Helsinki, 13 March 2018

Addressee
[redacted]

Decision number: TPE-D-2114394286-38-01/F
Substance name: Chloroethane
EC number: 200-830-5
CAS number: 75-00-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 15/12/2016
Registered tonnage band: Over 1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

Your testing proposal is accepted and you are requested to carry out:

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

Your testing proposal is modified and you are requested to carry out:

2. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, inhalation 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 an adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **21 September 2020**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons for 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

The decision of ECHA is based on the examination of the testing proposals submitted by you and scientific information submitted by third parties.

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

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

Examination of the testing proposal

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for 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 dossier contains a pre-natal developmental toxicity study in mice as first species. However, there is no information available for a pre-natal developmental toxicity study in a second species. Consequently there is an information gap for Annex X, Section 8.7.2. and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a pre-natal developmental toxicity study in a second species (rabbits) according to EU B.31./OECD TG 414 by the inhalation route.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA considers that the proposed study performed with the registered substance is appropriate to fulfil the information requirement of Annex X, Section 8.7.2. of the REACH Regulation.

The test in the first species was carried out with mice. According to the test method EU B.31./OECD 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 the rabbit as a second species.

ECHA agrees that the inhalation route is the most appropriate route of administration for gaseous substances 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 gas, ECHA concludes that testing should be performed by the inhalation route.

Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are thus requested to carry out the proposed study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a second species (rabbit), inhalation route (test method: EU B.31./OECD TG 414).

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, Section R.7.6.2.3.2.

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

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

a) Examination of the testing proposal

The basic test design of an extended one-generation reproductive toxicity study (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 of the REACH Regulation. 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 in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for an extended one-generation reproductive toxicity study according to EU B.56./OECD TG 443 by the inhalation route to be performed with the registered substance with the following justification and specification of the study design:

"SPECIFICATION OF STUDY DESIGN FOR EXTENDED ONE-GENERATION REPRODUCTION TOXICITY STUDY WITH JUSTIFICATIONS:
- Premating exposure duration for parental (P0) animals: 10 weeks due to the observed changes in oestrous cycle
- Basis for dose level selection: The dose levels will be determined based on the available relevant data, and taking into account the limit doses for the inhalation route (according to OECD 413 in the absence of data-based limits, the acute limits of the United Nations Globally Harmonized System of Classification and Labelling of Chemicals may be used (i.e., up to a maximum concentration of 5 mg/L for aerosols, 20 mg/L for vapours, and 20,000 ppm for gases).
- Inclusion/exclusion of extension of Cohort 1B: Cohort 1B will be extended to include the F2-generation (please see ' Justification for type of information' for more details).
- Termination time for F2: In accordance with ECHA's 'Chapter R.7a: Endpoint specific guidance, Version 4.1 (October 2015), the end of weaning (around PND 21) is proposed as the termination time for the F2 generation.

- Inclusion/exclusion of developmental neurotoxicity Cohorts 2A and 2B: Cohort 2A and 2B will not be included in the study design (please see ' Justification for type of information' for more details).
- Inclusion/exclusion of developmental immunotoxicity Cohort 3: Cohort 3 will not be included in the study design (please see ' Justification for type of information' for more details).
- Route of administration: Since the test substance is a gas, the substance will be administered via inhalation.
- Other considerations, e.g. on choice of species, strain, vehicle and number of animals: The study will be performed in the rat, as this is the default species according to the OECD guideline 443."

In addition, you submitted in the CSR document justification for the testing proposal, including a summary of the available repeated dose toxicity, carcinogenicity, reproductive and developmental toxicity data on the registered substance and considerations on the neurotoxic and immunotoxic potential of the registered substance.
Furthermore, you provided consideration on the general and specific adaptation possibilities of Annex VI to Annex X (column 2) and Annex XI of the REACH regulation.
You conclude that *"For chloroethane, there is no available in vivo animal data that meet the requirements for an extended one-generation reproductive toxicity study."* and that based on the available data *"for this endpoint (Annex X, 8.7) the 'specific rules for adaptation from Column 1' given in Column 2"* are not applicable. Consequently, you propose to test the registered substance in an extended one-generation reproductive toxicity study according to EU B.56./OECD TG 443 by the inhalation route, in rat.

ECHA observes that for the extension of Cohort 1B you have not provided detailed justification. ECHA examined your proposal in view of the available data on the registered substance and concluded that the criteria to mate the Cohort 1B animals to produce the F2 generation are no fulfilled. For more details please refer to section *"Extension of Cohort 1B"* of the current decision.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA considers that based on the currently available information the proposed study designs requires modification to fulfil the information requirement of Annex X, Section 8.7.3. 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. Thus, an extended one-generation reproductive toxicity study according to column 1 of 8.7.3., Annex X is required. The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You proposed 10 weeks due to the observed changes in oestrous cycle.

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* ECHA 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 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.

Extension of Cohort 1B

If the column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.

