EUROPEAN CHEMICALS AGENCY

Helsinki, 17 June 2015

Decision number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)

DECISION ON SUBSTANCE EVALUATION PURSUANT TO ARTICLE 46(1) OF REGULATION (EC) NO 1907/2006

For 3,5,5-trimethylcyclohex-2-enone, CAS No 78-59-1 (EC No 201-126-0), hereinafter "isophorone"

Addressees: Registrant(s)[1] of isophorone (Registrant(s))

This decision is addressed to all Registrant(s) of the above substance with active registrations on the date on which the draft for the decision was first sent for comment, with the exception of the cases listed in the following paragraph. A list of all the relevant registration numbers subject to this decision is provided as an annex to this decision.

Registrant(s) holding active registrations on the day the draft decision was sent are *not* addressees of this decision if they are: i) Registrant(s) who had on that day registered the above substance exclusively as an on-site isolated intermediate under strictly controlled conditions and ii) Registrant(s) who have ceased manufacture/import of the above substance in accordance with Article 50(3) of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation) before the decision is adopted by ECHA.

Based on an evaluation by Anses for the Competent Authority of France (evaluating MSCA), the European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 52 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

This decision is based on the registration dossiers on 29 April 2014, the day on which the draft decision was notified to the Registrant(s) pursuant to Article 50(1) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant(s) in the registrations is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossiers of the Registrant(s) at a later stage, nor does it prevent a new substance evaluation process once the present substance evaluation has been completed.

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of France has initiated substance evaluation for isophorone, CAS No 78-59-1 (EC No 201-126-0) based on registration(s) submitted by the Registrant(s) and other relevant and available information and prepared the present decision in accordance with Article 46(1) of the REACH Regulation.

[1] The term Registrant(s) is used throughout the decision, irrespective of the number of registrants addressed by the decision.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to Human health/CMR (initially focusing on carcinogenicity and mutagenicity); Exposure/Workers exposure, high aggregated tonnage, isophorone was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2013. The updated CoRAP was published on the ECHA website on 20 March 2013. The Competent Authority of France was appointed to carry out the evaluation.

In the course of the evaluation, the evaluating MSCA noted additional concerns regarding environment, endocrine disruption and reproductive toxicity. Exposure assessment calculations must be detailed considering that some estimated risk characterization ratios are not negligible.

The evaluating MSCA considered that further information was required to clarify the concerns regarding Human health, Workers exposure, General population exposure assessment, Environment. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 19 March 2014.

On 29 April 2014 ECHA sent the draft decision to the Registrant(s) and invited them pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

Registrant commenting phase

By 5 June 2014 ECHA received comments from the Registrant(s) of which it informed the evaluating MSCA without delay. The evaluating MSCA considered the comments received from the Registrant(s).

The information contained therein is reflected in the Statement of Reasons (Section III Point 4 – General population exposure assessment) whereas no amendments to the Information Required (Section II) were made.

Commenting by other MSCAs and ECHA

In accordance with Article 52(1) of the REACH Regulation, on 31 October 2014 the evaluating MSCA notified the Competent Authorities of the other Member States and ECHA of its draft decision and invited them pursuant to Articles 52(2) and 51(2) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, three Competent Authorities of the Member States and ECHA submitted proposals for amendment to the draft decision.

On 5 December 2014 ECHA notified the Registrant(s) of the proposals for amendment to the draft decision and invited them pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

The evaluating MSCA reviewed the proposals for amendment received and amended the draft decision.

On 15 December 2014 ECHA referred the draft decision to the Member State Committee.

By 5 January 2015, in accordance to Article 51(5), the Registrant(s) provided comments on

the proposed amendments. The Member State Committee took into account the comments the Registrant(s) made on the proposals for amendment.

After discussion in the Member State Committee meeting on 3-5 February 2015, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 4 February 2015.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit the following information using the indicated test method/instructions (in accordance with Article 13 (3) and (4) of the REACH Regulation) and the registered substance subject to the present decision:

1. Full study reports of endocrine assays submitted under the Endocrine Disruptor Screening Program of US-EPA;

2. Prenatal developmental toxicity study (inhalation, rat) (OECD TG 414) as specified in section III;

3. Revised worker exposure assessment;

4. Revised general population exposure assessment;

5. Detailed information on the environmental exposure assessment.

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA by **24 June 2016** an update of the registration(s) containing the information required by this decision[2], including robust study summaries and, where relevant, an update of the Chemical Safety Report.

