

Helsinki, 22 March 2018

Addressee: [REDACTED]

Decision number: TPE-D-2114394001-60-01/F
Substance name: Dichloromethylbenzene
EC number: 249-854-8
CAS number: 29797-40-8
Registration number: [REDACTED]
Submission number: [REDACTED]
Submission date: 15/04/2016
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 modified and you are requested to carry out:

- 1. 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:**
 - 1.1.1. Ten weeks pre-mating exposure duration for the parental (P0) generation;**
 - 1.1.2. Dose level setting shall aim to induce some toxicity at the highest dose level;**
 - 1.1.3. Cohort 1A (Reproductive toxicity);**
 - 1.1.4. 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 **30 March 2020**. You also have to update the chemical safety report, where relevant.

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>.

Authorised¹ 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 proposal submitted by you.

1. 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.

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 to be performed with the registered substance with the following justification and specification of the study design:

*"- without extension of Cohort 1B to include the F2 generation (the comprehensive sub-acute and sub-chronic studies do not indicate any potential endocrine effect);
- without Cohorts 2A and 2B or 3 (there is no trigger to include specific immunotoxicity and/or neurotoxicity endpoints);
- No extension of the 2 week pre-mating period (Based on the alpha 2u globulin nephropathy in males a prolonged exposure of males will result in male rat specific toxicity not relevant for human risk assessment).*

Exposure based consideration:

The dichloromethylbenzene mixture dossier supports exclusively industrial uses. According to the risk assessment human exposure in all uses is well controlled as all RCRs are below 1. .

Also for the remaining environmental risks of the industrial uses – there are no wide dispersive uses supported in the dossier - RCRs are < 1 based on CHESAR - EUSIS 2.1.2 modelling.

All volumes at the end of the life cycle are incinerated as hazardous waste in appropriate hazardous waste incineration plants operated according to Directive 2000/76/EC on the incineration of hazardous waste, Council Directive 2008/98/EC.

Off gas from processes is treated by waste gas incineration or adsorption technology.

Only small volumes of dichloromethylbenzene mixture from facility cleaning with water can be released to waste water from industrial processes.

These industrial releases are insignificant and very well controlled as demonstrated by RCRs <1 for all Exposure Scenarios.

Consequently the risk of men via environment is also very well controlled as all RCRs are below 0.01.

Based on these considerations the implementation of an EOGRTS seems not to be of high priority."

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 for which testing is proposed. ECHA has taken these considerations into account.

ECHA considers that the proposed study design requires modification to fulfil the information requirement of Annex X, Section 8.7.3. of the REACH Regulation. More specifically, you proposed no extension of Cohort 1B to include F2 generation, no inclusion of Cohorts 2A and 2B or 3as no triggers were identified, and the 2 weeks pre-mating period. ECHA agrees that extension of Cohort 1B to include F2 generation is not triggered as no professional or consumer uses or significant exposure are identified for the registered substance. ECHA also agrees that currently the conditions to include Cohorts 2A and 2B and/or Cohort 3 are not met. However, the proposed pre-mating exposure duration requires modification as explained below.

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.

Pre-mating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the pre-mating 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 pre-mating 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 pre-mating exposure duration is required when there is no substance specific information in the dossier supporting shorter pre-mating 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).

You proposed no extension of the 2 week pre-mating period. You provided the following justification: "*Based on the alpha 2u globulin nephropathy in males a prolonged exposure of males will result in male rat specific toxicity not relevant for human risk assessment*".

ECHA notes that alpha 2u globulin nephropathy is not considered as such a substance specific property that would require a shorter pre-mating exposure duration. Nephrotoxicity does not affect spermatogenesis in male rats and thus it may require considerations in relation with dose level setting but not regarding pre-mating exposure duration.

Ten weeks exposure duration is supported also by the lipophilicity of the substance (log Pow is 4.25) to ensure that the steady state in parental animals has been reached before mating.

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. You indicate that "*based on the alpha 2u globulin nephropathy in males a prolonged exposure of males will result in male rat specific toxicity not relevant for human risk assessment.*" Although alpha 2u globulin nephropathy may limit the highest dose level used in males, it does not limit the dose level setting in females. Thus, if a higher dose level is possible for females than for males this should be considered in order to fully evaluate the potential hazardous properties of the substance for reproduction. The selected highest dose level used with females should aim to produce some toxicity in females. The selected highest dose level used with males should aim to produce some toxicity in males.

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 not to include an extension of Cohort 1B 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 extend the Cohort 1B are not met and concludes that Cohort 1B must not be extended to include mating of the animals and production of the F2 generation.

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 did not specify the species for testing. 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 should consider if strains which are not sensitive to male-specific nephrotoxicity are available.

You did not specify the route for testing. 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.

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, oral route, according to the following study-design specifications:

- Ten weeks pre-mating 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 27 April 2017.

ECHA held a third party consultation for the testing proposals from 22 June 2017 until 7 August 2017. ECHA did not receive information from third parties.

This decision does not take into account any updates after **13 December 2017**, 30 calendar days after the end of the commenting period.

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 proposal(s) 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 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.