~~Confidential~~

Helsinki, 24 August 2021

Addressees
Registrants of JS_diisopropylamine as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
03/04/2013

Registered substance subject to this decision ("the Substance")
Substance name: Diisopropylamine
EC number: 203-558-5
CAS number: 108-18-9

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 ***3 March 2025***.

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. Justification for an adaptation of short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.) based on the results of the Long-term toxicity testing on aquatic invertebrates requested below (Annex IX, Section 9.1.5.)

2. 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. 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, with a neutralised form of the Substance.

2. Justification for an adaptation of short-term toxicity testing on fish (Annex VIII, Section 9.1.3.) based on the results of the Long-term toxicity testing on fish requested below (Annex IX, Section 9.1.6.)

3. Simulation testing on ultimate degradation in surface water also requested below (triggered by Annex VIII, Section 9.2.)

4. Soil simulation testing also requested below (triggered by Annex VIII, Section 9.2.)

5. Sediment simulation testing also requested below (triggered by Annex VIII, Section 9.2.)

6. Identification of degradation products also requested below (triggered by Annex VIII, Section 9.2)

7. Bioaccumulation in aquatic species also requested below (triggered by Annex I, sections 0.6.1. and 4.; Annex XIII, Section 2.1.)

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

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

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats, with a neutralised form of the Substance.

2. 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), with a neutralised form of the Substance.

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

4. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)

5. Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.; 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.

6. Soil simulation testing (Annex IX, Section 9.2.1.3.; test method: EU C.23./OECD TG 307) 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.

7. Sediment simulation testing (Annex IX, Section 9.2.1.4.; test method: EU C.24./OECD TG 308) 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.

8. Identification of degradation products (Annex IX, 9.2.3.; test method: using an appropriate test method)

9. Bioaccumulation in aquatic species (Annex IX, Section 9.3.2; test method: OECD TG 305, aqueous exposure)

Reasons for the request(s) are explained in the following appendices:

- Appendix entitled "Reasons common to several requests"; and
- Appendices entitled "Reasons to request information required under Annexes VII to IX 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), or as a transported isolated intermediate in quantity above 1000 tpa;

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

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

For certain endpoints, ECHA requests the same study from registrants at different tonnages. In such cases, only the reasoning why the information is required at lower tonnages is provided in the corresponding Appendices. For the tonnage where the study is a standard information requirement, the full reasoning for the request including study design is given. Only one study is to be conducted; the registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the other registrants under Article 53 of REACH.

How to comply with your information requirements

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

You must follow the general 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 on Reasons common to several requests

1. **Assessment of your read-across approach under Annex XI, Section 1.5.**

You seek to adapt the following standard information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5:

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

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

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 (addressed under 'Assessment of prediction(s)').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6 and related documents[2, 3].

A. Predictions for toxicological properties

You have provided a read-across justification document in IUCLID Section 13.2.

You read-across between

- Diethylamine, EC No. 203-716-3, and
- Dimethylamine hydrochloride, i.e. dimethylammonium chloride, EC No. 208-046-5

as source substances and the Substance as target substance.

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

- "*The analogue approach is based on read-across to substances with the same chemical structure (low molecular weight secondary alkyl amine), similar physicochemical properties and similar toxicological profiles*". You refer to the similarity in acute toxicity, skin irritation/corrosivity, skin sensitisation and *in vitro* genotoxicity/mutagenicity properties.
- "*These three secondary amines are structurally similar showing trend in physical-chemical properties and similar toxicological properties. The read across is justified as below:*
    - *a structure which contains only aliphatic organic substituents; elemental compositions of carbon, hydrogen and nitrogen;*
    - *a consistent incremental change across the group consisting of an increasing number of carbon atoms or branching. The change is constant in that it is restricted to adding elements that do not greatly change the physico-chemical properties of the amino moiety. This is evidenced by the consistency of pKa values of the protonated forms, which vary across the narrow range of 10.73*

[2] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[3] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

to 11.13; and
  - *molecular weights of < 500 Dalton, classifying these secondary amines as low molecular weight aliphatic amines*";
- "*In general, the secondary amines can be considered to be comparable in metabolism. Metabolism of secondary amines to aldehydes can be viewed as a bioactivation reaction since aldehydes are biologically reactive*".

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 to be quantitatively equal to those of the source substance.

ECHA notes the following shortcomings with regards to predictions of toxicological properties:

A. Relevance of the supporting information

According to the ECHA Guidance R.6.2.2.1.f, "*it is important to provide supporting information to strengthen the rationale for the read-across approach. Thus, in addition to the property/endpoint being read-across, it is also useful to show that additional properties, relevant to the endpoint, are also (qualitatively or quantitatively) similar between the source and target chemicals*".

In order to support your claim that your Substance and source substance(s) have similar properties for the endpoints under consideration in the read-across approach, you refer to their similarity in acute toxicity, skin irritation, skin sensitisation and *in vitro* genotoxicity/mutagenicity properties.

Whilst this data set suggests that the substances may have similar properties for acute toxicity, skin and eye irritation, and skin sensitisation and *in vitro genotoxicity/mutagenicity*, these studies do not inform on the repeated dose toxicity, and reproductive and developmental toxicity properties of the target and source substances. Accordingly, this information is not considered as relevant to support prediction of all the endpoints under consideration.

B. Supporting information

Annex XI, Section 1.5 of the REACH Regulation states that "*human health effects may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*" (ECHA Guidance R.6.2.2.1.f). 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(s).

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm that both substance 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).

In support of your adaptation, you have provided information on studies showing that the source substances and the Substance are corrosive; show a similar acute toxicity profile; and are negative in *in vitro* gene mutation studies in bacteria and mammalian

cells, and in *in vitro* cytogenicity studies. You have not provided bridging studies with comparable design and duration on the source substances and the Substance to inform on the repeated dose toxicity, and reproductive and developmental toxicity.

In the absence of such information, you have not established that the Substance and of the source substance are likely to have similar properties. Therefore, you have not provided sufficient supporting information to strengthen the rationale for the read-across.

C. *Adequacy and reliability of source studies for a sub-chronic toxicity study*

In addition, we have identified deficiencies with the source studies provided on the selected source substances for sub-chronic toxicity. These deficiencies are addressed under the corresponding appendix (Appendix C.1).

B. **Conclusions on the read-across approach**

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substances. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

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

1. **Justification for an adaptation of Short-term toxicity testing on aquatic invertebrates based on the results of the Long-term toxicity study on aquatic invertebrates**

Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.). This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Annex VII, Section 9.1.1., Column 2 or a general adaptation rule under Annex XI.

You have provided the following information:

i. a key study according to "*Methods outlined by the committee of Methods for Toxicity Tests with Aquatic Organisms*" on the Substance ([redacted], 1986);
ii. a supporting study according to N.F.T. 90-301 (1974) on the Substance ([redacted], 1980);
iii. a supporting study according to ISO 6341-1989 on the Substance ([redacted], 1989).

