ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 15 December 2016

Addressee: [redacted]

Decision number: CCH-D-2114350941-50-01/F
Substance name: CYCLOHEX-1,4-YLENEDIMETHANOL
EC number: 203-268-9
CAS number: 105-08-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 28.05.2015
Registered tonnage band: 1000+T

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]

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), oral route with the registered substance;**

2. **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 of the REACH Regulation. In order 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 are required to submit the requested information in an updated registration dossier by **23 December 2019**. You shall also update the chemical safety report, where relevant.

[1] No testing for endpoints listed in Annexes IX or X of the REACH Regulation may be started or performed at this moment: Only after a decision has been adopted pursuant to Article 51 of the REACH Regulation it becomes legally effective and binding for you. ECHA will take the decision either after the date it has become clear that Member State competent authorities have not made any proposals for amendment to the draft decision or, where proposals for amendment have been made, after the date the ECHA Member State Committee reached unanimous agreement on the draft decision.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. 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, shall 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[2] by Claudio Carlon, Head of Unit, Evaluation E2

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of 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 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 contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material.

You have sought to adapt this information requirement of pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on a second species according to Annex X, Section 8.7.2., column 2. You provided the following justification for the adaptation:

> *"For reproductive toxicity tests under Sections 8.7 of Annexes IX and X of the REACH Regulation (Regulation), Column 2 provides that studies do not need to be conducted if the substance is of low toxicological activity (i.e., no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure.*

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex X, Section 8.7.2., column 2, because low toxicological activity has not been demonstrated. More specifically, evidence of toxicity was observed in several studies; e.g.:

- 90-day oral toxicity study (OECD 408): mortality, abnormalities in the urine and faeces, and increase in urinary protein was observed in animals dosed with 861 mg/kg bw/d (males) and 1752 mg/kg bw/d (females);
- OECD TG 421 screening study: mortality, bloody or brown/red discolored urine, , dehydration, decreased sperm motility, decreased postnatal pup survival at 1360 mg/kg bw/d;
- Pre-natal developmental toxicity study (OECD TG 414): significant increase in the absolute and relative adrenal weights of the dams at 1000 mg/kg bw/d.

Moreover, it has not been proven from toxicokinetic data that no systemic absorption occurs. In addition, you did not demonstrate that there is no or no significant human exposure.

Therefore, your adaptation cannot be accepted.

Furthermore, you provided the following justification for not providing the standard information required:

> *"For substances manufactured or imported in quantities of 100 tonnes or more (Annex IX) or 1000 tonnes or more (Annex X), Column 2 requires the registrant to make a decision on the need to perform another pre-natal developmental study on a second species based upon the results of the first study and all other relevant data.*
>
> *Following a careful review of the prenatal developmental toxicity study in the first species and all other relevant data for 1,4-cyclohexane dimethanol (CHDM) in accordance with the specific rules set forth in Column 2, the Lead Registrant has determined that performing another pre-natal developmental study in a second species is not warranted. Specifically, the data from an OECD 422 study, wherein CHDM was administered to rats for 13 weeks in drinking water at concentrations up to 12.5 mg/ml, indicated that at exposure concentrations of up to 861 and 1360 mg/kg/day for male and female rats, respectively, there was no evidence of developmental toxicity. Moreover, an OECD 422 study also was done in rats that were treated with a compound (1,4-cyclohexane dimethanol; DMCD) that is metabolized in vivo to produce CHDM, and the data indicate that no evidence of developmental toxicity were observed following treatment with up to 15 mg/g of diet, which corresponded to doses of 888 and 1124 mg/kg/day for males and females, respectively.*
>
> *Based on these results, the LR concludes that there is no data suggesting that developmental toxicity is a concern and that a pre-natal developmental toxicity study using a second species is not warranted."*

ECHA notes that your conclusion that "*performing another pre-natal developmental study in a second species is not warranted*" is based on information on rats only. More specifically, you provided a pre-natal developmental toxicity study in rats according to OECD 414 and an OECD TG 421 screening study in rats both performed with the registered substance. You also provided an OECD TG 421 screening study in rats performed with an analogues substance without an appropriate read-across justification.

ECHA would like to point out that for dossiers registered at ≥1000 tonnes per year, a pre-natal developmental toxicity study in a second species is a standard information requirement according to Annex X, Section 8.7.2. This information requirement cannot be adapted solely on the basis that no developmental effects were seen in existing studies, which only cover the first species (rats).

Finally, you also refer to the provisions on data sharing and avoidance of unnecessary testing in your adaptation justification. However, in the absence of a justification that would meet the requirements for an adaptation in accordance with the rules set in Annex X, Section 8.7., Column 2 or Annex XI to the REACH Regulation, ECHA is held to require you to bring your registration into compliance with the relevant information requirement.

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.

The test in the first species was carried out by using rats. According to the test method EU B.31./OECD 414, the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbits as a second 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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

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) by the oral route.

Deadline to submit the requested Information

In the draft decision communicated to you the time indicated to provide the requested information was 30 months from the date of adoption of the decision. In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you requested an extension of the timeline by an additional 9 months to 39 months.

ECHA notes that you sought to justify this request based on difficulties in dosing of the substance which you experienced with a substance different from the registered substance. However, you do not base your request for an extended deadline upon a timetable provided by a CRO for the registered substance. Hence, it is not obvious from the provided documentation if such extensive problems would also be expected for the registered substance to a similar extent. However, based on the general information you provided from a CRO that it takes 10.4 months to perform a pre-natal developmental toxicity study in rabbits, ECHA decided to provide you 6 additional month (in total 12 months) to perform a pre-natal developmental toxicity study in rabbits including associated dose-range finding studies and other necessary preparations.

