ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 27 September 2019

Addressee: [redacted]

Decision number: TPE-D-2114484215-48-01/F
Substance name: Zinc O,O,O',O'-tetrabutyl bis(phosphorodithioate)
EC number: 230-257-6
CAS number: 6990-43-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 06/03/2019
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 proposals are accepted and you are requested to carry out:

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats using the registered substance.**
2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rats or rabbits), oral route using the registered substance.**

The testing material used for performing the required studies shall be selected and reported in accordance with the specifications prescribed in Appendix 3 of this decision.

You are required to submit the requested information in an updated registration dossier by **4 April 2022**. You shall also update the chemical safety report, where relevant. The deadline 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 specifications regarding the testing material are provided in Appendix 3.

This decision does not address the information requirement of the Extended one-generation reproductive toxicity study according to Annex IX, Section 8.7.3. of the REACH Regulation. The results of the Sub-chronic toxicity study (90-day) will be used, among other relevant information, to decide on the study design of the Extended one generation reproductive toxicity study. Therefore, your testing proposal for Extended one-generation reproductive toxicity study will be addressed after having received the results of the Sub-chronic toxicity study (90-day).

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

The decision of ECHA is based on the examination of the testing proposals submitted by you, for the registered substance: Zinc O,O,O',O'-tetrabutyl bis(phosphorodithioate) (CAS No 6990-43-8, EC No: 230-257-6) hereafter referred to as "registered substance".

In the original dossier you have proposed to test the analogue substance phosphorodithioic acid, mixed O,O-bis(iso-Bu and pentyl) esters, zinc salts (CAS No 68457-79-4, EC no 270-608-0), to fulfil the following standard information requirements, by using a grouping and read-across approach according to Annex XI, Section 1.5. of the REACH Regulation, as proposed for the "ZDDP category":

- Repeated-dose oral toxicity study (Annex IX, Section 8.6.2)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

ECHA notes that in your updated dossier (submission number [redacted]) you have modified your testing strategy and proposed testing for the above mentioned information requirements with the registered substance.

In the updated dossier you have considered that the registered substance can be grouped with 12 other substances in a category ("ZDDP category") for the purpose of a read-across approach. You have provided the justification documents "[redacted] *and* "[redacted]. These documents outline your testing strategy, including the proposal to test 4 category members, including the substance subject to the present decision as part of the read-across and grouping approach, in accordance with Annex XI, Section 1.5. of the REACH Regulation. ECHA has assessed the read-across approach and prediction possibility in the respective draft decisions on the substances that are members of the ZDDP category.

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

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

A sub-chronic toxicity study (90 day) is a standard information requirement as laid down in Annex IX, Section 8.6.2. 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.

In the updated dossier you have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to EU B.26./OECD TG 408 to be performed on the registered substance.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Sub-chronic toxicity (90-day): oral. 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.

You proposed testing by oral route. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA agrees that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure. Uses with industrial / professional spray application are reported in the chemical safety report. However, the reported concentrations for those uses are low (<[redacted]%). Hence, the test shall be performed by the oral route using the test method OECD TG 408.

Therefore, ECHA considers that the proposed study performed by the oral route with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

You proposed testing in rats. According to the test method OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

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: Sub-chronic toxicity study (90-day) in rats, oral route (test method: OECD TG 408).

The testing material used for performing the required study shall be selected and reported in accordance with the specifications prescribed in Appendix 3 of this decision.

Notes for your considerations:

You submitted a testing proposal for an Extended one-generation reproductive toxicity study (Annex X, 8.7.3.). However, this testing proposal is not addressed in this decision because the results of the Sub-chronic toxicity study (90-day) are considered crucial to inform on the study design of the Extended one-generation reproductive toxicity study. Therefore, you are required to perform the Sub-chronic toxicity study (90-day) first, and submit the results by the deadline indicated above.

Together with providing the results for the requested Sub-chronic toxicity study (90-day), you may also consider updating your testing proposal for the Extended one-generation reproductive toxicity study. The updated testing proposal should include a justification for the design of the Extended one-generation reproductive toxicity study following ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017), taking into account the results of the Sub-chronic toxicity study (90-day).

2. 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.

In the updated dossier you have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to OECD TG 414 by the oral route to be performed on the registered substance.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental 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 a study performed with the registered substance according to OECD TG 414 is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

You proposed testing with the rat as a first species. According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with the rat or rabbit as a first species.

You proposed testing by the oral route. ECHA agrees 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) 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.

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 (rats or rabbits), oral route (test method: OECD TG 414).

The testing material used for performing the required study shall be selected and reported in accordance with the specifications prescribed in Appendix 3 of this decision.

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.

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 up to 45 months for the conduct of the requested tests (OECD TG 408, OECD TG 414 in rat), and provided supporting information from two CROs.

The information provided indicates timelines for conducting 3 studies: the two above mentioned studies and in addition an OECD TG 414 test in rabbits, in a step-wise manner. It considers 36-40 months as sufficient, including the "*study completion, reporting, risk assessment and dossier completion*".

Taking into account that you are not requested to provide 3 but 2 studies a reasonable time period for providing the required information in the form of an updated registration is 24 months from the date of the adoption of the decision. However, taking into account the possible lab capacity issues, ECHA gives you 6 more months. Therefore, the deadline for the submission of the results from the OECD TG 408 and OECD TG 414 in one species is extended from 24 to 30 months. The decision was therefore modified accordingly.

Appendix 2: Procedural history

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 25 June 2018 following the necessary clarification of the substance identity issues related to several members of the ZDDP category.