We have assessed this information and identified the following issues:

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

   For studies i. to iii. above, as reported in your dossier, you have identified the test material as "Diisopropylamine" with CAS 108-18-9 without further information, including composition, purity and the presence of impurities. In your comments on the draft decision, you agree "*that the current acute studies on daphnia of the dossier present a gap around substance identification*". However, with regard study i. above, you state that the purity of the Substance is reported in the study report (i.e. purity of [redacted]% with no impurities > 0.1%).

While you have provided clarifications on the composition of the test material used in study i., you will have to add this information to your dossier in order to remove the incompliance. With regard studies ii. and iii., in the absence of appropriate information, you have not demonstrated that the test material is representative for the Substance. Therefore, the information form studies ii. and iii. is rejected.

B. To fulfil the information requirement, a study must comply with OECD TG 202 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
   - the percentage of immobilised daphnids is ≤ 10% at the end of the test in the controls (including the solvent control, if applicable);

   Technical specifications impacting the sensitivity/reliability of the test
   - the test duration is 48 hours or longer;
   - young daphnids, aged less than 24 hours at the start of the test, are used;
   - at least 20 animals are used at each test concentration and for the controls;
   - the test medium fulfils the following condition(s): particulate matter ≤ 20 mg/L, total organic carbon (TOC) ≤ 2 mg/L, hardness between 140 and 250 mg/L (as $CaCO_3$), pH between 6 and 9;

Characterisation of exposure

- the concentrations of the test material are measured at least at the highest and lowest test concentration, at the beginning and end of the test;

Reporting of the methodology and results

- the test procedure is reported (*e.g.* composition of the test medium, loading in number of *Daphnia* per test vessel);
- the number of immobilised daphnids is determined at 24 and 48 hours. Data are summarised in tabular form, showing for each treatment group and control, the number of daphnids used, and immobilisation at each observation;
- adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations are provided;

Your registration dossier provides a key study (study i. above) showing the following:

- no analytical monitoring of exposure is reported;
- on the test procedure, you have not specified the number of test animals used at each concentration and for the controls, the life-stage of the test animals, the composition of the test medium;
- tabulated data on the number of immobilised daphnids after 24 and 48 hours for each treatment group and control are not reported. However, you have provided this information as part of your comments on the draft decision. This information must be added to your dossier in order to remove the incompliance.

Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the study does not provide an analytical monitoring of exposure concentrations which is a mandatory element of OECD TG 202 in conjunction with OECD GD 23.

- in the absence of adequate reporting of the elements of the study procedure listed above, it is not possible to conduct an independent assessment of the reliability of this study.

Your registration dossier also provides a supporting study (study ii. above) showing the following:

- the test duration was 24 hours;
- you have not provided performance parameters of the analytical method;
- the results of the analyses to determine the concentration of the test substance in the test vessels are not provided;
- on the test procedure, you have not specified the number of test animals used at each concentration and for the controls, the life-stage of the test animals, the composition of the test medium;
- tabulated data on the number of immobilised daphnids for each treatment group and control are not reported.

Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the exposure duration was shorter than the minimum requirement specified in OECD TG 202;
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically:
    - you have not provided adequate documentation to demonstrate the validity of the analytical method and you have not reported the results of the

analytical verification of exposure concentrations. Therefore, you have not demonstrated that exposure was satisfactorily maintained over the duration of the test.
    - As you have not reported a number of key information on the study procedure and study results, it is not possible to verify that the validity criteria of OECD TG 202 were met and that experimental conditions were consistent with this test guideline.

In your comments on the draft decision, you agree that this study does not provide sufficient data to fulfil the information requirement. But you state that you consider this information only as supporting information to the key study.

Finally your registration dossier also provides a supporting study (study iii. above) showing the following:

- the test duration was 24 hours;
- no analytical monitoring of exposure was conducted;
- on the test procedure, you have not specified the number of test animals used at each concentration and for the controls, the life-stage of the test animals, the composition of the test medium;
- tabulated data on the number of immobilised daphnids for each treatment group and control are not reported.

Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the exposure duration was shorter than the minimum requirement specified in OECD TG 202;
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically:
    - you have not provided adequate documentation to demonstrate the validity of the analytical method and you have not reported the results of the analytical verification of exposure concentrations. Therefore, you have not demonstrated that exposure was satisfactorily maintained over the duration of the test.
    - As you have not reported a number of key information on the study procedure and study results, it is not possible to verify that the validity criteria of OECD TG 202 were met and that experimental conditions were consistent with this test guideline.

In your comments on the draft decision, you agree that this study does not provide sufficient data to fulfil the information requirement. But you state that you consider this information only as supporting information to the key study.

Therefore, none of the provided studies meet the specifications of OECD TG 202 in conjunction with OECD GD 23.

In your comments on the draft decision, you also consider that the "*lack of analytical monitoring does not jeopardize the results of any study in general, nor the studies on the registered substance in particular*". To support your claim, you provide the following justification:

i. You state that the analytical monitoring of exposure concentrations is not a validity criteria of OECD TG 202.

   However, paragraph 23 of OECD TG 202 specifies that the concentration of the test

substance should be measured, as a minimum, at the highest and lowest test concentration, at the beginning and end of the test. The guideline recommends that the results are based on measured concentrations. However, if evidence is available to demonstrate that the concentration of the test substance has been satisfactorily maintained within 20 per cent of the nominal or measured initial concentration throughout the test, then the results can be based on nominal or measured initial values.

Therefore, the analytical monitoring of exposure concentrations during the test cannot be regarded as an optional specification as it is required to evaluate whether or not results can reliably be based on nominal or measured initial values. Therefore, the justification under point i. above does not provide a valid basis to omit this information.

ii. You explain that the three studies listed above were performed before OECD TG 202 was adopted and that "*ECHA did not consider that the guidance documents at the time the latest study was performed were not as demanding as nowadays*".

However, the purpose of the adaptation set out under section 1.1.2. ("use of existing data") of Annex XI to REACH is precisely to enable registrants to demonstrate that existing data may be considered to be equivalent to data generated by the corresponding test methods referred to in Article 13(3) if the conditions set out in this provision are met. However, neither your dossier nor your comments on the draft decision demonstrate that the conditions set out in section 1.1.2. are met.

iii. You explain that based on "*the hydrolysis argumentation and biodegradation test, the substance is considered as stable in the environment*".

However, under the Appendix R.7.8-1 of the ECHA Guidance, Table R.7.8-2 lists critical parameters for aquatic toxicity testing. In this context, ionic substances are considered to be subject to loss from the test system as cationically charged substances bind to e.g. negatively charged humic acids, clay, glassware, microorganisms.

The substance is a secondary amine and you report, under Section 4.21 of your technical dossier, a pKa of 11. Hence, the Substance is ionised over the range of environmentally relevant pH.

Therefore, your justification, that the Substance shows limited degradation potential in the ready biodegradability test and that is not expected to be subject to fast hydrolysis, is not sufficient to exclude that significant loss (e.g. through adsorption) from the test system over the course of aquatic toxicity tests is unlikely.

iv. You consider that the statement by [redacted] 1980 that "*the substance was expected in ± 10% of nominal concentration*" supports that no significant loss of the test material occurred in the above studies.

