ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000001589-63-09/F Helsinki, 27 March 2012

DECISION ON A TESTING PROPOSAL SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide, CAS No 162881-26-7 (EC No 423-340-5), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined testing proposals set out in the registration dossier for phenyl bis(2,4,6-trimethylbenzoyl)-phosphine oxide, CAS No 162881-26-7 (EC No 423-340-5), submitted by [redacted] (the Registrant), latest submission number [redacted] for the tonnage band of 100 to 1000 tonnes per year.

In accordance with Articles 10(a)(ix) and 12(1)(d) of the REACH Regulation, the Registrant submitted the following testing proposals as part of the registration dossier to fulfil the information requirements set out in Annex IX:

- Annex IX, 8.6.2: Sub-chronic toxicity study (90-day) in rat, following the oral route of application
- Annex IX, 8.7.2: Pre-natal developmental toxicity study
- One-generation reproductive toxicity study
- Annex IX, 9.4.1: Short-term toxicity to invertebrates, for which, in view of the properties of the substance, a long term test was proposed using earthworms.

The examination of the testing proposal was initiated on 11 October 2010.

ECHA opened a third party consultation for testing proposals including testing on vertebrate animals that was held from 22 December 2010 until 7 February 2011. ECHA received following comments from third parties:

1. *"Evaluate the need to conduct a two-generation reproductive toxicity study (OECD Guideline 416)* [EU Method B.35] *in light of the results of the existing 28-day sub-chronic toxicity study (OECD 407)* [EU Method B.7] *and other toxicological data."*
2. *"Conduct a sub-chronic toxicity study (90-day oral Toxicity Study, OECD Guideline 408)* [EU Method B.26] *with additional reproduction toxicity parameters instead of a two-generation reproductive toxicity study (OECD Guideline 416)* [EU Method B.35]."
3. *"Perform in vitro (pre-) validated tests for the evaluation of the embryotoxic and endocrine disruption potential and apply QSAR classification models for*

developmental toxicity. Use results to waive developmental toxicity study (Prenatal Developmental Toxicity Study, OECD Guideline 414) [EU Method B.31]."

4. *"Conduct an Extended One Generation Reproduction Toxicity Study (EOGRTS, Draft OECD Guideline 17 November, 2010) instead of a two-generation reproductive toxicity study (OECD Guideline 416)* [EU Method B.35]."
5. *"Use the results of the EOGRTS to waive the sub-chronic toxicity study (90-day oral Toxicity Study, OECD Guideline 408)* [EU Method B.26] *and the developmental toxicity study (Prenatal Developmental Toxicity Study, OECD Guideline 414)* [EU Method B.31]."
6. *"Exposure considerations: use the TTC for repeated dose and reproduction toxicity endpoints."*
7. *"Use of a non-linear classification ANN QSAR Model for the prenatal developmental toxicity endpoint."*

ECHA examined the testing proposal and drafted a decision in accordance with Article 40 of REACH.

On 8 April 2011 ECHA notified the Registrant of its draft decision and invited him pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

On 10 May 2011 the Registrant provided to ECHA comments on the draft decision.

ECHA reviewed the further information received and decided not to amend the draft decision.

On 4 November 2011 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals to amend the draft decision within 30 days. Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision.

On 8 December 2011 ECHA notified the Registrant of proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

ECHA reviewed the proposals for amendment received and decided to modify the draft decision.

On 19 December 2011, the draft decision was referred to the Member State Committee.

On 6 January 2012 the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 6-10 February 2012, the Member State Committee further modified the draft decision and a unanimous agreement of the Member State Committee on the draft decision was reached on 9 February 2012.

This decision does not imply that the information provided by the Registrant in the registration dossier is in compliance with the requirements of the REACH Regulation. The decision does not prevent ECHA to initiate a compliance check on the present dossier at a later stage.