III. Statement of reasons

1. Study reports of endocrine assays submitted under the Endocrine Disruptor Screening Program

The evaluating MSCA was aware that EPA issued test orders for isophorone in 2010 under the Endocrine Disruptor Screening Program (EDSP). At this time, EPA assessment of these data is not available. After request, only posters presented at the Society of Toxicology meeting in San Francisco in 2012 were submitted by the Registrant(s). Based on these posters, it is unlikely that isophorone induces endocrine disruptions. However, the results cannot be adequately assessed based on the insufficient level of information described in the posters.

Therefore, the submission of the study reports is required in order to properly conclude on the endocrine disruption endpoint.

[2] The deadline set by the decision already takes into account the time that registrants may require to agree on who is to perform any required tests and the time that ECHA would require to designate a registrant to carry out the test(s) in the absence of the aforementioned agreement by the registrants (Article 53(1) of the REACH Regulation).

The Evaluating MSCA may identify further information required if concerns are raised during the evaluation of the endocrine disruption assays. In particular, the design of the Extended One Generation Reproductive Toxicity Study (EOGRTS) described below depends on the outcome of this evaluation.

During consultation of MSCAs, a proposal for amendment was submitted by one Member State for generation of a EOGRTS in rats, oral route (test method OECD TG 443) with DNT and DIT cohorts. ECHA acknowledges that no definitive conclusions on reproductive toxicity, specifically on peri- and post-natal development, can be drawn because of the current lack of required standard information in the registration dossier. Therefore, a concern for reproductive toxicity is identified and needs to be clarified.

However, in the absence of the study reports on endocrine assays, no definitive design of the EOGRTS (OECD TG 443) can be currently defined in regard of the different cohort options described in the OECD guideline. Such a study with adequate design would be requested after the submission of the study reports and based on the entire dataset, unless equivalent information can be provided to fulfill this standard information requirement.

2. Prenatal developmental toxicity study (inhalation, rat) (OECD TG 414)

During the conduct of a preliminary teratogenicity study by inhalation in rats (Strain Fisher 344), there was one exencephaly (1/12 litters) noted in one late resorption at 144 ppm. In dams, decrease of body weight on day 12 (-6%) and body weight gain (days 0-16; -20%) was reported at 144 ppm and clinical signs (alopecia, excessive lacrimation, staining) from 100 ppm. Increased relative weights of liver, spleen and kidneys were noted in all treated groups. However, in the absence of histopathological analysis, the relevance of these changes is unknown.

In the main study with rats (Strain Fischer 344), isophorone elicited minor effects in the pregnant dams in the form of decreased food consumption (days 6-20 and 0-20), lower body weights (on days 12 and 15 of gestation (< 7%)) and dose related increases in alopecia and staining of the cervical and anogenital areas at 111 ppm (640 mg/m^3). No histopathological examination was performed. No developmental effect was reported except a decrease of crown-rump distance in females at 111 ppm that could indicate growth retardation. However, this was mainly due to two foetuses from two different litters.

During the conduct of a preliminary teratogenicity study by inhalation in mice (Strain CD-1), there were three exencephalies noted in mouse fetuses: in a late resorption in one litter and in two alive fetuses in a second litter (3/12 litters). In dams, decreased body weight gain (days 6-16; -9%) and decreased spleen weight were reported at 144 ppm. However, in the absence of histopathological analysis, the relevance of this latter effect is unknown.

In the main teratogenicity study with mice (CD-1), isophorone elicited very minor effect in the pregnant dams in the form of lower body weights (on day 18 of gestation < 6%) at 111 ppm (640 mg/m^3). No histopathological examination was performed. No developmental effect was reported at the higher tested concentration of 111 ppm.

Overall, the choice of the concentrations tested in the main studies in rats and mice is questionable since no major toxicity was noted in dams at 144 ppm in the range-finding study and this does not justify lowering the concentrations.

The observation of exencephaly, which is a rare and serious teratogenic effect, in two species at 144 ppm in a context of low maternal toxicity raises a concern for teratogenicity.

Furthermore, because this concentration was not tested in the main test, it cannot be excluded that this lesion is related to treatment.

In this context, a new developmental study is required in order to clarify this point and to conclude on the developmental toxicity potential of isophorone. In case of positive test results, a classification for developmental toxicity and/or further risk management measures could be considered.

