ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114308985-40-01/F Helsinki, 16 October 2015

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

For Octene, hydroformylation products, low-boiling, CAS No 68938-03-4 (EC No 273-110-1), 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 the following testing proposal submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for Octene, hydroformylation products, low-boiling, CAS No 68938-03-4 (EC No 273-110-1, submitted by [redacted] (Registrant).

Mammalian Erythrocyte Micronucleus Test (OECD Guideline 474)

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 20 May 2015, i.e. 30 calendar days after the end of the commenting period.

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 registration at a later stage.

ECHA received the updated registration dossier containing the above-mentioned testing proposal for further examination pursuant to Article 40(1) on 2 December 2013.

ECHA held a third party consultation for the testing proposal from 17 June 2014 until 1 August 2014. ECHA did not receive information from third parties.

On 13 March 2015 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

By 20 April 2015 the Registrant did not provide any comments on the draft decision to ECHA.

On 11 June 2015 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 for amendment of the draft decision within 30 days of the receipt of the notification.

Subsequently, a proposal for amendment to the draft decision was submitted.

On 17 July 2015 ECHA notified the Registrant of the proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposal for amendment received and amended the draft decision.

On 27 July 2015 ECHA referred the draft decision to the Member State Committee.

By 17 August 2015, in accordance to Article 51(5), the Registrant provided comments on the proposal for amendment. The Member State Committee took the comments on the proposal for amendment of the Registrant into account.

A unanimous agreement of the Member State Committee on the draft decision was reached on 31 August 2015 in a written procedure launched on 20 August 2015.

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

II. Testing required

A. Tests required pursuant to Article 40(3)

The Registrant shall carry out either of the following tests pursuant to Article 40(3)(a) and 13(4) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

> *In vivo* mammalian erythrocyte micronucleus test, oral route (Annex IX, Section 8.4., column 2; test method B.12./OECD 474) under conditions as described in Section III;
> *or*
> *In vivo* mammalian alkaline comet assay (Annex IX, Section 8.4., column 2; test method OECD 489) under conditions as described in Section III.

Note for consideration by the Registrant:

The Registrant may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

Finally, ECHA reminds the Registrant that, as outlined in the paragraph 7 of the OECD 489 guideline, "*to fulfil animal welfare requirements, <...> the endpoint can be combined with other genotoxicity endpoints such as in vivo mammalian erythrocyte micronucleus assay*".

B. Deadline for submitting the required information

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation, the Registrant shall submit to ECHA by **24 October 2016** an update of the registration dossier containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposal submitted by the Registrant for the registered substance.

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test. "Mutagenicity" is an information requirement as laid down in Annex VIII, Section 8.4. of the REACH Regulation. Column 2 of Annex IX, Section 8.4. provides that "If there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already, an appropriate *in vivo* somatic cell genotoxicity study shall be proposed by the Registrant."

An appropriate *in vivo* genotoxicity study to follow up the concern on chromosomal aberrations identified *in vitro* is not available for the registered substance but shall be proposed by the Registrant. Consequently, there is an information gap. The Registrant proposed to generate information for this endpoint with a testing proposal for a Mammalian Erythrocyte Micronucleus Test (OECD 474) with the following justification: [redacted] showed evidence of "causing an increase in the frequency of structural chromosome aberrations in the absence of S9 mix only", in an *in vitro* human lymphocyte cytogenetic test (OECD 473).

ECHA notes that this test is an appropriate test to investigate further effects on chromosomal aberrations *in vivo* as described in the ECHA Guidance document on information requirements and chemical safety assessment R.7a, chapter R.7.7.6.3 and figure R.7.7-1 (August 2014).

ECHA notes further that the Registrant did not specify the route of administration intended to be used in the proposed test. In light of the physicochemical properties of the substance, ECHA considers that testing by the oral route is appropriate. However, ECHA further notes that, in absence of further toxicokinetics data, the absence of observed effects of the registered substance in presence of S9 mix in the *in vitro* mammalian chromosome aberration test raises a concern on potential deactivation of the registered substance after oral administration and first pass (liver) metabolism.

Taking into account the above considerations, ECHA is of the opinion that the test proposed by the Registrant is an appropriate test to investigate further effects on chromosomal aberrations *in vivo* provided that exposure of the target tissue (i.e. bone marrow) to the test substance or its metabolites is not ruled out by available information and is demonstrated to have occurred, as described in the updated OECD 474 guideline (September 2014), paragraphs 10, 40 and 48. In the case that exposure of the target tissue cannot be ensured, the genotoxicity of the substance subject to the present decision should be investigated in site of contact tissues and in the liver. ECHA is of the opinion that the comet assay (OECD 489 guideline, adopted on 26 September 2014) is an adequate test method to conduct such investigation. ECHA considers that the most appropriate tissues to be investigated in case of comet assay via the oral route are either the glandular stomach or the duodenum/jejunum, together with the liver.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out either of the following studies with the registered substance subject to the present decision:

In vivo mammalian erythrocyte micronucleus test, oral route (Annex IX, Section 8.4., column 2; test method B.12./OECD 474, under conditions as described above);
or
In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2; test method OECD 489, oral route, under conditions as described above).

Notes for consideration by the Registrant

In case the micronucleus test is performed, the Registrant is reminded of paragraph 10 of the OECD 474 (Mammalian Erythrocyte Micronucleus Test, updated on 26 Sept 2014) "*If there is evidence that the test substance(s), or its metabolite(s), will not reach the target tissue, it may not be appropriate to use this tes*t". Additionally, according to paragraph 48 (d) of the OECD 474, a test chemical is considered clearly negative if "*Bone marrow exposure to the test substance(s) occurred*". Accordingly, if a substance is negative in this test, and if it is not possible to demonstrate that bone marrow exposure to the substance occurred, then ECHA will consider any remaining uncertainty concerning the mutagenic potential of the substance and whether to request any further information.

The Registrant is reminded that according to Annex X, Section 8.4., column 2 of the REACH Regulation, if positive results from an *in vivo* somatic cell study are available, "the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered".

In case the Registrant decides to perform the comet assay, he may consider examining gonadal cells, as it would optimise the use of animals. ECHA notes that a positive result in whole gonads is not necessarily reflective of germ cell damage since gonads contain a mixture of somatic and germ cells. However, such positive result would indicate that the substance and/or its metabolite(s) have reached the gonads and caused genotoxic effects. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new study meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for examination of the testing proposal. The Registrant must note, however, that this information has not been subject of a full review of the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In addition, it is important to ensure that the particular sample of substance tested in the new study 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 study must be suitable to assess these.

Finally, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the study to be assessed.

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://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[1] by Leena Ylä-Mononen, Director of Evaluation

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.