EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-0000003215-82-04/F Helsinki, 13 December 2013

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

For 2-(2-(4-methyl-3-cyclohexen-1-yl)propyl)cyclopentanone, CAS No 95962-14-4 (EC No 404-240-0), 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 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration dossier for 2-(2-(4-methyl-3-cyclohexen-1-yl)propyl)cyclopentanone, CAS No 95962-14-4 (EC No 404-240-0) submitted by [redacted] (Registrant).

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 10 to 100 tonnes per year. This decision does not take into account any updates after 8 March 2013, 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.

This compliance check decision does not prevent ECHA from initiating further compliance checks on the registration at a later stage.

The compliance check was initiated on 28 September 2010.

On 27 September 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. That draft decision was based on submission number [redacted].

On 21 October 2011 the Registrant provided comments on the draft decision to ECHA.

On 23 January 2012 the Registrant updated his registration dossier (submission number [redacted]).

ECHA considered the Registrant's comments and update received. On the basis of the comments and update, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 8 March 2013 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, one Competent Authority of a Member State submitted a proposal for amendment to the draft decision.

On 11 April 2013 ECHA notified the Registrant of the proposal for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on that proposal for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposal for amendment received and did not amend the draft decision.

On 22 April 2013 ECHA referred the draft decision to the Member State Committee.

By 13 May 2013 the Registrant did not provide any comments on the proposal for amendment but only comments on the draft decision. These comments were considered outside the scope of Article 51(5) and hence the Member State Committee did not take them into account.

A unanimous agreement of the Member State Committee on the draft decision was reached on 28 May 2013 in a written procedure launched on 17 May 2013. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

1) Pursuant to Articles 41(1)(a), 41(3) and 10(a)(ii) as well as Annex VI , section 2 of the REACH Regulation the Registrant shall submit for the registered substance:

   a. Typical ratio of (stereo) isomers (Annex VI, 2.2.2.);
   b. The description of the analytical methods or the appropriate bibliographical references for the identification of the substance (Annex VI, 2.3.7.).

2) Pursuant to Articles 41(1)(a) and (b), 41(3), 10(a)(vi), 12(1)(c), 13 and Annex VIII of the REACH Regulation the Registrant shall submit the information using the test method as indicated on:

   a. Mutagenicity - in vitro gene mutation study in mammalian cells (Annex VIII, 8.4.3.; EU Method B.17/ OECD TG 476);
   b. Screening for reproductive/developmental toxicity test in the rat by the oral route (Annex VIII, 8.7.1.; test method OECD Guideline 421 or 422).

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated registration to ECHA by **14 December 2015.**

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 the column 2 provisions of the respective Annex and those contained in Annex XI of the REACH Regulation.

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 10 to 100 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 VI and VIII** 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.

1) Missing information related to substance identity

Pursuant to Article 10(a)(ii) and Annex VI, section 2 of the REACH Regulation, the technical dossier of the registration shall include information on the identity of the substance that shall be sufficient to identify it.

a. Typical ratio of (stereo) isomers

The registered substance contains three chiral centers covering eight different stereoisomers. However, the Registrant did not provide any information on the ratio of stereoisomers present in the composition of the substance, as required under Annex VI, Section 2.2.2. of the REACH Regulation.

In response to ECHA's draft decision sent on 27 September 2010, the Registrant updated the dossier on 23 January 2012. The information requested, however, has been only partially included in an analytical report attached in section 1.4 of the IUCLID dossier. Such analytical report shows the ratio of certain groups of isomers present in the substance. Information on the ratio of each stereoisomer present in the substance has not been provided.

The Registrant is therefore requested to specify the identity and typical ratio of the different stereoisomers of 2-(2-(4-Methyl-3-cyclohexen-1-yl)propyl)cyclopentanone.
Regarding how to report the information on the ratio of stereoisomers in IUCLID, the following applies: The Registrant shall report the chemical name and the corresponding typical ratio of the 8 different stereoisomers in the Remarks field under the reference substance assigned in IUCLID section 1.2 of the registration dossier.
The Registrant shall ensure that the IUPAC name and the molecular and structural information assigned in IUCLID section 1.1 for the registered substance are consistent with the identity of the main stereoisomers present in the composition.

b. The description of the analytical methods

The technical dossier does not contain any details on the analytical methods used for the identification and quantification of the different stereoisomers present in the composition of the registered substance, as required pursuant to Annex VI, Section 2.3.7 of the REACH Regulation. In response to ECHA's draft decision sent on 27 September 2010 the Registrant updated the dossier on 23 January 2012. The information requested, however, has been only partially included in an analytical report attached in section 1.4 of the IUCLID dossier. Such analytical report shows the ratio of certain groups of isomers present in the substance. Information on the ratio of each stereoisomer present in the substance has not been provided.