II. Testing required

Pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant shall carry out the following tests using the indicated test method:

a. Sub-chronic toxicity study (90-day) (Annex IX, 8.6.2) in rat by the oral route (EU Method B.26 or OECD 408);
b. Prenatal developmental toxicity study (Annex IX, 8.7.2) in rat by the oral route (EU Method B. 31 or OECD 414);

Pursuant to Article 40(3)(c) of the REACH Regulation the Registrant shall carry out the following tests using the indicated test method:

c. Effect on terrestrial organisms (Annex IX, 9.4.; Test on toxicity to invertebrates: OECD 222);
d. Effect on terrestrial organisms (Annex IX, 9.4.; Test on toxicity to soil micro-organisms: EU Method C.21 or OECD 216); and
e. Effect on terrestrial organisms (Annex IX, 9.4.; Test on toxicity to terrestrial plants : ISO standard 22030 or OECD 208).

Pursuant to Article 40(3)(d) of the REACH Regulation the originally proposed test:

f. One-generation reproductive toxicity study (OECD 415).

is rejected.

If the results of the sub-chronic toxicity study (90-day) required by this decision indicate adverse effects on reproductive organs or tissues then the Registrant shall submit a testing proposal to cover the endpoint of Annex IX, 8.7.3. for reproductive toxicity unless the Registrant considers that the specific rules for adaptation from this information requirement mentioned in Column 2, Annex IX, 8.7. apply.

The Registrant may also consider submitting a testing proposal for this end-point at any time on the basis of other considerations.

The Registrant shall determine the appropriate order of the studies taking into account the possible outcomes and considering the possibilities for adaptations of the standard information requirements according to column 1 or 2 provisions of the relevant Annexes of the REACH Regulation. More specifically, prior to conducting the second long term toxicity test to terrestrial organisms, the Registrant shall take into account the guidance on information requirements and chemical safety assessment (see later in Section III of this draft decision) related to integrated testing strategy for terrestrial toxicity testing to determine the sequence in which the tests are to be conducted.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **27 March 2014** an update of the registration dossier containing the information required by this decision.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other registrants.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals of the Registrant for the registered substance and scientific information submitted by third parties.

1. Sub-chronic toxicity study (90-day) (Annex IX, 8.6.2) in rat by the oral route (EU Method B.26 or OECD 408)

According to Annex IX, section 8.6.2, of the REACH Regulation the sub-chronic toxicity study is required to fulfil the standard information requirements.

The Registrant thus proposed the sub-chronic toxicity test to fulfil this information requirement.

As further explained in section 5 below, neither the information in the registration dossier nor the information received from third parties following the public consultation permits an adaptation of this standard information requirement in accordance with the second column of Annex IX and the general rules set out in Annex XI of the REACH Regulation.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the testing proposal is accepted and the Registrant is requested to carry out the following test: Sub-chronic toxicity study (90-day) (Annex IX, 8.6.2) in rat by the oral route (EU Method B.26 or OECD 408).

2. Pre-natal developmental toxicity study (Annex IX, section 8.7.2) in rat by the oral route (EU Method B.31 or OECD 414)

According to Annex IX, section 8.7.2, of the REACH Regulation a pre-natal developmental toxicity study is required to fulfil the standard information requirements.

The Registrant has thus proposed to perform the pre-natal developmental toxicity study to fulfil this information requirement.

As further explained in section 5 below, neither the information in the registration dossier nor the information received from third parties following the public consultation permits an adaptation of this standard information requirement in accordance with the second column of Annex IX and the general rules set out in Annex XI of the REACH Regulation.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the testing proposal is accepted and the Registrant is requested to carry out the following test: Pre-natal developmental toxicity study (Annex IX, section 8.7.2) in rat by the oral route (EU Method B.31 or OECD 414).

3. Effects on terrestrial organisms (Annex IX, section 9.4 of the REACH Regulation)

In order to fulfil the standard information requirements set out in Annex IX, section 9.4., the Registrant should provide the following studies: (i) short term toxicity to invertebrates (section 9.4.1), (ii) effects on soil micro-organisms (section 9.4.2) and (iii) short term toxicity to plants (section 9.4.3). Column 2 of Annex IX, section 9.4 advises the Registrant to consider long term toxicity testing instead of short term in particular for substances that have a high potential to adsorb to soil or that are very persistent.

