EUROPEAN CHEMICALS AGENCY

Helsinki, 19 February 2020

Addressees
Registrants of [redacted] listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of a decision
11/03/2019

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Propylidynetrimethyl trimethacrylate
EC number: 221-950-4
CAS number: 3290-92-4

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format TPE-D-XXXXXXXXXX-XX-XX/F)]

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***27 May 2022***.

A. Requirements applicable to all the Registrants subject to Annex IX of REACH

1. Extended one-generation reproductive toxicity study, also requested under Annex X (triggered by Annex IX, section 8.7.3) – see request B.1 for details.

B. Requirements applicable to all the Registrants subject to Annex X of REACH

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route specified as follows:

   - **At least two weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic 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 which shall be followed to weaning; and**
   - **Cohorts 2A and 2B (Developmental neurotoxicity).**

You must report the study performed according to the above specifications. Any expansions of the study design must be scientifically justified.

How to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.

To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annexes VII to IX of REACH, if you have registered a substance at 100-1000 tpa;
- you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

The Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

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.

Approved[1] under the authority of Christel Schilliger-Musset, Director of 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 A: Reasons for the requirement applicable to all the Registrants subject to Annex IX of REACH

This decision is based on the examination of the testing proposals you submitted.

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

The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement under Annex IX to REACH, if the available repeated dose toxicity studies indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. Furthermore, column 2 defines when the study design needs to be expanded.

ECHA considers that adverse effects on reproductive parameters or other concerns in relation with reproductive toxicity are observed in the available study, Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test (OECD TG 422; [redacted], 2010). That study showed reduced litter size as a consequence of reduced implantation sites. A statistically significant reduction in the number of implantation sites in the high dose females (900 mg/kg bw/day) was observed compared to the control group. Average values were slightly outside the historical control data range, giving more importance to the finding. The number of *corpora lutea* present for each animal was not determined in this study. Therefore ECHA could not assess if this finding was a reduction in the number of eggs available for fertilization or indicative of a treatment-related pre-implantation loss. Therefore as a worst-case scenario, ECHA considers the findings as a substance related adverse effect.

In the same study, changes in gestation length were observed, suggesting a minor shift towards a longer gestation length for females: *"At 900 mg/kg bw/day group, no females had a 22-day gestation length compared with 3, 5 and 4 females at 0, 100 and 300 mg/kg bw/day, respectively. The incidence of females with a 23.5 day gestation length was marginally outside the Historical control data range."* This finding is considered to be an indication of an endocrine-disrupting mode of action of the Substance.

Therefore the condition of Annex IX, Section 8.7.3. column 1 is fulfilled and the EOGRTS is an information requirement for your registration.

For the specifications of the study design, see the request B.1.

Appendix B: Reasons for the requirement applicable to all the Registrants subject to Annex X of REACH

This decision is based on the examination of the testing proposals you submitted.

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

Examination of the testing proposal

The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement under Annex X to REACH. Furthermore, column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have submitted a testing proposal for an EOGRTS according to OECD TG 443 by the oral route in rats, including the extension of Cohort 1B, the inclusion of Cohorts 2A/2B and of Cohort 3. You have provided the following justification according to the criteria described in Column 2 of Section 8.7.3, Annex X:

- Regarding the triggering of the extension of Cohort 1B: Consumer and professional uses related to the Substance are reported, and "*No Endocrine Disrupting effects were observed in the previous studies. A statistically significant reduction in the mean number of implantation sites, associated with low litter size were observed at the high dose (900 mg/kg bw/d) in the OECD 422 study.*"
- Regarding the triggering of Cohort 2: In the 90-days repeated dose study (OECD TG 408; Braun, 2015) "*reductions were seen in the mean locomotor activity of the males treated with 1000 mg/kg bw/day and were considered to be test item-related*".
- Regarding the triggering of Cohort 3*:* you report that an increase in white cell counts related to the Substance was observed in the male rats treated with 1000 mg/kg/day in the 90-day repeated toxicity study: "*The mean absolute leukocyte count was significantly elevated ($p<0.05$); this aberration was almost exclusively ascribed to a marked increase in absolute lymphocytes ($p<0.05$), although the mean absolute monocyte subpopulation was also significantly elevated ($p<0.01$) when compared to the control males.*"

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.

The proposed study design requires modification to fulfil the information requirement. The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

ECHA considers that a minimum of 2-week premating exposure duration for P0 animals is required because the full spectrum of parameters on sexual function and fertility will be covered in the F1 animals.

