EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000002211-91-05/F Helsinki, 20 December 2012

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

**For Reaction mass of 2,6-Octadien-1-ol, 3,7-dimethyl-, (E) and 2,6-Octadien-1-ol, 3,7-dimethyl-, (Z)-, EC No. 906-125-5, registration number:** [redacted]

**Addressee:** [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined testing proposals set out in the registration dossier for Reaction mass of 2,6-Octadien-1-ol, 3,7-dimethyl-, (E) and 2,6-Octadien-1-ol, 3,7-dimethyl-, (Z)-, EC No. 906-125-5, submitted by [redacted] (Registrant).

In accordance with Articles 10(a)(ix) and 12(1)(e) of the REACH Regulation, the Registrant submitted the following testing proposals as part of the registration dossier to fulfil the information requirements set out in Annex X:

- Developmental toxicity / teratogenicity study, test guideline, species, route of administration or test material not specified.
- Toxicity to reproduction, test guideline, species, and route of administration or test material not specified.

The present decision relates solely to the examination of the testing proposal for a Developmental toxicity / teratogenicity study. The testing proposal for the Toxicity to reproduction study is addressed in a separate decision although the testing proposals were initially addressed together in the same draft decision.

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 19 July 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 decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the present dossier at a later stage.

The examination of the testing proposals was initiated on 2 December 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 1 July 2011 until 15 August 2011. ECHA did receive information from a third party (see section III below).

On 6 March 2012 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 19 March 2012 ECHA received comments from the Registrant.

ECHA considered the Registrant's comments received. The comments are reflected in the Statement of Reasons (Section III) whereas no amendments to the Testing Required (Section II) were made.

On 19 July 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, the Competent Authorities of the Member States submitted proposals for amendment to the draft decision.

On 22 August 2012 ECHA notified the Registrant of proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

ECHA reviewed the proposals for amendment received and decided not to amend the draft decision.

On 3 September 2012 ECHA referred the draft decision to the Member State Committee.

On 21 September 2012 the Registrant provided comments on the proposed amendments. The Member State Committee took the comments of the Registrant into account.

The draft decision was split into two draft decision documents: one relating to the testing proposal for Toxicity to reproduction study and one relating to the testing proposal for a Developmental toxicity/teratogenicity study.

After discussion in the Member State Committee meeting on 23-24 October 2012, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 24 October 2012. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

## II. Testing required

Pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant shall carry out the following modified tests using the indicated test methods and the substance subject to the present decision:

- Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, 8.7.2.; test method: EU B.31/OECD 414).

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **20 December 2014** an update of the registration dossier containing the information required by this decision.

Data from a second pre-natal developmental toxicity study on another species is a standard information requirement according to Annex X, 8.7.2. of the REACH Regulation. The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI. If the Registrant considers that testing is necessary to fulfill this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other Registrants.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance and scientific information submitted by third parties.

**Pre-natal developmental toxicity study**

a) Examination of the testing proposal

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

Pre-natal developmental toxicity studies are part of the standard information requirements as laid down in Annexes IX and X, section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The Registrant has therefore submitted a testing proposal in IUCLID, section 7.8.2 – Developmental toxicity/teratogenicity. The principle of the test is described by the Registrant in its dossier as: *"approach / design of a suitable study to be discussed, e.g. enhanced one generation or cross fostering study"*. Furthermore, the Registrant did not specify the species, route of administration, or the substance to be used for testing. In order to meet the standard information requirement in Annex IX, section 8.7.2., ECHA decided to modify the test proposed by the Registrant.

Therefore, a pre-natal developmental toxicity study is required according to the test method EU B.31/OECD 414. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

In his comments on the draft decision submitted on 19 Mar 2012, the Registrant states that the registered substance Reaction mass of 2,6-Octadien-1-ol, 3,7-dimethyl-, (E) and 2,6-Octadien-1-ol, 3,7-dimethyl-, (Z)- consists of: [redacted]% geraniol, i.e. 2,6-Octadien-1-ol, 3,7-dimethyl-, (E), CAS 106-24-1 (EC 203-377-1) and [redacted]% nerol, i.e. 2,6-Octadien-1-ol, 3,7-dimethyl-, (Z)-, CAS 106-25-2 (EC 203-378-7). The Registrant argues that the results from another experimental study on geraniol, proposed by the Registrant to be performed according to OECD 443 with Cohort 1A but not Cohort 1B can be used to fulfil the information requirements for the registered substance of the present decision. The other experimental study on geraniol may be performed by the Registrant as a result of a

separate testing proposal decision taken by ECHA (TPE-D-0000002210-93-01/D). The Registrant suggests that this study could possibly be used to fulfil both the information requirement for a first pre-natal developmental toxicity study (Annex IX, 8.7.2.) and a two-generation reproductive toxicity study (Annex X, 8.7.3.). Therefore, the Registrant proposes not to test the registered substance and await the results from the study on geraniol. Only thereafter, if the results on geraniol show that additional information is needed, the Registrant proposes that ECHA should take into account the information that possibly will be provided (by a different Registrant) through a future registration of nerol(*i.e.* the second constituent of the registered substance subject to the present decision).

