EUROPEAN CHEMICALS AGENCY

Decision number TPE-D-0000002592-75-05/F Helsinki, 10 January 2013

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

For 4-tert-butylpyrocatechol, CAS No 98-29-3 (EC No 202-653-9), 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 4-tert-butylpyrocatechol, CAS No 98-29-3 (EC No 202-653-9), by [redacted] (Registrant):

- Fish, juvenile growth test (OECD 215)
- *Daphnia magna* reproduction test (OECD 211)
- Two-generation reproduction toxicity study (OECD 416)
- Prenatal developmental toxicity study (OECD 414)

The present decision relates to the examination of the testing proposals for a fish, juvenile growth test, a *Daphnia magna* reproduction test, and a pre-natal developmental toxicity study. The testing proposal for the two-generation reproductive toxicity study is addressed in a separate decision although all testing proposals were initially addressed together in the same draft decision.

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.

On 25 November 2010, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposals set out by the Registrant in the registration dossier for the substance mentioned above.

ECHA held a third party consultation for the testing proposals from 29 April 2011 until 14 June 2011. ECHA did receive information from third parties (see section III below).

On 31 July 2012 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

By 30 August 2012 the Registrant did not provide any comments on the draft decision to ECHA.

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, Competent Authorities of Member States submitted proposals for amendment to the draft decision.

On 10 October 2012 ECHA notified the Registrant of the 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 amend the draft decision.

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

The Registrant did not provide any comments on the proposed amendments.

The draft decision was split into two draft decision documents: one relating to the testing proposal for a two-generation reproductive toxicity study and one relating to the testing proposals for a fish, juvenile growth test, a *Daphnia magna* reproduction test, and a pre-natal developmental toxicity study.

A unanimous agreement of the Member State Committee on the draft decision relating to the testing proposals for a fish, juvenile growth test, a *Daphnia magna* reproduction test, and a pre-natal developmental toxicity study was reached on 26 November 2012 in a written procedure launched on 14 November 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 REACH requirements. The decision does not prevent ECHA to initiate a compliance check on the present dossier at a later stage.

II. Testing required

The Registrant shall carry out the following proposed tests pursuant to Article 40(3)(a) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

1. Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211).
2. Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, 8.7.2.; test method: EU B.31/OECD 414).

The Registrant shall carry out the following additional test pursuant to Article 40(3)(c) of the REACH Regulation using the indicated test method and the registered substance subject to the present decision:

3. Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.; test method: Fish, early-life stage toxicity test, OECD 210)

while the originally proposed test for a Fish, juvenile growth test (test method: OECD 215) is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

The Registrant shall determine the appropriate order of the studies taking into account the possible outcome 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.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **10 October 2014** an update of the registration dossier containing the information required by this decision.

Before conducting any of the tests mentioned above in points 1 and 3 the Registrant shall consult the ECHA *Guidance on information requirements and chemical safety assessment (version 1.1., August 2008)*, Chapter R7b, Section R.7.8.5 to determine the sequence in which the aquatic long-term toxicity tests are to be conducted and the necessity to conduct long-term toxicity testing on fish.

Data from a second pre-natal developmental toxicity study on another species is a standard information requirement according to Annex X, 8.7.2. of the REACH Regulation. If the Registrant considers that testing is necessary to fulfil this information requirement taking into account the outcome of the pre-natal developmental toxicity study on a first species and all other relevant and available data, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species.

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 submitted by the Registrant for the registered substance and scientific information submitted by third parties.

1. Long-term toxicity testing on aquatic invertebrates

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.

According to column 1 of Section 9.1.5 of Annex IX of the REACH Regulation, long-term toxicity testing on invertebrates is required to fulfil the standard information requirements. 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.

The Registrant provided the following justification for conducting the proposed test in section 7.6 of the CSR and the summary of IUCLID section 6:
"In order to refine the PNEC aquatic, in view of the chemical safety assessment, testing proposals are made to investigate the long-term toxicity to daphnids and fish. Studies according to OECD guidelines 211 and 215 are suggested for daphnids and fish, respectively. The OECD 215 test is proposed among the three available chronic tests on fish as it is considered as a sensitive indicator of toxicity, which is adapted to substance with a Log Kow value inferior to 5. Once obtained, such data will allow reducing the assessment factors applied to derive the PNEC aquatic, though it will impact the PNECs sediment and soil."

