EUROPEAN CHEMICALS AGENCY

Helsinki, 18 June 2012

Decision number: CCH-D-0000002035-85-06/F

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For Tetrahydro-4-methyl-2-(2-methylpropyl)-2H-pyran-4-ol, CAS No [redacted] (EC No 405-040-6), 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 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration dossier for the ECHA has performed a compliance check of the registration dossier for Tetrahydro-4-methyl-2-(2-methylpropyl)-2H-pyran-4-ol, CAS No. [redacted] (EC No. 405-040-6) submitted [redacted] (Registrant), latest submission number [redacted], for the tonnage band of 100 to 1000 tonnes per year.

The compliance check was initiated on 11 October 2011.

On 2 November 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.

On 1 December 2011 the Registrant provided to ECHA comments on the draft decision.

ECHA reviewed the further information received and amended the draft decision accordingly.

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.

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 the proposals for amendment within 30 days of the receipt of the notification.

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

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

On 22 March 2012 the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant into account.

A unanimous agreement of the Member State Committee on the draft decision was reached on 11 April 2012 in a written procedure launched on 28 March 2012.

This compliance check decision does not prevent ECHA to initiate further compliance checks on the present dossier at a later stage.

II. Information required

Pursuant to Articles 41(1)(a) and (b), 41(3), 10(a)(vii), 12(1)(a), 13 and Annexes VIII - IX of the REACH Regulation the Registrant shall submit the following information using the test method as indicated on:

a. Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, 8.6.2.; test method: EU B.31/OECD 408);
b. Screening for reproduction/developmental toxicity in rats, oral route (Annex VIII, 8.7.1.; test method: OECD 421);
c. Pre-natal developmental toxicity study in rats, oral route (Annex IX, 8.7.2.; test method: EU B.31/OECD 414).

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated IUCLID dossier to ECHA **by 18 June 2014**.

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. The Registrant shall consult the Guidance on information requirements and chemical safety assessment (Version 1.1., May 2008, Chapter R.7.A, Section R.7.6.6.3., page 365) to follow the integrated testing strategy for reproductive toxicity testing. In general, it should be noted that the OECD TG 414 (EU B.31) study does not incorporate post-natal parameters and therefore it is advisable not to bypass the screening study when a prenatal developmental toxicity study is triggered.

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

Based on the examination of the technical dossier, ECHA concludes that the information therein, submitted by the Registrant for registration of the above mentioned substance for the purpose of registration within the applicable tonnage band of 100 to 1000 tonnes per year in accordance with Article 6 of the REACH Regulation, does not comply with the requirements of Articles 10, 12 and 13 and with Annexes VIII, IX and XI thereof. Consequently, the Registrant is requested to submit the information mentioned above that is needed to bring the registration into compliance with the relevant information requirements for the endpoints subject to this decision.

Missing information related to endpoints

Pursuant to Articles 10(a)(vii), 12(1)(d) of the REACH Regulation, a registration for a

substance produced in quantities of 100 – 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

a. Sub-chronic toxicity study (90-day) (Annex IX, 8.6.2.)

A 90-day repeated dose toxicity study is a standard information requirement of Annex IX, 8.6.2. at the present tonnage level. The data is not available in the registration dossier.

The Registrant proposes to adapt the standard information requirements based upon exposure scenarios developed in the chemical safety assessment with reference to Annex XI, section 3 of the REACH Regulation.

The Registrant states that adequate risk assessment can be derived based on extrapolation from existing data. Moreover, the Registrant claims that appropriate assessment factors would have been taken into account for the derived no effect level (DNEL) derivation concerning workers and consumers.

The justification provided by the Registrant does not meet the conditions of Annex XI, section 3.2. Section 3.2(a) requires that all of the following conditions are met:

1) The results of the exposure assessment covering all relevant exposures through the life-cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses referred to in Annex VI, section 3.5.
2) A DNEL can be derived from results of available test data for the substance concerned taking full account of the increased uncertainty resulting from the omission of the information requirement. The footnote to this subparagraph clarifies that without prejudice to column 2 of section 8.6 of Annexes IX and X, a DNEL derived from a 28-day repeated dose toxicity study shall not be considered appropriate to omit a 90-day repeated dose toxicity study.
3) The comparison of the derived DNEL with the results of the exposure assessment shows that exposures are always well below the derived DNEL.

As to the first point, the exposure assessment does not demonstrate the absence of or no significant exposure in all scenarios. For example, the risk characterisation ratios derived for workers in manufacturing process (PROC 8b RCR combined [redacted]) and in compounding (PROC 8a RCR combined [redacted]) cannot be seen as non significant.

As to the second point, the DNELs have not been derived according to the ECHA Guidance document (http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r8_en.pdf), but using ECETOC assessment factors without any further justification. When using the default assessment factors provided in the ECHA Guidance document R.8 the risks are not controlled for workers in manufacturing process and compounding (risk characterisation ratios >1). Moreover and decisively, the footnote to Annex XI section 3.2(a)(ii) states that use of additional assessment factors to derive a DNEL from a 28-day repeated dose toxicity study cannot be used to omit the 90-day repeated dose toxicity study.

As to the third point, due to the lack of a no observed adverse effect level (NOAEL) from a 90-day repeated dose toxicity study it is impossible to conclude that the exposures are always below the derived DNELs and hence give sufficient evidence that the substance can be used safely (Annex I, section 5).

For these reasons, the exposure based adaptations fail to meet the requirements of Annex XI, section 3 and cannot be considered as a valid adaptation of the information requirement. There is no data provided for this endpoint on the registered substance, and the information requirement for sub-chronic repeated dose toxicity (90-day) (Annex IX, section 8.6.2) has not been met.

