~~CONFIDENTIAL~~

European Chemicals Agency

Decision number: TPE-D-0000001585-71-05/F Helsinki, 24 October 2011

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

For Mono- and/or di- and/or tri(1-phenylethyl)-m-cresol and p-cresol, EC No 700-427-9, 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 testing proposals set out in the registration dossier for **Mono- and/or di- and/or tri(1-phenylethyl)-m-cresol and p-cresol, EC No 700-427-9**, submitted by [redacted] (Registrant), latest submission number [redacted] for 100-1000 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, 7.16. Dissociation constant;
- Annex IX, 7.17. Viscosity;
- Annex IX, 8.7.3. Two-generation reproductive toxicity study in rats: oral route;
- Annex IX, 8.7.2. Pre-natal developmental toxicity study: oral route; and
- Annex IX, 8.6.2. Repeated dose toxicity, sub-chronic toxicity study in rats: oral route.

The examination of the testing proposal was initiated on 1 October 2010.

ECHA opened a third party consultation for testing proposals including testing on vertebrate animals that was held from 1 December 2010 until 17 January 2011 and received some comments (see Section III below).

On 31 March 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.

The Registrant did not provide any comments on the draft decision.

On 17 June 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 20 July 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 within 30 days of the receipt of the notification.

ECHA reviewed the proposals for amendment received and modified the draft decision accordingly.

On 1 August 2011, the modified draft decision was referred to the Member State Committee.

On 19 August 2011 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 20-23 September 2011, the Member State Committee further modified the draft decision. A unanimous agreement of the Member State Committee on the modified draft decision was reached in written procedure on 30 September 2011.

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 tests using the indicated test method while taking full account of the obligation to possibly agree on sharing of information and costs with other registrants at a later stage:

- Dissociation constant using the partition coefficient method, as described in the ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7a, p.174, Annex IX, 7.16.;
- Viscosity according to OECD Guideline 114, Annex IX, 7.17.;
- Pre-natal developmental toxicity study in rats: oral route, according to EU Method B.31 (OECD Guideline 414), Annex IX, 8.7.2.;
- Sub-chronic toxicity study (90-day) in rats: oral route, according to EU Method B.26 (OECD Guideline 408), Annex IX, 8.6.2.;

Pursuant to Article 40(3)(d) of the REACH Regulation the proposed two-generation reproductive toxicity study in rats, oral route, for provision of Annex IX, 8.7.3. is currently 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.

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation, the Registrant shall submit to ECHA an update of the dossier by **24 April 2013**.

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.

a) Dissociation constant

According to Section 7.16. of Annex IX of the REACH Regulation dissociation constant is standard information requirement that is currently not available in the technical dossier. Therefore, the test for dissociation constant is required.

b) Viscosity

According to Section 7.17. of Annex IX of the REACH Regulation viscosity is standard information requirement that is currently not available in the technical dossier. Therefore, the test for viscosity is required.

c) Pre-natal developmental toxicity study

According to Section 8.7.2. of Annex IX of the REACH regulation the pre-natal developmental toxicity study is a standard information requirement that is currently not available in the technical dossier.

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

1. A third party suggested the use of a qualitative or quantitative structure-activity relationship model ((Q)SAR), the nonlinear classification ANN QSAR Model for Combined Repeated Dose Toxicity Study with the Reproduction Developmental Toxicity (QMRF reference number: Q17-10-31-264).

ECHA examined the model and its results and concluded the following:

1) In order to use results of a QSAR model instead of testing as required by Annex XI, 1.3 of the REACH Regulation, the results should be adequate

and for the purpose of classification and labelling and/or risk assessment. However, the model output of the QSAR model provided is only in the form "toxic/non-toxic" which is sufficient neither for the purpose of classification and labelling nor for risk assessment (especially for derivation of DNEL).The endpoint concerned in the model is combined repeated dose toxicity with reproduction/developmental toxicity screening which cannot be considered equivalent to the information that a developmental toxicity test would provide. Therefore the information for this endpoint in the Molcode model cannot be considered adequate for providing information for developmental toxicity as standalone information. In addition, in the evaluation made by the Joint Research Centre (24522/2010), evaluation on QSAR models and software tools for predicting developmental and reproductive toxicity, Molcode models were referred as "a range of modules for predicting toxicological endpoints and ADME (absorption, distribution, metabolism, elimination) properties between the endocrine activity". Endocrine activity could be relevant for the endpoint of the testing proposal. However, since the mechanisms of pre-natal developmental toxicity can be some other than endocrine activity, the QSAR model results provided alone are not sufficient to be used instead of testing.

