Helsinki, 7 March 2018

Addressee: [redacted]

Decision number: CCH-D-2114394599-25-01/F
Substance name: Exo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl acetate
EC number: 204-727-6
CAS number: 125-12-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 08/10/2014
Registered tonnage band: 100-1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. ***In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 with the registered substance;**

2. ***In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance, provided that the study requested under 1. has negative results;**

3. **Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: *Daphnia sp.* Acute immobilisation test, EU C.2./OECD TG 202) with the registered substance;**

4. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: Alga, growth inhibition test, EU C.3./OECD TG 201) with the registered substance;**

You have to submit the requested information in an updated registration dossier by **14 May 2019**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Kevin Pollard, Head of Unit, Evaluation E1

[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.

Appendix 1: Reasons

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: S. typhimurium TA1535; TA1537 or TA97a or TA97; TA98; TA100; S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). This includes four strains of *S. typhimurium* (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four *S. typhimurium* strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by E.coli WP2 strains or *S. typhimurium* TA102 which have an AT base pair at the primary reversion site.

You have provided a test from the year 1988 according to OECD TG 471 and GLP with an assigned reliability score of 1. The test used five different strains of *S. typhimurium* TA 1535, TA 1537, TA 1538, TA 98 and TA 100 and it did not include tests with strains S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). However, since the test was conducted, significant changes have been made to OECD TG guideline 471 so that additionally testing with S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is now required. Therefore, the provided study does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

ECHA concludes that a test using *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 has not been submitted and that the test using one of these is required to conclude on *in vitro* gene mutation in bacteria.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

From your comments according to article 50(1), ECHA notes that you agree to this request.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to complete the following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

2. *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained. ECHA notes that the registration dossier does not contain appropriate study records for several of these information requirements. Therefore, adequate information on *in vitro* gene mutation in mammalian cells needs to be present in the technical dossier for the registered substance to meet this information requirement, provided that the study requested under 1. has negative results.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2. ECHA has evaluated your adaptation and concludes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.2, which provides that "there may be sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion."

More specifically, the adaptation includes QSAR predictions for *in vitro* mutagenicity, generated with the Danish QSAR database, dated [redacted] 2011. The use of the Danish database in Chapter R.6 of the Guidance on information requirements on QSAR and grouping of chemicals for REACH provides that the Danish QSAR database is compiled to support the self-classification process (known as "Danish self-classification advisory list for dangerous substances"). It does not state that the predictions are suitable for replacement of the standard test. The data used in a hazard or risk assessment should be relevant, reliable and sufficient for the regulatory purpose.

ECHAs assessment of the QSAR predictions

The two first assays were submitted as separate endpoint records under the section in vitro toxicity (7.6.1) section in IUCLID 6.

- QSAR for mouse lymphoma cells
- QSAR for Chinese hamster ovary cells (CHO), chromosome aberration
- QSAR for HGPRT locus in Chinese hamster ovary cells
- Unscheduled DNA Synthesis (UDS) in Rat Hepatocytes
- Syrian Hamster Embryo (SHE) Cell Transformation

All five predictions were negative, and shown to be in domain. However, ECHA notes that the predictions were derived from an older version of the Danish QSAR database. ECHA notes further that the documentation of the QSAR predictions is incomplete, lacking information about training sets and QSAR model reporting format (QRMF) documents from the 2011 version for all endpoint study records. Therefore ECHA cannot verify the usefulness of the models, or the correctness of the calculated applicability domains.

Predictions made with the current version of the Danish QSAR database (17.08.2017), reproduce the negative prediction, in domain, only for chromosomal aberration CHO, in three QSARs now available (CaseUltra, Leadscope and SciQSAR). For the mouse lymphoma cell assay, the prediction is inconclusive, and out of the applicability domain in all three models. For the HGPRT locus CHO assay, one of the models (CaseUltra) gives inconclusive result, and is out of domain. For the UDS assay in rat hepatocytes and the SHE cell transformation assay, the consensus predictions are inconclusive and out of domain.

In addition, the isobornyl substructure is not among the experimental data used for the prediction for predicting the mouse lymphoma assay, and the HGPRT locus CHO assay. Therefore ECHA cannot verify the usefulness of the models or the correctness of the calculated applicability domains. Hence, the prediction cannot accepted. Therefore ECHA concludes that the provided data is insufficient to conclude on the hazardous properties of the substance for regulatory purposes and does not comply with the general rules of adaptation as set out in Annex XI, Section 1.2., which is therefore rejected.

ECHAs assessment of the read-across

Furthermore, you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a mammalian cell gene mutation assay (gene mutation) (OECD TG 476) with the analogue substance 2-isopropyl-5-methylcyclohexanol (EC no 201-939-0). However, there is no documentation for the read-across. Therefore, your dossier is lacking a basis for predicting relevant human health properties of the registered substance from data for the source substances.