The Registrant is therefore requested to provide the necessary description of the analytical methods for the identification of the registered substance. The information shall be sufficient for the methods to be reproduced and shall therefore include complete details of the experimental protocol followed, the calculation made and the results obtained.
This information should be attached in IUCLID section 1.4 of the registration dossier.

The Registrant shall provide any information that is suitable and appropriate to meet the above-mentioned objectives.

2) Missing information related to endpoints

Pursuant to Articles 10(a)(vi), 12(1)(c) of the REACH Regulation, a registration for a substance produced in quantities of 10 – 100 tonnes per year shall contain as a minimum the information specified in Annexes VII - VIII of the REACH Regulation.

a. Mutagenicity - *in vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3.)

The technical dossier contains the results of an *in vitro* gene mutation study in bacteria, showing negative results and an *in vitro* micronucleus test, showing negative results. According to Annex VIII, 8.4.3. of the REACH Regulation information on *in vitro* gene mutation study in mammalian cells is required, if the negative results are obtained in the tests in *in vitro* gene mutation study in bacteria and the *in vitro* micronucleus test or *in vitro* cytogenicity study.

However, the *in vitro* gene mutation study in mammalian cells is not included in the technical dossier. The Registrant provides a waiving justification for omitting this information based on the fact that the substance was previously notified by another registrant under Council Directive 67/548/EEC.

The waiving justification provided by the Registrant does not meet the specific rules for adaptation of the information requirement for mutagenicity under column 2 of Annex VIII, 8.4.3., nor the general rules contained under Annex XI of the REACH Regulation.

In response to ECHA's draft decision the Registrant in the updated dossier provided the following waiving justification under section In vitro genetic toxicity (7.6.1.) of the technical dossier:

"Data from a reliable in vivo mammalian gene mutation test (an *in vivo* mouse micronucleus assay according to OECD 474) are available and reported in the IUCLID dossier. Therefore, according to the specific rules for adaptation in Annex VIII of the REACH regulation, under point 8.4.3, this study does not need to be conducted".

Therefore, the Registrant provided a waiving justification for omitting the required information based on the fact that there is an in vivo mammalian gene mutation test available in the technical dossier.

However, ECHA notes that the test "*in vivo* mouse micronucleus assay according to OECD 474" referred to by the Registrant in accordance to ECHA guidance on R.7.7.6.3., Chapter R.7a, page 344 of the Guidance on information requirements and chemical safety assessment (version 2.0., November 2012),) is not considered as an *in vivo* mammalian gene mutation test. The following test methods are suitable *in vivo* mammalian gene mutation tests: Unscheduled DNA synthesis (UDS) test with mammalian lever cells in vivo (EU B.39, OECD 486), Transgenic rodent gene mutation assays (OECD 488) and in vivo Comet assay (no EU or OECD guideline), none of which are available in the technical dossier.

The *in vivo* micronucleus study, provided in the technical dossier does not address the ability to induce gene mutation in mammalian cells, because it covers only the chromosomal aberration and aneugenic potential. Therefore, the waiving justification provided by the Registrant does not meet the specific rules for adaptation of the information requirement for mutagenicity under column 2 of Annex VIII, 8.4.3., nor the general rules contained under Annex XI of the REACH Regulation.

Therefore, the currently available results from the test battery on genotoxicity in the technical dossier do not cover gene mutation in mammalian cells. Consequently, the Mutagenicity - in vitro gene mutation study in mammalian cells (Annex VIII, 8.4.3.; EU Method B.17/ OECD TG 476) testing is required.

b. Screening for reproductive/developmental toxicity (Annex VIII, 8.7.1.;)

According to Annex VIII, 8.7.1. of the REACH Regulation information on screening for reproductive/developmental toxicity, one species is required if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. However, the screening for reproductive/developmental toxicity is not included in the technical dossier. The Registrant provides a waiving justification for omitting this information based on the fact that the substance was previously notified by another registrant under Council Directive 67/548/EEC.

The waiving justification provided by the Registrant does not meet the specific rules for adaptation of the information requirement for reproductive toxicity under column 2 of Annex VIII, 8.7.1., nor the general rules contained under Annex XI of the REACH Regulation.

