EUROPEAN CHEMICALS AGENCY

Helsinki, 5 April 2019

Addressee: [redacted]

Decision number: TPE-D-2114465871-41-01/F
Substance name: Phenol, isopropylated, phosphate (3:1)
EC number: 273-066-3
CAS number: 68937-41-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 30/10/2017
Registered tonnage band: Over 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 modified and you are requested to carry out:

1. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, via 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; and**
   - **Cohorts 2A and 2B (Developmental neurotoxicity).**

You have to submit the requested information in an updated registration dossier by **12 October 2021**. You also have to update the chemical safety report, where relevant.

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 Ofelia Bercaru, Head of Unit, Hazard Assessment C4

[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 proposal you submitted.

1. Extended one-generation reproductive toxicity study (Annex X, 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 (EOGRTS) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X 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 an EOGRTS according to OECD TG 443 by the oral (gavage) route in rats to be performed with the registered substance. You have provided the following justification, according to the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA Guidance[2]: *"An extended one-generation reproductive toxicity - basic test design (Cohorts 1A, and 1B without extension) is proposed. Developmental toxicity has been addressed using a current OECD 414 study. The substance is proposed to have effects relating to fertility that warrant further investigation, but not developmental toxicity. Adverse effects on fertility and reproductive performance were documented during the screening studies. These effects were reversible, however, and were not apparent in the recovery phase of the study. Test article-related reductions in male fertility and copulation indices were noted. Decreased epididymal weights were considered test article-related. As these are screening studies, a further assessment of prolonged effects is proposed to adequately investigate this endpoint.*
[...] the substance does not display genotoxic effects nor is there sufficient evidence from the 90-day study or developmental toxicity study relating to resolution of steady state or endocrine disruption.
[...]the substance does not display significant effects in the developmental toxicity conducted to OECD 414.
There are multiple studies for neurotoxicity on the substance, carried out over a number of years and using a variety of dose levels. On a weight of evidence basis, it appears that a neurotoxic response is only triggered for the substance at higher dose levels which are outside of the scope of the general usage. Further investigation is not warranted. On the basis of the available data, immunotoxicity effects are also not proposed. Extension of the above cohorts is not required.
On the basis of the above, the registrant considers that there is sufficient information already available for neurotoxicity on the substance, and immunotoxicity is not considered to be a concern on the basis of the data available. It is considered therefore that the proposed basic test design will be adequate to determine the potential reproduction fertility effects noted in the 28-day screening studies."

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 provided your considerations concluding that there were no

[2] ECHA Guidance *on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017)

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 designs requires modification to fulfil the information requirement of Annex X, Section 8.7.3. of the REACH Regulation, as elaborated in details below. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. Therefore, ECHA concludes that an EOGRTS according to columns 1 and 2 of Section 8.7.3., Annex X is required. The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You did not specify the premating exposure duration.

In this specific case, 2-week premating exposure duration for P0 animals is sufficient, because the F1 animals of Cohort 1B are mated to produce the F2 generation and, thus, the premating exposure duration will be 10 weeks for these animals. Consequently the fertility parameters will be covered allowing an evaluation of the full spectrum of effects on fertility in these animals.

Therefore, the requested premating exposure duration is at least two weeks.

ECHA emphasises that 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 relevant data to be used for dose-level setting, it is recommended that a range-finding study (or range finding studies) is performed and that its results 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

You proposed testing by oral (gavage) route in rats. ECHA agrees with the proposed species (rat) and concludes that gavage-dosing seems appropriate based on previous oral studies.

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. This extension provides information also on the sexual function and fertility of the F1 animals.

You proposed not to include an extension of Cohort 1B and provided justifications following the criteria of ECHA Guidance[3].

ECHA notes that the criteria to extend the Cohort 1B are met, because:

- The use of the registered substance in the joint submission is leading to significant exposure of consumers and professionals. The registered substance is used by professionals in many applications (among which sealants and adhesives, coatings and paints, within photochemicals, indoor and outdoor use of fire resistant plastics [...] or foams [...], ... application of lubricant to work pieces [...] by dipping, brushing or spraying, ..., according to the PROCs 4, 8a, 8b, 9, 10, 11, 13, 19), and by consumers as sealants and adhesives, in coatings and paints, within photochemicals, in fire resistant

plastics and related products containing the substance, indoor and outdoor functional fluids in machines, vehicles etc. containing the substance.

