EUROPEAN CHEMICALS AGENCY

Helsinki, 10 March 2020

Addressees
Registrant of JS_290822-07-0 listed in the last Appendix of this decision

Date of submission for the dossier subject of this decision
14 June 2012

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 1-(2-hydroxy-2-methylpropoxy)-2,2,6,6-tetramethylpiperidin-4-yl octadecanoate
EC number: 433-060-5
CAS number: NS

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

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by ***17 March 2021***.

A. Requirements applicable to all the Registrants subject to Annex VIII of REACH

1. *In vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) with the Substance;

2. Only if a negative result in Annex VIII, Section 8.4.2. is obtained, *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method OECD TG 476 or TG 490) with the Substance;

3. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method OECD 421/422) in rats, oral route with the Substance.

Conditions to comply with the requests

You are bound by the requests for information corresponding to the REACH Annexes applicable to your own registered tonnage of the Substance at the time of evaluation.

Therefore you have to comply with the requirements of Annexes VII and VIII of REACH, if you have registered a substance at 10-100 tpa.

Registrants are only required to share the costs of information that they must submit to fulfil the information requirements for their registration.

Appendix A states the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach

for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

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.

Approved[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[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 A: Reasons for the requests to comply with Annex VIII of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 10 to 100 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII and VIII to REACH.

1. ***In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, Section 8.4.2.)**

An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is a standard information requirement in Annex VIII to REACH.

To fulfil the information requirement for the Substance, both *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) and *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

You have provided a key study in your dossier:

- *In vitro* cytogenicity/chromosome aberration study in mammalian cells (equivalent to OECD TG 473, GLP compliant, [redacted] 2000) with negative results.

We have assessed this information and identified the following issue(s):

To fulfil the information requirement, the study has to be an *in vitro* chromosomal aberration test or an *in vitro* micronucleus test, conducted in mammalian cells in accordance with OECD TG 473 or OECD TG 487, respectively[2]. The key parameters of these test guidelines include, among others:

- At least 300 well-spread metaphases must be scored per concentration;
- Determination and reporting data on the cytotoxicity and the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures must be provided.

The reported data for the study you have provided in your dossier did not include:

- information on the number of metaphases scored;
- data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures.

In the absence of detailed information on those critical aspects of the study, we cannot evaluate the reliability of the conclusions derived from this data.

In your comments on the draft decision you agree that the robust study summary (RSS) is lacking the above mentioned information.

Based on the above, ECHA concludes that the information provided in your registration dossier does not meet the requirements of Annex VIII, Section 8.4.2, and therefore requests information on this endpoint.

[2] ECHA Guidance R.7a, Table R.7.7-2, p.557.

In your comments you have further provided tabulated data reporting the cytotoxicity and the frequency of cells with the structural chromosomal aberrations. You state you will update the RSS in the registration dossier accordingly "*as soon as possible*".

ECHA confirms that the data reported in your comments provides adequate and reliable information on the cytotoxicity and the frequency of cells with the structural chromosomal aberrations.

A registration update with such a robust study summary of the existing study would be adequate to fulfill the information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation. As you were already informed in the notification letter accompanying the initial draft decision of 30 August 2019, dossier updates will be considered in the follow-up evaluation which ECHA will perform after expiry of the deadline set by this decision.

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

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test in mammalian cells or the *in vitro* micronucleus study.

Your dossier contains an *in vitro* gene mutation study in mammalian cells.

We have assessed this information and identified the following issue(s):

A. The information for the *in vitro* cytogenicity study in mammalian cells provided in the dossier are rejected for the reasons provided in section A.1.

   The result of the request for information in section A.1 will determine whether the present requirement for an *in vitro* gene mutation study in mammalian cells in accordance with Annex VIII, Section 8.4.3 is triggered.

   In your comments to the draft decision you have provided a robust study summary (RSS) for the *in vitro* cytogenicity study, which, as explained above under A.1., ECHA considers adequate to fulfill the information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation. Provided that you update your registration with this information, your dossier will contain negative results for both an Ames test and an *in vitro* cytogenicity study. Such a finding triggers the information requirement for an *in vitro* gene mutation study in mammalian cells.