There were no indications in the dossier from the short-term toxicity studies on aquatic species that the fish would be substantially more sensitive than *Daphnia*.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 1.1., August 2008), Chapter R7b, Figure R.7.8-4 page 53, if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. According to the integrated testing strategy, the Daphnia study is to be conducted first. If based on the results of the long-term Daphnia study and an applied assessment factor of 50 no risks are indicated, no long-term fish testing may need to be conducted.

b) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211).

2. Pre-natal developmental toxicity study

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.

Pre-natal developmental toxicity studies are part of the standard information requirements as laid down in Annexes IX and X, 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.

The Registrant did not specify the species and route to be used for testing. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

Third party information 1:

A third party presented a nonlinear ANN QSAR Model for prenatal developmental toxicity study. The third party has indicated that their information is confidential and, as such, this information is not provided to the Registrant.

The result from the QSAR classification model (i.e. "toxic" or "non-toxic") is not suitable for the purposes of classification and labelling and/or risk assessment for the endpoint for which testing has been proposed to meet the information requirement (Annexes IX or X, 8.7.). In addition, the submitted information does not exclude the possibility that the registered substance might be outside the applicability domain of the model. The (Q)SAR Model

Reporting Format (QMRF) does not provide sufficient information to deduce whether the training set was constructed from studies that cover the information requirements of the OECD 414 guideline, or important study aspects, such as the species, dose selection and number of animals used. In addition, the submitted QPRF does not contain any indication on the adequacy in relation to a defined regulatory purpose of the Testing Proposal. Therefore, ECHA concludes that on this occasion, the information submitted does not meet the conditions for the adaptation on the basis of QSAR models set out in Annex XI, Section 1.3. Therefore, it cannot constitute an acceptable adaptation to standard information requirements.

Third party information 2:

A third Party has firstly indicated that due to the corrosive property of the substance, *in vivo* testing should be prevented, has secondly proposed a strategy for ECHA to consider before further tests on animals are requested, and has thirdly proposed a weight-of evidence approach for ECHA to take into account before further tests on vertebrate animals are required. As part of weight-of evidence approach, the third party refered to the results from a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) and to the results of non-guideline single exposure developmental toxicity study conducted on the read-across substance pyrocathecol (CAS No 120-80-9), and suggested using future results from a pre-natal developmental toxicity study which has been proposed by another registrant to ECHA to be conducted with pyrocathecol.

In response to the first point, ECHA notes that under certain conditions *in vivo* testing with corrosive substances is technically possible. As specified in the general part of Annexes VII-X "*in vivo* testing with corrosive substances at concentration/dose levels causing corrosivity shall be avoided". The test methods for repeated dose toxicity and reproductive toxicity specify that the highest dose level should induce "toxicity but not death or severe suffering". It is the Registrant's responsibility to ensure that appropriate dose/exposure levels are used. Therefore, the information submitted does not provide a sufficient basis on which to reject the proposed test.

In response on the second point, ECHA notes that 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.

On the third point, ECHA has taken the information provided by the third party on read-across substance into account and concludes that it is insufficient for demonstrating that the conditions of Annex XI, Section 1.2 and 1.5 of the REACH Regulation are met. More specifically, the proposed weight-of-evidence approach is not sufficient to assume that the substance has or has not a particular dangerous property after gestational exposure and that the standard information requirement for a prenatal developmental toxicity study could be adapted. Furthermore, the proposed read-across approach as an element of the weight of evidence justification did not demonstrate that human health effects of the registered substance may be predicted from data on the reference substance.

Although ECHA recognises that the information as provided by the third party might be scientifically valid, it does not fulfil Annex XI requirements and is therefore not sufficient to allow ECHA to reject the testing proposal. Nevertheless, ECHA acknowledges that the Registrant may himself supplement under its own responsibility the argumentation and information provided by the third party in order to make use of adaptation possibilities. This would require that the Registrant documents, using several independent sources of

information, that there is a sufficient weight of evidence leading to the assumption/conclusion that a substance has or has not particular dangerous properties, according to the criteria laid down in Annex XI of the REACH Regulation.

