EUROPEAN CHEMICALS AGENCY

Helsinki, 10 December 2018

Addressee: [redacted]

Decision number: TPE-D-2114453635-45-01/F
Substance name: Reaction products of pentaerythritol, propoxylated and 1-chloro-2,3-epoxypropane with hydrogen sulfide
EC number: 701-196-7
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 20.12.2017
Registered tonnage band: 100-1000

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 accepted and you are requested to carry out:

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route using the registered substance.**

Your testing proposal is modified and you are requested to carry out:

2. **Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: 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 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;**
   - **Cohorts 2A and 2B (Developmental neurotoxicity)**

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 ***17 June 2021***. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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.

Authorised[1] by Kevin Pollard, Head of Unit, Evaluation, E1

[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 proposals submitted by you.

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2., of the REACH Regulation. 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 a pre-natal developmental toxicity study according to OECD TG 414.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal develomental toxicity). ECHA notes that 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.

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation. ECHA notes that you have not identified the test material to be tested. However ECHA considers that the study shall be performed with the registered substance.

You did not specify the species to be used for testing. According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent. On the basis of this default consideration, ECHA considers testing should be performed with rats or rabbits as a first species.

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) R.7a, chapter 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)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rat or rabbit), oral route (test method: OECD TG 414).

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, section R.7.6.2.3.2.

2. Extended one-generation reproductive toxicity study (Annex IX, 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 IX of the REACH Regulation if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. If the conditions described in column 2 of Annex IX 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 ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017).

ECHA considers that effects in the thyroid gland which reveals concerns related to reproductive toxicity are observed in the 90-day study with the registered substance ([redacted] 2012). More specifically, in this study increase in absolute and relative weight of thyroid glands in females at 1000 mg/kg bw/day, and increase in incidence of minimal or slight diffuse follicular hypertrophy/hyperplasia in thyroid glands in males at 250 mg/kg bw/day and in both sexes at 1000 mg/kg bw/day were reported. As the condition of Annex IX, Section 8.7.3., is fulfilled, an extended one-generation reproductive toxicity study is an information requirement for the registered substance pursuant to Annex IX, Section 8.7.3.

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 OECD TG 443 with inclusion of Cohort 3. In addition, you have the following justification and specification on the study design: "[...] *The extended one-generation study is proposed to contain the developmental immunotoxicity cohort (DIT) due to the thyroid effects observed in the 90-day study.* [...] *Hormones made in the thyroid gland are involved in the regulation of T-lymphocyte development and growth*".

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 have 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.

In the comments to the draft decision, you stated that relevant exposure to professionals and consumers can be excluded due to risk management measures that need to be applied by professional workers and because very small quantities of material are handled, the low incidence of use, the fast curing time, no ingestion and minimal dermal contact, the low toxicity of the material and that RCRs were less than 1. Based on this exposure information, you have deemed to meet the conditions for adaptation according to Annex XI, Sections 3.1 and 3.2, specifically 3.2.(c), and you concluded that no vertebrate testing is required.

You further noted that ECHA suggested such an adaptation during the informal communication. ECHA would like to clarify that during the informal communication ECHA indicated to you to consider the specific adaptation rules outlined in column 2 of Annexes VI to IX and/or the general rules outlined in Annex XI of the REACH Regulation. This reminder of the adaptation rules is not to be confused with a suggestion. It is your responsibility to adapt the standard information and thus avoid the proposed testing to provide the required information. For any such adaptation to comply with the respective information requirement, it needs to be scientifically justified, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation must be provided in the registration dossier.

ECHA notes that Annex XI, Section 3.1 is a general introduction to the adaptation according to Annex XI, Section 3 where testing may be omited based on exposure scenario(s) developed in the CSR. To meet this adaptation, you are required to fulfill any one of the conditions specified in Section 3.2 (a), (b), or (c) of Annex XI. In your comments, you refer to the adaptation according to Annex XI, Section 3.2 (c).

However, in your case the conditions of Annex XI, Section 3.2 (c) are not met due to the following reasons:

With regard to Annex XI, Section 3.2 (c) (i), you have not provided some relevant documentation, e.g. the measured data demonstrating that there is no releases from the article. You claim that the substance "[..] *is a liquid curing agent with unique rapid-cure characteristics for epoxy resins at ambient temperatures. GPM-800 imparts rapid cure rates (1 to 5 minutes) on systems at low temperatures and in thin films, and with exceptional color.*" and "*Fast curing time (1 to 5 minutes) where after the material becomes an inert article*". However, there could be exposure to the substance before curing and you did not demonstrate that there is no release from the article. Hence, your justification is not sufficient to fulfil the first point of the exposure based adaptation.