However, a mere statement, that the authors of this publication expected the Substance to be stable, is not a valid evidence to demonstrate that the test material concentrations' were satisfactorily maintained in the studies listed above.

On this basis, the information requirement is not fulfilled.

The present decision requests the registrant(s) concerned to conduct and submit a long-term toxicity study on aquatic invertebrates (OECD TG 211; see Appendix C.3 for details).

According Annex VII, Section 9.1.1., Column 2 and to prevent unnecessary animal testing, a short-term toxicity study on aquatic invertebrates does not need to be provided.

Because you still must comply with the information requirement in Annex VII, Section 9.1.1., you are requested to submit a justification for the adaptation provided in Annex VII, Section 9.1.1, Column 2, second indent.

2. 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:

i. a key study according to "*EPA, National Eutrophication Research Program, U.S. Environmental Protection Agency, Corvallis, Oreg. (1971)*" on the Substance ([redacted] 1980).

We have assessed this information and identified the following issue:

A. 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

- exponential growth in the control cultures is observed over the entire duration of the test;
- at least 16-fold increase in biomass is observed in the control cultures by the end of the test;
- 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%;
- the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures is ≤ 10%;

Characterisation of exposure

- the concentrations of the test material are measured at least at the beginning and end of the test:
  1) at the highest, and
  2) at the lowest test concentration, and
  3) at a concentration around the expected EC_{50}.

  For volatile, unstable or strongly adsorbing test substances, additional samplings for analysis at 24 hour intervals is required.

Reporting of the methodology and results

- the test design is reported (*e.g.*, number of replicates, number of test concentrations and geometric progression used);
- the test conditions are reported (*e.g.*, composition of the test medium, test temperature, test species, biomass density at the beginning of the test);
- the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form;
- adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations is provided;

Other considerations

- Algal biomass is 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.

Your registration dossier provides a key study showing the following:

- exposure concentrations were monitored using GC-FID. You have not provided performance parameters of the analytical method;
- the results of the analyses to determine the concentration of the test substance in the test vessels are not provided;
- on the test design, you have not specified, the number of replicates for each test concentrations and for the controls;
- on the test procedure, you have not specified the initial cell density and the composition of the test medium;
- tabulated data on the algal biomass determined daily for each treatment group and control are not reported;
- biomass was determined based on *in vivo* fluorescence. No data to support the validity of this approach is provided;

Based on the above, the reporting of this study is not sufficient to conduct an independent assessment of its reliability. More specifically:

- As you have not provided adequate information on the analytical method and the results of the analytical determination of exposure concentrations, you have not demonstrated that exposure was satisfactorily maintained over the duration of the test.
- As you have not reported the key information on the study design and procedure listed above, you have not demonstrated that the test was conducted under conditions that are consistent with the specifications of OECD TG 201;
- As you have not provided tabulated data on the algal biomass determined during the test, it is not possible to verify if validity criteria consistent with the specifications of OECD TG 201 were met;

  In your comments on the draft decision, you explain that "*the validity criteria are not fulfilled as the guidance OECD TG 201 was not adopted on the 23 March 2006*". Furthermore, you state that "*the data on algal growth were not mathematically elaborated, the usual statistical method being considered not applicable owing to the high number of organisms* […]" and "*the 96h EC5O were extrapolated from the eye fitted empirical curve*".

  As already explained under Appendix A.1., the purpose of the adaptation set out under section 1.1.2. ("use of existing data") of Annex XI to REACH is precisely to enable registrants to demonstrate that existing data may be considered to be equivalent to data generated by the corresponding test methods referred to in Article 13(3), if the conditions set out in this provision are met. However, neither your dossier nor your comments on the draft decision demonstrate that the conditions set out in section 1.1.2. are met. Furthermore, the high number of organisms in an algae test is neither a valid justification for omitting to report tabulated data on the algal biomass as determined during the test, nor to conduct an appropriate mathematical analysis of the data. In this regard, Annex 5 of OECD TG 201 provides guidance on how to conduct such analysis using non linear regression.

- As you have not provided any supporting information to demonstrate that *in vivo* fluorescence provides an adequate determination of algal biomass, 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. You have not addressed this uncertainty.

In your comments on the draft decision, you explain that "*the protocol of fluorescence study was reported in* [redacted] *(1966), which indicated that generally each pure culture or mixed population has a different chlorophyll-fluorescence relationship which must be established by standardization. As the chlorophyll is a major compound of algae, if the fluorescence increase it is possible to conclude there is an algae growth*".

While it may be expected that an increase in fluorescence is indicative of an increase in algal biomass, you have not provided any justification that both parameters are linearly related over the range of biomass measured during the test and that that the potential physiological stress induced by the exposure to the test material did not bias this relationship.

Therefore, this study does not meet the specifications of OECD TG 201 in conjunction with OECD GD 23.

In your comments on the draft decision, you consider that the absence of analytical monitoring of exposure concentrations or the absence of performance parameters of the analytical method should not be regarded as a valid reason to reject this study. To support your claim, you provided the following justification:

i. "*the performance, accuracy, and other parameters of analytical methods were not mandatory in 1980, but only since the SANCO method/3029/99 revised in august 2000*".

This comment is already addressed under issue A.1. above.

ii. "*Analytical monitoring in OECD TG 201 is not regulatory mandatory this is not a validation criteria*".

However, under paragraph 37 of OECD TG 201 specifies that the analysis of the concentration of the test substance at the start and end of the test of a low and high test concentration and a concentration around the expected EC50 may be sufficient where it is likely that exposure concentrations will vary less than 20% from nominal values during the test. Analysis of all test concentrations at the beginning and at the end of the test is recommended where concentrations are unlikely to remain within 80-120 % of nominal. Under paragraph 39, the guideline explains that if the deviation from the nominal or measured initial concentration is not within the range of ± 20 %, analysis of the results should be based on geometric mean concentration during exposure or on models describing the decline of the concentration of the test substance.

Therefore, the analytical monitoring of exposure concentrations during the test cannot be regarded as an optional specifications as it is required to evaluate whether or not results can reliably be based on nominal or measured initial values. Hence, your justification does not provide a valid basis to omit this information.

iii. "*Calamari indicated in the publication that the substance was ±10 % of the nominal*

concentration. This information is supported by substance property considered as stable as previously explained".

This comment is already addressed under Appendix A.1. above.

On this basis, the information requirement is not fulfilled.

You further explain that if the additional information is considered as not sufficient by ECHA, you will perform an OECD TG 201 study under GLP condition. As explained above, the additional justification provided as part of your comments on the draft decision does not address the deficiencies identified in the draft decision.

Study design

The Substance is difficult to test as it is ionised under relevant environmental pH and therefore it has a high adsorption potential. 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. Screening for reproductive/developmental toxicity

A Screening for reproductive/developmental toxicity study is an information requirement under Annex VIII to REACH (Section 8.7.1.), if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

You have provided the following information:

i. An adaptation under Annex VIII, Section 8.7.1, Column 2 with the following justification: "[the study] *does not need to be conducted since a pre-natal developmental toxicity study (Annex IX, 8.7.2) is available on a structural analogue (dimethylamine)*".

