Helsinki, 31 October 2018

Addressee: [redacted]

Decision number: CCH-D-2114448613-48-01/F
Substance name: 2-methylpentane-1,5-diamine
EC number: 239-556-6
CAS number: 15520-10-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 27/11/2017
Registered tonnage band: over 1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **High-pressure liquid chromatogram, gas chromatogram (Annex VI, Section 2.3.6.) of the registered substance;**
   - **Identification and quantification of the main constituent and impurities**
2. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats with the registered substance;**
3. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral] route with the registered substance;**
4. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) in a second species (rat or rabbit), oral route with the registered substance;**
5. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation**

6. **Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: Daphnia sp. Acute immobilisation test, EU C.2./OECD TG 202) with the registered substance;**

   or

   Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) with the registered substance;

7. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: Alga, growth inhibition test, EU C.3./OECD TG 201) with the registered substance;**

8. **Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: Fish, acute toxicity test, OECD TG 203) with the registered substance**

   or

   Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance.

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by ***9 May 2022*** except for the information requested under point 2 for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **7 November 2019**. You may only commence the extended one-generation reproductive toxicity study as requested under point 5 after **7 February 2020**, unless an indication to the contrary is communicated to you by ECHA before that date. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Kevin Pollard, Head of Unit, Evaluation E1

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

Appendix 1: Reasons

IDENTIFICATION OF THE SUBSTANCE

1. **High-pressure liquid chromatogram, gas chromatogram (Annex VI, Section 2.3.6.)**

   - **Identification and quantification of the main constituent and impurities**

In accordance with Article 10(a)(ii) of the REACH Regulation, the technical dossier must contain information on the identity of the substance as specified in Annex VI, Section 2 to the REACH Regulation. In accordance with Annex VI, Section 2 the information provided has to be sufficient to enable the identification of the registered substance.

According to Annex VI, section 2.3.6 of the REACH Regulation, the registration needs to contain a chromatogram (Gas Chromatogram, or High Pressure Liquid Chromatogram). According to the Guidance, the information provided with the chromatogram shall include the chromatogram itself and the other analytical relevant results, e.g, indicate the main peaks important for substance identification.

You provided in your dossier a report with chromatographic data [redacted]. The report describes the quantification of impurities at ppm(parts per million) levels.

The information in the report is not sufficient and not consistent with the composition reported in section 1.2 of your dossier. In particular:

- there is no information on the quantification of the main constituent 2-methylpentane-1,5-diamine
- there is no information on the quantification of the impurities 3-methylcyclopentane-1,2-diamine and 2-ethylbutane-1,4-diamine reported in section 1.2.
- none of the impurities listed in the chromatography report are reported in section 1.2 of your dossier.

Therefore, the provided chromatographic data does not support the composition of your substance as reported in in section 1.2 of your dossier and you did not provide any other quantification method. Hence, your dossier does not have sufficient information to verify the composition of the registered substance and therefore its identity.

Therefore, you need to provide chromatographic data that is sufficient to verify the composition of your substance as reported in section 1.2. The data must include the method description together with the chromatogram and corresponding peak table with the identification of the peaks, peak areas and area %. The identification and values of each peak (main constituent and impurities) provided in the chromatographic report to be consistent with the information reported in section 1.2 so that the composition of the substance can be verified.

As for the reporting of the data in the registration dossier, the information should be attached in IUCLID section 1.4.

You submitted comments to the draft decision agreeing with the request.

TOXICOLOGICAL AND ECOTOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for multiple endpoints adaptation arguments in the form of a grouping and read-across approach according to Annex XI, Section 1.5. of the REACH Regulation. ECHA has assessed first the scientific and regulatory validity of your grouping and read-across approach in general before the individual endpoints listed below by bullet points.

Grouping and read-across approach for toxicological and ecotoxicological information

You have sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5, for the endpoints:

- a sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.)
- pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)
- short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- growth inhibition study on aquatic plants (Annex VII, Section 9.1.2)
- short-term toxicity testing on fish (Annex VIII, Section 9.1.3)
- long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5).