With regard to Annex XI, Section 3.2 (c) (ii), you have not demonstrated negligible exposure. You indicated that the package of the system for professional workers and consumers typically contains [redacted] of the registered substance. However, this information does not prove that the exposure for consumers and professionals is negligible. In addition, the exposure estimations in the provided CSR do not support this either, since the calculated RCRs are as high as [redacted] and [redacted], which do not describe negligible exposure.

With regard to Annex XI, Section 3.2 (c) (iii), you have not demonstrated that the registered substance is handled under strictly controlled conditions set out in Article 18(4) (a) to (f) during all manufacturing and production stages. The information in the CSR indicates "*Use of the substance and use of products containing the substance (with significant contact to the substance) (PROC 5), and Transfer of the substance and transfer of products containing the substance (with significant contact to the substance) (PROC*

8a)". These uses do not indicate uses under strictly controlled conditions rather they indicate potential for exposure.

For all the reasons explained above, ECHA concludes that the conditions for an exposure based adaptation under Annex XI, Section 3.1. and Section 3.2 (c) are not met.

Furthermore, you have stated that, if ECHA rejects exposure based adaptation of the current information requirement of Annex IX of REACH Regulation (according to Annex XI, Section 3.1 and 3.2 (c)) at your tonnage band 100-1000 tonnes, then you plan to reduce the import of your substance below 100 tonnes (which is relevant to Annex VIII requirements). However, ECHA notes that as you currently hold a registration for the tonnage band of 100 - 1000 tpa, you are responsible to comply with the standard information requirements of Annex IX.

ECHA considers that based on the currently available information the proposed study method according to OECD TG 443 is appropriate to fulfil the information requirement of column 1 of Section 8.7.3., Annex IX, of the REACH Regulation. However, ECHA considers that your proposed study design does not meet the conditions of column 2 of Section 8.7.3., Annex IX for the reason described below under section *"the specification of the study design"*.

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 columns 1 and 2 of Section 8.7.3., Annex IX is required. The following refers to the specifications of this required study.

The specifications for the study design

Premating exposure duration and dose-level setting

You have not included a proposal for appropriate premating exposure duration. 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 R.7.6., 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 ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7.a, Section R.7.6 (version 6.0, July 2017). In this specific case, animals of Cohort 1B are mated to produce the F2 generation 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. Thus, 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 R.7.6. 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 R.7.6.

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow 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.

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. 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 Section 8.7.3., Annex IX 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 have not included a proposal for the extension of Cohort 1B to produce F2 generation. However, the extension of Cohort 1B is met based on the criteria described in column 2 of Section 8.7.3. of Annex IX and further detailed in ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). More specifically, the use of the registered substance in the joint submission is leading to significant exposure of consumers and professionals because the registered substance uses include "*use of the substance and use of products containing the substance (with significant contact to the substance*" (PROC 5), and "*transfer of the substance and transfer of products containing the substance (with significant contact to the substance) (PROC 8a)*" by professionals, and as adhesives, sealants (PC 1: in glues, as hobby uses) by consumers.

Furthermore, there are indications for endocrine-disrupting modes of action because of the observed effects in the thyroid gland from the provided 90-day study with the registered substance ([redacted], 2012). More specifically, in this study an increase in absolute and relative weight of thyroid glands in females at 1000 mg/kg bw/day, and an increase in incidence of minimal or slight diffuse follicular hypertrophy/hyperplasia in thyroid glands in males at 250 mg/kg bw/day and in both sexes at 1000 mg/kg bw/day were reported.

In the comments to the draft decision, you have stated that the observed effects in the thyroid gland from the 90-day study do not indicate a link to endocrine disruption, but merely that the thyroid is more active. Furthermore, you mentioned your experience that a change in thyroid weight is not always accompanied by a change in T4/TSH and that effects on the thyroid are observed already after an exposure of about 4 weeks and certainly after 8 week exposure. However, you have no knowledge that thyroid weight/follicular hypertrophy/hyperplasia would occur only after a 90-day exposure duration.
You have proposed two options for way forward:

1. To perform an OECD TG 421 study as a dose range finding study and to investigate the potential link between thyroid effects (thyroid weight and histopathology) and hormonal activity of the substance (T4/THS measurements, anogenital distance, nipple retention and sex ratio). If no link is observed, then no extension of Cohort 1B would be justified.

2. If blood levels of T3/T4 and TSH measured in parent animals after extended exposure (to 90 days) will show a change, then thyroid function may be affected and the substance may have an effect on reproduction. In this case an extension of Cohort 1B would be justified.

Furthermore, you have stated that sperm parameters, oestrous cycle or reproductive organs were not affected in the 90-day study, indicating that effects of thyroid on fertility is unlikely. However, anogenital distance, nipple retention and sex ratio will be examined to investigate possible endocrine disruptive effects.