We have assessed this information and identified the following issue:

A. According to Annex VIII, Section 8.7., Column 2, first paragraph, fourth indent, the study does not need to be conducted if a pre-natal developmental toxicity study (OECD TG 414) is already available.

   You justified the adaptation by stating that a prenatal developmental toxicity study is available and, therefore an EU B.63/OECD TG 421 or EU B.64/OECD TG 422 study does not need to be conducted. However, as explained under C.2. (below) the provided prenatal developmental toxicity study is not adequate. Therefore, your Column 2 adaptation is rejected.

On this basis, the information requirement is not fulfilled.

Study design

The Substance is a corrosive liquid. It has harmonised classification as Skin Corr. 1B (H314) and you apply self-classification as Skin Corr. 1A (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.

Therefore, 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 with oral administration of a neutralised form the Substance.

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

2. Justification for an adaptation of Short-term toxicity testing on fish based on the results of the Long-term toxicity study on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.). This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Annex VIII, Section 9.1.3, Column 2 or a general adaptation rule under Annex XI.

You have provided the following information:

i. a key study not performed according to any guideline on the Substance ([redacted] 1989);

ii. a supporting study according to "*Methods outlined by the committee of Methods for Toxicity Tests with Aquatic Organisms*" on the Substance ([redacted] 1984a; Report no. [redacted]
iii. a supporting study according to "*Methods outlined by the committee of Methods for Toxicity Tests with Aquatic Organisms*" on the Substance ([redacted], 1984b; Report no. [redacted])
iv. a supporting study according to "*Methods outlined by the committee of Methods for Toxicity Tests with Aquatic Organisms*" on the Substance ([redacted], 1986)
v. a supporting study according to "IRSA, Quaderni dell'Istituto di Ricerca sulle Acque, 11, Consiglio Nazionale delle Ricerche - Roma, (1973)" on the Substance ([redacted] 1980);
vi. a supporting study according to DIN 38412 part 15 on the Substance ([redacted] 1985)
vii. a non guideline study on the Substance ([redacted] 1952).

We have assessed this information and identified the following issues:

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

For studies ii. to iv. and vi. to vii. above, you have identified the test material as "Diisopropylamine" with CAS 108-18-9 without further information, including composition, purity and the presence of impurities. In your comments on the draft decision, you state that study ii. and iii. were performed "*with a high purity similar to the registered substance*". You also state that study iv. was "*performed with an high purity compound ([redacted]%)*".

While you have provided clarifications on the composition of the test material used in studies ii. to iv., you will have to add this information to your dossier in order to remove the incompliance. With regard studies vi. and vii., in the absence of appropriate information, you have not demonstrated that the test material is representative for the Substance. Therefore, the information form studies vi. and vii. is rejected.

B. To fulfil the information requirement, a study must comply with OECD TG 203 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
- mortality in the control(s) is ≤ 10% (or one fish, if fewer than 10 control fish are tested) at the end of the test;
- the analytical measurement of test concentrations is conducted;

Technical specifications impacting the sensitivity/reliability of the test
- the test duration is 96 hours or longer;
- the test is conducted on juveniles of similar age (or size);
- the test medium fulfils the following condition(s): particulate matter ≤ 5 mg/L, total organic carbon (TOC) ≤ 2 mg/L or carbon oxygen demand (COD) ≤ 5 mg/L;
- the fish-to-water loading rate is ≤ 0.8 g of fish (wet weight) per litre of water for static and semi-static tests;

Characterisation of exposure
- in semi-static tests, test concentrations are measured at least twice over one exposure period (before and after renewal of test solutions). If the concentrations

of the test material:

1) are expected to remain within ± 20 % of the nominal, then the test substance concentration is determined) in the highest and lowest test concentrations, and a concentration around the expected LC50;
2) are expected to decline by more than 20%, analytical monitoring is conducted on all test concentrations with an additional determinations on the other exposure period(s);

Reporting of the methodology and results

- the test procedure is reported (*e.g.* composition of the test medium, fish loading);
- adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations are provided;
- mortalities and sub-lethal effects (*e.g.* with regard to equilibrium, appearance, ventilator and swimming behaviour) are reported. The frequency of observations includes at least 2 observations within the first 24 hours and at least two observations per day from day 2 to 4.

Your registration dossier provides a key study (study i.) showing the following:

- you specified that only exposure concentrations in the test system at the beginning of the test were verified;
- you have not provided performance parameters of the analytical method;
- the test was conducted under semi-static conditions and the results of the analyses to determine the concentration of the test substance in the test vessels are not provided;
- tabulated data on mortalities and sub-lethal effects are not reported.

Based on the above,

- there are critical methodological deficiencies resulting in the rejection of this study. More specifically, the validity criteria of the TG 203 are not fulfilled as you have not provided adequate monitoring of exposure concentrations;
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, you have not reported key information required to verify that the other validity criteria of OECD TG 203 were met.

Your registration dossier also provides three supporting studies by [redacted] (1984a, 1984b, 1986) (study ii. to iv.) all showing the following:

- no analytical monitoring of exposure is reported;
- on the test procedure, you have not specified the composition of the test medium (including particulate matter and TOC or COD). In your comments on the draft decision, you have provided some physico-chemical information on the well water used to perform the study. However, this information does not include the concentration in particulate matter and TOC or COD. We also note that the sampling was conducted after the completion of the corresponding studies and the relevance of this information is therefore questionable;
- tabulated data on mortalities and sub-lethal effects are not reported. In your comments on the draft decision, you provided this missing information. This information must be added to your dossier in order to remove the incompliance.

Based on the above,

- there are critical methodological deficiencies resulting in the rejection of these studies. More specifically, the validity criteria of the TG 203 are not fulfilled as no monitoring of exposure concentrations was conducted;
- the reporting of the study is not sufficient to conduct an independent assessment

of their reliability. More specifically, you have not reported a number of key information required to verify that the other validity criteria of OECD TG 203 were met and that experimental conditions were consistent with this test guideline. However, we note that in your comments on the draft decision, you have provided information that would partially resolve this issue. Nevertheless, key information on the composition of the test medium is still missing.

In your comments on the draft decision, you also provide information to support that the test organisms used in studies ii. to iv. had appropriate length to be considered as juveniles. However, we note that the lack of information on the test organisms life-stage is not a deficiency identified in the draft decision.

Your registration dossier provides another supporting study (study v.) showing the following:
- you have not provided performance parameters of the analytical method;
- the results of the analyses to determine the concentration of the test substance in the test vessels are not provided;
- on the test procedure, you have not specified the life-stage of the test animals and the composition of the test medium (including particulate matter and TOC or COD);
- tabulated data on mortalities and sub-lethal effects are not reported.

