ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000001886-63-05/F Helsinki, 21 June 2012

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

For 947-19-3_Hydroxycyclohexyl phenyl ketone, CAS 947-19-3 (EC No 213-426-9), 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 **947-19-3_Hydroxycyclohexyl phenyl ketone**, CAS 947-19-3 (EC No 213-426-9), submitted by [redacted] (Registrant), latest submission number [redacted] for > 1000 tonnes per year.

In accordance with Articles 10(a)(ix) and 12(1)(e) 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 Annexes IX and X:

- Sub-chronic oral toxicity study (90-day) (OECD Guideline 408)
- Pre-natal developmental toxicity study (OECD Guideline 414)
- One-generation reproduction toxicity study (OECD Guideline 415)

The present decision relates solely to the examination of the testing proposals for sub-chronic oral toxicity study (90-day) and pre-natal developmental toxicity study. The testing proposal for the one-generation reproductive toxicity study is addressed in a separate decision although all testing proposals were initially addressed together in the same draft decision.

The examination of the testing proposals was initiated on 3 August 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 28 February 2011 until 14 April 2011. ECHA received the comments from the third party concerning:
Comment 1: the use of existing toxicological data, *in vitro* tests, QSAR modelling, and TTC (Threshold of Toxicological Concern) concept, and conducting an extended one-generation reproductive toxicity study.
Comment 2: the use of nonlinear classification ANN QSAR Model for pre-natal developmental toxicity study.

On 15 November 2011 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 15 December 2011 the Registrant did not provide any comments on the draft decision to ECHA.

On 20 January 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. Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision. ECHA has reviewed the proposals for amendment received and decided not to modify the draft decision.

On 23 February 2012 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 within 30 days of the receipt of the notification.

On 5 March 2012 ECHA referred the draft decision to the Member State Committee.

On 19 March 2012 following an informal discussion the Member State Committee amended the draft decision.

On 23 March 2012 the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant into account.

The draft decision was split into two draft decision documents: one relating to the testing proposal for a one-generation reproductive toxicity study and one relating to the testing proposals for a sub-chronic toxicity study and a pre-natal developmental toxicity study.

After discussion in the Member State Committee meeting on 24-27 April 2012, the Member State Committee reached unanimous agreement on the draft decision relating to the testing proposal for a sub-chronic toxicity study and a pre-natal developmental toxicity study at the meeting on 25 April 2012 and 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 tests using the indicated test method:

1. Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, 8.6.2., test method: EU B.26 /OECD 408),
2. Pre-natal developmental toxicity study in rats, oral route (Annex IX, 8.7.2., test method: EU B.31 /OECD 414).

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. The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI. If the Registrant considers that testing is necessary to fulfil this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species.

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.

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation, the Registrant shall submit to ECHA **by 23 December 2013** 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.

a) Examination of the testing proposals

- Sub-chronic toxicity study (90-day)

A sub-chronic toxicity study (90-day) is a standard requirement as laid down in Annex IX, 8.6.2., of the REACH Regulation. The information for 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 generate the data for this endpoint.

The Registrant proposed testing by the oral route. In the 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. The Registrant did not specify the species to be tested. According to the test method EU B.26/OECD 408 the rat is the preferred rodent species. ECHA considers this species as being appropriate.

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.

- Pre-natal developmental toxicity study

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 for 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 generate the data 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 as a first species to be used.

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, oral route (test method: EU B.31/OECD 414) using the registered substance.

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

b) Consideration of the third party consultation

ECHA reviewed third party information concerning the testing proposals during the public consultation. For the reasons further below the information provided by third parties is not sufficient to fulfil these information requirements.

Comment 1:
A third party has proposed the following information for ECHA to consider, i.e. the use of *in vitro* tests, QSAR modelling, and TTC (Threshold of Toxicological Concern) concept.

Considering that ECHA invited submission of "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal", as specified by Article 40(2), ECHA concludes that the proposed information does not sufficiently address the relevant endpoint. Consequently, ECHA concludes that the information provided is not a basis for rejecting the testing proposed.

In addition, the third party proposed to use the existing toxicological data and to conduct an extended one-generation reproductive toxicity study to waive the pre-natal developmental toxicity test.

ECHA notes that the pre-natal developmental toxicity study is a standard information requirement according to Annexes IX and X, 8.7.2. of the REACH Regulation. The information provided by the third party does not meet the specific

rules for adaptation of the information requirement for reproductive toxicity studies under column 2 of Annexes IX and X, 8.7. Specifically, it was shown from toxicokinetic data that systemic absorption occurs via relevant routes of exposure. Therefore, the third party proposal does not provide a sufficient basis on which to reject the proposed tests.

The third party has further proposed to conduct an extended one-generation reproductive toxicity study (EOGRTS) instead of pre-natal developmental toxicity study.

(i) The third party has proposed to conduct an extended one-generation reproductive toxicity study (EOGRTS) instead of a pre-natal 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.

Therefore, ECHA concludes that the third party proposal does not provide a sufficient basis on which to reject the proposed tests.

Comment 2:
A prediction using the ANN QSAR Model for pre-natal developmental toxicity study giving the result toxic was provided. The dependent variable of the model is in the form "toxic/non-toxic". Annex XI, 1.3 governing QSAR models requires that information concerning the validity, applicability domain, adequacy for classification and labelling and/or risk characterisation, and documentation of the method to be provided. As this information was not provided, ECHA concludes that the model fails to meet the criteria of Annex XI, 1.3. The predicted result can therefore not be directly used or extrapolated to fill the information requirement in question.

In the draft decision 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 decision also requested a reproductive toxicity study according to the standard information requirements of Annex X, 8.7.3 of the REACH Regulation. As the testing proposal for this study is not addressed in the present draft decision, ECHA considers that a reasonable time period for providing the 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. 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."*

ECHA
EUROPEAN CHEMICALS AGENCY

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 the technical progress. 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.

[redacted]
Jukka Malm
Director of Regulatory Affairs