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. 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 (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

You consider to achieve compliance with the REACH information requirements for the registered substance 2-methylpentane-1,5-diamine (MPMD, EC No. 239-556-6; CAS No 15520-10-2, 'the target substance') using data of structurally similar substances (hereafter the 'source substances'):

[1] cyclohexane-1,2-diamine (DCH; EC No. 211-776-7; CAS No 694-83-7),
[2] hexane-1,6-diamine (HMD) dihydrochloride (EC No 227-977-8; CAS No 6055-52-3),
[3] hexane-1,6-diamine (HMD; EC No 204-679-6; CAS No 124-09-4), and
[4] amine heads mixture (no identifier available).

You have provided a read-across documentation as a separate attachment registration.

You use the following arguments to support the prediction of properties of the target substance from data for the source substances within the group:

"*The category members are structurally similar, with minor differences in their physico-chemical properties (i.e.state at ambient temperature, molecular weight, melting point, flammability, solubility, octanol-water partition coefficient) as well as in their toxicological and ecotoxicological behaviour.*"

"*As a consequence of the high basicity, the substances show pronounced irritating properties and are toxic to the immediate site of contact. All substances are classified as corrosive to skin and as causing severe eye damage. The corrosive properties govern the toxicity profile of the substances. Local effects (in the respiratory tract) are also the most relevant endpoint in repeated dose toxicity studies with inhalation exposure, whereas systemic effects are only reported at concentrations well below the doses critical for classification.*

[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

For the basic biological effects, i.e.
-toxic effects after single oral, dermal or inhalation exposures,
-toxicity after repeated oral or inhalation exposure,
-skin irritation/ corrosion,
-eye irritation,
-skin sensitizing effects,
-mutagenic properties and
-toxic effects to aquatic, terrestrial and sediment organisms as well as bacteria

the members of the amine heads category reveal comparable toxicological and ecotoxicological profiles. This conclusion is based on experimental data on one or more members of the group as well as a mixture containing several members of the amine heads category. These data cover the following endpoints: Acute oral, dermal and inhalation toxicity, skin and eye irritation, skin sensitization, genotoxicity in vitro and in vivo, subacute and subchronic oral toxicity, acute toxicity to aquatic organisms, daphnia reproduction, acute toxicity to soil and sediment dwelling organisms, activated sludge respiration inhibition and ready biodegradability (for details see section 1.3, data matrix)."

Your suggestion that the target and source substances reveal comparable toxicological and ecotoxicological profiles is supported by a data matrix for mammalian toxicity and data matrix for environmental fate properties and ecotoxicity. As an integral part of this prediction, you propose that the source and registered substance(s) have similar properties for the above-mentioned information requirements. ECHA considers that this information is your read-across hypothesis.

ECHA's evaluation and conclusion

ECHA considers that the suggested category of three C6 diamines (DCH, MPMD and HMD) cannot be accepted as category boundaries and category membership criteria have not been defined. ECHA also notes that there are isomers that are structurally similar to the proposed category members which have not been included in the category. No exclusion criteria for such category members have been provided. Therefore, ECHA assessment below has been conducted as for endpoint-to-endpoint read-across adaptations.

Your proposed adaptation argument is that the similarity in chemical structure, ecotoxicological and toxicological properties and minor differences in physico-chemical properties between the source and target substance is a sufficient basis for predicting the properties of the registered substance for other endpoints. Structural similarity is a prerequisite for applying the grouping and read-across approach. ECHA notes first that there are structural differences between the target and source substances (for example branched vs. unbranched substances) that you have not discussed in the context of your read-across justifications. You state also in your read-across justifications that the majority of the amine substances in general are excreted unmetabolised.

Second ECHA considers that, as no biotransformation to common products has been demonstrated, you have not sufficiently explained why potential structural dissimilarity between metabolic products would not lead to differences in the toxic properties.