Based on the above, the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically:
- you have not provided adequate documentation to demonstrate the validity of the analytical method and you have not reported the results of the analytical verification of exposure concentrations. Therefore, you have not demonstrated that exposure was satisfactorily maintained over the duration of the test;
- you have not reported a number of key information required to verify that the other validity criteria of OECD TG 203 were met and that experimental conditions were consistent the specifications of OECD TG 203.

Your registration dossier provides a further supporting study (study vi.) showing the following:
- no analytical monitoring of exposure was conducted;
- the test was conducted under static conditions and the fish-to-water loading rate was 3.6 g of fish (wet weight) per litre of water;
- tabulated data on mortalities and sub-lethal effects are not reported.

Based on the above,
- there are critical methodological deficiencies resulting in the rejection of this study. More specifically, the validity criteria of the TG 203 are not fulfilled as no monitoring of exposure concentrations was conducted Furthermore, the test was conducted at very high loading rate which may have impacted the reliability of the study;
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, you have not reported tabulated data on mortalities and it is not possible to verify that the other validity criteria of OECD TG 203 were met

Finally, your registration dossier provides another supporting study (study vii.) showing the following:
- the test duration was 24 hours;
- no analytical monitoring of exposure is reported;

- on the test procedure, you have not specified the life-stage of the test animals and the composition of the test medium (including particulate matter and TOC or COD);

Based on the above,

- there are critical methodological deficiencies resulting in the rejection of this study. More specifically, the validity criteria of the TG 203 are not fulfilled as no monitoring of exposure concentrations was conducted. Furthermore, exposure duration was shorter than the minimum requirement of OECD TG 203;
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, you have not reported a number of key information required to verify that the experimental conditions were consistent with this test guideline.

Therefore, none of the provided studies meet the specifications of OECD TG 203 in conjunction with OECD GD 23.

In your comments on the draft decision, you acknowledge that "*the current acute studies on fish in the dossier present an analytical method gap*". However, you consider that the absence of analytical monitoring of exposure concentrations or the absence of performance parameters of the analytical method should not be regarded as a valid reason to reject the provided studies. To support your claim, you provide the following justification:

i. "*the analytical monitoring is not a validity criteria* [in OECD TG 203]";

However, under paragraph 7 ('Validity of the test') of the OECD TG 203 (2019), the guideline specifies that analytical measurement of test concentrations is compulsory. The previous version of the test guideline (OECD TG 203, 1992) already specified under the same section that "there must be evidence that the concentration of the substance being tested has been satisfactorily maintained".

Therefore, the analytical monitoring of exposure concentrations is to be regarded as a validity criteria of this test guideline.

ii. "*As indicated in the hydrolysis robust study summary and biodegradation test, the substance is considered as stable in the environment*";

This comment is already addressed under Appendix A.1. above.

iii. "[redacted] *1980 indicated that the substance was expected in ± 10% between observed and expected concentrations*";

This comment is already addressed under Appendix A.1. above.

iv. "*the performance, accuracy, and other parameters of analytical methods were not mandatory in 1980, but only since the SANCO method/3029/99 revised in august 2000*".

This comment is already addressed under Appendix A.2. above.

On this basis, the information requirement is not fulfilled.

The present decision requests the registrant(s) concerned to conduct and submit a long-term toxicity study on fish (OECD TG 210; see Appendix C.4 for details). According Annex VIII,

Section 9.1.3., Column 2 and to prevent unnecessary animal testing, a short-term toxicity study on fish does not need to be provided.

Because you still must comply with the information requirement in Annex VIII, Section 9.1.3., you are requested to submit a justification for the adaptation provided in Annex VIII, Section 9.1.3, Column 2, second indent.

3. Simulation testing on ultimate degradation in surface water

and

4. Soil simulation testing

and

5. Sediment simulation testing

and

6. 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).

These information requirement are 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 301D), and
- 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 has a calculated BCF > 2000;
- 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.

Your registration dossier provides the following:

- The Substance is not readily biodegradable (11% degradation after 28 days in OECD TG 301D);
- The Substance is ionisable and therefore high potential for bioaccumulation cannot be excluded based on available information;

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 C.9. of this decision), and
- it is not possible to conclude on the toxicity of the Substance see Appendices A.2., B.1., and C.1 to C.4. this decision).

In your comments on the draft decision, you argue that the Substance should not be regarded as ionisable with the following justification: "*it has been concluded that the pKa of [the Substance] is 11 at 20°C, so the substance is predominantly not ionised at the environmentally relevant pH range (4-9)*".

However, the pKa value of 11 (supported by open literature and modelling on secondary amines) is that of the conjugate acid or protonated form. Therefore, the substance is in fact protonated at all environmentally relevant pHs.

Accordingly, ECHA maintains that the information above indicates that the Substance is a potential PBT/vPvB substance.

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

The examination of the available information or adaptations, as well as the selection of the requested tests and the tests design are addressed in Appendices C.5. to C.8.

In your comments on the draft decision, you state that based on QSAR predictions "*the substance is not B and not vB. Taking into account this information, the substance is not PBT/vPvB, so it is not need to pursue the P assessment and the registrants do not agree to perform the simulation studies*". However, for the reasons explained under Appendix C.9., neither your dossier nor your comments on the draft decision include reliable information to conclude on the bioaccumulation potential of the Substance.

You further explain that, if ECHA still requires all studies, you intend to first conduct a simulation test according to OECD TG 309. If the Substance is concluded as fulfilling the criteria for P or vP, you will perform an OECD TG 305.

However, as explained in ECHA Guidance R.11.4.1.1., results of a single simulation degradation study cannot be directly extrapolated to other environmental compartments. Therefore, if for the first tested compartment a conclusion "not P" can be derived, but the available data is not sufficient for drawing conclusions in (an)other compartment(s), further data generation would be required to complete the assessment for the compartments for which a conclusion could not be drawn.

7. 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 investigation on bioaccumulation in aquatic species (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 301D), and
- 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 has a calculated BCF > 2000;
- 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.

As already explained under Apendices B.3. to B.6. above, the Substance is a potential PBT/vPvB substance. Therefore, the chemical safety assessment (CSA) indicates the need for

further degradation investigation.

Therefore, the chemical safety assessment (CSA) indicates the need for further investigation on bioaccumulation in aquatic species.

The examination of the available information or adaptations, as well as the selection of the requested test and the test design are addressed in Section C.9.

8. Adsorption/ desorption screening

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

You have provided the following information:

i. an adaptation under Annex XI, Section 1.3 ('Qualitative or Quantitative structure-activity relationship ((Q)SAR)'). In support of you adaptation you have provided a predicted Log Koc based on the approach described in Franco & Trapp (2008) and Franco *et al.* (2009).

Additionally, in your comments on the draft decision, you explain that you intend to support the above adaptation using the following information:

ii. a predicted Koc for the Substance using the OPERA model from US EPA.

We have assessed this information and identified the following issues:

A. The selected QSAR models do not provide information on pH-dependence of the adsorption/deosprtion potential for the Substance

Annex XI, Section 1.3. states that (Q)SAR results must be adequate for the purpose of risk assessment, including PBT assessment. ECHA Guidance 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. The guidance further clarifies that, if estimation methods are not appropriate (e.g. because the substance is a surfactant or ionisable at environmentally-relevant pH), then a batch equilibrium test is essential under Annex VIII.

