EUROPEAN CHEMICALS AGENCY

Helsinki, 21 March 2017

Addressee: [redacted]

Decision number: CCH-D-2114356723-46-01/F
Substance name: PROPYLIDYNETRIMETHANOL
EC number: 201-074-9
CAS number: 77-99-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 17.05.2016
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:

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 **28 March 2019**. You also have to update the chemical safety report, where relevant.

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.

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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

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

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

The basic test design of an extended one-generation reproductive toxicity study (test method 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 provided

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

You have sought to adapt this information requirement. While you have not explicitly claimed a specific 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.

You have provided the following justification for the weight of evidence adaptation:
"*There is no two generation reproductive toxicity study available. In a combined repeat dose and reproductive/developmental toxicity study according to OECD TG 422 and GLP the NOAEL (general toxicity) is 200 mg/kg bw based on pathological changes in liver and kidneys whereas reproductive organs were not affected by the treatment. In addition, there were no effects on fertility index, copulation index, and viability index at PN day 4 as indication of toxicity in the offspring up to and including the highest test dose of 800 mg/kg bw/day (MHLW1994). In a repeat dose toxicity study over a period of 90 days reproductive organs were not affected by treatment up to and including the highest concentration (de Knecht van Eekelen 1969) thus confirming the results of the combined repeat dose and reproductive / developmental toxicity study. Therefore based on the available data there is no reason to expect a specific reproductive toxicity of TMP. As confirmed by recent literature (Mangelsdorf et al 2003, Ulbrich & Palmer 1995, Janer et al 2007a, Dent 2007, Sanbuissho et al. 2009) in rodents, histopathological examination of reproductive tissues in repeated dose toxicity studies is of high value and high sensitivity for evaluation of reproductive toxicity in males and females.*

Histopathological changes on the reproductive organs in repeated dose toxicity studies are indicative for effects on fertility. With this respect repeated dose toxicity studies should be considered sensitive and sufficient information is obtained to evaluate toxicity on fertility if histological examination of the reproductive organs is performed. Based on the considerations above no further testing is required for the fertility assessment as TMP has not shown specific effects on reproductive organs in male and female rats in the lower effect dose ranges even at dose levels where general toxicity was noted and there was no evidence of a specific reproductive toxicity of TMP in a combined repeated dose and reproductive/developmental screening assay."

To support your weight of evidence adaptation you have provided the following sources of individual information:

1. Key study: Trimethylolpropane CAS-No. 77-99-6: Repeat dose and reproductive /Developmental Toxicity Study, rat gavage, oral (OECD TG 422; GLP) with the registered substance, MHLW, 1994 (Toxicity Reports of Environmental Chemicals 1, 55-58, 59-68, 519-524), reliability 1;
2. Key study: Sub-chronic (90-day) toxicity study with trimethylolpropane (TMP 99) in albino rats, oral diet (no test guideline indicated, no GLP) with the registered substance (de Knecht-van Eekelen,1969; [redacted], reliability 2;
3. Literature references with regard to the value of histopathological examination of reproductive tissues in repeated dose toxicity studies for the evaluation of reproductive toxicity in males and females (Mangelsdorf *et al* 2003, Ulbrich & Palmer 1995, Janer *et al* 2007a, Dent 2007, Sanbuissho *et al* 2009).

b) ECHA's evaluation and conclusion of the provided Weight of Evidence adaptation

Criteria applied

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property with respect to the information requirement in question.

Your adaptation based on Annex XI, Section 1.2. needs to address the properties of the registered substance by covering the relevant elements investigated in an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443) as requested in this decision. ECHA considers that this study type provides relevant information on two aspects, namely on sexual function and fertility in parental (P) and filial (F1) generations (further referred to as "sexual function and fertility") and on developmental toxicity observable peri- and postnatally in the F1 generation (further referred to as "post-natal developmental toxicity").