In response to ECHA's draft decision the Registrant provided comments and updated the dossier with an exposure based waiving justification as an attachment in the technical dossier under Toxicity reproduction (section 8.7.1) and as part of the Chemicals Safety Report (CSR). As a justification the Registrant puts forward the following considerations: 1) Exposure considerations, 2) Adequate risk assessments based on existing data and 3) Consideration of the low toxicological activity of the substance. The Registrant states 'testing in accordance with section 8.7 (Reproductive toxicity) of Annex VIII may be omitted, based on exposure scenario(s) developed in the Chemical Safety Report (Annex XI, section 3).

With respect to point 3) Consideration of the low toxicological activity of the substance, the Registrant states the following:

"According to 8.7.1 of Annex IX of the REACH Regulation, testing does not need to be considered 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 relevant routes 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.

The substance is of low toxicological activity, it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure and there is no or no significant human exposure. Low toxicological activity of the substance. Studies on [redacted] *show no toxicological concerns and support the expected low toxicological activity of this substance.*
- [redacted] *is not mutagenic nor genotoxic in in vitro and in vivo studies.*
- A 28-day study via the dermal route (most relevant route of human exposure) showed no effects at the limit dose and provided a NOAEL of 1000mg/kg. No effects were seen on reproductive organs in this study. This information, in addition to the low human exposure as described above will be included in the updated waiving justification of the updated dossier".

ECHA has analysed the exposure scenarios (use of the registered substance as a [redacted] substance) and risk characterisation contained in the registration dossier.

ECHA considers that justifications provided by the Registrant do not meet any of the criteria specified in Annex XI, section 3.2. nor specific rules for adaptation under Annex VIII, section 8.7.1., column 2 of the REACH Regulation. The detailed reasoning in respect to both provisions is provided below.

Firstly, the justifications provided by the Registrant do not meet the conditions of Annex XI, section 3.2. (a) (i – iii) where all of the following conditions have to be met:

i. 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.

ii. 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 and that DNEL is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes.

iii. The comparison of the derived DNEL with the results of the exposure assessment shows that exposures are always well below the derived DNEL.

The specified above conditions are not met for the following reasons:

a. The quantitative Tier 1 exposure assessment provided, based on the ECETOC TRA assumption of 1% incorporation of the registered substance, indicates that exposure levels are beyond insignificant for occupational industrial exposure and occupational professional exposure as the majority of risk characterisation ratios are above 1 (some are significantly above 1; for example Proc 11 public domain (professional) RCR = [redacted]). The Registrant indicates that with personal protective equipment (wearing of gloves and protective clothing) and good manufacturing practice, "the real exposure values will be at least 5 fold lower". Given the uses listed in the

registration dossier, and the details presented in the CSR, worker exposure is likely in particular during the preparation of [redacted] (duration of exposure for this task is indicated as 1 – 4 hrs) and transfer to final small packaging container in the mixing room (duration of exposure for this task is indicated as > 4hrs). The Registrant indicated "Worker exposure to undiluted and diluted (in mixture) registered substance (and other substances) may occur". Therefore the criterion set out in 3.2.(a)(i) is not satisfied from the perspective of worker exposure.

b. Furthermore, the Registrant has stated that exposure of consumers is expected because the substance is used in a variety of consumer products. '[redacted] is a [redacted] of which 85% of the quantity produced is incorporated in to [redacted]. The remaining 15% is employed in [redacted] Production of the pure substance is outside of EU' and that '[redacted] is generally incorporated at up to [redacted]% in [redacted] (pre-formulations), which are then sold and incorporated into final consumer products at low levels'. Thus exposure to consumers cannot be ruled out and the criterion set out in 3.2.(a)(i) is not satisfied from the perspective of consumer exposure.

c. For the purpose of criterion 3.2(a)(ii) the Registrant has derived a DNEL using the available NOAEL for the registered substance; based on a 28-day repeated dose toxicity study via the dermal route this is 1000mg/kg bw/day. ECHA considers that the derived DNEL for a 28-day repeated dose toxicity study based on the dermal route is not relevant to the information requirement to be omitted and for risk assessment purposes as it may not be the *"most appropriate route of administration, having regard to the likely route of human exposure".* In accordance with column 2 of Annex VIII, section 8.6.1 testing via dermal route is appropriate if,

- Inhalation of the substance is unlikely; and
- Skin contact in production and/or use is likely; and
- The physicochemical and toxicological properties suggest potential for a significant rate of absorption through the skin.