The Registrant has not provided scientific justification as to how test results from pure geraniol can be used to predict the effects on reproduction of the registered substance. The possible contribution to toxicity of the other component ([redacted]% nerol) is not addressed. Moreover, the Registrant has not updated his dossier with a suitable adaptation of the standard information requirements according to Column 2, Annex X 8.7 or Annex XI, and ECHA accordingly is not able to accept this as a valid adaptation.

Against this background ECHA concludes that the suggested study on geraniol, OECD 443 with Cohort 1A but not Cohort 1B, does not meet the information requirement for a pre-natal developmental toxicity study (OECD 414; at Annexes IX-X, 8.7.2).

In his comments on the proposal for amendments from the Member States Competent Authorites, the Registrant indicated his intention to fulfil the standard information requirement of the registered substance by providing information on both individual components (*i.e.* geraniol and nerol) of the registered substance.

ECHA recognises that the Registrant has in his comments proposed a tiered testing strategy that involves taking into account the results of the OECD 416/443 that is to be conducted on geraniol and the information that may be provided on nerol in an "intended registration" before initiating any tests on the registered substance. The current registration dossier contains testing proposals for the information requirements of Annex IX, 8.7.2 and Annex X, 8.7.3. ECHA however notes that the proposed testing strategy as outlined above is not reflected in the technical dossier of geraniol as this dossier only contains a testing proposal for the information requirement at Annex X, 8.7.3 but not for Annex IX, 8.7.2.

Furthermore, ECHA considers that testing both of the components to cover the potential effects of the registered substance (*i.e.* a reaction mass of the two components) may be plausible, provided that any remaining uncertainty of the predicted combined toxicity effects are adequately and reliablly documented and justified. However, the Registrant has not provided adequate and reliable documentation for this approach in his dossier as required by Annex XI, 1.5. Consequenty, this does not fulfil the criteria for adaptation set out in Annex XI, 1.5. ECHA emphasises that if the registrant chooses to provide information on the individual components rather than on the registered substance additional testing proposals for pre-natal studies are required for the individual components of the registered substance.

Therefore, ECHA has considered the Registrants comments to the proposals for amendments and decided not to amend the draft decision.

b) Consideration of third party information

ECHA received third party information concerning the testing proposal during the public consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

A third party has proposed a weight-of-evidence approach for ECHA to consider before further tests on animals are requested. As part of this approach, the third party provided references to several scientific review papers that summarise results mostly from subchronic studies on read-across substances. The third party also supplied a reference to the dermal OECD 421 study performed by the Registrant. From the limited data available the third party conclude that geraniol shows no concern for reproductive or developmental effects but does show systemic toxicity and dermal effects.

ECHA has taken the information provided into account and concludes that it is insufficient for demonstrating that the conditions of Annex XI, Section 1.2 and 1.5 of the REACH Regulation are met. More specifically, the proposed weight-of-evidence approach is not sufficient to assume that the substance has or has not a particular dangerous property after gestational exposure and that the standard information requirement for a pre-natal developmental toxicity study could be adapted. Furthermore, the proposed read-across approach as an element of the weight of evidence justification did not demonstrate that human health effects of the registered substance may be predicted from data on the reference substance.

Although ECHA recognises that the information as provided by the third party might be scientifically valid, it does not fulfil Annex XI requirements and is therefore not sufficient to allow ECHA to reject the testing proposal. Nevertheless, ECHA acknowledges that the Registrant may himself supplement under its own responsibility the argumentation and information provided by the third party in order to make use of adaptation possibilities. This would require that the Registrant documents, using several independent sources of information, that there is a sufficient weight of evidence leading to the assumption/conclusion that a substance has or has not particular dangerous properties, according to the criteria laid down in Annex XI of the REACH Regulation.

In addition, the Registrant has submitted information during the public consultation. The public consultation is reserved to third parties; this covers anybody not directly and individually concerned by the dossier. Specific procedures are available to Registrants to provide additional information or modify a testing proposal. Modification of a testing proposal before the reception of a draft decision can be done by submitting at any time a dossier update that amends the initial testing proposal, or by commenting on the draft decision in accordance with Article 51 of the REACH Regulation. The comments provided by the Registrant during the public consultation have therefore not been considered at that stage in the procedure. ECHA also stresses that the procedure to assess testing proposals also reserves explicitly to the registrant concerned by a draft decision a period of 30 days during which he may submit his comments.

c) Conclusion

On the basis of the considerations set out above and pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant is required to carry out the following study: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414) using the registered substance Reaction mass of 2,6-Octadien-1-ol, 3,7-dimethyl-, (E) and 2,6-Octadien-1-ol, 3,7-dimethyl-, (Z)-, EC No. 906-125-5.
When considering the need for a testing proposal for a prenatal developmental toxicity

study in a second species, the Registrant should take into account the outcome of the pre-natal developmental toxicity study on the first species and all available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if Weight of Evidence assessment of all relevant available data provides a scientific justification for omitting the study in a second species.

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 appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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