Third, based on Table 3a: Data matrix for mammalian toxicity, the toxicity studies show partly different toxic effects (as set out below under the endpoint concerned) and a comparison of developmental toxic profiles of the target and source substances is not possible as there is no information on the target substance. Moreover, based on Table 2a: Data matrix for environmental fate properties and ecotoxicity, the ecotoxicity studies show (based on unreliable studies on the registered substance) that the target substance is slightly more toxic than the source substance.

ECHA concludes therefore that your justification based on structural similarity, similar physico-chemical, ecotoxicological and toxicological properties has not established why the prediction is reliable for the human health and environmental endpoints for which the read-across is claimed.

Additionally, ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across. Secondly, the defects of each individual argument are not mitigated by the other arguments you have provided, and so ECHA considers that the arguments when taken all together do not provide a reliable basis for predicting the properties of the registered substance.

Therefore, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects and environmental effects of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. ECHA notes that there are specific considerations for the individual endpoints which also result in a failure to meet the requirement of Annex XI, Section 1.5., and these are set out under the endpoint concerned.

You acknowledge in your comments to the draft decision that "*a more robust documentation has to be provided in order for the category to be used for the purposes of (grouping and) read-across*" and express your intentions to improve the documentation in line with the observations made in this decision and ECHA's Read-Across Assessment Framework (RAAF). More specifically, you state that you are "*committed to provide a broader data base to substantiate the category approach.*"

You expressed your intention to conduct the requested testing in three tiers requiring an extension of the current decision deadline for sub-chronic toxicity study, extended one-generation reproductive toxicity study and pre-natal developmental toxicity study in a second species. In addition, you consider that the two C6 diamine category members (the source substance DCH and the target substance MPMD) currently subject to a respective compliance check "*have to be seen in combination and having the results of an EOGRTS with one substance first would increases the likelihood of getting higher quality results for the second substance.*" More specifically, you intend to expand the sub-chronic toxicity study with MPMD with "*in-depth histopathological examination of reproduction-associated organs*" and to compare the results of the screening study and the extended one-generation reproductive toxicity study performed with DCH, when available.

You also state that your proposed sequential testing plan and schedule would "*secure more realistic schedules established by the contract research organisations performing the tests.*"

ECHA acknowledges your intentions. However, as explained above, the read-across does not seem to be acceptable based on the current information because comparison of the toxicity studies show partly different toxic effects. In addition, a sub-chronic toxicity study does not investigate reproductive function directly and cannot therefore be used for comparing the reproductive function of MPMD and DCH.

ECHA notes that, the deadline of this decision has been set to accommodate sequential testing of the requested studies with the registered substance MPMD. In addition, ECHA notes based on the current information, there appears to be currently no basis to apply read-across between DCH and MPMD. Therefore, ECHA considers delaying the pre-natal developmental toxicity study in a 1st species with MPMD is not adequate and the requested prolongation of the decision deadline to allow sequential testing of DCH and MPMD for the higher tier tests not justified. Based on this, ECHA did not ask you to substantiate your testing strategy scheduling with a selected contract research organisation. The deadline was not changed.

Any additional data in support of your read-across adaptation will be assessed in follow-up evaluation stage after the deadline of the decision has passed.

As described above, further elements are needed to establish a reliable prediction for a toxicological or ecotoxicological property, based on recognition of the structural similarities and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health and environmental properties.

2. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided a study records for a "*repeated dose 28-day oral toxicity study*" (according to OECD TG 407) and a "*two-week inhalation toxicity study*" with the registered substance. However, these studies do not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days and the number of animals per dose group is significantly lower than in the 90 day sub-chronic toxicity study (OECD TG 408). Therefore, the sensitivity of a 28-day oral study (OECD TG 407) and the provided two-week inhalation toxicity study is much lower than that of a 90-day study.