However, you have not provided any experimental data to determine adsorption/desorption for the Substance. Instead, you have provided a QSAR predicted Log Koc. The log Koc is predicted to be 1.82 at 20°C and pH 5-8.

As further explained under section B. below, there are issues with the reliability of the reported predicted value. In addition, the reported value does not provide information on pH-dependence of the adsorption potential of the Substance. Considering the properties of the Substance and the tonnage band of the joint submission, an experimental confirmation of the adsorption potential of the Substance must be provided. Therefore, your adaptation is rejected. This issue equally applies to the additional QSAR prediction provided as part of your comments on the draft decisions (see source of information ii. above).

B. The QSAR adaptation from your dossier (point i. above) is not supported by adequate documentation

Under Annex XI, Section 1.3., the study may be omitted if results obtained from valid QSAR models are available. Therefore, the following cumulative conditions must be met:

1. The results are derived from a QSAR model whose scientific validity has been established;
2. the substance falls within the applicability domain of the QSAR model;
3. adequate and reliable documentation of the applied method is provided; and
4. the results are adequate for classification and labelling and/or risk assessment.

According to ECHA's Practical guide "How to use and report (Q)SARs", section 3.4, a QSAR Model Reporting Format (QMRF) and a QSAR Prediction Reporting Format (QPRF) are required to establish the scientific validity of the model, to verify that the Substance falls within the applicability domain of the model, and to assess the adequacy of the prediction for the purposes of classification and labelling.

You have not provided any documentation for the QSAR prediction. In particular, you have not included a QMRF and a QPRF in your technical dossier.

In the absence of this information, ECHA cannot establish whether the model is scientifically valid, whether the Substance falls within the applicability domain of the model, and whether the results are adequate for classification and labelling and/or risk assessment. Therefore your adaptation is rejected.

C. *The QSAR adaptation from your comments on the draft decisions (point ii. above) provides 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.

The documentation available on the model does not include adequate information on experimental protocol and data quality for the data used to develop the model.

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

D. *The QSAR adaptation from your comments on the draft decisions (point ii. above) is not adequate due to low reliability*

Under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. ECHA Guidance R.6.1.5.3. specifies that, among others, the following condition must be met:

- the model predicts well substances that are similar to the substance of interest, and
- reliable input parameters are used.

Your comments on the draft decision provides the following information:

- a predicted Koc value of 37.4 L/kg based on the OPERA model from US EPA which uses log Kow as an input parameter;
- a link to the QMRF provided by the model developer. This documentation indicates that Log Kow is used as input parameter to the prediction;
- a link to a prediction report for the Substance indicating the 5 nearest neighbours (i.e. most structurally similar substances) used for the prediction. Among these

substances only one is an ionisable substance.

The prediction for the Substance is not reliable because log Kow is not considered a valid descriptor of the adsorption/desoprtion potential of ionisable substances.

In your comments on the draft decision, you further state that the Substance "*the substance does not ionize at the environmentally relevant pH range (4-9)*". However, as already explained under Appendices B.3-6, ECHA disagrees with this conclusion.

Furthermore, as explained under issue *B*. above, adequate information to assess the reliability of the data used to develop the model are missing. Furthermore, as the selected nearest neighbours have limited structural similarity with the Substance, you have not demonstrated that the model predicts well substances that are similar to the substance of interest.

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

On this basis, the information requirement is not fulfilled.

Appendix C: Reasons to request information required under Annex IX of REACH

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

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

You have adapted this information requirement under Annex XI, Section 1.5 ('Grouping of substances and read-across approach').
In support of your read-across adaptation you have provided the following information:

i. a key study similar to OECD TG 413 via inhalation route in rats with an analogue substance, diethylamine with EC 203-716-3 ([redacted] 2011);
ii. a supporting study similar to OECD TG 413 via inhalation route in mice with an analogue substance, diethylamine with EC 203-716-3 ([redacted] 2011);
iii. a non-guideline supporting study via inhalation route in rats with an analogue substance, diethylamine with EC 203-716-3 ([redacted] 1986).

We have assessed this information and identified the following issues:

A. As explained in the Appendix on Reasons common to several requests your read-across adaptation under Annex XI, Section 1.5 is rejected.

B. Under Annex XI, Section 1.5., the results to be read across must provide adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 413. Therefore, the following specifications must be met:
   - ophthalmological examination must be conducted;
   - examination of haematology and clinical chemistry parameters must be conducted;
   - examination of bronchoalveolar lavage must be conducted;
   - the weight of the following organs must be recorded: adrenals, brain, epididymides, heart, kidneys, liver, lung, ovaries, spleen, testes, thymus, thyroid and uterus

   However, the studies (i.) to (iii.) did not include ophthalmological examination and bronchoalveolar lavage. In addition, only limited number of organs weights were recorded. OECD TG 413 requires 13 organs to be weighed. In studies (i.) and (ii.) only heart, right kidney, liver, lung, right testis and thymus were weighed, and in study (iii.) only weights of lung, liver, kidneys, heart and reproductive organs were recorded. The clinical chemistry was not examined in study (ii.) and only limited clinical chemistry parameters were examined in studies (i.) and (iii.).

   Therefore, the studies (i.) to (iii.) do not provide an adequate and reliable coverage of the key parameters of the OECD TG 413.

On this basis, the information requirement is not fulfilled.

In your comments on the draft decision, you refer to a recent decrease of tonnage band of joint submission and therefore you consider that the requested information is not needed. This comment is addressed under Appendix F of this decision.

Study design

Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because the

Substance is a corrosive liquid. It has harmonised classification as Skin Corr. 1B (H314) and you apply self-classification as Skin Corr. 1A (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. These specifications are valid also for testing of repeated dose toxicity.

Therefore the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of a neutralised form of the Substance.

2. Pre-natal developmental toxicity study in one species

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

You have adapted this information requirement under Annex XI, Section 1.5 (Grouping of substances and read-across approach). In support of your adaptation you provided the following information:

i. A key study according to OECD 414 via oral route (gavage) in rats with an analogue substance, dimethylamine hydrochloride with EC No. 208-046-5 ([redacted] 2009).

We have assessed this information and identified the following issue:

A. As explained in the Appendix on Reasons common to several requests your read-across adaptation under Annex XI, Section 1.5 is rejected.

On this basis, the information requirement is not fulfilled.

Study design

The Substance is a corrosive liquid. It has harmonised classification as Skin Corr. 1B (H314) and you apply self-classification as Skin Corr. 1A (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.

Therefore, a PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral administration of a neutralised form the Substance.

In your comments on the draft decision, you state that "*although this information is no more required in the revised tonnage band registration (< 100 T/year)*" you agree to perform the requested study.

3. Long-term toxicity testing on aquatic invertebrates

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

You have provided the following information:

i. a justification to omit the study which you consider to be based on Annex IX, Section 9.1, Column 2. In support of your adaptation, you provided the following justification: "*As the CSA indicates no risk, there are no further requirements for aquatic toxicity*

testing".