The Registrant considered that long term toxicity testing is necessary and proposed an earthworm reproduction test according to OECD 222 in order to fulfil all three standard information requirements in section 9.4 of Annex IX of the REACH Regulation. The

registration dossier does not contain any valid justification for waiving the studies in sections 9.4.2 and 9.4.3 in accordance with the specific rules for adaptation indicated in column 2 of Annex IX, section 9.4 or the general rules for adaptation under Annex XI.

The test proposed by the Registrant is therefore not sufficient, on its own accord, to fulfil all the information requirements outlined in Annex IX, 9.4., since it does not fulfil the information requirements laid down in Annex IX, sections 9.4.2 and 9.4.3. The proposed test only addresses invertebrates (i.e. the information requirement in Annex IX, section 9.4.1) and does not address the other two trophic levels requested for this tonnage band (i.e. the information requirements in Annex IX, sections 9.4.2 and 9.4.3).

Based on the available aquatic toxicity information and the physico-chemical properties of the substance ECHA considers that according to ECHA Guidance section R.7.11.6 the substance can be considered as a Hazard Category 3. In the context of an integrated testing strategy for soil toxicity, this would allow the Registrant to perform an initial screening assessment in order to identify the need to perform further studies. The screening assessment should include the evaluation of Equilibrium Partitioning Method (EPM; with the application of an appropriate correction factor), together with a confirmatory long term soil toxicity test. Based on the result of the initial screening, further long term testing may be needed.

The Registrant has proposed to undertake a long term toxicity test to earthworms (OECD 222). According to Table R.7.11.-2, Guidance R7.C, this test could be considered as the confirmatory long term soil toxicity test. The Registrant could opt to start with the long term plant test (ISO 22030 or OECD 208) as an alternative confirmatory test.

According to the guidance the PNECscreen is calculated through EPM on the basis of aquatic toxicity data only. Intrinsic properties of soil microbial communities however are not addressed through the EPM extrapolation method. Thus, ECHA considers that the hazard to soil microbial communities needs to be evaluated as a standard information requirement under Annex IX. 9.4.2. Therefore ECHA concludes that the application of an integrated testing strategy could only be applied to the need to perform either a long term toxicity test for soil invertebrates or plants, or to perform both of them, and that the effects on soil micro-organisms need to be ascertained by performing a relevant test (EU Method C.21 or OECD 216).

Furthermore, ECHA considers that it is not possible to determine *a priori* whether the results obtained from the toxicity screening assessment will be sufficient to fulfil the information requirement in section 9.4. of Annex IX of the REACH Regulation.

Pursuant to Article 40(3)(c) ECHA may take a decision permitting the registrant to carry out the proposed test in accordance to Article 40(3)(a) but requiring the registrant to carry out one or more additional tests in cases of non-compliance of the testing proposal with Annexes IX, X, and XI of the REACH Regulation.

Therefore, pursuant to Article 40(3)(c) ECHA has accepted the Registrant's testing proposal and the Registrant is requested to perform a long-term toxicity to invertebrates (Annex IX, 9.4.1, OECD 222). In light of the guidance mentioned above, the Registrant is also required to carry out the following tests to fulfil the information requirements in Annex IX, sections 9.4.2 and 9.4.3 of the REACH Regulation:

- Toxicity to micro-organisms (Annex IX, 9.4.2, EU Method C.21 or OECD 216)

- Toxicity to plants (Annex IX, 9.4.3, ISO Method 22030 or OECD 208).

The Registrant shall determine the need to perform the plant toxicity test based on the outcome of the OECD 222 test and the considerations set out in Table R.7.11.-2 of Guidance R7.C.

4. One-generation reproductive toxicity study (OECD 415) – Annex IX section 8.7.3)

The standard information requirements according to Annex IX, section 8.7.3. are warranted if the 28-day or the 90-day study indicates adverse effects on the reproductive organs or tissues.

The Registrant proposed a one-generation reproductive toxicity study (OECD 415) to fulfil this information requirement depending on the outcome of the sub-chronic toxicity study.