ECHA held a third party consultation for the testing proposals from 4 October 2018 until 19 November 2018. ECHA did not receive information from third parties.

This decision does not take into account any updates after **6 March 2019**, 30 calendar days after the end of the commenting period.

The registrants updated the registration with submission number [redacted] on 06 March 2019. ECHA took the information in the updated registration and in the registrants' comments into account and modified the draft decision.

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: Specifications regarding the testing material

Issues related to the composition of the registered substance and its consequence on the test material for requested studies

You reported within the joint submission the registered substance as Zinc O,O,O',O'-tetrabutyl bis(phosphorodithioate) (EC number: 230-257-6). The substance is registered as Unknown or Variable Composition, Complex reaction products and Biological materials (UVCB Substance). It is a zinc dithiodialkylphosphate (ZDDP) consisting of neutral and basic zinc salts as constituents. In addition, base oils are reported as constituents. The base oils are refined crude oils and UVCB substances.

The main constituents and their concentration ranges in the boundary composition are:

[redacted]

Due to the wide ranges of reported constituent concentrations for the joint submission, possible compositions may be e.g.

[redacted]

- any composition between these concentration values.

It is not clear whether [redacted] is also a realistic possibility. In addition, different base oils with non specified compositions may be present at various concentrations. You state in your testing strategy for the ZDDP category that the ratio of the constituents does not influence the potential for systemic toxicity, since the constituents are not absorbed at a significant level. However, you did not provide any experimental proof for this assumption and in fact it is contradicted by the information (see Appendix 1, section B.2).

ECHA therefore considers it likely that the different possible constituent ratios result in different hazard properties, if tested in toxicity studies. To avoid underestimation of the hazard caused by the inappropriate selection of the test material, the test material should represent a worst case in terms of expected absorption and expected toxicity. ECHA therefore provides considerations on the selection of the test material and how it should be reported below.

1- Selection of the test material(s)

It is the responsibility of all registrants of the substance to agree on the composition of the test material in carrying out the tests required by the present decision. It is important to select the test material so that it is relevant for all the registrants of the substance, i.e. it takes into account the variation in compositions reported by all members. The composition of the test material(s) must fall within the boundary composition(s) of the substance. Studies conducted to investigate the hazardous properties need to use test material representative for the registered 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 registered substance is known to have an impact on (eco)toxicity, the selected test material shall contain that constituent/impurity.

As explained above, the registrants of the joint submission for this substance should select a composition of the test material for the conduct of the requested studies, which represents a worst case in terms of expected absorption and expected toxicity for the possible constituent ratios. In this regard the specification of the ratio between the concentrations of the [redacted] and the concentration of the [redacted] and the concentration of the base oils appears to be a relevant consideration. You also state that the [redacted] exist in reversible monomeric and dimeric forms. It is not clear which conditions lead to which form in this equilibrium. Therefore, the extent of dimer formation from the [redacted] appears to be also a relevant consideration for the selection of the appropriate test material. You also provide the structure of a [redacted], which may be formed from the [redacted]. The possible formation of such hydrolysis/ degradation product during the test material administration appears to be also a relevant consideration for the selection of the appropriate test material.

The following aspects therefore may facilitate the selection of the appropriate test material. ECHA considers that in the absence of toxicity data for the individual constituents, one parameter currently available to support the selection of the test material in a worst-case approach is the molecular weight. The [redacted] consists of [redacted] whereas the [redacted] consists of [redacted]. In addition, due to the difference in molecular weight between the monomer and the dimer, it is important to know what percentage of the [redacted] exists as dimer in the test material. In general, the [redacted] is more likely to be absorbed than the dimer or than the [redacted]. Moreover, the [redacted] may be more easily hydrolysed/degraded to the [redacted] in the stomach thereby further increasing the likelihood of absorption. Furthermore, the different base oils possibly present in the composition have an unknown impact on the absorption of the ZDDP constituents. Lower concentrations of base oils likely will have a smaller impact and their presence in the test material should be as low as technically possible.

2- 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 registered substance and to all the registrants of the registered substance.

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers" on the ECHA website (https://echa.europa.eu/documents/10162/22308542/manual_regis_and_ppord_en.pdf).

In that respect, ECHA notes that the substance is registered as Substance of Unknown or Variable Composition, Complex reaction products and Biological materials (UVCB Substance). By definition, the composition of such substances is complex, the number of constituents is relatively large, the composition is, to a significant part, unknown, and/or the variability of the composition is relatively large. All of the constituents identified in the composition reported in the dossier have a broad variation.

According to Article 13(4) of REACH, tests and analyses required under this Regulation shall be carried out in compliance with the principles of Good Laboratory Practice (GLP). The OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 11 [ENV/MC/CHEM(98)16] requires a careful identification of the test item and description of its characteristics.

More specifically, according to Article 13(3) of REACH, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation. The Test Methods Regulation (EU) 440/2008, as amended by Regulation (EU) 2016/266, requires that "*if the test method is used for the testing of a* [...] *UVCB* [...] *sufficient information on its composition should be made available, as far as possible, e.g. by the chemical identity of its constituents, their quantitative occurrence, and relevant properties of the constituents*".

To conclude, for the test material selected to conduct the requested studies, information as specified below has to be provided:

Detailed information on the composition of the test material using appropriate analytical techniques. The reporting must include the concentration values of [redacted], the concentration values of the [redacted], the concentration values of the [redacted], and the concentrations, identities and compositions of the base oils.

You have to justify the test material selected for testing taking into account the aspects on absorption described under 1 above.