In the preliminary studies, 3 cases and 1 case of exencephaly were found in mice and rats, respectively. No study was performed in rabbits. Therefore, mouse seems to be the most sensitive species to the developmental toxicity of isophorone. However, it is not considered the most suitable species for testing developmental toxicity based on the high intraspecies variability and its sensitivity to stress-related teratogenicity. According to the OECD guideline 414, rats and rabbits are the preferred species for testing pre-natal developmental toxicity. The reason of this choice is probably based on the large historical control database available and the low intraspecies difference in background malformation rate. Furthermore, the rat is likely the rodent species which is most similar to humans with respect to metabolism, pharmacokinetics, excretion. In this context, ECHA considers that the rat is the most relevant species for the required pre-natal developmental toxicity study to confirm or not the concern of teratogenicity. The same strain as in the original study should be used in the requested study.

During the consultation of MSCAs, a proposal for amendment was submitted to remove the request for the study or to conduct the study as a limit test with one concentration of 144 ppm. The Registrants, in their comments on proposal for amendment supported the removal of the request believing that the observed exencephaly in rats appears to be a chance event and that there is no sufficient concern to conduct an additional prenatal developmental toxicity study.

However, it cannot be concluded that the effect is a chance event because no concentration above 144 ppm was tested. This concentration was not associated with overt maternal toxicity and therefore an additional assay using the maximum tolerated and attainable concentration is needed.

As a conclusion, the requested study should be performed as a limit test described in the OECD 414 guideline using the maximum tolerable and attainable concentration established on a basis of suitably designed sighting study.

This study must be performed by inhalation route due to the volatile nature of isophorone and because inhalation is expected to be a major route of exposure considering the identified uses.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant(s) are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD 414) in Fischer 344 rats by the inhalation route.

3. Worker exposure assessment

- Perform a refined exposure assessment for PROC 11 using adequate models

ECETOC TRA only predicts vapour phase exposure and was not appropriate to evaluate exposure to spray aerosol. In this context, the inhalation exposure of isophorone can be

underestimated. An estimation of inhalative exposure to aerosols during professional spraying (PROC 11) is thus required.

For PROC 11 in agrochemical use, it is considered more relevant to use the specific exposure models available for plant protection products. A refined risk assessment for this scenario is thus required using more adequate exposure models depending of the type of application (for example, German BBA model or UK-POEM).

- Perform an acute risk assessment

Isophorone is classified H302/H312 (harmful if swallowed and in contact with skin), H319 (causes serious eye irritation) and H335 (may cause respiratory irritation). Furthermore, ECHA considers that the available data indicate that isophorone may also cause drowsiness or dizziness.

High peaks of exposure can be anticipated considering the volatility of isophorone and the use pattern (spray application). In this context, the long-term risk assessment will not take into account these effects. Therefore, an acute risk assessment is required since acute toxicities are identified and high peak of exposure can be anticipated for isophorone. This is also in accordance with Annex R8.8 of the ECHA Guidance on information requirements on chemical safety assessment Chapter R.8: Characterisation of dose [concentration]- reponse for human health, Version 2.1, November 2012[3].

4. General population exposure assessment

- Provide a risk assessment for bystanders and residents for agrochemical uses

Bystanders and residents can be exposed to the mixture containing isophorone during professional spraying in agrochemical use. Furthermore, specific exposure models are available for plant protection products to estimate these exposures.

No risk assessment has been performed by the Registrant(s) and no argumentation was provided to rule out these scenarios. A risk assessment for this scenario is thus required.

- Provide risk assessment for secondary exposure after coating and cleaning uses

As mentioned in the Chemical Safety Report (CSR), isophorone is used in coating ([redacted]) and cleaning agents in sector of use "SU22 public domain (administration, education, entertainment, services, craftsmen)". Therefore, even if all consumer uses are strongly advised against, general population can have access to locations where formulated products containing isophorone are applied. Considering the vapour pressure of isophorone (0.4 hPa), inhalation exposure to residues can be expected.

No risk assessment has been estimated by the Registrant(s) and no argumentation was provided to rule out this scenario. A risk assessment for secondary exposure or RM management measures (RMMs) applied to prevent this exposure are thus required.

In their comments on the initial draft decision, the Registrant(s) agreed that SU22 will be deleted from the CSR. Therefore, coating and cleaning uses would only concern industrial

[3] http://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf

sector. If the CSR is updated accordingly and use in public domain (SU22) is advised against, this request is out of date.

5. Detailed information on the environmental exposure assessment

In order to clarify the exposure assessment calculations, the following information must be provided considering that the estimated risk characterization ratios are not negligible.