More explicitly, the relevant elements for sexual function and fertility are, in particular, functional fertility in the parental generation after 10 weeks pre-mating exposure to cover the spermatogenesis and folliculogenesis before mating, sperm parameter analysis, oestrus cyclicity and histopathological examinations of reproductive organs in both P and F1 generations, and ability to support intrauterine and postnatal development of offspring until weaning.

Furthermore, the relevant elements for post-natal developmental toxicity are, in particular, peri- and post-natal investigations of the F1 generation up to adulthood (such as growth, survival/mortality, external malformations, sexual maturation and certain investigations related to hormonal modes of action like anogenital distance, nipple retention, and thyroid hormone measurements).

Sexual function and fertility

With respect to the aspect of sexual function and fertility of P and F1 generations, you have provided reliable information on histopathological changes in major reproductive organs (OECD TG 422 screening study). You have also provided reliable information on male and female reproductive performance such as gonadal function, mating behaviour, conception, development of the conceptus and parturition (OECD TG 422 screening study). However, ECHA notes that the statistical power of OECD TG 422 study is lower than that of the extended one-generation reproductive toxicity study, and certain investigations are not included, such as functional fertility after 10 weeks premating exposure to cover spermatogenesis and folliculogenesis before mating, histopathology of the reproductive organs in F1 animals in adulthood, sexual maturation, oestrous cycle measurements in F1 animals, and investigations related to hormonal modes of action. Furthermore, you did not provide information on sperm parameters in P and F1 generations. You claim that the available information from the sub-chronic toxicity (90-days) study in the rat confirms that the reproductive organs are not affected after repeated exposure to the registered substance. The study has been conducted prior to approval of current guidelines and GLP. With regard to the examination of the reproductive tissues/organs this means that there is limited evidence from these studies that such reproductive organs/tissues are not affected. In comparison to current methods the past histopathological methods used fixation methods which are no longer recommended and furthermore lack the sensitivity of the modern methods.

The literature references cited in your adaptation justification do not contain information on the registered substance, nor do you explain why and how the information on the various aspects of reproduction provided by an extended one-generation reproductive toxicity could be replaced or predicted for your substance by histopathological examinations only.

Thus, the information you provided does not support your conclusion that the substance does not have a dangerous property with respect to sexual function and fertility.

Post-natal developmental toxicity

ECHA notes that your adaptation justification does not address the post-natal developmental toxicity. The provided information does also not cover the key elements which need to be investigated in this regard. The OECD TG 422 screening study investigates developmental toxicity only until postnatal day 4. The studies according to OECD TG 414 in the rat and the rabbit (also available in the registration dossier but not mentioned in your adaptation justification) provide information only on pre-natal developmental toxicity. ECHA notes that in the PNDT study in the rat malformations at 1000 mg/kg bw/day (related to eye and eyehole) but also dysplasia of limb bones was observed. In respect of the eye malformations, these especially seem to be substance specific as they are not commonly associated with secondary toxicity (maternal toxicity) in rats.

There are a few cases observed also at 300 mg/kg bw/day supporting the dose-dependent nature of the eye and some other malformations, however, as they are associated with significant maternal toxicity the toxicological significance is not clear. Eye malformations were not reported in the OECD TG 422 study, but those may have not been specifically investigated in that study. In the rabbit, malformations or other pre-natal developmental effects were not observed.

These data do not allow a conclusion to be drawn that developmental effects are not observed at all in studies conducted with the registered substance, and in particular do not cover the peri-and postnatal developmental toxicity. Thus, the information you provided does not support the conclusion that the substance does not have a hazardous property with respect to postnatal developmental toxicity.

Conclusion

Hence, from the information you provided to support your adaptation, considered individually or together, it cannot be assumed or concluded that the substance does not have a particular dangerous (hazardous) property with respect to the information requirement for Annex X, Section 8.7.3.

Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2 of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

c) 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.

d) Outcome

In the comments to the draft decision you have accepted to perform an extended one-generation reproductive toxicity study according to OECD 443 with the registered substance in the design described.
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 7 October 2016.

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.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request(s).

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

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

Appendix 3: Further information, observations and technical guidance

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

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

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

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

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