You have sought to adapt this information requirement according to Annex IX, Section 8.6.2., column 2. You provided the following justification for the adaptation:

"According to REACH Annex IX, No. 8.6, Column 2, information shall be provided for at least one appropriate route. The submission substance is part of the amine heads category and various subacute and subchronic studies are available for the different category members:
- Oral toxicity data are available from a subacute screening study with DCH.
- As well as there are data after subacute expusure to inhalation of an aerosol/vapour mixture of DCH and MPMD.
- A 90 day oral toxicity study is available for a mixture (consisting approx. to 55% of the members of the amine heads category). Effects observed and effect level seen are comparable to subacute studies with single substances as test materials.
- Moreover there is a subchronic study conducted with HMD-dihydrochloride exposing rats via inhalation (which covers for systemic effects) and another subchronic inhalation study in rats was performed with HMD.

As sufficient subchronic data are provided for the inhalation route no oral 90 day study is required."

In addition to the two studies with the registered substance you have provided the following study records with source studies in support of your adaptation:

- study record for a "*repeated dose 90-day oral toxicity in rodents*" (equivalent or similar to OECD TG 408) with the source substance **[4]** (amine heads)
- study record for a "*subchronic inhalation toxicity: 90-day study*" (equivalent or similar to OECD TG 413) with the source substance **[2]** (HMD dihydrochloride)
- study record for a "*subchronic inhalation toxicity: 90-day study*" (equivalent or similar to OECD TG 413) with the source substance **[3]** (HMD)
- study record for a "*screening for reproductive/developmental toxicity*" (according to OECD TG 422) with the source substance **[1]** (DCH)
- study record for a "*two-week inhalation toxicity study*" with the source substance **[1]** (DCH)

ECHA has first evaluated your adaptation according to Annex XI, Section 1.5 of the REACH Regulation (grouping and read-across). However, as explained above in Appendix 1, section Grouping and read-across approach for toxicological and ecotoxicological information of this decision, your adaptation of the information requirement according to Annex XI, Section 1.5 is rejected. Hence, as the sub-chronic studies referred to in your adaptation have been conducted using analogue substances, your adaptation does not meet the requirements for adaptation of Annex IX, Section 8.7.2., column 2.

Furthermore, ECHA has made the following observations while assessing your read-across adaptation of the sub-chronic toxicity endpoint:

1. With regard to the applicability of the 13-week oral toxicity study with the source substance **[4]** (amine heads), i) the composition of the multi-constituent test item has not been reported in sufficient detail, ii) low doses were used while "*no signs of toxicity associated with treatment were observed*", which is not in accordance with the respective guideline and iii) deviations compared to the reference study guideline (no neurobehavioural examinations were included).

2. Target and source substances show inconsistent systemic toxicity profiles in the repeated dose toxicity studies provided: only local respiratory tract effects were seen in the 14-day sub-acute toxicity studies via inhalation route with the target substance (MPMD), and no toxic findings were reported in the sub-acute toxicity study via the oral route with the target substance. For the source substances lymphocytic alveolar inflammation (significant increase in females and positive trend in males) was observed in the screening study via oral route with the source substance **[1]** (DCH), significant changes in haematological parameters were observed in the sub-chronic toxicity study via inhalation route with the source substance **[2]** (HMD dihydrochloride), and local respiratory tract effects were seen in the sub-chronic toxicity study via inhalation route with the source substance **[3]** (HMD).

Therefore, your adaptations of the information requirement are rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA Guidance on information requirements and chemical safety assessment (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, potential inhalation-specific effects due to corrosive property of the registered substance are already addressed by deriving a long-term DNEL for inhalation for local effects and by self-classifying the substance accordingly. Hence, the test shall be performed by the oral route using the test method OECD TG 408.

According to the test method OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

In your comments to the draft decision you agreed to perform the requested test in TIER-1 of your testing plan (within 15 months from the date of this decision). However, as explained above in Appendix 1, section Grouping and read-across approach for toxicological and ecotoxicological information of this decision, ECHA considers the requested prolongation of decision deadline not justified. Hence, there is no need to extend the deadline for testing.

