EUROPEAN CHEMICALS AGENCY

Helsinki, 13 February 2018

Addressee: [redacted]

Decision number: CCH-D-2114392123-54-01/F
Substance name: 2-(2-AMINOETHOXY)ETHANOL
EC number: 213-195-4
CAS number: 929-06-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 11/01/2017
Registered tonnage band: [redacted]

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. **Assessment of the toxicokinetic behaviour of the substance (Annex VIII, Section 8.8.1.);**

2. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. /OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 with the registered substance;**

3. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance provided that studies requested under 2. have negative results;**

4. **Available human data on skin sensitisation (Annex I, Sections 0.5, 1.0.3 and 1.2 and Annex X, second paragraph) for the registered substance;**

5. **Available assessment from national programme (Annex I, Section 0.5) for the registered substance;**

6. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

7. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit or rat), oral route with the registered substance;**

8. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./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 some 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;**

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 have to submit the requested information in an updated registration dossier by **20 August 2021**. You also have to 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 Ofelia Bercaru, Head of Unit, Evaluation E3

[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

1. **Assessment of the toxicokinetic behaviour of the substance (Annex VIII, Section 8.8.1.)**

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered [redacted] 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 assessment of the toxicokinetic behaviour of the substance to the extent that can be derived from the relevant available information is a standard information requirement as laid down in Annex VIII, Section 8.8.1. of the REACH Regulation.

You have sought to adapt this information requirement. You provided the following justification for the adaptation *"No data are available on Toxicokinteics, metabolism and distribution."*

ECHA notes that the registration dossier does not provide any assessment on the toxicokinetics properties of the registered substance. Although REACH does not specifically require generation of toxicokinetic information, it does require that all relevant available information is used to assess the toxicokinetic behaviour of a substance, and that the human health hazard assessment considers the toxicokinetic profile of the substance. The toxicokinetic profile of a substance describes its absorption, distribution, metabolism and excretion. Consequently the statement *"No data are available on Toxicokinteics, metabolism and distribution."* is not a valid adaptation. Therefore there is a data gap for this information requirement.

In your comments to the draft decision you agreed to provide the information.

Therefore, pursuant to Article 41(1)(b) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: assessment of the toxicokinetic behaviour of the substance to the extent that can be derived from the relevant available information (Annex VIII, 8.8.1.).

Notes for your consideration

Guidance on Toxicokinetics is available in ECHA Guidance on information requirements and chemical safety assessment (version 3.0, June 2017), Chapter R.7c, Section R.7.12.

2. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)**

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at [redacted] 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.

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. 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.

According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: S. typhimurium TA1535; TA1537 or TA97a or TA97; TA98; TA100; S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). This includes four strains of *S. typhimurium* (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four *S. typhimurium* strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by E.coli WP2 strains or *S. typhimurium* TA102 which have an AT base pair at the primary reversion site.

You have provided a test from the year 1990 according to OECD TG 471 ([redacted] 1990) and GLP with an assigned reliability score of 2. The test used four different strains of *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 and it did not include tests with strains S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). In addition, you have provided a test from the year 1982 according to OECD TG 471 ([redacted] 1982) and GLP with an assigned reliability score of 1. The test used five different strains of *S. typhimurium* TA 1535, TA 1537, TA 98, TA 1538 and TA 100 and it did not include tests with strains S. typhimurium TA 102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101).However, since the test was conducted, significant changes have been made to OECD TG guideline 471 so that additionally testing with S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is now required. Therefore, the provided study does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

ECHA concludes that a test using *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 has not been submitted and that the test using one of these is required to conclude on *in vitro* gene mutation in bacteria.

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 considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

In your comments to the draft decision you agreed to conduct the study.

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: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

3. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered [redacted] 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.

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

You have not provided any study record of an *in vitro* gene mutation study in mammalian cells in the dossier that would meet the information requirement of Annex VIII, Section 8.4.3.

You have provided in your technical dossier an *in vitro* mammalian cell transformation test, a non-guideline study, with an assigned reliability score of 2 (key study, [redacted] 1982). ECHA notes that the provided study is an *in vitro* method for screening of potential carcinogens and not a specific method to test gene mutation in mammalian cells.
In addition, you have provided an *in vitro* UDS test according to OECD TG 482, with an assigned reliability score of 2 (key study, [redacted] 1982). ECHA notes that the *in vitro* UDS test is an indicator assay detecting putative DNA lesions followed by DNA repair (measured as unscheduled "DNA" synthesis) and hence not a specific method to test gene mutation in mammalian cells. Therefore the above mentioned studies cannot be considered as providing equivalent data according to the criteria in Annex VIII section 8.4.3. of the REACH Regulation.

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 considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) or the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

In your comments to the draft decision you agreed to conduct the study.

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: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that the studies requested under 2. have negative results.

