ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-0000003041-91-04/F Helsinki, 22 March 2013

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

**For (E)-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one CAS No 79-77-6 (EC No 201-224-3), 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 the ECHA has performed a compliance check of the registration dossier for (E)-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one CAS No 79-77-6 (EC No 201-224-3) submitted by [redacted] (Registrant).

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after 2 November 2012, 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 to initiate further compliance checks on the registration at a later stage.

The compliance check was initiated on 21 December 2010 on the registration dossier with submission number: [redacted].

On 20 December 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 23 January 2012 the Registrant provided to ECHA comments on the draft decision.

On 7 May 2012 the Registrant updated his registration dossier (submission number [redacted])

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

On 2 November 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.

On 5 December 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.

ECHA reviewed the proposals for amendment received and decided to amend the draft decision.

On 17 December 2012 ECHA referred the draft decision to the Member State Committee.

On 3 January 2013 the Registrant provided comments on the proposed amendments. 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 21 January 2013 in a written procedure launched on 11 January 2013. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

1) Pursuant to Articles 41(1)(a) and 41(3), as well as Annex X of the REACH Regulation the Registrant shall submit the information using the test method as indicated on:

    a. ***Pre-natal developmental toxicity study on rabbit via the oral route*** (Annex X, 8.7.2.; test method: EU Method B.31/OECD test guideline 414).

2) Pursuant to Articles 41(1)(c), 41(3), 10(b) and 14 as well as Annex I of the REACH Regulation the Registrant shall submit in the chemical safety report (CSR):

    a. ***A transparent documentation for the derivation of PNECs, PECs and risk characterisation ratios (RCRs) for the soil and sediment compartments*** (Annex I, 3.3, 5. and 6. of the REACH Regulation). The Registrant shall provide the calculations used in his derivation of all the PNECs and PECs for his environmental risk assessment as an appendix to his CSR. This shall include numerical values for all constants and default input parameters.

    b. ***Revised risk characterisation ratios (RCRs) for microbial activity in sewage treatment systems*** (Annex I, 6. of the REACH Regulation). The Registrant shall provide correct calculations for RCR for microbial activity in sewage treatment systems.

    c. ***A transparent documentation for the environmental exposure assessment for exposure scenario "Production"*** (Annex I, 5.1. and 5.2. of the REACH Regulation; section 9.1 of the CSR). The Registrant shall provide as an appendix to his CSR numerical values for all constants and input parameters as well as the full output of the ECETOC TRA or EUSES models.

d. ***A transparent documentation for the environmental exposure assessment for exposure scenario "Compounding"*** (Annex I, 5.1. and 5.2. of the REACH Regulation; section 9.2 of the CSR). The Registrant shall provide evidence for justifying the wastewater emission value used to estimate environmental releases for all compounders. In addition he shall provide clear justification for the value of [redacted]% applied for the fraction used at main local source for the compounders.

e. ***A transparent documentation for the environmental exposure assessment for exposure scenario "Formulation"*** (Annex I, 5.1. and 5.2. of the REACH Regulation; section 9.3 of the CSR). The Registrant shall provide as an appendix to his CSR numerical values for all constants and default input parameters as well as the full output of the ECETOC TRA or EUSES models.

f. ***A full justification for the derivation of DNELs for workers and for the general population*** (Annex I, 1.4.1 of the REACH Regulation; section 5.11 of the CSR) in order to demonstrate that the following factors have been taken into account:
   - the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
   - the nature and severity of the effect;
   - the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies; and
   - that the DNELs reflect the likely route(s), duration and frequency of exposure.

   If the current derivation is not fully justified, the Registrant should reconsider the present DNEL and reassess related risks.

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 **22 March 2014.**

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, if relevant.

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 over 1000 tonnes per year in accordance with Article 6 of the REACH Regulation, does not comply with the requirements of Articles 10, 12, 13 and 14, as well as with Annexes I and VI-X 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 endpoints

Pursuant to Articles 10(a)(vii) and 12(1)(e) of the REACH Regulation, a registration for a substance produced in quantities above 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

a. Pre-natal developmental toxicity study on rabbit via the oral route (Annex X, 8.7.2.)

A prenatal developmental toxicity study on a first species is required under Annex IX, 8.7.2 to the REACH Regulation, and a developmental toxicity on a second species is required according to Annex X, 8.7.2, subject to all appropriate column 2 or Annex XI data adaptations.

The Registrant has provided data on developmental toxicity, and no adverse effects on prenatal development were observed in a study on rats up to and including the high dose level of 400 $mg/kg_{bw}/day$.