B. To fulfil the information requirement, the *in vitro* gene mutation study on mammalian cells has to meet the requirements of OECD TG 476 or OECD TG 490. The key parameter(s) of these test guidelines include, among others, the determination and reporting of the cytotoxicity and the mutation frequency for the treated and control cultures.

You have provided a key study in your dossier:

- *In vitro* gene mutation study in mammalian cells (equivalent to OECD TG 476, GLP compliant, [redacted] 2010) with negative results.

The reported data for the *in vitro* study you submitted did not include information on the cytotoxicity and the mutation frequency for the treated and control cultures.

In the absence of detailed information on this critical aspect of the study, we cannot evaluate the reliability of the conclusions derived from this data.

In your comments to the draft decision you agree that the robust study summary (RSS) is lacking the above mentioned information.

Based on the above, ECHA concludes that the information provided in your registration dossier does not meet the requirements of Annex VIII, Section 8.4.3, and therefore requests information on this endpoint.

In your comments, you have further provided tabulated data reporting the cytotoxicity and the mutation frequency. You state you will update the RSS accordingly "*as soon as possible*".

ECHA has assessed the provided data and identified the following issue:

According to the OECD TG 476 (from 1997) you have followed, one of the key requirements to obtain reliable results, is that the cell type used should have a stable spontaneous mutant frequency.

The results you have provided show inconsistencies in the reporting of the mutation frequency, as follows:

- Vehicle control: the reported values vary significantly: from 0.5 (at 4 h without S9/trail 1) to 6.92 (at 4 h with S9/trail 2). It is noted that the spontaneous mutant frequency measured under the conditions of metabolic activation is nearly 90 % higher compared to some of the treatment groups under the same conditions.
- Treatment groups: values from 0 to 9.68 (with 5.84 for the lowest dose in 24-h treatment without S9/trial 2; 5.10 for the lowest dose in 4-h treatment with S9/trial 1). ECHA points out that it is unusual to report values of 0 (zero) for a mutation frequency. This may be a sign that the test system is not completely mastered by the operators.

Therefore, the information requirement is not fulfilled.

To fulfil the information requirement for the Substance, both the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) and the thymidine kinase gene (OECD TG 490) are considered suitable

3. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

In your dossier you have reported a running OECD TG 421 study with the Substance ([redacted] 2012). We note that you have not updated your dossier since submission [redacted] (14 June 2012).

In your comments to the draft decision you state that "*The requested reproductive/developmental toxicity screening study has been completed following OECD*

guideline 421 in 2013, however, this information was unfortunately never submitted to ECHA".

Based on the above, ECHA concludes that the information provided in your registration dossier does not meet the requirements of Annex VIII, Section 8.7.1, and therefore requests information on this endpoint.

In your comments, you have further provided a summary of the study and you stated that you will update your dossier with the missing information *"as soon as possible"*.

Based on the summary information provided, ECHA notes that the reproductive/developmental toxicity screening study is performed in accordance with OECD TG 421 and that no systemic and reproductive effects were reported up to the highest dose of 1000 mg/kg bw/day. Therefore, ECHA considers that the data provided in your comments provides adequate and reliable information on the sexual function and fertility and development of the offspring.

A registration update with such a robust study summary of the existing study would be adequate to fulfill the information requirement of Annex VIII, Section 8.7.1. of the REACH Regulation. As you were already informed in the notification letter accompanying the initial draft decision of 30 August 2019, dossier updates will be considered in the follow-up evaluation which ECHA will perform after expiry of the deadline set by this decision.

Information on study design

A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats with oral[3] administration of the Substance.

[3] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Appendix B: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

The compliance check was initiated on 28 May 2019.

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 within 30 days of the notification.

ECHA took into account your comments and did not amend the requests.

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix C: Observations and technical guidance

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

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 the Member States.

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries'[4].

4. Test material

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/ impurity.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[5].

[4] https://echa.europa.eu/practical-guides
[5] https://echa.europa.eu/manuals

5. List of references of the ECHA Guidance and other guidance/ reference documents[6]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[7]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents[8]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[8] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix D: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]