EUROPEAN CHEMICALS AGENCY

For final decision: TPE-D-0000001985-63-05/F Helsinki, 29 January 2013

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

For 2,6-di-tert-butylphenol, CAS No 128-39-2 (EC No 204-884-0), 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 the following testing proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for 2,6-di-tert-butylphenol, CAS 128-39-2 (EC No 204-884-0) submitted by [redacted] (Registrant).

- Annex IX, 8.6.2: Subchronic toxicity study (90-day) by oral route according to OECD 408);
- Annex IX 9.1.5. Long-term toxicity testing on aquatic invertebrates, according to OECD Guideline 211 (Daphnia magna Reproduction Test).

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after 6 September 2012, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

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

The examination of the testing proposals was initiated on 14 October 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 16 May 2011 until 30 June 2011 and received some comments (see Section III below).

On 17 October ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 7 November ECHA received comments from the Registrant.

ECHA considered the Registrant's comments received. The comments are reflected in the Statement of Reasons (Section III) whereas no amendments to the Testing Required

(Section II) were made.

On 6 September 2012 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 of the receipt of the notification.

Subsequently, one Competent Authority of a Member State submitted a proposal for amendment to the draft decision.

On 10 October 2012 ECHA notified the Registrant of the proposal for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposal for amendment within 30 days of the receipt of the notification.

ECHA reviewed the proposal for amendment received and did not amend the draft decision.

On 22 October 2012 ECHA referred the draft decision to the Member State Committee.

On 9 November 2012 the Registrant provided comments on the proposed amendment. The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 10-14 December 2012, a unanimous agreement of the Member State Committee on the draft decision was reached on 12 December 2012. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant in his 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 proposed tests using the indicated test methods and the registered substance:

1. Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, 8.6.2., (EU method B.26 or OECD 408);
2. Long-term toxicity testing on aquatic invertebrates (Annex IX 9.1.5., EU Method C.20 or OECD 211 - *Daphnia magna* Reproduction Test).

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit the information on the form of an updated IUCLID dossier to ECHA by **29 July 2014**.

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. Subchronic toxicity study (90-day)

a) Examination of the testing proposal

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

Subchronic toxicity study (90 day) is part of the information requirements as laid down in section 8.6.2 of Annex IX of the REACH Regulation. As 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, it follows that there is an information gap and that it is necessary to generate the data for this endpoint.

The Registrant proposed testing by the oral route. In light of the physico-chemical properties of the substance and the information provided on the uses and human exposure, ECHA considers that testing by the oral route is appropriate. According to the test method EU B.26/OECD 408 the rat is the preferred rodent species. ECHA considers this species as being appropriate.

b) Consideration of the information received during third party consultation

During the third party consultation, ECHA received following comments/information on the testing proposal for the sub-chronic toxicity study:

(1) A third party has provided QSAR model results.

ECHA examined the proposal and concluded the following:

According to Annex XI, 1.3 of the REACH Regulation, the results of the QSARs may be used instead of testing when the following conditions are met: a) the results are derived from a QSAR model whose scientific validity has been established; b) the substance falls within the applicability domain of the QSAR model; c) results are adequate for the purposes of classification and labelling and/or risk assessment; and d) adequate and reliable documentation of the applied method is provided.

The evaluation of the submitted information according to the conditions described above showed that:

- Contrary to point a) above, the dependent variable of the 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 or extrapolated to fill a data gap according to the information requirements of the REACH Regulation.
- Contrary to point b) above, based on the information in the QPRF (QSAR Prediction Reporting Format), the possibility that the substance does not fall in the applicability domain of the model could not be ruled out. In fact, there is only evidence that the parameters of the chemical, used for prediction, fall within the ranges of the individual descriptors, used in the model. The provided QPRF contains analogues, which do not look similar to the two constituents of the registered substance.
- Contrary to point c) above, the results are not adequate for the purposes of classification and labelling and/or risk assessment, because the estimated endpoint does not have adequate and reliable coverage of the key parameters in the corresponding test method as described in the 414 OECD guideline.
- Contrary to point d) above, the level of detail in the documentation of the algorithm in the QMRF (QSAR Model. Reporting Format) was not considered sufficient to

transparently describe the model. The algorithm does not appear in the QMRF in formalised mathematical form that can be reproduced from the documentation. In addition, the training, selection and test sets were not found available.

In conclusion, the conditions for using QSAR instead of testing, as required under Annex XI, section 1.3, are not met. Therefore, the third party has not provided scientifically valid information or studies (Annex XI 1.3 and Article 40(2)).

(2) Another third party referred to the above QSAR model results and also provided results of the OECD QSAR Toolbox and proposed to consider the following weight-of-evidence arguments:
a) Evaluate the need for conducting sub-chronic toxicity study in the light of 28-day study, the existing pre-natal study and other toxicological data
b) Evaluate the need conducting a sub-chronic study on the basis of the presence/absence of structural alerts for chronic toxicity and the NOAEL estimation of a QSAR model.
c) Exposure considerations: use the Threshold for Toxicological Concern (TTC) for repeated dose endpoint
d) Concluding remarks (on the basis of data on related substances and a 28-day study robust risk assessment can be done without 90-day study).

ECHA examined the proposal and concluded the following:

The third party has provided results of the OECD QSAR Toolbox. However, OECD QSAR Toolbox results are only predictions for specific structural alerts (e.g. estrogen receptor binding, mutagenicity). The provided information is not sufficient for classification and labelling or for risk assessment, as required in Annex XI, 1.3. This third party also refers to a QSAR, which is commented separately above in point 1.

The third party has also proposed weight-of-evidence arguments for ECHA to consider. However, ECHA has invited submission, pursuant to Article 40(2) of the REACH Regulation of *"scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal"*, and the weight-of-evidence arguments are not "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". Consequently, ECHA concludes that this is not a sufficient basis for rejecting the Testing Proposal.

Therefore, the third party did not provide scientifically valid information or studies.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408) using the registered substance.

2. Long-term toxicity to aquatic invertebrates

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

According to Section 9.1.5 of Annex IX of the REACH Regulation, long-term toxicity testing on aquatic invertebrates is required to fulfil the standard information requirements. As the proposed test for long-term toxicity to aquatic invertebrates is not available for the registered substance but needs to be present in the technical dossier to meet the

information requirement of Section 9.1.5 of Annex IX of the REACH Regulation, it is necessary to generate the data and to perform the test. The need for testing for the specific endpoint is, finally, supported by the fact that daphnia was found to be the most sensitive species in the acute aquatic tests.

Consequently, pursuant to Article 40(3)(a) of the REACH Regulation the Registrant is requested to carry out the proposed test: long-term toxicity testing on aquatic invertebrates (Annex IX 9.1.5., EU Method C.20 or OECD 211 - *Daphnia magna* Reproduction Test).

3. Non-extension of timeline

The Registrant, in his comments (pursuant to Article 51(1) of the REACH Regulation) on 7 November 2011 asked for prolongation of the deadline for submission of information due to long lead times for contract institutes. However, on 23 February 2012 the Registrant indicated that the lead times for contract institutes had shortened. In light of the information provided, ECHA believes that the timeline indicated in the draft decision is sufficient and did therefore not extend the timeline.

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 ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

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.

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.

Jukka Malm
Director of Regulatory Affairs