You proposed to include an extension of Cohort 1B but provided no justifications following the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

ECHA has evaluated your proposal to include the Cohort 1B with extension to mate the Cohort 1B animals to produce the F2 generation and considers the followings:

The use of the registered substance in the joint submission is leading to significant exposure of professionals because the registered substance is used by professionals in medical applications, in wide dispersive indoor/outdoor use of processing aids in open systems (PROC 11).

However, the registered substance is not classified as Mutagen Category 2 and does not display genotoxic effects in somatic cell mutagenicity tests *in vivo* which could lead to classifying it as Mutagen Category 2.

Furthermore, there are no indications that the internal dose for the registered substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure.

Finally, there are no indications for endocrine-disrupting (ED) modes of action and ECHA considers that the registered substance is not an endocrine disruptor. In this respect, ECHA observes that the following effects are observed in the following studies:

- Breslin, W.J. et al. (1988) inhalation (whole body) 15000 ppm (39577 mg/m³) Exposure: 6 hours/day (minimum of 14 consecutive days; changes (prolongation) in oestrous cycle is observed;
- OECD 451, 2 years, NTP (1989a), mice: inhalation: vapour (whole body) 15000 ppm, 39577 mg/m3) (nominal conc.): highly significant incidence (86%) of uterine carcinomas of endometrial origin, clearly associated with chloroethane exposure, was observed in exposed female mice;
- Fedtke et al. (1994): Effects on uterine weights were examined in B6C3F1 mice and rats exposed to 15000 ppm chloroethane 6 hours/day for 5 days (Fedtke et al., 1994). In female mice, the absolute and relative uterus weights were decreased by approximately 35% compared with unexposed controls. The body weight of mice was also reduced by 16.4% in mice. No effect on uterus weight or body weight was observed in the rats.

Although the effects seen in these studies could indicate an ED mode of acion, ECHA considers that chloroethane (small linear monohalogenated C2 alkane) gives no alert with respect to ED mode of action. Furthermore, the above described effects are isolated, high dose effects observed at 15 000 ppm (39577 mg/m3). The carcinogenicity study is considered by the authors inadequate to determine carcinogenicity based on the significant lower survival rate of the treated animals and the uterine carcinoma observed in these carcinogenicity studies with mice was considered as isolated high dose phenomena by the authors, more likely related to metabolism/metabolites of the substance: "*It is proposed that the mechanism of tumor induction is a high dose phenomenon and more likely related to GSH conjugation than to the oxidative metabolism or to possible genotoxic effects of chloroethane or its metabolites.*" No uterine carcinoma were observed in the carcinogenicity study in rats. In addition, in the other reapeat-dose toxicity studies reported in the dosssier, no effects on ED-sensitive organs was observed which would indicate endocrine mode of action of the substance: For example, no organ weight change and/or no histopathological changes in ovary, uterus/cervix, vagina and female mammary gland; no organ weight change and/or no histopathologic changes in testes, epididymides, male accessory sex organs and male mammary glands; no thyroid related activity in any of these studies: no histopathologic changes in thyroid gland or increased thyroid weight.

Therefore, ECHA concludes that Cohort 1B shall not be extended to include mating of the animals and production of the F2.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of 8.7.3., Annex X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

You proposed not to include Cohorts 2A and 2B and provided justifications following the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

ECHA considers that the criteria to include Cohorts 2A and 2B are not met and concludes that the developmental neurotoxicity Cohorts 2A and 2B need not to be conducted.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of 8.7.3., Annex X.

You proposed not to include Cohort 3 and provided justifications following the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

Therefore, ECHA agrees that the criteria to include Cohort 3 are not met and concludes that the developmental immunotoxicity Cohort 3 needs not to be conducted.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Species and route selection

You proposed testing in rats. According to the test method EU B.56./ OECD TG 443, the rat is the preferred species. On the basis of this default consideration, ECHA considers that testing should be performed in rats.

You proposed testing by the inhalation route.

ECHA agrees that the inhalation route is the most appropriate route of administration for gaseous substances 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 gas, ECHA concludes that testing should be performed by the inhalation route.

Outcome

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the modified study 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, inhalation 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 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.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 16 December 2016.

ECHA held a third party consultation for the testing proposals from 10 March 2017 until 25 April 2017. ECHA did not receive information from third parties.

This decision does not take into account any updates after **1 August 2017**, 30 calendar days after the end of the commenting period.

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 did not receive any comments by the end of the commenting period.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment on 7 September 2017 for the MSCA 30-day consultation phase 8 September 2017 – 9 October 2017. ECHA received proposal(s) for amendment and invited you to comment on the proposed amendment(s). However, ECHA considered and decided to withdraw the draft decision from the MSC-57 decision making procedure.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment on 26 October 2017 for the MSC 58 decision making procedure.

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 during its MSC-58 meeting and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the 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 the Member States.

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.