The Registrant has proposed that should a study be requested, this should be performed via the dermal route as the most relevant route of exposure. In his comments to the draft decision on 1 December 2011 the Registrant referred to column 1 of Annex IX section 8.6.2. "most appropriate route of administration, having regard to the likely route of human exposure" emphasised that dermal administration would be most appropriate for testing because exposure for workers and consumers would occur via dermal route and oral exposure would be unlikely. However, column 2 of Annex IX, section 8.6.2 of the REACH Regulation specifies further criteria for the selection of the most appropriate route of administration mentioned in column 1. Column 2 of Annex IX, section 8.6.2 specifies that testing via dermal route is appropriate if,

1) Skin contact in production and/or use is likely; and
2) The physicochemical properties suggest a significant rate of absorption through the skin; and
3) One of the following conditions are met:
   a) Toxicity is observed in acute dermal toxicity test at lower doses than in the oral toxicity test, or
   b) Systemic effects or other evidence of dermal absorption is observed in skin and/or eye irritation study, or
   c) *In vitro* tests indicate significant dermal absorption, or
   d) Significant dermal toxicity or dermal penetration is recognised for structurally-related substances.

Whereas skin contact of the registered substance is likely and dermal absorption is possible due to the properties of the substance, toxicity in acute dermal toxicity tests was not observed at lower doses than in the oral toxicity test, no systemic toxicity effects were reported in the endpoint study records for skin and eye irritation, and no data is available from *in vitro* tests indicating significant dermal absorption. No data is available either that would show significant dermal toxicity or dermal penetration for structurally-related substances.

Moreover, oral exposure cannot be excluded, since it is known that oral exposure will happen even if primary exposure is dermal (inadverted ingestions from dermal to oral e.g. by touching mouth (Cherrie et al. 2006)) and indirectly via air exposure.

Hence, the conditions specified in the column 2 of Annex IX, section 8.6.2 have not been met. The oral route is the default route of exposure in the absence of specific reasons to choose another route as specified in the ECHA Guidance document R.7.5.(May 2008).

The Registrant is accordingly requested to submit the missing information for sub-chronic repeated dose toxicity (rat, oral route) for the registered substance by using the EU test method B.26 (or OECD 408).

b. Screening for reproductive/developmental toxicity (Annex VIII, 8.7.1) and,
c. Pre-natal developmental toxicity study (Annex IX, 8.7.2)

A screening study for reproductive/developmental toxicity is a standard information requirement of Annex VIII, 8.7.1 at the present tonnage level. A pre-natal developmental toxicity study is a standard information requirement of Annex IX, 8.7.2 at the present tonnage level. These data are not available in the registration dossier.

The Registrant proposes to adapt the standard information requirements based upon column 2 of Annexes VIII and IX, 8.7, respectively. The Registrant justifies adapting the standard information requirements as follows: "The substance is of low toxicological activity, it can be proven from toxicokinetic data that no systemic absorption occurs via relevant route of absorption and there is no or no significant human exposure. The column 2 of Annex VIII section 8.7.1 adaptation rules do not contain the possibility to adapt the standard information requirement based on low toxicity." In addition the Registrant states that adequate risk assessment can be built based on extrapolation from existing data.

The justification provided by the Registrant does not meet the conditions of column 2 of Annex IX, section 8.7. The column 2, third indent, provides that reproductive toxicity studies do not need to be conducted if the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via the relevant route of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure.

Firstly, the condition that specifies that no evidence of toxicity is seen in any of the test available has not been met. The results of the sub-acute toxicity study (28-day) showed effects at the test concentration of 625 mg/kg bodyweight/day. Secondly, the condition that it can be proven from toxicokinetic data that no systemic absorption occurs via the relevant route of exposure is not met. The Registrant has provided estimations in his justification to adapt the standard information requirement, that indicate that absorption occurs via the dermal route (estimated at <30 %), also the physico-chemical properties of the substance favours dermal penetration. In addition, the Registrant proposes to perform *in vitro* dermal penetration study with human and rat skin, and depending on the results of the *in vitro* study they may like to perform an *in vivo* toxicokinetic study via dermal route. This indicates as well that systemic absorption may occur. Consequently, there is no available toxicokinetic data that would prove that systemic absorption does not occur via the relevant route of exposure.

As to the last point, the technical dossier shows that there the condition of no or no significant exposure is not met, as pointed out above for the 90-day repeated dose toxicity study.

For the above reasons, the exposure based adaptation fails to meet the requirements of conditions of column 2 of Annexes VIII and IX, section 8.7 and cannot be considered as a valid adaptation of the information requirement. There is no data provided for these endpoints on the registered substance, and so the information requirements for screening study on reproductive/developmental toxicity (Annex VIII, 8.7.1) and for pre-natal developmental toxicity study (Annex IX, 8.7.2) have not been met.

The Registrant has proposed that should a study be requested in the future this should be performed via the dermal route as the most relevant route of exposure. In his comments on the draft decision on 1 December 2011 the Registrant referred to column 1 of Annex IX section 8.6.2. "most appropriate route of administration, having regard to the likely route of human exposure". The reasoning for the selection of the appropriate route for the screening and pre-natal developmental toxicity study is the same as specified under section III.a above.

The Registrant is accordingly requested to submit the missing information for the screening study on reproductive/developmental toxicity (rat, oral route) for the registered substance by using OECD TG 421 and for the pre-natal developmental toxicity study (rat, oral route) for the registered substance by using EU test method B.31 (or OECD 414).

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 an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on 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]

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