EUROPEAN CHEMICALS AGENCY

Helsinki, 26 August 2019

Addressee: [redacted]

Decision number: CCH-D-2114482123-55-01/F
Substance name: Propyl acetate
EC number: 203-686-1
CAS number: 109-60-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 08/12/2017
Registered tonnage band: Over 1000

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:

- **At least two weeks premating exposure duration for the parental (P0) generation;**
- **Dose level setting shall aim to induce toxicity at the highest dose level;**
- **Cohort 1A (Reproductive toxicity);**
- **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation.**

You have to submit the requested information in an updated registration dossier by ***7 March 2022***. 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.

The scope of this compliance check decision is limited to the standard information requirements of Annex X, Section 8.7.3. to the REACH Regulation.

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, Hazard Assessment

[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. 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 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 decision CCH-D-2114340407-54-01/F (enclosed), ECHA concluded, after evaluating the relevant information in your registration dossier, that an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. In that compliance check decision, ECHA first concluded on your read-across adaptation as *"currently the adaptation does not comply with the general rules of adaptation as set out in Annex XI, 1.5."* and subsequently that *"the information provided on this endpoint [extended one-generation reproductive toxicity study] for the registered substance in the technical dossier does not meet the information requirement."*

In the same decision on the same ground that *"your adaptation of the information requirement cannot be accepted"*, ECHA also required you to provide a sub-chronic toxicity study (90-day), by inhalation route with the registered substance. The decision indicated that the 90-day study shall be conducted before the extended one generation reproductive toxicity study and the results from the 90-day study shall be used, among other relevant information, to decide on the study design of the extended one generation reproductive toxicity study.

ECHA notes that you have submitted the requested sub-chronic toxicity study (90-day), by inhalation route with the registered substance, as well as an updated testing proposal to fulfil the information requirement for an Extended one-generation reproductive toxicity study (test method OECD TG 443), together with your views on the study design for this study.

ECHA also notes that your adaptation justification for the information requirement of Section 8.7.3., Annex X is based on the same documentation as analysed in decision CCH-D-2114340407-54-01/F: *"according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for a two-generation study (OECD TG 416) with the analogue substances propan-1-ol and n-butyl acetate (EC numbers 200-746-9 and 204-658-1 respectively)"*. Therefore, your adaptation justification is rejected for the same reasons set

out in that decision (enclosed), which remain valid.

Consequently there is an information gap and it is necessary to provide information for this endpoint. 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.

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 if 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). In this specific case, animals of Cohort 1B are mated to produce the F2 generation (see below) and, thus, the premating exposure duration will be 10 weeks for these Cohort 1B animals and the fertility parameters will be covered allowing an evaluation of the full spectrum of effects on fertility in these animals. Consequently, shorter premating exposure duration for parental (P) animals may be considered. However, the premating period shall not be shorter than two weeks and must be sufficiently long to reach a steady-state in reproductive organs, as advised in the ECHA Guidance. The consideration should take into account whether the findings from P animals after a longer premating exposure duration would provide important information for interpretation of the findings in F1 animals, e.g. when considering the potential developmental origin of such findings as explained in ECHA guidance.

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.

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. The extension is *inter alia* required, if the use of the registered substance is leading to significant exposure of consumers or professionals (column 2, first paragraph, lit. (a) of section 8.7.3., Annex X) and if there are indications of one or more relevant modes of action related to endocrine disruption from available *in vivo* studies or non-animal approaches (column 2, first paragraph, lit. (b), third indent of section 8.7.3., Annex X).

The use of the registered substance in the joint submission is leading to significant exposure of consumers and professionals because the registered substance is used by consumers and professionals e.g in coatings and paints, thinners, paint removes, inks, adhesives and sealants (PROCs 1, 2, 3, 4, 5, 8a, 8b, 9, 10, 11, 13, 19).

In addition there are indications for endocrine-disrupting modes of action because the repeated dose toxicity study ([redacted] 2017; according to OECD TG 413) you submitted, shows biologically significant changes in the reproductive organ weights. You conducted the OECD TG 413 study with the registered substance (according to GLP) in the rat (10 animals/ sex/ dose), by inhalation route (6h/exposure), at the following doses: 148.5 ppm, 505.2 ppm and 1528.7 ppm.

Mean terminal body weights of the females of the high dose group were statistically significantly decreased (-9%). According to the study report, this was regarded to be treatment-related "*resulting secondarily in weight changes of different organs*". However, the absolute uterus weights were decreased in the mid- and top-dose group animals (-34% and -39%), respectively; being statistically significant at the high dose) which cannot be explained by the slight reduction in body weight.

In your comments you disagree with ECHA that Cohort 1B must be extended to include mating of the animals and production of the F2 generation.

With your comments you provided an overview of historical control data (1/1/2012 - 10/11/2018) of uterus weights. You claimed that this supports demonstrating that the values obtained (in mg – and which were not reported in your dossier) were falling within the historical control ranges. However you have not clarified the significant reduction in the top dose (and remarkable reduction in the mid-dose) groups in relation to the concurrent control group.

In addition in your comments you refer to a metabolome analysis for which you did not provide the study report. In general ECHA does not consider that such analysis would allow you to conclude "*that there is no indication for an endocrine disrupting mode of action*".

Finally, you refer to a recent pre-natal developmental toxicity study with n-Propyl acetate which "*caused neither evidence of maternal nor developmental toxicity*", and you conclude that "*there were also no effects observed that could serve as indication for endocrine-disrupting modes of action*". ECHA notes that a pre-natal developmental toxicity study does not remove the concern stemming from the sub-chronic toxicity study (90-day).

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because the uses of the registered substance is leading to significant exposure of professionals and consumers and because there are indications of modes of action related to endocrine disruption from the available repeated dose toxicity study for the registered substance.

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) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is an organic liquid, with a vapour pressure of 33 hPa at 20 °C and boiling point of 101°C, 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:

- At least two weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation.

While the specifications for the study design are given above, you shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the premating exposure duration and dose level selection, 2) reasons for why or why not Cohort 1B was extended, 3) termination time for F2 generation, and 4) reasons for why or why not Cohorts 2A/2B and/or Cohort 3 were included.

Notes for your consideration

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 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.

Extension of deadline

In the draft decision communicated to you, the time indicated to provide the requested information was 24 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline to 36 months, claiming that 24 months is too short (i) to conduct an appropriate range-finder and the definite study and (ii) to update the dossier. You referred to a letter to support your claim

ECHA reminds you that the deadline applies only to testing for endpoints listed in Annexes IX or X which may not be started before the decision is adopted. You are responsible to start any dose range-finding study at any time. Furthermore ECHA notes that the letter you referred to was not provided as part of your comments.
Therefore, ECHA has only partially granted the request and set the deadline to 30 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 01 October 2018.

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, did not amend the request and amended the deadline.

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. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for the start of substance evaluation in 2019.

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

3. 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.

4. 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.