According to the Registrant's conclusions, the oral 28-day study showed no adverse effects on reproductive tissues or organs and accordingly there would currently be no grounds indicating the need to fulfil the information requirement set out in Annex IX, section 8.7.3. On this basis the testing proposal is rejected. In the comments to the proposals for amendment the Registrant agreed that generation toxicity testing should not be performed at this point in time. If the 90-day study shows adverse effects on reproductive organs or tissues, the Registrant shall submit a testing proposal to cover the information requirement of Annex IX, 8.7.3., as this would then constitute a standard information requirement for substances registered at 100 to 1000 tonnes per year.

In any event based on the information generated from the other studies or on the basis of any other considerations the Registrant may also consider submitting a testing proposal for the information requirement of Annex IX, 8.7.3. Such reasons for testing should be specified.

It should be noted that currently neither the specific rules for adaptation set out in Annex IX of REACH nor the general rules for adaptation in Annex XI consider that the one-generation reproductive toxicity study (OECD 415) is sufficient to fulfil this information requirement.

5. Comments from third parties.

ECHA has examined the comments received from third parties, listed under (1)-(7) in Section I.

1. *"Evaluate the need to conduct a two-generation reproductive toxicity study (OECD Guideline 416)* [EU Method B.35] *in light of the results of the existing 28-day sub-chronic toxicity study (OECD 407)* [EU Method B.7] *and other toxicological data."*

   ECHA has taken into account the information provided by the third parties as stated under point (4) above. According to Annex IX, 8.7.3, a two-generation reproductive toxicity study has to be conducted if the 28-day or 90-day study indicates adverse effects on reproductive organs or tissues. Since the 28-day study submitted by the Registrant does not indicate adverse effects on reproductive organs up to 1000 mg/kg bw/day, a two-generation study need not be performed. However, if the 90-day study requested by ECHA would show such effects, this will trigger the need for the two-generation study.

2. *"Conduct a sub-chronic toxicity study (90-day oral Toxicity Study, OECD Guideline 408)* [EU Method B.26] *with additional reproduction toxicity parameters instead of a two-generation reproductive toxicity study (OECD Guideline 416)* [EU Method B.35]."

   ECHA has considered this comment and has concluded that the 90-day study cannot replace the two-generation reproduction toxicity study on the basis that in the 90-day study no multi-generational effects are investigated.

3. *"Perform in vitro (pre-) validated tests for the evaluation of the embryotoxic and endocrine disruption potential and apply QSAR classification models for developmental toxicity. Use results to waive developmental toxicity study (Prenatal Developmental Toxicity Study, OECD Guideline 414)* [EU Method B.31]."

   A third party has proposed a strategy for ECHA to consider before further tests on animals are requested. However, third parties were invited, as specified by Article 40(2) to submit "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". As the proposal for a strategy as such cannot be regarded as information or studies, ECHA concludes that this is not a sufficient basis for rejecting the Testing Proposals.

   Additionally, ECHA notes the following. For *in vitro* tests (embryonic stem cell test, the limb bud micromas culture and the whole embryo culture), the Guidance on information requirements and chemical safety assessment R.7, chapter R.7.6, states that these tests have limited value in a regulatory context. Considering the possibility of establishing a weight of evidence approach on the basis of such tests and existing *in vivo* data, which could fulfil the information requirements of REACH, it is the registrant's responsibility and cannot be requested by ECHA.

   Therefore, ECHA concludes that on this occasion, the information submitted does not meet the conditions for the adaptation on the basis of *in vitro* methods set out in Annex XI, Section 1.4. Therefore, it cannot constitute an acceptable adaptation to standard information requirements.

4. *"Conduct an Extended One Generation Reproduction Toxicity Study (EOGRTS, Draft OECD Guideline 17 November, 2010) instead of a two-generation reproductive toxicity study (OECD Guideline 416)* [EU Method B.35]."

   For the reasons indicated in sub-section 1 above ECHA has decided that at this stage the Registrant does not need to fulfil the information requirements laid down in section 8.7.3.

   For the sake of completeness however ECHA addresses the third parties' proposal to have as an alternative testing strategy to conduct an Extended One-Generation Reproductive Toxicity Study (EOGRTS) instead of a Two-Generation Reproductive Toxicity Study. ECHA acknowledges that the OECD test guideline for an extended one generation reproductive toxicity study may be used as a valid option by the Registrant, if appropriate specifications to the study design are provided.