Furthermore, you expressed your intention to extend the sub-chronic toxicity study with in-depth histopathological examination of reproduction-associated organs and additional determinations of clinical-biochemical parameters associated with reproduction for better comparison of relevant effects in the available screening study with the source substance **[1]** (DCH).

ECHA acknowledges your intentions. While comparing registered substance (MPMD) and source substance **[1]** (DCH) toxic properties in context of read-across justifications is possible, ECHA notes that the results of the sub-chronic toxicity study (even with extended investigations related to reproductive toxicity) cannot negate the already observed adverse effects related to reproductive function in the OECD TG 422 study performed with the source substance **[1]** (DCH) that trigger further investigations for reproductive toxicity for the source substance under the respective registration. The information requirement for an extended one-generation reproductive toxicity study therefore remains to be addressed under the respective registration.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: OECD TG 408) in rats.

3. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "pre-natal developmental toxicity study" (test method OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not submitted a study record for a "pre-natal developmental toxicity study" with your registered substance. Instead you have sought to adapt this information requirement by providing the following justification:

"In accordance with column 2 of REACH Annex IX, section 8.7.2, a developmental toxicity/ teratogenicity study is not necessarily required. There are no adverse effects on reproductive organs or tissues in repeated dose toxicity studies (28 day or 90 day study; one and two generation study conducted with members of the category) and no indications for reproductive toxic effects in the prenatal developmental toxicity study for one member substance of the category with rats. Moreover there are no effects on reproduction and no malformation or adverse effects on pups were identified in a two generation study with rats as well as in one generation studies performed with rats or mice. Effects (i.e. increased postnatal loss and thus reduced viability index) in a COMBINED 28-DAY REPEATED DOSE TOXICITY STUDY WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST with rats were not found to occur in a dose-dependent manner and were therefore not accounted for as adverse (test material: DCH). In accordance with REACH provisions a developmental toxicity/ teratogenicity study with e.g. rabbits is not envisaged."

You have provided the following study records in support of your adaptation:

- study record for a "*prenatal developmental toxicity study*" (equivalent or similar to OECD TG 414) with the source substance **[3]** (HMD)
- study record for a "*screening for reproductive/developmental toxicity*" (according to OECD TG 422) with the source substance **[1]** (DCH) in IUCLID Section 7.8.1.
- study record for a "*repeated dose 90-day oral toxicity in rodents*" (equivalent or similar to OECD TG 408) with the source substance **[4]** (amine heads) in IUCLID section 7.5.1.
- study record for a "*subchronic inhalation toxicity: 90-day study*" (equivalent or similar to OECD TG 413) with the source substance **[2]** (HMD dihydrochloride) in IUCLID section 7.5.2.
- study record for a "*subchronic inhalation toxicity: 90-day study*" (equivalent or similar to OECD TG 413) with the source substance **[3]** (HMD) in IUCLID section 7.5.2.
- study record for a "*two-week inhalation toxicity study*" with the source substance **[1]** (DCH) in IUCLID section 7.5.2.
- study record for a "*two-week inhalation toxicity study*" with the target substance (MPMD) in IUCLID section 7.5.2.
- study record for a "*repeated dose 28-day oral toxicity study*" (according to OECD TG 407) with the target substance (MPMD) in IUCLID section 7.5.1.

ECHA has first evaluated your adaptation according to Annex XI, Section 1.5 of the REACH Regulation (grouping and read-across). However, as explained above in Appendix 1, section Grouping and read-across approach for toxicological and ecotoxicological information of this decision, your adaptation of the information requirement according to Annex XI, Section 1.5 is rejected.

ECHA further notes that, apart from the pre-natal developmental toxicity study with source substance **[3]** (HMD), none of the supporting studies cover key parameters of a pre-natal developmental toxicity study, such as examinations of foetuses for skeletal and visceral alterations.

Regarding your adaptation according to Annex IX, Section 8.7.2., Column 2., ECHA points out that the adaptation rule is for the information on a second species and not adapting information on a first species which is a standard information requirement of Annex IX.