4. Available human data on skin sensitisation (Annex I, sections 0.5, 1.0.3 and 1.2 and Annex X, second paragraph) for the registered substance

Pursuant to Articles 10(a) and Annex I of the REACH Regulation, a technical dossier registered at [redacted] per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation and the available human information.

In the IUCLID file in section 7.1.4 (sensitisation data (humans)) you have included the results of a publication "Contact allergy to diglycolamine in water-based metalworking fluid (Geier et al. 2002). ECHA notes that other relevant human data have been reviewed by the

[redacted]MAK-Commission (MAK Collection for Occupational Health and Safety, 5. [redacted] 2014[redacted] version, 2-2-Aminoethoxy)ethanol). These data include additional case studies (Frosch et al. 2002, Geier et al. 2011) and several systematic investigations of the IVDK on cohorts (Geier et al 2002, Geier et al. 2003, Geier et al. 2004, Geier et al. 2006, IVDK 2013). The results of these studies as reported by the MAK assessment are highly relevant to the safe handling of the registered substance, since they indicate a skin sensitising potential in humans, and there is no indication that the studies are not available.

In your comments to the draft decision you agreed to include the above mentioned available human data on skin sensitisation in your updated registration dossier.

Therefore, pursuant to Annex I, Sections 1.0.3, 0.5 and 1.2 and Annex X, second paragraph of the REACH Regulation you are requested to include the above mentioned, available human data on skin sensitisation in your registration dossier and in the CSR.

5. Available assessment from national programme (Annex I, Section 0.5) for the registered substance;

Pursuant to Articles 10(b) and 14(1) of the REACH Regulation, the registration shall contain a chemical safety report (CSR) which shall document the chemical safety assessment (CSA) conducted in accordance with Article 14(2) to (7) and with Annex I of the REACH Regulation. Pursuant to Annex I, Section 0.5. of the REACH Regulation *"Available information from assessments carried out under other international and national programmes shall be included."*

ECHA observes that you have provided results obtained in an animal test according to OECD TG 406 with an assigned reliability score of 2 (Huntsman, 1991). You concluded that *"Altough 10 % of the animals showed a positive result, a minimum figure of 15% under any study would be necessary for classification as a sensitizer under EU standards. No EU classification according to Annex I of Directive 67/548/EEC."* In addition, you provided under IUCLID section 7.1.4 the results of the above mentioned publication (Geier et al. 2002) with an assigned reliability score of 4. Based on this information you concluded that the substance has no sensitisation properties and *"No EU and / or GHS classification warranted".*

ECHA notes that the MAK assessment on 2-(2-aminoethoxy)ethanol (see above in section 4) evaluated the available human information including clinically-relevant test reactions to 2-(2-aminoethoxy)ethanol as being positive. Consequently, 2-(2-aminoethoxy)ethanol is labelled with "Sh" for skin sensitisation by the MAK Commission. There is no indication that the MAK assessment is not available.

ECHA considers that in contrast to the current conclusion in your dossier, the data described for the registered substance may well meet the criteria for classification and labelling as skin sensitizer, as provided in the CLP Regulation, Section 3.4. Currently, the relevant human data (see section 3.), the assessment of these data by the MAK Commission, and a discussion of the relevance of such data for classification and labelling according to the CLP regulation is missing from your registration dossier.

In your comments to the draft decision you agreed to include the available assessment from national programme in your updated dossier. You also indicate your intention to discuss in the updated dossier the available human case studies and the results of the Buhler test in a

weight of evidence approach. In addition, in your comments you consider that this weight of evidence from all the available information will support your disagreement with the conclusion that the registered substance is a skin sensitizer.

ECHA notes that this information needs to be included in the technical dossier in the formats requested by the REACH Regulation. While for the purpose of this decision making, ECHA does not take into account any dossier updates after the notification of this draft decision under Article 50(1) of the REACH Regulation, ECHA notes that dossier updates and any adaptations therein will be evaluated by ECHA at the follow up stage.

Therefore, pursuant to Article Annex I, Section 0.5 of the REACH Regulation you are requested to include the outcome of the available assessment from national programme (MAK Commission) on the skin sensitising properties of the registered substance in the registration dossier and in the CSR. The consequences for classification and labelling according to the CLP Regulation have to be documented with a view to avoid underestimation of the hazard for skin sensitisation.