However, there is no information provided for the prenatal developmental toxicity test on a second species, nor is there any adequate adaptation of the information requirement. Therefore there is an information gap.

In response to ECHA's draft decision, the Registrant submitted new information and expressed his view that systemic exposure of humans could be regarded as being low and that the additional benefit of a pre-natal developmental toxicity on rabbits was debatable.

However, the new information provided by the Registrant still does not meet the specific rules for adaption of the information requirement according to Annex X, 8.7, column 2:

- the substance is not known to be a genotoxic carcinogen and to have corresponding appropriate risk management measures implemented, or
- the substance is not known to be a germ cell mutagen and to have corresponding appropriate risk management risk measures implemented, or
- evidence of toxic effects has been shown in the available tests, and absence of systemic absorption and of human exposure has not been demonstrated. In his comment and in his updated dossier, the Registrant has explained that systemic absorption and human exposure are low, however this statement is not justified properly. Documentation should be included with data on 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 that there is no or no significant human exposure.

According to Annex XI, section 3 of the REACH Regulation, testing may also be omitted based on exposure scenario(s) developed in the chemical safety report (CSR). However, in the CSR the Registrant has provided to ECHA (latest available update dated 15 March 2012), he has not performed a human health exposure assessment.

In order to adapt the standard information requirement for a pre-natal developmental toxicity study in the second species, the registration dossier would need to demonstrate in the chemical safety report that the above mentioned criteria of Annex X, 8.7, column 2 or of Annex XI section 3 of the REACH Regulation are met. As this is not the case, the Registrant is requested to submit information on a developmental toxicity study for a second species, namely in the rabbit via the oral route by using EU Method B.31 or OECD test guideline 414.

2) Missing information related to Chemical Safety Report

Annex I sets out the general provisions for assessing substances and preparing chemical safety reports (CSR).

a. A transparent documentation for the derivation of PNECs, PECs and risk characterisation ratios (RCRs) for the soil and sediment compartments (Annex I, 3.3, 5. and 6. of the REACH Regulation)

In his updated dossier, the Registrant has proposed new values for soil and sediment PECs and PNECs. However it is not clear how the new PECs and PNECs have been calculated for sediments (freshwater and marine). After further review of the dossier, ECHA could not reproduce Registrant's calculations[1]. Therefore the CSR needs to be more transparent concerning how the new PECs and PNECs values proposed by the Registrant were derived. In particular, the Registrant shall provide the calculations he used for the derivation of all PECs and PNECs for his environmental risk assessment as an appendix to his CSR. This shall include numerical values for constants and default input parameters he applied.

b. Revised risk characterisation ratios (RCRs) for microbial activity in sewage treatment systems (Annex I, 1.6. of the REACH Regulation)

In the updated dossier, RCRs for microbial activity in sewage treatment plants (STP) are incorrect for all exposure scenarios. There are systematically 10 times lower than RCRs calculated based on the PNEC and PECs provided in the dossier. The Registrant is therefore requested to correct RCRs for STP, for all exposure scenarios.

c. A transparent documentation for environmental exposure assessment for exposure scenario "Production" (Annex I, 5.1. and 5.2. of the REACH Regulation; section 9.1 of the CSR)

For exposure scenario "Production", PEC values presented in the updated dossier are much lower than those presented in the previous version of the dossier (e.g. more than 2 orders of magnitude lower for PECsoil), whereas input parameters presented in both dossiers are mostly unchanged (same tonnage, same release factors, same RMM). After further review of the updated dossier, ECHA could not reproduce the PECs presented by the Registrant. PECs calculated by ECHA using the input parameters presented in the updated dossier were found to be much higher than the PECs presented by the Registrant in that dossier. This raises doubt about the figures in the updated dossier being correct. Therefore the Registrant shall provide as an appendix to his CSR the numerical values he used for all constants and input parameters for his exposure assessment, as well as the full output of the ECETOC TRA or EUSES models.

d. A transparent documentation for the environmental exposure assessment for exposure scenario "Compounding" (Annex I, 5.1. and 5.2. of the REACH Regulation; section 9.2 of the CSR)

For exposure scenario "Compounding", the Registrant has set the release factor to wastewater to 0.05%. This is lower than the release factor recommended by the International Fragrance Association (IFRA). In his comments, the Registrant explained that the value of 0.05% originated from information provided by a downstream user. However the Registrant shall provide clear justification for why emission at one compounder can be read-across to others (e.g. has there been any consultation or monitoring conducted at several downstream user sites to verify the value of 0.05%?). While site-specific measurements for one site could justify an emission for that site, wider information is needed to support the use of the value the Registrant applied for all compounders.