2) In order to use results of a QSAR model instead of testing as required by Annex XI, 1.3 of the REACH Regulation, the substance should fall within the applicability domain of the QSAR model. However, the third party did not provide QPRF (QSAR Prediction Reporting Format), therefore no assessment of the accuracy of the model prediction can be made. Based on the information provided in the QMRF(QSAR Model Reporting Format), the possibility that the registered substance does not fall within the structural applicability domain of the model cannot be ruled out.

3) In order to use results of a QSAR model instead of testing as required by Annex XI, 1.3 of the REACH Regulation, adequate and reliable documentation of the applied method should be provided. However, 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. 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. For application of the model, an access to specific software is required.

Therefore, ECHA concludes that on this occasion, the information submitted does not meet the conditions for the (Q)SAR adaptation set out in Annex XI, Section 1.3. Therefore, it cannot constitute an acceptable adaptation to the standard test in question.

2. A third party proposed to perform a validated *in vitro* test for the evaluation of the embryotoxic potential instead of a developmental toxicity study (prenatal developmental toxicity study, OECD Guideline 414).

ECHA examined the proposal and concluded the following:

According to Article 13(1) and Annex XI, 1.4 of the REACH Regulation, confirmation of negative results obtained using *in vitro* methods is required. However, such confirmation may be waived if: a) results are derived from an *in*

vitro method whose scientific validity has been established by a validation study, according to internationally agreed validation principles, b) results are adequate for the purpose of classification and labelling and/or risk assessment, and c) adequate and reliable documentation of the applied method is provided.

The evaluation of the submitted information shows that:

- The three suggested tests have been declared to be scientifically validated according to ECVAM. This is also stated in the REACH Guidance, Chapter R.7a (R.7.6 Reproductive and developmental toxicity). However, the REACH Guidance R.7a (R.7.6 Reproductive and developmental toxicity) also states that there are a number of weaknesses in the design of both the validation study and of the *in vitro* tests that have been identified, such as the limited number and range of substances tested, and absence of a biotransformation system, which have led to the conclusion that the tests currently have limited value in a regulatory context. The REACH Guidance also states that while a positive result in an *in vitro* test could provide justification for further testing, such a result in isolation would not be adequate to support hazard classification.
- The comments do not provide information on the registered substance or a prediction of its properties, and cannot be deemed as providing adequate results for its classification and labelling and/or risk assessment, as required by point b) above. As such, they cannot be considered an adaptation of the standard information requirements according to Annex XI, 1.4.

Therefore, ECHA concludes that in 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 testing in question.

3. A third party proposed the use of the TTC concept (Threshold of Toxicological Concern) in order to evaluate if exposure is negligible. However, the Registrant has not proposed to adapt the information requirement on the basis of Annex XI, Section 3 of the REACH Regulation. Furthermore, based on the exposure assessment carried out by the Registrant the conditions in Annex XI, Section 3.2 (a) (i) "absence or no significant exposure" are not met.

The argumentation provided by the third party does not allow an adaptation of the information requirement for a pre-natal developmental toxicity study using the specific rules under column 2 of Annex IX, 8.7.2 of the REACH Regulation.

d) Repeated dose toxicity: oral route

According to Section 8.6.2. of Annex IX of the REACH regulation the sub-chronic toxicity study (90 day) is a standard information requirement that is currently not available in the technical dossier.

During the third party consultation, ECHA received following comments/information on the testing proposal for the repeated dose toxicity study:

1. A third party proposed to use extended one-generation study to waive/evaluate the need for sub-chronic study: It was stated that "Offspring is indirectly exposed to the chemical during lactation and can be directly treated at weaning (21 days after

delivery) up to 90 days after delivery." and "On the extended one-generation study clinical observations and pathology examinations are performed on all animals for sign of toxicity."

ECHA examined the proposal and concluded the following:

Since the extended one-generation study is not accepted to replace both two-generation study and prenatal developmental toxicity studies or either of these, there is no point to replace 90-day study by an extended one-generation study, since it requires more animals when offspring is included. Furthermore, the extended one-generation study does not fully correspond to a 90-day study, since in extended one-generation study offspring is exposed even before delivery and during lactation whereas in the 90-day study animals are exposed only after weaning. Therefore, the extended one-generation study cannot be used to fulfil the data gap concerning sub-chronic toxicity study.

2. A third party proposed the use of the TTC concept (Threshold of Toxicological Concern) in order to evaluate if exposure is negligible. However, the Registrant has not proposed to adapt the information requirement on the basis of Annex XI, Section 3 of the REACH Regulation. Furthermore, based on the exposure assessment carried out by the Registrant the conditions in Annex XI, Section 3.2 (a) (i) "absence or no significant exposure" are not met.