6. 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 [redacted] 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 EU B.31./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 provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex IX/X, Section 8.7., column 2. You provided the following justification for the adaptation: *"2-(2-Aminoethoxy)ethanol is in accordance with EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008 classified as corrosive (Cat. 1B; H318: Causes severe skin burns and eye damage). In an inhalatory (aerosol) combined repeated dose toxicity study with the reproduction/developmental toxicity screening test the no observed adverse effect concentration (NOAEC) for reproductive performance and fertility in male and female Wistar rats was 40 mg/m³. The NOAEC for local signs of toxicity in male and female Wistar rats was 4 mg/m³. In a subchronic dermal study following OECD test guideline 411 no effects on the male and female reproductive organs were observed up to the highest dose tested (175 mg/kg/day). The NOAEL for local effects was 17 mg/kg bw/d. Industrial and professional worker exposure is controlled by the use of closed systems, industrial hygiene controls, and personal protective equipment. No exposure of the general population is expected. Therefore, it is concluded that reproductive toxicity should not be an endpoint of concern."*

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX/X, Section 8.7., column 2. as explained below. Firstly, classification as corrosive is not an adaptation rule for reproductive toxicity studies. Secondly, ECHA notes that the combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test was conducted via the inhalation route and the exposure concentrations ranged from 0, 4, 16 to 40 mg/m³/day; while the sub-chronic toxicity study was conducted via the dermal route (OECD 411) with applied doses of 0, 17, 87, 175 mg/kg bw/d. ECHA observes that predominantly local toxicity has been observed in both studies. As there are effects observed, it cannot be concluded that "*the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available*)" and, thus, the first aspect of the specific rule for adaptation of Annex IX/X, Section 8.7., column 2 (indent 3) is not met. ECHA also observes that you do not explain the rationale for setting the administered exposures/doses and/or the choice of route of administration. In view of the administered exposures/doses and given the lack of toxicokinetic information on the registered substance, ECHA is not in the position to independently evaluate whether systemic absorption took place in the above mentioned studies and/or whether the low incidence of systemic effects are arising from the applied low dosing regimen which may lead to under-estimation of the reproductive toxicity potential. Hence, your conclusion that based on the absence of observed effects on the reproductive organs and fertility parameters there is no concern for reproductive toxicity cannot be confirmed.
Moreover, ECHA observes that no repeated dose toxicity studies or screening studies via the oral route are available with the registered substance, which would address whether or not the substance displays effects on the reproductive organs and/or fertility parameters. Therefore, the second aspect of the specific rule for adaptation of Annex IX/X, Section 8.7., column 2 (indent 3) "*it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure*" is not met.

In addition, ECHA notes that according to your registration dossier besides the uses in closed systems the substance is used by professional workers in processes where exposure of workers can occur e.g. PW-7 (Professional use of ADG in metal working fluids and lubricants) and PW-10 (Professional use as processing aid for paper, textile, leather, coatings). Hence, ECHA considers that the use of the registered substance is leading to significant exposure of professionals. Therefore, the third aspect of the specific rule for adaptation of Annex IX/X, Section 8.7., column 2 (indent 3) "*there is no or no significant human exposure*" is not met. It is to be noted that all three aspects required in column 2 (indent 3) should be fulfilled.

In summary, 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 EU B.31./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 conduct the study.

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: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

7. 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 [redacted] 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 EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for [redacted] 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.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex X, Section 8.7., column 2. You provided the same justification for the adaptation as quoted in section 6.
However, as explained under section 6., ECHA considers that your adaptation does not meet the specific rules for adaptation of Annex IX/X, Section 8.7., column 2 and your adaptation of the information requirement is rejected.
According to the test method EU B.31./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 consider conduct of the study depending on the outcome of the first study.

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: EU B.31./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.

8. 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 [redacted] 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 EU B.56./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

In the technical dossier you have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422; [redacted] 2010) . However, this study does not provide the information required by Annex X, Section 8.7.3. because it does not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. More specifically, the main missing key elements are: 10 weeks pre-mating exposure duration, at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation.

In addition, while you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex X, Section 8.7., column 2. You provided the same justification for the adaptation as quoted in section 6.
However, as explained under section 6., ECHA considers that your adaptation does not meet the specific rules for adaptation of Annex IX/X, Section 8.7., column 2 and your adaptation of the information requirement is rejected.

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.

a) *The specifications for the study design*

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 some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of 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 existing relevant data to be used for dose level setting, it is recommended that results from a conducted 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 EU B.56./ 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.

In your comments to the draft decision you agreed to conduct the study.

b) 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 EU B.56./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 some 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;

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with the new information, shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Extension of the deadline

In the draft decision communicated to you the time indicated to provide the requested information was 34 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline to 42 months. You sought to justify this request by difficulties in the scheduling timelines for the studies in question in the selected laboratory facility. Furthermore, you indicated additional obstacles related to the time required for the test material characterization under GLP. Following ECHA's request you have provided documentary evidence from the selected test laboratories on the above mentioned.

ECHA considered your request and the provided evidences. Therefore, ECHA has granted the request and set the deadline to 42 months.

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 22 February 2017.

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 amended the deadline.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-58 written procedure and ECHA took the decision according to Article 51(6) 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.