[1] Default parameters used by ECHA for recalculating the PEC and PNEC values were those recommended by ECHA guidance documents (i.e. Fwater: 0.9, Fsolid: 0.1, Foc: 0.1, RHOsolid: 2500, RHOsusp: 1150). Other input parameters were taken from the registration dossier (i.e. Koc value of 625.1, Henry's Law constant of 17.63 Pa.m3/mol and PNECwater value of 0.00403 mg/L for freshwater or PNEC water value of 0.0004 mg/L for marine water).

Therefore, the Registrant shall provide evidence for justifying the wastewater emission value used to estimate environmental releases for all compounders. This shall include reference to the methods outlined in ECHA guidance R16 on Environmental Exposure Estimation, in particular section R16.4 "Measured data".

Moreover, the CSR assumes that the maximum amount used at a site per year is [redacted]% of the total tonnage ([redacted]). As justification, the Registrant explained that he assumed at least 5 compounders in the EU, but he did not provide more information to substantiate this assumption. In particular, he needs to prove that each of the five compounders receives an equivalent volume of the chemical. Therefore the Registrant should also provide evidence for justifying the value of [redacted]% applied for the fraction used at the main local source for the compounders.

e. A transparent documentation for the environmental exposure assessment for exposure scenario "Formulation" (Annex I, 5.1. and 5.2. of the REACH Regulation; section 9.3 of the CSR)

After further review of the dossier, ECHA has recalculated PECs for exposure scenario "Formulation" based on the input parameters presented in the dossier. PECs calculated by ECHA are much higher (systematically more than 2 orders of magnitude higher, except for the air compartment) compared to both those presented the updated version and those presented in the previous version of the dossier. Consequently, RCRs predicted by ECHA for this exposure scenario are very high for every compartment (e.g. >100 for soil and sediment).
Therefore the Registrant shall provide as an appendix to his CSR the numerical values he used for all constants and input parameters for his exposure assessment, as well as the full output of the ECETOC TRA or EUSES models.

f. A full justification for the derivation of DNELs for workers and for the general population (Annex I, 1.4.1. of the REACH Regulation; section 5.11 of the CSR)

Annex I, 1.4.1 of the REACH Regulation requires that the following factors shall, among others, be taken into account when deriving DNELs:
- the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
- the nature and severity of the effect;
- the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies.

Annex I, 1.4.1 also requires that a full justification for the establishment of DNELs is given specifying, among others, the choice of information used, the route of exposure and the duration and frequency of exposure of the substance.

The ECHA "Guidance on information requirements and chemical safety assessment" (Volume 8, R8) provides further details and specifically provides default factors which should be applied to derive DNELs in the absence of substance specific information.

The assessment factors (AF) applied by the Registrant and the default assessment factors recommended in the ECHA Guidance[2] are given in detail in Annex I attached to this decision.

[2] Link to ECHA guidance document R.8 is: http://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf

ECHA observes that the Registrant has not followed recommendations of ECHA's Guidance R.8 and has not provided a full justification for the derivation of DNELs in line with Annex I, 1.4.1. Instead, the Registrant has applied less protective assessment factors than those recommended by the ECHA guidance for the intraspecies extrapolation and has not applied assessment factors to cover uncertainties due to remaining interspecies differences (i.e. not related to allometric scaling).

In response to ECHA's draft decision, the Registrant submitted additional information in the updated registration dossier.

In the updated chemical safety report, under heading "Intraspecies extrapolation" the Registrant argues that a default assessment factor of 5 is sufficient to cover the "intraspecies variability" in the general population and a factor of 3 to cover for the "intraspecies variability" in the worker population. These factors are lower than the ones presented in ECHA's guidance, recommended ECHA's factors being 10 and 5 respectively. Moreover, the Registrant states that "*the 95th percentile is considered sufficiently conservative to account for intraspecies variability in the general population*". This is an arbitrary opinion of the Registrant on the level of protection regarded sufficient for the human population; it is not a scientific justification. ECHA notes further that the Registrant's arguments are only based on general considerations and do not provide substance-specific information. ECHA points out that default factors recommended in ECHA's guidance are established after ample consultation with stakeholders, taking into account the various opinions on the matter. ECHA's default factors are furthermore based on the available relevant publications and reports. The Registrant's reasoning does not provide ECHA with reasons to alter its default assessment factors.