The inhalation exposure may occur, since the substance is used in [redacted], however in very low concentrations as explained by the Registrant. Skin contact of the registered substance is likely. The physical chemical properties of the substance i.e. logPow of 5.4 and water solubility of 4.6 mg/L do not indicate a potential for significant rate of absorption through the skin and hence dermal absorption may not be favoured. Moreover, no systemic toxicity effects were reported in the endpoint study records for the 28-day repeated dose toxicity study via dermal route and for the acute dermal toxicity nor for skin and eye irritation, and no data is available from in vitro tests indicating significant dermal absorption. Hence, the existing information, together with the physicochemical properties and toxicological properties does not suggest a potential for a significant rate of absorption through the skin. Based on the aforementioned, all the conditions necessary for the dermal route selection are not met.

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.

Thus the derived DNEL based on a 28-day repeated dose toxicity study via the dermal route, may underestimate the risk.

Additionally, ECHA considers that the derived DNEL for a 28-day repeated dose toxicity study based on the dermal route is not appropriate to the information requirement to be omitted and for risk assessment purposes as the parameters addressed by a screening for reproductive/developmental toxicity test are not the same as by a 28-day repeated dose toxicity study. A screening for reproductive/developmental toxicity test addresses mating behaviour, fertility and peri-natal effects in accordance with the endpoint (Guidance on information requirements and chemical safety assessment (version 2.0., November 2012) paragraph 7.6.6.3., page 321). Whilst the Registrant notes that there are no adverse effects on the reproductive organs in the 28-day repeated dose toxicity study, the reason for that is that the above parameters are not assessed during a 28-day toxicity study.

Thus the criterion set out in 3.2.(a)(ii) is not satisfied as the derived DNEL is considered by ECHA not to be relevant and appropriate to the information requirement of a screening for reproductive/developmental toxicity test and for risk assessment purposes concerning effects on development.

d. Regarding criterion 3.2(a)(iii) requires that a comparison of the derived DNEL with the results of the exposure assessment shows that exposures are well below the derived DNEL. The Registrant indicates that the drived DNEL "provides a margin of safety of >1,000,000 over consumer exposures assuming 100% dermal penetration, and likely >>1,000,000 once dermal penetration is taken into account". However due to the lack of a no observed adverse effect level (NOAEL) from a 28-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). Also as the derived DNEL is considered not relevant and appropriate, ECHA consideres a comparison cannot be established.

Thus ECHA considers none of the conditions of criterion 3.2(a) for exposure-based adaptation are satisfied.

Secondly, the justifications provided by the Registrant do not meet conditions for Annex XI, section 3.2. (b) exposure based adaptation. Strictly controlled conditions as set out in Article 18(4)(a) to (f) are not demonstrated. In particular, condition (a) as set out in Article 18(4) does not appear to be fulfilled because it has not been demonstrated that the registered substance is rigorously contained by technical means during its whole lifecycle. Thus ECHA considers criterion 3.2(b) is not satisfied.

Thirdly, the criterion 3.2(c) of Annex XI concerns the substance incorporated in an article. Since the substance is not incorporated in an article within the meaning of Article 3(3) of the REACH Regulation, this criterion does not apply to this case.

Fourthly, ECHA considers that an adaptation of the Registrant based on column 2 of Annex IX section 8.7.1. does not apply to the current case.

The test requested by the current decision is the screening study for reproductive/developmental toxicity pursuant to Annex VIII, section 8.7.1. of the REACH Regulation. The adaptation referred to by the Registrant is relevant only for the tests requested under section 8.7.1. of Annex IX.

Additionally, ECHA points out that the assumptions of the Registrant that the registered substance is not mutagenic nor genotoxic in *in vitro* and *in vivo* studies are incorrect as no conclusion can be yet drawn based on available information and testing is requested in the current decision on an *in vitro* gene mutation study in mammalian cells study.

ECHA also notes that there is no available toxicokinetic data that would prove that systemic absorption does not occur via the relevant route of exposure. It is noted that there is only a sub acute 28-day repeated dose toxicity study via the dermal route and that the physico-chemical properties of the substance do not favour dermal penetration.).

For all of the above stated reasons, ECHA concludes that the justifications provided by the Registrant do not meet conditions specified in Annex XI, section 3.2. or Annex IX, section 8.7.1.. Consequently there is an information gap. Therefore the screening for reproductive/developmental toxicity in the rat, by the oral route (test method OECD Guideline 421 or 422) shall be performed with the registered substance.

IV. Adequate identification of the composition of the tested material

In carrying out the studies required by the present decision it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new studies must be suitable to assess these.

Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) 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 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]

Leena Ylä-Mononen
Director of Evaluation