ECHA
EUROPEAN CHEMICALS AGENCY

For final decision: TPE-D-0000001878-60-05/F Helsinki, 13 June 2012

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

For 2-hydroxy-2-methylpropiophenone, CAS No 7473-98-5 (EC No 231-272-0), 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 testing proposals set out in the registration dossier for 7473-98-5_2-hydroxy-2-methylpropiophenone, CAS No 7473-98-5 (EC No 231-272-0) 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 Annex X:

- Sub-chronic toxicity study (90-day), in combination with a 1-generation study
- Pre-natal developmental toxicity study
- One-generation reproductive toxicity study, which "might be combined with a 90-day oral toxicity study", to meet the requirement of a two-generation reproductive toxicity study.

The present decision relates solely to the examination of the testing proposal for a Sub-chronic toxicity study (90-day), in combination with a 1-generation study, and for 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.

The examination of the testing proposals was initiated on 6 September 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 15 March 2011 until 29 April 2011. ECHA received comments from third parties following this public consultation.

On 4 January 2012 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 1 February 2012, the Registrant commented on the draft decision by expressing agreement with the draft decision.

ECHA considered the Registrant's comments received and did not amend the draft decision.

On 2 March 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 the Member States submitted proposals for amendment to the draft decision. ECHA has reviewed the proposals for amendment received and decided not to amend the draft decision.

On 4 April 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 for amendment within 30 days of the receipt of the notification.

On 16 April 2012 ECHA referred the draft decision to the Member State Committee.

On 3 May 2012 April the Registrant provided comments on the proposed amendments. 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 two-generation reproductive toxicity study and one relating to the testing proposals for sub-chronic toxicity study 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 sub-chronic toxicity study and a pre-natal developmental toxicity study was reached on 21 May 2012 in a written procedure launched on 10 May 2012.

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)(b) of the REACH Regulation the following testing proposals have been accepted subject to the conditions set out further below:

a. Sub-chronic toxicity study (90-day) (Annex IX, 8.6.2, EU method B.26) in rat by the oral route
b. Pre-natal developmental toxicity study (Annex IX, 8.7.2, EU Method B 31) in rat by the oral route

while the originally proposed one-generation reproduction toxicity study, in an unspecified combination with a 90-day oral toxicity study" for provision of Annex IX 8.7.2. and 8.7.3. is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **13 June 2014** an update of the registration dossier containing the information required by this decision.

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 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 draft decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 24 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

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.

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.

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

For the reasons set out below ECHA has pursuant to Article 40(3)(b) imposed the following tests subject to certain conditions.

a. Sub-chronic toxicity study: oral route

Pursuant to Article 40(3)(b) of the REACH Regulation ECHA may adopt a decision requiring the Registrant to carry out the proposed tests but modifying the conditions under which the test is to be carried out.

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. The Registrant did not propose a guideline for conducting the study, and further stated "a combination with a 1-Generation study is anticipated". The Registrant did not provide a test guideline, or detailed methods, for conducting such a study. According to Article 13(3), "[w]here tests on substances are required to generate information on intrinsic properties of

substances, they 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 Agency as being appropriate." Accordingly, the conditions of the testing proposal of the Registrant have been modified in so far as (i) the test shall be performed in accordance with EU method B.26, in rat by the oral route, to meet the requirement of Annex IX, 8.6.2 and (ii) the test should not be performed in combination with a 1-Generation study.

For the reasons set out below the arguments provided by the third party do 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, or under Annex XI of the REACH Regulation. Therefore, the Registrant is required to carry out the test.

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

1. Use data from 28-day dose range finding study and other toxicological data (IUCLID dossier) as Weight of Evidence
2. Inclusion in CANADA domestic substance list (2007)
3. Alternatively, apply the grouping approach on repeated dose toxicity assessment for 2-hydroxy-2-methylpropiophenone and (1-hydroxycyclohexyl) (phenyl)methanone
4. Exposure considerations: use the TTC for repeated dose end point.