In the updated chemical safety report, under heading "Remaining interspecies differences" the Registrant argues that the default assessment factor for the remaining interspecies variation of 2.5, as presented in ECHA's guidance can be omitted. However, the Registrant's reasoning is unclear and misses details. He bases his opinion only on preliminary results and on assumptions which do not constitute arguments strong enough for ECHA to reconsider its default assessment factors for interspecies variation. Firstly, the fact that the average interspecies difference has been observed to approach the allometric difference between species does not invalidate the use of an additional factor for remaining interspecies differences, as the Registrant seems to claim. For a given substance, the interspecies difference may be larger than the average interspecies difference for reasons not related to allometry. The purpose of the default factor of 2.5 recommended by ECHA guidance is precisely to reduce the underestimation of hazard that may occur when the interspecies differences are larger than predicted by the differences in allometry alone. Secondly, the Registrant elaborates on the nature of the effects observed to support his opinion that the default factor of 2.5 can be omitted. According to the Registrant the main effects observed in repeated-dose toxicity studies with the registered substance are "*largely rat specific or adaptive responses, which are in worst case believed to be similar for humans*". ECHA considers this statement as an assumption that lacks scientific evidence. ECHA is of the opinion that the Registrant has not demonstrated that "*no remaining interspecies differences are expected*" for the registered substance.

Therefore, the Registrant is, in accordance with Annex I, 1.4.1, requested to fully justify the DNEL derivation for workers and for the general population provided in the chemical safety report by specifying

- the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;

- the nature and severity of the effect;
- the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies;
- and that the DNELs reflect the likely route(s), duration and frequency of exposure.

If the current derivation is not fully justified, the Registrant shall reconsider his DNELs and reassess related risks. The chemical safety report shall be amended 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 eco-toxicological 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]
Jukka MALM
Director of Regulatory Affairs

Annex I.

Assessment factors (AF) applied by the Registrant:

For workers - systemic long term – inhalation route:
- intraspecies: 3
- exposure duration: 2
  (overall AF: 6)

For workers - systemic long term – dermal route:
- interspecies: 4
- intraspecies: 3
- exposure duration: 2
- absorption difference dermal-oral: 0.5
  (overall AF: 12)

For the general population - systemic long term – inhalation route:
- intraspecies: 5
- exposure duration: 2
  (overall AF: 10)

For the general population - systemic long term – dermal route:
- interspecies: 4
- intraspecies: 5
- exposure duration: 2
- absorption difference dermal-oral: 0.5
  (overall AF: 20)

For the general population - systemic long term – oral route:
- interspecies: 4
- intraspecies: 5
- exposure duration: 2
  (overall AF: 40)

The default assessment factors recommended in the ECHA Guidance[3]:

For workers - systemic long term – inhalation route:
- interspecies: 2.5 (remaining differences between species non related to allometry)
- intraspecies: 5 (workers)
- exposure duration: 2 (sub-chronic to chronic)
  (overall AF: 25)

For workers - systemic long term – dermal route:
- interspecies - allometric correction: 4 (rat to human)
- interspecies - remaining differences: 2.5 (non-related to allometry)
- intraspecies: 5 (workers)
- exposure duration: 2 (sub-chronic to chronic)
- absorption difference dermal-oral[4]: 1
  (overall AF: 100)

[3] Link to ECHA guidance document R.8 is: http://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf
[4] In the absence of substance specific information, the ECHA Guidance R.8 (section R.8.4.2) recommends that a factor of 1 be applied for the extrapolation of the results from the oral route to the dermal route. In general, dermal absorption will not be higher than oral absorption and by default, the same bioavailability for experimental animals and humans should be assumed.

For the general population - systemic long term – inhalation route:
- interspecies: 2.5 (remaining differences between species non related to allometry)
- intraspecies: 10 (general population)
- exposure duration: 2 (subchronic to chronic)
  (overall AF: 50)

For the general population - systemic long term – dermal route:
- interspecies - allometric correction: 4 (rat to human)
- interspecies - remaining differences: 2.5 (non-related to allometry)
- intraspecies: 10 (general population)
- exposure duration: 2 (subchronic to chronic)
- absorption difference dermal-oral[5]: 1
  (overall AF: 200)

For the general population - systemic long term – oral route:
- interspecies - allometric correction: 4 (rat to human)
- interspecies - remaining differences: 2.5 (non-related to allometry)
- intraspecies: 10 (general population)
- exposure duration: 2 (sub-chronic to chronic)
  (overall AF: 200)