.

We have assessed this information and identified the following issues:

A. Annex VIII, Section 9.3.1., column 2 specifies that a study does not need to be conducted if the substance can be expected to have a low potential for adsorption.

In your adaptation under Annex VIII, Section 9.3.1., column 2, you state that the substance is *"ionized across the environmentally relevant pH range (pH 5 to 7)"* and therefore *"the test item is anticipated to lack mobility in soils".*

ECHA agrees that the substance is ionised at environmentally relevant pHs. On this basis the Substance is expected to have a high potential for adsorption and therefore your adaptation is rejected.

B. Assessment of your (Q)SAR adaptation

Annex XI, Section 1.3. specifies that the following conditions must be fulfilled whenever a (Q)SAR approach is used:

1. the prediction needs to be derived from a scientifically valid model,
2. the substance must fall within the applicability domain of the model,
3. results need to be adequate for the purpose of risk assessment or classification and labelling, and
4. adequate and reliable documentation of the method must be provided.

a. The substance is outside the applicability domain of the model.

Under ECHA Guidance R.6.1.5.3., a substance must fall within the applicability domain specified by the model developer.

Under ECHA Guidance R.6.1.5.3., a prediction is within the applicability domain of the model, when, among others, the substance and the structures selected for the prediction fall within descriptor, structural, mechanistic and metabolic domain.

The Substance is ionisable at environmentally relevant pHs and therefore the Substance and the fragments used in the prediction are out of the QSAR KOCWIN domain of applicability.

Therefore, you have not demonstrated that the Substance falls within the applicability domain of the model.

b. Selection of the representative structure(s)

Under ECHA Guidance R.6.1.7.3. a prediction is adequate for the purpose of classification and labelling and/or risk assessment if the following cumulative conditions are met:

- the composition of the substance is clearly defined, and

- representative structure(s) for the assessment are selected.

Your registration dossier provides the following information:

- In Section 1.1 of your technical dossier, you define the Substance as 1-Piperazineethanamine, N,N,4-trimethyl-.
- For the assessment, you provided predictions for the following structures: 1-Piperazineethanamine, N,N,4-trimethyl and with EC:255-615-9 and a different SMILES.

You have considered another substance and another SMILEs structure as representative structures. You failed to justify your selection.

However, ECHA disagrees with the representative structures you selected because of the mismatch between your Substance and the predicted one.

Therefore, you have not demonstrated that the prediction is adequate for the purpose of classification and labelling and/or risk assessment.

c. Inadequate documentation of the model (QMRF)

Under Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and ECHA Guidance R.6.1.6.3., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF) which reports, among others, the following information:

- the predicted endpoint, including information on experimental protocol and data quality for the data used to develop the model;
- an unambiguous definition of the algorithm, the descriptor(s) of the model and its applicability domain,
- an estimate of the goodness-of-fit and of the predictivity of the model, including information on training set and validation statistics.

The documentation available on the model refers to a molcode model, while the results are based on KOCWIN model. It is not described how the molcode model would relate to the KOCWIN model.

In absence of such information, ECHA cannot establish that the model can be used to meet this information requirement.

d. *Results not adequate for the purpose of risk assessment or classification and labelling*
ECHA Guidance R.7a, Section R.7.1.15.4 specifies that a measured adsorption coefficient is usually needed for ionising substances, since it is important to have information on pH-dependence. QSAR predictions cannot provide this pH dependence information.

Since the substance is ionised at environmentally relevant pHs, the QSAR information provided is not considered adequate for the purpose of risk assessment or classification and labelling.

In your comments on the draft decision, you stated that you intend to provide another QSAR method based data requirement using the equations developed by [redacted] (2008) and the requested information on the applicability domain by means of the QMRF and QPRF for this QSAR on ionised substances.You further stated that you will provide this information in an update of your registration dossier. However, as you have not provided this information as part of your comments, ECHA is not in a position to assess the corresponding information.

On this basis, your adaptation according to Annex XI, Section 1.3 is rejected and therefore the information requirement is not fulfilled.

Study design

You state that the Substance is "*ionized across the environmentally relevant pH range (pH 5 to 7)*". For such substance OECD TG 121 may not be applicable. Therefore, you are requested to generate information on adsorption/desorption using the OECD TG 106 (ECHA Guidance R.7.1.15.3).

Appendix C: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. 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].

B. 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.

1. 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.

2. 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 and other parameters relevant for the property to be tested.

This information is needed to assess 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[4].

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

Appendix D: General recommendations when conducting and reporting new tests for REACH purposes

A. Strategy for the PBT/vPvB assessment

Under Annex XIII, the information must be based on data obtained under conditions relevant for the PBT/vPvB assessment. You must assess the PBT properties of each relevant constituent of the Substance present in concentrations at or above 0.1% (w/w) and of all relevant transformation/degradation products. Alternatively, you would have to justify why you consider these not relevant for the PBT/vPvB assessment.

You are advised to consult ECHA Guidance R.7b (Section R.7.9.), R.7c (Section R.7.10) and R.11 on PBT assessment to determine the sequence of the tests needed to reach the conclusion on PBT/vPvB. The guidance provides advice on 1) integrated testing strategies (ITS) for the P, B and T assessments and 2) the interpretation of results in concluding whether the Substance fulfils the PBT/vPvB criteria of Annex XIII.

In particular, you are advised to first conclude whether the Substance fulfils the Annex XIII criteria for P and vP, and then continue with the assessment for bioaccumulation. When determining the sequence of simulation degradation testing you are advised to consider the intrinsic properties of the Substance, its identified uses and release patterns as these could significantly influence the environmental fate of the Substance. You must revise your PBT assessment when the new information is available.

Appendix E: 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 27 March 2020.

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.

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 F: List of references - ECHA Guidance[5] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[6]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[6]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[7]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

[5] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[6] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[7] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

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

You must provide the information requested in this decision for all REACH Annexes applicable to you.

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.