In conclusion, ECHA has evaluated your request and rejected an extension to 39 months. The deadline was instead extended to 36 months.

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

Pursuant to Articles 10(a)(vi) 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* R.7a, chapter R.7.6 (version 4.1, October 2015).

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 requirement

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.

In the technical dossier you have provided two study records for a OECD TG 421 screening test performed with the registered substance and an analogue substance. However, these studies do not provide the information required by Annex X, Section 8.7.3., because they do 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.

Furthermore, you have sought to adapt this information requirement. Whilst 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 XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this adaptation, as presented below
ECHA notes that an extended one-generation reproductive toxicity study with a design specific for the registered substance according to Annex X, Section 8.7.3., mainly addresses effects on "sexual function and fertility" and "postnatal developmental toxicity". Hence, ECHA has evaluated the information you provided on those elements of a one-generation reproductive toxicity study and your overall justification.

i. Information provided

You have provided the following justification for the adaptation: "*The Lead Registrant has conducted a pre-natal developmental toxicity test (OECD 414), and has completed a reproductive/developmental screen (OECD 421) and a 90-day repeat dose study with histological examination of reproductive tissues (OECD 408). The results of these studies have not suggested any evidence of toxicity to reproductive organs or reproduction and development in general. Thus, it is unlikely that a 2-generation study would result in any relevant results, especially when the REACH mandate of testing only when absolutely necessary is applied (Article 25(1)).*"
You have provided information from the following sources that addresses information on "sexual function and fertility":

- The screening study (OECD TG 421) provides information on histopathological changes in reproductive organs, male and female reproductive performance such as gonadal function, mating behaviour, conception and parturition. ECHA notes that the study provided was performed with 56 days pre-mating exposure. ECHA also notes that this study was performed according to the test method with 12 animals per sex and dose.

- The sub-chronic toxicity study (OECD TG 408) provides information on histopathological changes of reproductive organs. ECHA notes that this study was performed according to the test method by using 10 animals per sex and dose.

- The pre-natal developmental toxicity study (OECD TG 414) provides some information on maintenance of the pregnancy for the duration of exposure, which was gestation days 3 to 19 for the study provided in your dossier.

You have provided information from the following sources that address information on "postnatal developmental toxicity":

- The screening study (OECD TG 421) provides limited information on peri- and postnatal toxicity. More specifically, this study provided information on body weight and mortality of the offspring until termination of the study, which was post-natal day 4.

- The pre-natal developmental toxicity study (OECD TG 414) provides information on pre-natal developmental toxicity but no information on peri- or postnatal effects.

ii. ECHA's evaluation of the information provided

ECHA notes that the information you submitted on "sexual function and fertility" covers the main elements of the information an extended one-generation reproductive toxicity study performed for your substance would provide. However, in the OECD TG 421 screening study and the sub-chronic toxicity study, 12 and 10 animals per sex and dose, respectively, were used, whereas 20 animals per sex and dose are used in the extended one-generation reproductive toxicity study. Hence, your information provided a lower sensitivity than the extended one-generation reproductive toxicity study to detect effects on sexual function and fertility. ECHA further notes that in the OECD TG 421 screening study the following relevant findings have been reported: "*high-dose group males had decreased sperm motility although this did not affect reproductive performance. Reduced postnatal pup survival and lower mean pup body weights were observed in litters from high-dose group dams although these abnormalities were generally observed in dams that also exhibited systemic effects*." In light of those findings, ECHA considers that the sensitivity of the OECD TG 421 screening study does not allow an assumption/conclusion of whether or not the substance has a particular dangerous property with respect to sexual function and fertility.

Furthermore, ECHA notes that you did not provide sufficient information on "postnatal developmental toxicity" including sexual maturation and histopathological integrity of the reproductive organs at adulthood. Hence, it is not possible to assume/conclude whether or not the substance has a particular dangerous property with respect to postnatal developmental toxicity.
In addition, ECHA notes that the justification you provided "*The results of these studies have not suggested any evidence of toxicity to reproductive organs or reproduction and development in general"* does not consider the lower sensitivity of the information provided to detect effects on sexual function and fertility and the findings of the OECD TG 421 screening study on sperm parameters and offspring and is not based on sufficient information on post-natal developmental toxicity. Hence, ECHA concludes that your assumption "*Thus, it is unlikely that a 2-generation study would result in any relevant results, especially when the REACH mandate of testing only when absolutely necessary is applied (Article 25(1)"* is not sufficiently justified and supported by evidence.

iii. ECHA's conclusion

ECHA concludes that the evidence you provided to adapt the standard information requirement for an extended one-generation reproductive toxicity study based on Annex XI, Section 1.2. does not sufficiently cover the parameters and observations, which are addressed in the extended one-generation reproductive toxicity study, which is the standard information requirement. Furthermore, you have not provided a justification on how the studies, specified above, when taken as part of the Weight of Evidence approach, enable characterisation of the effects on fertility and sexual function. Therefore, the information which you have provided is not sufficient to assume/conclude that the substance does not have hazardous properties with regard to sexual function, fertility and development.

Therefore, your adaptation of the information requirement is rejected.

b) 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* R.7a, chapter R.7.6 (version 4.1, October 2015).

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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid, 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 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 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* R.7a, chapter R.7.6 (version 4.1, October 2015). 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

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 4 May 2016.

On 23 June 2016 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 30 July 2016 ECHA received comments from the Registrant on the draft decision.

The ECHA Secretariat considered the Registrant's comments.
On basis of this information, the deadline in the Decision was amended. The Statement of Reasons (Appendix 1) was changed accordingly.

On 3 November 2016 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

As no proposal for amendment was submitted, ECHA took the decision pursuant 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 request(s) in this decision, or to fulfil otherwise the information requirement(s) 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 test(s) 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 test(s) 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 test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.