Therefore, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision you agreed to perform the requested test with the registered substance in TIER-2 of your testing plan, without an extension to the deadline of this decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: OECD TG 414) in a first species (rat or rabbit) by the oral route.

4. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Pre-natal developmental toxicity studies (test method OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier does not contain information on a pre-natal developmental toxicity study with the registered substance.

You have sought to adapt the information requirement for a pre-natal developmental study in a first and second species according to Annex XI, Section 1.5 and Annex IX, Section 8.7.2., column 2, respectively. As explained above under request 3 above, your adaptation of the information requirement is rejected. Since your adaptation according to Annex XI, Section 1.5. is rejected, the listed study records with such analogous substances cannot be used as a basis for your adaptation according to Annex IX, Section 8.7.2, column 2 either.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision you agreed to perform the requested test with the registered substance in TIER-3 of your testing plan (within 69 months from the date of this decision), if the results from the pre-natal developmental toxicity study in the first species triggers the investigation in a second species.

ECHA reminds you of the fact that a pre-natal developmental toxicity study in second species is a standard information requirement for a technical dossier registered at more than 1000 tonnes per year which needs to be therefore addressed either by providing the requested study or by applying an appropriate adaptation as indicated below under "*Notes for your consideration*". Moreover, as explained above in Appendix 1, section Grouping and read-across approach for toxicological and ecotoxicological information of this decision, ECHA considers the requested prolongation of the decision deadline not justified and notes that the pre-natal developmental toxicity study in the second species can be performed in TIER-2 of your testing plan, without an extension to the deadline of this decision. Hence, there is no need to extend the deadline for testing.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: OECD TG 414) in a second species (rabbit or rat) by the oral route.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species with other available information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

5. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

The basic test design of an extended one-generation reproductive toxicity study (test method OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information provided

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

Instead, you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing the following information:

- study record for a *"one-generation reproductive toxicity"* (equivalent or similar to OECD TG 415; GLP) in rat and mouse via inhalation route with source substance **[2]** (HMD dihydrochloride), Hebert et al. 1993 (publication), rel 2.

- study record for a *"screening for reproductive/developmental toxicity"* (according to OECD TG 422) with source substance **[1]** (DCH), [redacted] 2007 (study report), rel 1. and

- study record for a *"two-generation reproductive toxicity"* (equivalent or similar to OECD TG 416; GLP) in rat via oral route with source substance **[3]** (HMD), [redacted] 1985 (study report) and Short et al. 1991 (publication), rel 1.

However, as explained above in Appendix 1, section Grouping and read-across approach for toxicological and ecotoxicological information of this decision, your adaptation of the information requirement is rejected. ECHA further notes that where the two-generation reproductive study could meet the column 2 specific adaptation rule if the read-across were accepted, while the one-generation reproductive toxicity study with the source substance does not provide equivalent information as of the extended one-generation reproductive toxicity study. More specifically, the study lacks investigations to detect certain endocrine modes of action and sexual development. In addition, extensive investigations in F1 generation was lacking.

Hence, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the study design

Information from studies to be conducted before the extended one-generation reproductive toxicity study

The sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from that study shall be used, among other relevant information, to decide on the study design of the extended one-generation reproductive toxicity study following ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).The sub-chronic toxicity study may provide information on effects that is relevant for triggers (e.g. weight changes and histopathological observations of organs as indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or as evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity which may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts).

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Species and route selection

According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

c) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation

While the specifications for the study design are given above, you shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the premating exposure duration and dose level selection, 2) reasons for why or why not Cohort 1B was extended, 3) termination time for F2 generation, and 4) reasons for why or why not Cohorts 2A/2B and/or Cohort 3 were included.