Finally, a third party has suggested conducting an extended one generation reproductive toxicity study (EOGRTS) and use results to waive a two-generation reproduction toxicity study and a prenatal developmental toxicity study. ECHA notes that in EOGRTS the developmental toxicity parameters such as skeletal and visceral malformations are not examined and, thus, EOGRTS do not provide adequate information on developmental toxicity to waive the prenatal developmental toxicity study.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414).

When considering the need for a testing proposal for a prenatal developmental toxicity study in a second species, the Registrant should take into account the outcome of the pre-natal developmental toxicity study on the first species and all available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if Weight of Evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed.

3. Fish, early-life stage (FELS) toxicity test

a) Examination of the testing proposal

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation.

According to column 1, Section 9.1.6 of Annex IX of the REACH Regulation, long-term toxicity testing on fish is required to fulfil the standard information requirements. 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.

The Registrant proposed to perform a long term toxicity study on fish according to OECD guideline 215 and provided the following justification for conducting the test in section 7.6 of the CSR and the summary of IUCLID section 6:
"In order to refine the PNEC aquatic, in view of the chemical safety assessment, testing proposals are made to investigate the long-term toxicity to daphnids and fish. Studies according to OECD guidelines 211 and 215 are suggested for daphnids and fish, respectively. The OECD 215 test is proposed among the three available chronic tests on fish as it is considered as a sensitive indicator of toxicity, which is adapted to substance with a Log Kow value inferior to 5. Once obtained, such data will allow reducing the assessment factors applied to derive the PNEC aquatic, though it will impact the PNECs sediment and soil."

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 1.1., August 2008), Chapter R7b, Figure R.7.8-4 page 53, if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. According to the integrated testing strategy, the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and an applied assessment factor of 50 no risks are indicated, no long-term fish testing may need to be conducted.

Further according to ECHA *Guidance on information requirements and chemical safety assessment* (version 1.1., August 2008), Chapter R7b, R.7.8.4.1 Data on aquatic pelagic toxicity p. 25 refers to the three studies mentioned in the legal text under section 9.1.6 of Annex IX. The guidance outlines that "Among the currently available standardised test methods, the FELS toxicity test is considered as the most sensitive of the fish tests." Currently, OECD 210 is the most widely used method for industrial chemicals for predicting chronic toxicity to fish according to the findings of the draft OECD workshop paper on fish toxicity testing framework (http://www.oecd.org/dataoecd/58/37/48699063.pdf, September 2010). In absence of a clear scientific justification in the dossier why other guidelines (such as OECD TG 215) are considered to be equally or more sensitive than OECD TG 210 for the registered substance, OECD TG 210 should be used for generating new long-term toxicity data on fish.

b) Outcome

Therefore, pursuant to Article 40(3)(c)of the REACH Regulation, the Registrant is required to carry out the proposed study: Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.; test method: Fish, early-life stage toxicity test, OECD 210) using the registered substance, while the originally proposed test for a Fish, juvenile growth test (test method: OECD 215) is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

4. Deadline for submitting the information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 30 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a two-generation reproductive toxicity study according to the standard information requirement of Annex X, 8.7.3 of the REACH Regulation. As the testing proposal for this study is not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 21 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

IV. Adequate identification of the composition of the tested material

The process of evaluation of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new studies meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for evaluation of the testing proposal. The Registrant must note, however, that this information, or the information submitted by other registrants of the same substance, has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In relation to the proposed tests, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given by the joint registrants. It is the responsibility of all joint registrants of the same substance to agree to the tests proposed (as applicable to their tonnage level) and to document the necessary information on their substance composition.

In addition, it is important to ensure that the particular sample of substance tested in the new studies 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies 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 studies to be assessed.

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

ECHA 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).

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.

VI. 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.

[redacted]
Jukka Malm
Director of Regulatory Affairs