- *Environmental exposure – Environmental release – Total release for regional exposure estimation*
  Regional concentrations are steady-state concentrations representing the background in environmental compartments. They are calculated considering all the releases to each environmental compartment for each use, summed up and averaged over the year. Consequently the regional PEC for each compartment must be the same value whatever the emission scenario. The estimate of a single regional PEC value for each environmental compartment whatever the emission scenario is thus required.
- *Environmental exposure – Exposure concentration – PEC (Predicted Environmental Concentrations) values for each environmental compartment at local scale and at regional scale*

  In order to correctly assess the environmental risk, it is required to provide in the CSR the regional PEC value for each environmental compartment. The regional concentrations are used as background concentrations in the calculation of the local concentrations. The recalculation of the local PECs values considering these new background concentrations is thus required.
- *Environmental exposure – Exposure concentration relevant for the food chain (Secondary poisoning)*

  More details about the calculations of the predicted environmental concentrations in food for secondary poisoning is required.

  The values in the CSR are not consistent with those after calculation of the PEC values for secondary poisoning, and taking into account equations given in the ECHA Guidance on information requirements and chemical safety assessment, Chapter R.16: Environmental Exposure Estimation, Version 2.1, October 2012 [4](Equation R.16-70 and Equation R.16-72
- *Emission scenario 1 - Manufacture. Environment related measures*
  In order to evaluate the quality of the campaign of measures conducted in the plant effluent and in the atmosphere, the monitoring data or all the information needed to fulfill the quality criteria for the use of exisiting measured data (based on OECD, 2013[5]) are required.
  In absence of monitoring data and in case of modelisation, the refined value for the release fraction to waste water is not properly justified. The refinement of the default worst case release factor to water (before sewage treatment plant STP) of 6%, described in the ERC 1 "Manufacture of chemicals", has to be argued with more justifications.
- *Emission scenario 1 - Intermediate use. Environment related measures*
  In order to evaluate the quality of the campaign of measures conducted in the plant effluent and in the atmopshere, the monitoring data or all the information needed to fulfill the quality criteria for use of exisiting measured data (based on OECD, 2013)

[4] http://echa.europa.eu/documents/10162/13632/information_requirements_r16_en.pdf

[5] Guidance document for exposure assessment based on environmental monitoring. Series on Testing and Assessment No 185. OECD 2013.

are required.
In absence of monitoring data and in case of modelisation, the refined value of the fraction used as main source, and the release fractions in each environmental compartment (waste water, air, soil) are not properly justified. The refinement of the values proposed in the SpERC "ESVOC 6.1a.v1" has to be argued with more justifications.

- *Emission scenario 4 – Uses in Cleaning Agents – Professional sector of use. Emission or release factors to the relevant compartments*
Verify the correct release fraction to waste water. In the SpERC "ESVOC 4a.v1", a value of 0.0001% is given instead of 0.01% as indicated in the CSR. Consequently and if necessary, the recalculation of the release from point source for aquatic compartment is required.
- *Emission scenario 5 – Agrochemical Uses – Environmental risk assessment*
Considering the Article 10(b) of REACH Regulation the EU manufacturer or importer has to develop a CSR which demonstrates that all uses of a substance are adequately controlled including co-formulants used in Plant Protection Products. European Crop Protection Association (ECPA) has developed a series of tools which are specifically designed to estimate exposure of the environment resulting from crop protection uses. Especially for the local environmental assessment, a Local Environmental Tool (ECPA LET) has been proposed[6]. A risk assessment for this use and with these tools is required.

Pursuant to Article 46(1) of the REACH Regulation the concerned Registrant(s) shall submit the detailed information as presented above on the environmental exposure assessment.

IV. Adequate identification of the composition of the tested material

In relation to the required experimental study, the sample of the substance to be used shall have a composition that is within the specifications of the substance composition that are given by all Registrant(s). It is the responsibility of all the Registrant(s) to agree on the tested material to be subjected to the test subject to this decision and to document the necessary information on composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation. Finally, the test must be shared by the Registrant(s).

V. Avoidance of unnecessary testing by data- and cost-sharing

In relation to the experimental study the legal text foresees the sharing of information and costs between Registrant(s) (Article 53 of the REACH Regulation). Registrant(s) are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who is to carry out the study on behalf of the other Registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at:
https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

Further advice can be found at http://echa.europa.eu/datasharing_en.asp.

If ECHA is not informed of such agreement within 90 days, it will designate one of the Registrant(s) to perform the study on behalf of all of them.

[6] ECPA Guidance on REACH Chemical Safety Assessment for Co-formulants Used in Crop Protection Products. European Crop Protection. 5 July 2013.

VI. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Articles 52(2) and 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 the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

[redacted]

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Director of Evaluation

Annex: List of registration numbers for the addressees of this decision. This annex is confidential and not included in the public version of this decision.