Currently, the extension of Cohort 1B and the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) are not requested. However, the sub-chronic toxicity study (90-day) requested in this decision and/or any other relevant information may trigger changes in the study design. Therefore, the sub-chronic toxicity study (90-day) is to be conducted first and the study results submitted to ECHA in a dossier update by the 12-month deadline indicated in this decision. If, on the basis of this update and/or other relevant information, a need for changes to the study design is identified, ECHA will inform you within three months after expiry of the 12-month deadline to provide the sub-chronic toxicity study (90-day)), as indicated in this decision, of its intention to initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study. If you do not receive a communication from ECHA by the expiry of the three months following the 12-month deadline for providing the results of the sub-chronic toxicity study (90-day), the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision.

In your comments to the draft decision you agreed to perform the requested test with the registered substance in TIER-3 of your testing plan (within 69 months from the date of this decision). However, as explained above in Appendix 1, section Grouping and read-across approach for toxicological and ecotoxicological information of this decision, ECHA considers the requested prolongation of decision deadline not justified. Hence, there is no need to extend the deadline for testing.

Notes for your consideration

When submitting the study results of the sub-chronic toxicity study (90-day) you are invited to also include in the registration update your considerations whether changes in the study design are needed (see also *ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a, Section R.7.6 (version 6.0, July 2017)*).

Furthermore, after having commenced the extended one-generation reproduction toxicity study in accordance with the ECHA decision, you may also expand this study to address a concern identified during the conduct of it and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the changes in the study design must be documented.

6. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.) or long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Short-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex VII, Section 9.1.1. of the REACH Regulation. This provision specifies that long-term toxicity testing on aquatic invertebrates may be considered instead of short-term and that the short-term study does not need to be conducted if a long-term study on aquatic invertebrates is available.

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. Adequate information on these endpoints needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt the information requirement on short-term toxicity testing on aquatic invertebrates according to Annex XI, Section 1.5. of the REACH Regulation by providing the following studies:

- study record for a *"short-term toxicity to aquatic invertebrates"* (equivalent or similar to OECD TG 202) with source substance **[3]** (HMD),
- study record for a *"short-term toxicity to aquatic invertebrates"* (equivalent to US EPA 660/3-75-009) with source substance **[3]** (HMD), and
- study record for a *"short-term toxicity to aquatic invertebrates"* (no guideline provided) with source substance **[3]** (HMD).

However, as explained above in Appendix 1, section Grouping and read-across approach for toxicological and ecotoxicological information of this decision, your adaptation of the information requirement cannot be accepted.

In addition, you have sought to adapt the information requirement for long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5. of the REACH Regulation) by providing the following study:

- study record for a *"long-term toxicity to aquatic invertebrates"* (equivalent to OECD TG 211) with source substance **[3]** (HMD).

However, as explained above in Appendix 1, section Grouping and read-across approach for toxicological and ecotoxicological information of this decision, your adaptation of these information requirements cannot be accepted.ECHA further notes that it was a static test with no analytical confirmation of the concentrations. The Vapour pressure for the registered substance is predicted to be 26 Pa at 20 °C. Thus, losses of the test substance due to volatilisation may have occurred.

As there is currently no valid information on aquatic toxicity, ECHA considers that the available information in your chemical safety assessment does not rule out the need to investigate further long-term effects on aquatic organisms.

In particular, you may need to perform long-term aquatic toxicity test(s) to refine the PNECs and the risk assessment. The magnitude of the assessment factors used for calculating the PNECs can indeed be reduced when information on long-term toxicity is available: this often leads to higher PNEC and to lower risk characterisation ratios.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

With regard to the test methods to be used, ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) indicates that Daphnia sp. acute immobilisation test (test method EU C.2. / OECD TG 202) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.1.

If you choose to perform a long-term test instead, ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) indicates that *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.

You submitted comments to the draft decision agreeing with the request.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *Daphnia* sp. Acute immobilisation test, EU C.2./OECD TG 202) or Daphnia magna reproduction test (test method: EU C.20./OECD TG 211.

Notes for your consideration

Once results of the test on long-term toxicity to aquatic invertebrates are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation.