The argumentation provided by the third party does not allow an adaptation of the information requirement for a 90-day sub-chronic toxicity study using the specific rules under column 2 of Annex IX, 8.6.2 of the REACH Regulation.

e) Reproductive toxicity study (two-generation study): oral route

According to Section 8.7.3. of Annex IX of the REACH regulation a two-generation reproductive toxicity study is required if the 28-day or 90-day study indicates adverse effects on reproductive organs or tissues. According to the Registrant's conclusions, the dermal 28-day study showed no adverse effects on reproductive tissues or organs and accordingly there would currently be no grounds for a two-generation study at this tonnage level. Therefore, the conditions for requiring a two-generation reproductive toxicity study are not currently fulfilled. ECHA concludes that at this moment in time the legal requirements of Annex IX for the mandatory performance of the two-generation study are not met. The Registrant in his comments on the proposals for amendment agreed that this test should be postponed until the results of the sub-chronic toxicity study are available. He did not indicate any reasons for performing the study immediately. On this basis the testing proposal is currently rejected. If the 90-day study shows adverse effects on reproductive organs or tissues, the Registrant shall submit a testing proposal to cover the endpoint 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 this end-point. Such reasons for testing should be specified.

During the third party consultation, ECHA received the following comments/information on the testing proposal for the two-generation reproductive study:

1. A third party proposed a strategy of four elements to avoid performance of a two-generation study:

    1) To conduct a sub-chronic toxicity study (90-day oral Toxicity Study, OECD Guideline 408) with additional reproduction toxicity parameters instead of a two-generation reproductive toxicity study (OECD Guideline 416). The third party refers to a previous decision taken by ECHA (((triethoxysilyl)methyl)morpholine, EC 480-370-1) in which a modified 90-day study was accepted to study reproductive toxicity.
    2) To 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). In addition, a study of Piersma and colleagues (2010) is referred which concludes that the second generation mating will rarely provide critical information and therefore supports the use of extended one-generation study in regulatory risk assessment.
    3) To use the threshold for toxicological concern (TTC) approach for reproduction toxicity endpoints.
    4) To use the results the combined reproduction/developmental toxicity study (OECD 421) and physico-chemical, toxicological and ecotoxicological characteristics to waive reproductive toxicity tests, since no evidence of toxicity was seen in any of the tests available.

ECHA examined this proposal and concluded the following:

ECHA agrees that dermal 28-day study or screening study for reproductive toxicity did not indicate the need for a two-generation study at this tonnage level. However, if the 90-day study shows adverse effects on reproductive organs or tissues the registrant shall submit a testing proposal for an appropriate highest tier reproductive toxicity study.

As this element of the third party comment is sufficient to reject the proposed two-generation reproductive toxicity study, there is no need to address the other elements submitted by the third party.

f) Deadline for submitting the required information

In the draft decisions communicated to the Registrant the time indicated to provide the requested information was 36 months from the date of adoption of the decision. This period of time took into account the fact that the draft decisions also requested a 2-generation reproductive toxicity study. As the testing proposal for this study has now been rejected, ECHA considers that a reasonable time period for providing the remaining required information in the form of an updated IUCLID5 dossier is 18 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

IV. Avoidance of unnecessary testing by data and cost sharing

The Registrant is hereby designated already now to perform the above mentioned tests in accordance with Article 53(1) of the REACH Regulation in case the same substance is registered by further registrant(s) at a later stage. This is to avoid unnecessary testing and the duplication of tests as a general aim of the REACH Regulation (Article 25). The legal text foresees the sharing of information between registrants.

In case a compliance check is carried out on another registration for the same substance and a standard information requirement is not met therein but requested from the Registrant of this decision, ECHA will inform the subsequent registrant of the this decision. The costs of the test shall be shared equally and the Registrant shall provide each of the other registrant(s) concerned with a copy of the full study report. This is stipulated by Article 53(2) and (3) of the REACH Regulation.

V. 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.*"

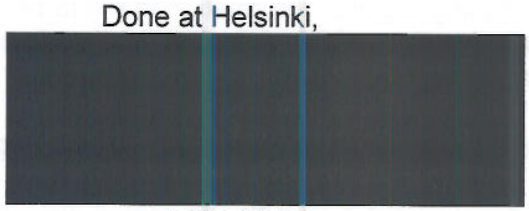
According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the 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 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.

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.

Done at Helsinki,



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