We have assessed this information and identified the following issue:

A. Annex IX, Section 9.1, Column 2 does not allow omitting the need to submit information on long-term toxicity to aquatic invertebrates under Column 1. It must be understood as a trigger for providing further information on long-term toxicity to aquatic invertebrates if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

Your adaptation is therefore rejected.

On this basis, the information requirement is not fulfilled.
You specify that you have no comments for this request.

Study design

OECD TG 211 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Section A.2.

4. Long-term toxicity testing on fish

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

You have provided the following information:
i. a key study equivalent/similar to OECD TG 210 on the Substance ([redacted] 1989);

We have assessed this information and identified the following issue:

A. To fulfil the information requirement, a study must comply with the OECD TG 210 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:

Technical specifications impacting the sensitivity/reliability of the test
- the stage of embryonic development at the start of the test is provided;
- the test medium fulfils the following condition(s): particulate matter ≤ 5 mg/L, total organic carbon (TOC) ≤ 2 mg/L.
- at least 80 eggs, divided equally between at least four replicate test chambers, are used per concentration;
- five concentrations are tested (or a justification must be provided if fewer than five concentrations are used);

Characterisation of exposure
- during the test, a minimum of five determinations of the concentrations of the test material are obtained;

Reporting of the methodology and results
- the test procedure is reported (*e.g.* number of eggs per replicate, composition of the test medium, fish loading);
- evidence that controls met the overall survival acceptability standard of the test species is reported;
- data on mortality at each stage (embryo, larval and juvenile) measured daily and

cumulative mortality are reported;
- days to hatch, numbers of larvae hatched each day, and end of hatching are reported;
- the number of healthy fish at end of test is reported;
- data for length (specify either standard or total) and weight of surviving animals at the end of the test are reported;
- the incidence, description and number of morphological abnormalities, if any, are reported;
- adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations is provided;

Your registration dossier provides a key study showing the following:
- on the test procedure, you have not specified the stage of embryonic development at the start of the test, the number of eggs used per test concentration, adequate information on the composition of the test medium (presence of sediment, particulate matter and TOC or COD);
- the test was conducted at only three concentrations with no justification;
- you specified that only exposure concentrations in the test system at the beginning of the test were verified;
- you have not provided the performance parameters of the analytical method;
- tabulated data on mortalities at each stage (embryo, larval and juvenile), days to hatch, numbers of larvae hatched each day, and end of hatching, data for length and weight of surviving animals at the end of the test and the incidence, description and number of morphological abnormalities, if any, are not reported

Based on the above,
- there are critical methodological deficiencies resulting in the rejection of this study. More specifically, the test was conducted with too few doses. Furthermore, as you have not provided adequate information on the analytical method and as exposure concentrations were only monitored at the beginning of the test, you have not demonstrated that exposure was satisfactorily maintained during the test.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, you have not reported a number of key information on the test procedure and test results. Therefore, you have not demonstrated that the experimental conditions were consistent with the test guideline and that the results and their interpretation are reliable.

Therefore, this study does not meet the requirements of OECD TG 210 in conjunction with OECD GD 23.

On this basis, the information requirement is not fulfilled.

You specify that you have no comments for this request.

Study design

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

OECD TG 210 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Section A.2.

5. Simulation testing on ultimate degradation in surface water

Simulation testing on ultimate degradation in surface water is an information requirement under Annex IX to REACH (Section 9.2.1.2.).

You have provided the following information:

i. a key study according to OECD TG 303A on the Substance ([redacted], 2013).

We have assessed this information and identified the following issue:

A. To fulfil the information requirement and to allow concluding on the P/vP criteria, ultimate biodegradation simulation tests must simulate degradation under relevant environmental conditions, such as those found in surface water, freshwater sediment or soil (Annex VIII, Section 9.2. and Annex XIII to REACH; ECHA Guidance R.11.4.).

   Your registration dossier provides an OECD TG 303A study, which is a simulation test in activated sewage units. You have not provided any other information on simulation testing on ultimate degradation in surface water.

   ECHA Guidance R.11.4.1.1. clarifies that, because it does not simulate degradation under relevant environmental conditions, the SCAS test (*i.e.* OECD TG 303A) does not provide relevant information for this information requirement and this information is rejected.

In your comments on the draft decision, you state that based on QSAR predictions "*the substance is not B and not vB. Taking into account this information, the substance is not PBT/vPvB, so it is not need to pursue the P assessment and the registrants do not agree to perform the simulation studies*". However, for the reasons explained under Appendix C.9., neither your dossier nor your comments on the draft decision include reliable information to conclude on the bioaccumulation potential of the Substance.

On this basis, the information requirement is not fulfilled.

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).

6. Soil simulation testing

Soil simulation testing is an information requirement under Annex IX to REACH (Section 9.2.1.3.) for substances with a high potential for adsorption to soil.

The Substance is ionisable and therefore has high potential for adsorption to soil.

You have provided the following information:

i. an adaptation under Annex IX, Section 9.2., Column 2 with the following justification: "*Due to the presented test results significant biodegradation of diisopropylamine (DIPA)cannot be expected for the substance in the environment. This finding is supported by the chemical structure of the substance which indicates a low potential for biodegradation. Therefore, no further tests on biodegradation are performed because it is not expected that further testing will significantly change this assessment. In addition, the PEC/PNEC ratio for soil obtained in the exposure assessment of DIPA is below 1. Based on the exposure assessment, the conduct of a simulation test of the degradation in soil is waived in accordance with column 2 of Annex IX chapter 9.2 of Regulation EC 1907/2006*".

We have assessed this information and identified the following issue:

A. Under Section 9.2., Column 2 of Annex IX to REACH, the study may be omitted if the chemical safety assessment (CSA) does not indicate the need for further biotic degradation testing. The CSA does indicate such need (Annex I, Section 4; Annex XIII, Section 2.1) if, for instance, 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, impurity or transformation/degradation product present in concentration ≥ 0.1% (w/w) meets the criteria already listed in Section B.5-B-8.

   As already explained under Section B.5-B-8, you have not demonstrated that the CSA does not indicate the need for further biotic degradation testing and your adaption is rejected.

In your comments on the draft decision, you state that based on QSAR predictions "*the substance is not B and not vB. Taking into account this information, the substance is not PBT/vPvB, so it is not need to pursue the P assessment and the registrants do not agree to perform the simulation studies*". However, for the reasons explained under Appendix C.9., neither your dossier nor your comments on the draft decision include reliable information to conclude on the bioaccumulation potential of the Substance.

On this basis, the information requirement is not fulfilled.

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.

In accordance with the specifications of OECD TG 307, you must perform the test using at least four soils representing a range of relevant soils (*i.e.* varying in their organic content, pH, clay content and microbial biomass).

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 307.

In accordance with the specifications of OECD TG 307, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents (ECHA Guidance R.7.9.4.1). 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 307; ECHA Guidance R.11.4.1).

7. Sediment simulation testing

Sediment simulation testing is an information requirement under Annex IX to REACH (Section 9.2.1.4.) for substances with a high potential for adsorption to sediment.