In the absence of this information, ECHA cannot verify that the properties of the registered substance can be predicted from the data on the source substance. Hence, you have not established that relevant properties of the registered substance can be predicted from data on the analogue substance. Since your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5., it is rejected and it is necessary to perform testing on the registered substance.

Therefore, your adaptations of the information requirement are rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

From your comments according to article 50(1), ECHA notes that you agree to this request.

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the*Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that the study requested under 1. has negative results.

3. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Short-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex VII, Section 9.1.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

While you have not explicitly claimed an adaptation, in the CSR you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.3.: *"The following ranges for mortalities are predicted using the available OASIS/EcoSAR models and trend analysis: Daphnia magna EC50(48h) _3.07 ÷ 4.09 [mg/L]."*

However, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.3. The predictions provided for acute aquatic toxicity of the registered substance (QSAR toolbox, TIMES and ECOSAR are all outside of the applicability domain and not adequate for the regulatory purpose (risk assessment and C&L). More specifically, the adaptation fails due to the following reasons:

- QSAR Toolbox prediction:

  As can be seen in your dossier in Tables 1 and 2 of the file named "[redacted]" none of the analogue substances used to do the prediction are close structural analogue to the registered substance. Indeed, the registered substance contains a carbocyclic structure and a specific spatial configuration, which is not represented in the analogue structures used by you.

- TIMES prediction:

  As indicated in your dossier in the file named "[redacted]": *"This [redacted] is the cut-off value calculated according to narcotic base-surface. However, the target chemical has excess toxicity based on the ester group. Hence prediction should be considered as equal to or less than threshold value of [redacted], defined by narcotic base-surface. Hence, no domain information is associated with this prediction."*

  In addition, with reference to above observations on the structure of the registered and the analogue substances, the training set of TIMES does not contain close structural analogues to the registered substance.

- ECOSAR prediction:

  The training set of ECOSAR does not contain close structural analogues to the registered substance.

- CATALOGIC prediction:

  As indicated in your dossier in the file named "[redacted]", there are some fragments that are unknown to the CATALOGIC 301C model and therefore the registered substance is out of the structural domain of the model. In addition:

  - It is uncertain that the three degradation products identified by you will occur;

  - It is uncertain that they will be stable and that they will not degrade rapidly into other compounds;

  - Other degradation products may be produced in addition to these three compounds.

Consequently, the identification of the degradation products provided in the technical dossier is also unreliable and prediction of their aquatic toxicity cannot be accepted, as they are outside of the applicability domain and not adequate for the regulatory purpose (risk assessment and C&L).

Therefore, your adaptation of the information requirement cannot be accepted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

From your comments according to article 50(1), ECHA notes that you agree to this request.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) Daphnia sp. acute immobilisation test (test method EU C.2. / OECD TG 202) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.1.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *Daphnia* sp. Acute immobilisation test, EU C.2./OECD TG 202).

Notes for your consideration for requests 3 and 4:

Due to the surface activity of the registered substance you should consult the OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and the ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

4. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. No such study is available from the registration dossier.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement Annex XI, Section 1.3.: *"The following ranges for mortalities are predicted using the available OASIS/EcoSAR models and trend analysis: Algae sp. EC50(96h) is between 1.31 and 1.45 mg/L."*

However, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.3. because the predictions given by the registrant for aquatic toxicity of the registered substance (QSAR Toolbox and ECOSAR for Algae) cannot be accepted as they are all outside of the applicability domain and not adequate for the regulatory purpose (risk assessment and C&L) due to the following reasons:

- QSAR Toolbox prediction:

  As can be seen in your dossier in Tables 1 and 2 of the file named "[redacted]" none of the analogue substances used to do the prediction are close analogue to the registered substance. Indeed, the target substance contains a carbocyclic structure and a specific spatial configuration, which is not represented in the analogue structures used by you.

- ECOSAR prediction:

  The training set of ECOSAR does not contain close structural analogues (source substances) to the registered substance (target substance).

Consequently, the identification of the degradation products provided in the technical dossier is also unreliable and prediction of their aquatic toxicity cannot be accepted, as they are outside of the applicability domain and not adequate for the regulatory purpose (risk assessment and C&L).

Therefore, your adaptation of the information requirement cannot be accepted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

From your comments according to article 50(1), ECHA notes that you agree to this request.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) Algae growth inhibition test (test method EU C.3. / OECD TG 201) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.2.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Algae growth inhibition test, EU C.3./OECD TG 201).

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide the requested information was 10 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline to 14 months. You sought to justify this request by providing quotes of testing laboratories to demonstrate the current low capacities. Therefore, ECHA has granted the request and set the deadline to 14 months.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 29 June 2017.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and amended the deadline.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests 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 or imported by each registrant.

If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.