In order to be compliant and not to be rejected due to too low dose levels, the study must include a highest dose level which must aim (i) at inducing systemic toxicity, but not death or severe suffering of the animals, and (ii) at allowing comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no existing 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.

You must provide a justification with your study report demonstrating that the dose level selection meets the conditions described above.

Extension of Cohort 1B

If the Column 2 conditions of Section 8.7.3., Annex X are met, Cohort 1B must be extended by mating the Cohort 1B animals to produce the F2 generation.

You proposed to include an extension of Cohort 1B and ECHA agrees that the criteria to extend the Cohort 1B are met, because:

- The use of the Substance reported in the joint submission leads to significant exposure of consumers and professionals: the Substance is used by professionals in adhesives/ inks/ coatings formulations (PROCs 8a, 8b, 10, 11, 28) and consumers as coatings, thinners and paint removers.

- In your justification you consider that no endocrine disrupting effects were observed in the available study, Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test (OECD TG 422; [redacted] 2010). However, there are indications for endocrine-disrupting modes of action resulting from changes in gestation length, suggesting a minor shift towards a longer gestation length for females: *"At 900 mg/kg bw/day group, no females had a 22-day gestation length compared with 3, 5 and 4 females at 0, 100 and 300 mg/kg bw/day, respectively. The incidence of females with a 23.5 day gestation length was marginally outside the Historical control data range."*

Therefore, the Cohort 1B must be extended.

The F2 generation must be followed to weaning allowing assessment of nursing and lactation of the F1 parents and postnatal development of F2 offspring. Investigations for F2 pups must be similar to those requested for F1 pups in OECD TG 443 and described in OECD GD 151. It is recommended to aim to 20 litter per dose group in order to have similar statistical power for investigations than in P0 generation.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity.

You proposed to include Cohorts 2A and 2B and ECHA agrees that the criteria to include Cohorts 2A and 2B are met, because existing information on the Substance derived from the existing 90-day sub-chronic study according to OECD TG 408 ([redacted] 2015) show evidence of significantly reduced locomotor activity in the mid- and high-dose males. Specifically in the mid-dose group, the reduction is up to 60% at the last time point, in the absence of systemic toxicity.

Therefore the developmental neurotoxicity cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity.

You proposed to include Cohort 3. However, ECHA does not agree that the criteria to include Cohort 3 are met, because existing information on the Substance derived from the available 90-day repeated dose toxicity study in the dossier (OECD TG 408; [redacted] 2015), show that although you justify the inclusion of the cohort based on an increase in white blood cells (see above), ECHA could not verify this statement as in the IUCLID dossier you merely reported: *"Although there were statistically significant differences in the haematology and clinical biochemistry parameters to the control values, only isolated parameters exceeded the lower limits of the historical control data (such as relative eosinophil count and cholesterol activity in males at 1000 mg/kg bw/day). Such differences are generally recognized as being of no toxicological relevance, and unrelated to the treatment with the test item."*

Therefore this finding cannot be considered as a trigger.

Furthermore your justification is most likely reflecting inflammation and can also not be considered as a trigger.

There is no particular concern on (developmental) immunotoxicity. Therefore, the developmental immunotoxicity Cohort 3 does not need to be included.

Species and route selection

You proposed testing by oral route in rats. ECHA agrees with your proposal.

Outcome

Under Article 40(3)(b) of REACH, you are requested to carry out the proposed test under modified conditions, as explained above, with the Substance.

Appendix C: Procedural history

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 12 March 2019.

ECHA held a third party consultation for the testing proposal from 26 April 2019 until 10 June 2019. ECHA did not receive information from third parties.

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

The decision making followed the procedure of Articles 50 and 51 of REACH, as described below:

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the requests.

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix D: Observations and technical guidance

1. This testing proposal examination decision does not prevent ECHA from initiating compliance checks at a later stage on the registrations present.

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(s).

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries'[2].

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/impurity is known to have or could have on the test results for the endpoint to be assessed. For example, if a constituent/impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/impurity.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[3].

[2] https://echa.europa.eu/practical-guides
[3] https://echa.europa.eu/manuals

5. List of references of the ECHA Guidance and other guidance/ reference documents[4]

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[5]

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents
Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

[4] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[5] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

Appendix E: Addressees of this decision and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fulfilled
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.