ECHA notes that in the well conducted 90-day study (OECD TG 408, GLP; [redacted], 2012) with the registered substance changes in organ weight and histopathology were shown in thyroid. No thyroid hormone measurement was performed in this study. However, histopathological analysis of thyroid gland may give more reliable information on identification on thyroid active chemicals than information based only on hormonal measurement. For the current case, you have not convincingly shown why T4 and TSH measurements would outweigh the findings on weight changes and histopathology of the thyroid. Hence, the results of the measurement of T4 and TSH will not negate the observed effects on the thyroid which are considered relevant triggers for the OECD TG 443 and the extension of Cohort 1B, Cohort 2A and 2B (see also ECHA Guidance R.7a, R.7.6. for reproductive toxicity). Thus, there is an indication of a relevant mode of action related to endocrine modes of action which is sufficient to trigger the extension of Cohort 1B.

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and to produce the F2 generation because the uses of the registered substance is leading to significant exposure of professionals and consumers and there is indication of endocrine-disruption modes of action for the registered substance from the 90-day study ([redacted] 2012).

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of Section 8.7.3., Annex IX. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

You have not included a proposal for the inclusion of Cohort 2A and 2B. However, the inclusion of Cohorts 2A and 2B are met based on the the criteria described in column 2 of Section 8.7.3. of Annex IX and further detailed in ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

ECHA notes that existing information on the registered substance itself derived from available *in vivo* study ([redacted] 2012) show evidence of specific mechanism/mode of action of the substance with an association to (developmental) neurotoxicity. More specifically, in this study an increase in absolute and relative weight of thyroid glands in females at 1000 mg/kg bw/day, and an increase incidence of minimal or slight diffuse follicular hypertrophy/hyperplasia in thyroid glands in males at 250 mg/kg bw/day and in both sexes at 1000 mg/kg bw/day were reported.

In the comments to the draft decision, you have presented your opinion that it is not clear why the neurotoxicity cohorts need to be performed if there is no effect on T4/TSH and that the observed effects, in the available 90-day study, are only adaptive. However, you have not convincingly explained why the observed thyroid effects are not linked to changed T4 and TSH levels. In addition, as explained above, the histopathological changes seen in the 90-day study are reliable to indicate thyroid activity. Therefore, the observed effects on thyroid indicate a particular concern for developmental neurotoxicity as it shows a specific mechanism/modes of action of the substance with an association to (developmental) neurotoxicity.

ECHA concludes that the developmental neurotoxicity cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified *in vivo* study on the registered substance itself.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of Section 8.7.3., Annex IX.

In your original testing proposal, ou proposed to include Cohort 3 and provided justifications stating that "*Hormones made in the thyroid gland are involved in the regulation of T-lymphocyte development and growth*". But in your comments to the draft decision, you have stated that the findings observed in the 90-day study do not support the inclusion of Cohort 3.

ECHA considers that thyroid hormones in general do have an important role in development, but information on specific mechanisms/modes of action of the substance with associatioin to (developmental) immunotoxicity is needed to include Cohort 3. However, you have not provided such information, supported by substance specific data, following the criteria described in column 2 of Section 8.7.3., of Annex IX and further detailed in ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). Furthermore, the available information on the technical dossier does not support the inclusion of Cohort 3 in the study design.

Therefore, ECHA concludes that based on the current available information the inclusion of Cohort 3 is not met.

Species and route selection

In your comments to the draft decision, you specified rat (Wistar) as the species for testing. According to the test method 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.

In your comments to the draft decision, you specified oral as 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 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.

Outcome

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 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 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;
- Cohorts 2A and 2B (Developmental neurotoxicity)

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

As stated above, the available information on the technical dossier does not support the inclusion of Cohort 3 in the study design. However, you may expand the study by including 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 IX 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.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 18 May 2016.

ECHA held a third party consultation for the testing proposals from 31 January 2018 until 19 March 2018. ECHA did not receive information from third parties.

This decision does not take into account any updates after **11 June 2018**, 30 calendar days after the end of the commenting period.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and did not amend the request(s).

Note due to an administrative error, in the orginal draft decision, the registered substance identifiers and submission number were referred to incorrectly as follows:
Substance name: Reaction products of a polyol of pentaerythritol and propylene oxide, epichlorohydrin and hydrogen sulfide
EC number: 615-735-8: CAS number: 72244-98-5: Submission number: [redacted]
Submission date: 18.05.2016

For the notification to the MSCAs, the information in the draft decision has been correctly updated as follows:
Substance name: Reaction products of pentaerythritol, propoxylated and 1-chloro-2,3-epoxypropane with hydrogen sulfide
EC number: 701-196-7: CAS number: NS: Submission number: [redacted]
Submission date: 20.12.2017

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 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.