- In addition, there are indications of one or more modes of action related to endocrine disruption because:
  (i) In oral repeated dose studies (OECD TG 422: [redacted] 2004; OECD TG 408: [redacted] 2015; OECD TG 421: [redacted], 2005) consistent adverse effects on adrenal gland such as increased organ weight and microscopic findings e.g. diffuse vacuolation of the adrenal cortex have been reported. These findings are further supported by the existing harmonised classification of the registered substance for STOT RE 2 (H373: May cause damage to adrenal gland after oral exposure).

  (ii) Furthermore, as also mentioned in your testing proposal, substance-related decrease of the epididymides weight was recorded in the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422; [redacted] 2004). Statistically significant decrease of the mean absolute and relative (to final body weight) right epididymis weights and lower, but statistically not significantly decreased left epididymis weights were reported in the 400 mg/kg/day group. Female fertility and conception indices were also affected: female fertility indices were 100.0%, 91.7%, 75.0% and 50.0% in the control, 25, 100 and 400 mg/kg/day groups, respectively, and female conception indices were 100.0%, 100.0%, 81.8% and 50.0% in these same respective dose groups, reaching statistical significance at the high dose level.

  (iii) Female reproductive organs and/or parameters have been affected in the sub-chronic repeated dose toxicity study as well (OECD TG 408; [redacted] 2015): most females dosed with the test article had interstitial cell vacuolation in the ovaries and fewer females had increased corpus luteum in the ovaries at 100 and 325 mg/kg/day (mid and high dose). The vacuolation was associated with slight increases in ovary weights at all dose levels.

  (iv) Finally, in a Reproduction/Developmental Toxicity Screening Test according to OECD TG 421 ([redacted] 2005) investigating four different mixtures of isopropyl phenol phosphates at a single dose level (400 mg/kg bw/day), effects on female reproductive organs and/or parameter were reported for all tested mixture, such as vacuolation of interstitial cells of the ovaries. Additionally, adverse effect on fertility and reproductive performance was seen in one of the tested isopropyl phenol phosphate mixture group (Reofos 65) for which fertility and fecundity indices were statistically lower than controls (50% vs. 100%).

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and to produce the F2 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. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.
You proposed not to include Cohorts 2A and 2B and provided a justification following the criteria of ECHA Guidance[3].

ECHA notes that existing information on the registered substance itself derived from available *in vivo* studies show evidence of neurotoxicity. More specifically, as an organophosphorus compound, the substance has been attributed to inhibit cholinesterase

(ChE). This has been confirmed in a neurotoxicity study in rats (European Chemicals Bureau (2000a)) showing decrease in serum ChE and significant inhibition of ChE and Neuropathy Target Esterase (NTE) in brain. Furthermore, numerous neurotoxicity studies in hens with various length (17 studies are available in the technical dossier), with the registered substance show consistent neurotoxicity findings such as ataxia in correlation with degenerative changes of the nervous system.

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* studies on the registered substance.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity. You proposed not to include Cohort 3 and provided an acceptable justification.

ECHA agrees that the criteria to include Cohort 3 are not met and therefore the developmental immunotoxicity Cohort 3 needs not to be conducted.

In your comments to the draft decision you agreed to conduct the study as requested by ECHA.

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, as specified above.

Notes for your consideration

No triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified.However, you may expand the study by including the extension of Cohort 3 if 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[3]. 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 the 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, based on the expert opinion of the selected laboratory indicating that *"from preparation of the first draft protocol to report finalisation, would be between 30 to 36 month"*. You have provided some documentary evidence from the selected test laboratory on the above mentioned.

ECHA considered your request and the provided evidence. As you have not provided a substance-related justification as to why more time is required, ECHA has partially granted you the request and set the deadline to 30 months.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 30 October 2017.

ECHA held a third party consultation for the testing proposals from 26 March 2018 until 11 May 2018. ECHA did not receive information from third parties.

This decision does not take into account any updates after **31 October 2018**, 30 calendar days after the end of the commenting period.

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 and amended the deadline.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) 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.