ECHA examined the proposals and concluded the following:

1. The information provided does not provide sufficient weight of evidence to adapt the information requirement. The availability of predictions (no "alerts"), a 28-day result on an analogous substance, and the use of Assessment Factors are not a basis individually for adapting the testing requirement, and do not add up to a sufficient weight of evidence. The Weight of Evidence fails the requirements of Annex XI, 1.2.
2. The 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 Proposal(s). Additionally, the reported findings from databases (US EPA ACTOR, JRC ESIS) do not provide a basis for adaptation of the testing requirement for repeated-dose toxicity according to column 1 or column 2 of Annex IX, 8.6.2, or Annex XI.
3. Grouping and read-across between the registered substance and (1-hydroxycyclohexyl) (phenyl)methanone is proposed. The proposed read-across is not adequately documented (a prerequisite for read-across), involves extrapolation (only interpolation allowed under Annex XI, 1.5), and does not allow the conclusion that the human health effects of the registered substance may be predicted from the reference substance. The read-across fails three requirements of Annex XI, 1.5.
4. The third party proposed the use of the TTC concept (Threshold of Toxicological Concern) in order to evaluate if exposure is negligible.

The 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 Proposal(s). Additionally, 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.

b. Pre-natal developmental toxicity study

Pursuant to Article 40(3)(b) of the REACH Regulation ECHA may adopt a decision requiring the Registrant to carry out the proposed tests but modifying the conditions under which the test is to be carried out.

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.

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.

For the reasons set out further below the arguments provided by the third party do 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, or under Annex XI, of the REACH Regulation. Therefore, the Registrant is required to carry out the proposed test.

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

1. 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).
2. Alternatively, apply the grouping approach on reproductive toxicity assessment (OECD 414, OECD 416) for 2-hydroxy-2-methylpropiophenone and (1-hydroxycyclohexyl) (phenyl)methanone

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3. Conduct and EOGRTS [[ECHA note- an Extended One-Generation Reproductive Toxicity Study]] instead of a 2-generation reproduction toxicity study (OECD Guideline 416) and use the results of the EOGRTS to waive the developmental toxicity study (Prenatal Developmental Toxicity Study, OECD Guideline 414).
4. Exposure considerations: use the TTC for reproduction toxicity end points.

ECHA examined the comments and concluded the following:

1. The 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 Proposal(s). Additionally, ECHA notes the following. Scientifically validated in vitro methods such as the embryonic stem cell test, the limb bud micromass culture and the whole embryo culture may provide additional information which can be assessed together with existing in vivo data in a weight of evidence approach. However, the mentioned in vitro tests only cover some of the reproductive toxicity endpoints, modes of action and mechanisms covered by the in vivo pre-natal developmental toxicity study and therefore they cannot be used on their own as replacement to testing according OECD Guideline 414. Furthermore, these alternative methods are not part of the information requirements laid down in Annex VII to X of REACH and can therefore not be requested by ECHA in the context of a testing proposal examination. ECHA notes that it is the Registrant's responsibility to establish the weight of evidence justification which demonstrates that any data that may be obtained from the conduct of the proposed tests would be sufficient to meet the information requirements when submitting and/or updating its registration dossier.
2. Grouping and read-across between the registered substance and (1-hydroxycyclohexyl) (phenyl)methanone is proposed. The proposed read-across is not adequately documented (a prerequisite for read-across), involves extrapolation (only interpolation allowed under Annex XI, 1.5), and does not allow the conclusion that the human health effects of the registered substance may be predicted from the reference substance. The read-across fails three requirements of Annex XI, 1.5.
3. The 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 Proposal(s). Additionally, the availability of a two-generation study is not, in itself, a basis for adaptation of the information requirement for Annex IX, 8.7.2 according to column 1 or 2, or Annex XI.
4. The third party proposed the use of the TTC concept (Threshold of Toxicological Concern) in order to evaluate if exposure is negligible. The 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 Proposal(s). Additionally, 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.

IV. Deadline for submitting the information

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 2-generation reproductive toxicity study. 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 24 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

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 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.

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.

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