5. *"Use the results of the Extended One Generation Reproduction Toxicity Study (EOGRTS, Draft OECD Guideline 17 November, 2010) to waive the sub-chronic toxicity study (90-day oral Toxicity Study, OECD Guideline 408)* [EU Method B.26] *and the developmental toxicity study (Prenatal Developmental Toxicity Study, OECD Guideline 414)* [EU Method B.31]."

   Third parties proposed as an alternative testing strategy to conduct an Extended One-Generation Reproductive Toxicity Study (EOGRTS) instead of a 90-day oral Toxicity Study and the Developmental Toxicity/Teratogenicity Study.
   However, third parties were invited, as specified by Article 40(2) of the REACH Regulation to submit "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". As the proposal for a strategy as such cannot be regarded information or studies, ECHA concludes that this is not a sufficient basis to fulfil the data/information requirement.

6. *"Exposure considerations: use the TTC for repeated dose and reproduction toxicity endpoints."*

   According to Annex XI, Section 3 of the REACH Regulation, the testing can be omitted if it can be demonstrated that there is no or no significant exposure. The Registrant did not use substance-tailored exposure-driven testing according to Annex XI. Furthermore, the concept of Threshold of Toxicological Concern (TTC) does not meet the specific rules of column 2 for adaption from Annex IX, 8.6.2 and 8.7.2. Consequently, ECHA concludes that this is not a sufficient basis for rejecting the Testing Proposal.

7. *"Use of a non-linear classification ANN QSAR Model for the prenatal developmental toxicity endpoint."*

   According to Annex XI, 1.3 of the REACH Regulation, the results of (Q)SARs may be used instead of testing when the following conditions are met: a) the results are derived from a (Q)SAR model whose scientific validity has been established; b) the substance falls within the applicability domain of the (Q)SAR model; c) results are adequate for the purpose of classification and labelling and/or risk assessment, and; d) adequate and reliable documentation of the applied method is provided. Requirement c) refers to the relevance of the predicted endpoint to meet the information requirement, for which a testing proposal has been made. The evaluation of the submitted information according to the conditions described above showed that:
   a) The dependent variable of the Molcode model is in the form "toxic/non-toxic". In the absence of additional information on the meaning of these terms, the predicted result could not be directly used to fill a data gap according to the information requirements of the REACH Regulation.
   b) In addition, in the evaluation made by the Joint Research Center (24522/2010), evaluation on QSAR models and software tools for predicting developmental and reproductive toxicity, Molcode models were referred to as "a range of modules for predicting toxicological endpoints and ADME properties between the endocrine activity." Endocrine activity could be relevant for the endpoint of the testing proposal, but not sufficient, since the mechanisms of pre-natal developmental toxicity can be some other than ER binding affinity and AhR binding affinity.
   c) Contrary to point b) above, based on the information provided in the QMRF,

the possibility that the registered substance does not fall within the structural applicability domain of the model cannot be ruled out. Information is needed on how the query chemical falls within the applicability domain of the model.
Contrary to point d) above, the level of detail in the documentation of the algorithm in the Q()SAR Model Reporting Format (QMRF) was not considered sufficient to transparently describe the model. Information is needed on how the descriptors were selected, on how descriptors are computed, and on how the final algorithm was derived as a result of a formalised mathematical approach.
d) According to the REACH Guidance (R.6: QSARs and grouping of Chemicals, section R.6.1.6.4), the explanation on how an estimate has been derived by applying a specific model to a specific substance would appear in the QSAR Prediction Reporting Format (QPRF).
Therefore, ECHA concludes that the information submitted does not meet the conditions for the (Q)SAR adaptation set out in Annex XI, Section 1.3 and, as such, it cannot constitute an acceptable adaptation to the standard test in question.

IV. General requirements for the generation of information and Good Laboratory Practice

ECHA always reminds registrants of the requirements of Article 13(4) of the REACH Regulation that reads:

> *"Ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or the Agency and with the provisions of Directive 86/609/EEC, if applicable."*

According to Article 13(3) of the REACH Regulation, 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 or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as adapted to technical progress or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

National authorities monitoring good laboratory practice (GLP) maintain lists of test facilities indicating the relevant areas of expertise of each facility.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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