Due to the high volatility you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

7. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing the following studies:

- study record for a *"toxicity to aquatic algae and cyanobacteria"* (equivalent to OECD TG 201) with source substance **[3]** (HMD),

However, as explained above in Appendix 1, section Grouping and read-across approach for toxicological and ecotoxicological information of this decision, your adaptation of these information requirements cannot be accepted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.
According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) Algae growth inhibition test (test method EU C.3. / OECD TG 201) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.2.

You submitted comments to the draft decision agreeing with the request.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Algae growth inhibition test, EU C.3./OECD TG 201).

Notes for your consideration

Due to high volatility you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

8. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.) or long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Short-term toxicity testing on fish" is a standard information requirement as laid down in Annex VIII, Section 9.1.3. of the REACH Regulation. This provision specifies that long-term toxicity testing on fish may be considered instead of short-term and that the short-term study does not need to be conducted if a long-term study on fish is available.

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation.
Adequate information on these endpoints need to be present in the technical dossier for the registered substance to meet these information requirements.

In the technical dossier you have provided a study record for a Short-term toxicity to fish ([redacted]) with the registered substance. However, this study does not provide the information required by Annex VIII, Section 9.1.3., because, as already claimed by you in the technical dossier, it is not reliable. ECHA notes that the total exposure duration (48hrs) is less than required by the guideline (96hrs). Moreover, there is an uncertainty with the pH value of the test media. Hence, it is not clear if the effects seen in the test were due to the pH effect or the toxicity of the test substance.

Additionally, you have sought to adapt the information requirement on short-term toxicity to fish according to Annex XI, Section 1.5. of the REACH Regulation by providing the following studies:

- study record for a *"short-term toxicity to fish"* (equivalent or similar to EU Method C.1) with source substance **[3]** (HMD),
- study record for a *"short-term toxicity to fish"* (equivalent to "Deutsches Einheitsverfahren" DIN 38 412, Part 15, "Bestimmung der Wirkung von Wasserinhaltsstoffen auf fische", Fischtest L15; equivalent or similar to OECD TG 203) with source substance **[1]** (DCH), and
- study record for a *"short-term toxicity to fish"* (equivalent or similar to OECD TG 203) with source substance **[3]** (HMD).

However, as explained above in Appendix 1, section Grouping and read-across approach for toxicological and ecotoxicological information of this decision, your adaptation of the information requirement cannot be accepted. ECHA further notes that it was a static test with no analytical confirmation of the concentrations. The Vapour pressure for the registered substance is predicted to be 26 Pa at 20 °C. Thus, losses of the test substance due to volatilisation may have occurred.

However, ECHA notes that you have sought to adapt the information requirement for long-term toxicity testing on fish (Annex IX, Section 9.1.6. of the REACH Regulation) by providing the following justification:

> *"Waiving according to "column 2" in Annex IX of REGULATION (EC) No 1907/2006 (CSA does not indicate need for further investigations)".*

As there is currently no valid information on aquatic toxicity, ECHA considers that the available information in your chemical safety assessment does not rule out the need to investigate further long-term effects on aquatic organisms.

In particular, you may need to perform long-term aquatic toxicity test(s) to refine the PNECs and the risk assessment. The magnitude of the assessment factors used for calculating the PNECs can indeed be reduced when information on long-term toxicity is available: this often leads to higher PNEC and to lower risk characterisation ratios.

With regard to the test methods to be used, ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) indicates that fish acute toxicity test (test method EU C.1. / OECD TG 203) is the preferred test to cover the standard information requirement of Annex VIII, Section 9.1.3.

If you choose to perform a long-term test instead, the fish early-life stage (FELS) toxicity test according to OECD test guideline 210 is to be preferred since it covers several life stages of the fish from the newly fertilised egg, through hatch to early stages of growth (see ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), *Chapter R7b, Figure R.7.8-4).*
You submitted comments to the draft decision agreeing with the request.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Fish, acute toxicity test (test method: EU C.1./OECD TG 203) or Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

Notes for your consideration

Once results of the test on long-term toxicity to fish are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation.

Due to the high volatility you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 12 January 2018.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

ECHA took into account your comments and did not amend the request(s) or the deadline.

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.