The Substance is ionisable and therefore has high potential for adsorption to soil.

You have provided the following information:

ii. a key study according to OECD TG 303A on the Substance (Roulstone, 2013).

However, for the reasons already explained under Section C.5, this study does not meet the information requirement.

In your comments on the draft decision, you state that based on QSAR predictions "*the substance is not B and not vB. Taking into account this information, the substance is not PBT/vPvB, so it is not need to pursue the P assessment and the registrants do not agree to perform the simulation studies*". However, for the reasons explained under Appendix C.9., neither your dossier nor your comments on the draft decision include reliable information to conclude on the bioaccumulation potential of the Substance.

You further explain that "*EPisuite (EPI SUMMARY v4.11) simulation and fugacity model indicate that water and soil would be the main compartment of the emission of the substance*

in the environment. The emission to the sediment is not expected. Therefore, the sediment compartment is not relevant for P assessment". ECHA understands that through this statement you consider that this information requirement may be adapted under Annex IX, Section 9.2.1.3., column 2.

ECHA Guidance R.11.3.3.3. specifies that, if no conclusion can be reached whether or not a substance fulfils the PBT and/or vPvB criteria, a registrant must generate relevant additional information (as described under Seection 2.1. of Annex XIII) until such conclusion can be reached. In case you intend to submit a Column 2 adaptation based on limited or unlikely exposure, it is important to note that, if you are not able to conclude that "*The substance does not fulfil the PBT or vPvB criteria*", you need to carry out the tests you wished to waive in order to be able to conclude the PBT/vPvB, unless you decide to treat the substance "*as if it is a PBT or vPvB*".

On this basis, the information requirement is not fulfilled.

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.

In accordance with the specifications of OECD TG 308, you must perform the test using two sediments. One sediment should have a high organic carbon content (2.5-7.5%) and a fine texture, the other sediment should have a low organic carbon content (0.5-2.5%) and a coarse texture. If the Substance may also reach marine waters, at least one of the water-sediment systems should be of marine origin.

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 308.

In accordance with the specifications of OECD TG 308, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents (ECHA Guidance R.7.9.4.1). 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 308 ECHA Guidance R.11.4.1).

8. Identification of degradation products

Identification of degradation products is an information requirement under Annex IX to REACH (Section 9.2.3.).

You have provided no information on the identity of transformation/degradation products for the Substance.

You provided no specific comments for this request and referred to your comments provided on simulation studies.

On this basis, the information requirement is not fulfilled.

This information is required for the purpose of the PBT/vPvB assessment (Annex I, Section 4) and the risk assessment (Annex I, Section 6) of the Substance.

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 studies requested in Sections C.5 to C.7 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 (Section C.5) 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).

To determine the degradation rate of the Substance, the requested studies according to OECD TG 308/307 (Sections C.6 and C.7) must be conducted at 12°C and at test material application rates reflecting realistic assumptions. 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) and at higher application rate (*e.g.* 10 times).

9. Bioaccumulation in aquatic species

Bioaccumulation in aquatic species is a standard information requirement under Annex IX to REACH (Section 9.3.2.).

You have provided the following information:

i. an adaptation under Annex IX, Section 9.3.2., Column 2 with the following justification: "*the substance has a low octanol water partition coefficient and therefore diisopropylamine is expected to have a low potential for bioaccumulation or for crossing biological membranes*".

In addition, in your comments on the draft decision, you explain that you intend to support the above adaptation based on an adaptation under Annex XI, Section 1.3. ('QSAR'). In support of this adaptation, you provide the following information:

ii. a predicted BCF for the Substance using the OPERA model from US EPA.

We have assessed this information from your registration dossier as well as the additional information provided as part of your comments on the draft decision and identified the following issues:

A. *Your adaptation under Annex IX, Section 9.3.2., Column 2*

Under Section 9.3.2., Column 2, first indent of Annex IX to REACH, the study may be omitted if the substance has a low potential for bioaccumulation and/or a low potential to cross biological membranes. A low log Kow (*i.e.* log Kow < 3) may be used to support low potential for bioaccumulation if the partitioning to lipids is the sole mechanism driving the bioaccumulation potential of a substance. For some groups of substances (e.g. organometals, ionisable substances, surfactants) other partitioning mechanisms may drive bioaccumulation (e.g. binding to protein/cell membranes). For this reason log Kow is not considered a valid descriptor of the bioaccumulation potential for such substances (ECHA Guidance R.7c, Appendix R.7.10-3).

Your registration dossier provides an adaptation stating that the log Kow is low without further explanation. The Substance is ionisable at all relevant pHs (pKa of conjugate acid = 11)

As the Substance is ionisable, log Kow is not a valid descriptor of the bioaccumulation potential of the Substance and your adaptation is rejected.

In your comments on the draft decision, you consider that the reported pKa value of the Substance indicates that it is not ionised under environmentally relevant pHs. However, as already explained under Appendices B.3-6, this statement is erroneous.

B. *Inadequate documentation of the model (QMRF) for the QSAR prediction provided in your comments*

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.

The documentation available on the model does not include adequate information on experimental protocol and data quality for the data used to develop the model.

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

C. *Your QSAR predicted BCF is not adequate due to low reliability*

Under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. ECHA Guidance R.6.1.5.3. specifies that, among others, the following condition must be met:

- reliable input parameters are used.

Your comments on the draft decision provides the following information:

- a predicted BCF value of 6.16 based on the OPERA model from US EPA which uses log Kow as an input parameter;
- a link to the QMRF provided by the model developer. This documentation indicates that Log Kow is used as input parameter to the prediction.

The prediction for the Substance is not reliable because as already explained under

issue *A*. above, log Kow is not considered a valid descriptor of the bioaccumulation potential of ionisable substances as other mechansims than partitioning to lipid may drive the bioaccumulation. Furthermore, as explained under issue B. above, adequate information to assess the reliability of the data used to develop the model are missing.

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

On this basis, the information requirement is not fulfilled.

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).

Appendix D: 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[4].

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,
   - as explained under Appendices B.1., C.1. and C.2., the use of a neutral salts of the Substance (*e.g.* hydrochloride salt of the Substance) is more appropriate for conducting the tests requested under Appendices B.1., C.1. and C.2. as it allows the investigation of intrinsic properties at adequate dose levels. When selecting a neutral salt, the potential impact of the counterion must be considered. The counterion must have no known systemic toxicity.
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[5].

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

Appendix E: 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.

B. Environmental testing for substances containing multiple constituents

Your Substance contains multiple constituents and, as indicated in ECHA Guidance R.11 (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.

Appendix F: 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 24 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.

In its comments on the draft decision, the registrant [redacted] raised the issue of updating the registration tonnage band of their registration. However, ECHA does not take into account new information on volumes or tonnage band after the date on which the draft decision is notified to the registrants according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation). Therefore, the comment on this matter does not impact the decision.

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 G: List of references - ECHA Guidance[6] 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)[7]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[7]

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[8]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[8] 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 H: 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]
[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.