EUROPEAN CHEMICALS AGENCY

Helsinki, 25 April 2018

Addressee: [redacted]

Decision number: CCH-D-2114408329-49-01/F
Substance name: (Z)-2-butene-1,4-diol
EC number: 228-085-1
CAS number: 6117-80-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 15/12/2017
Registered tonnage band: 10-100T

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]

1. ***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;**

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

You have to submit the requested information in an updated registration dossier by **2 May 2019**. You also have to update the chemical safety report, where relevant.

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[2] by Kevin Pollard, Head of Unit, Evaluation E1

[1] No testing for endpoints listed in Annexes IX or X to the REACH Regulation may be started or performed at this moment: A decision only becomes legally effective and binding for you after it has been adopted according to Article 51 of the REACH Regulation. ECHA will take the decision either after the date it has become clear that Member State competent authorities have not made any proposals to amend the draft decision or, where proposals to amend it have been made, after the date the Member State Committee reached a unanimous agreement on the draft decision.
[2] 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

TOXICOLOGICAL INFORMATION

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

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

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 contains negative results for both 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.

You have not provided any study record of an *in vitro* gene mutation study in mammalian cells in the dossier that would meet the information requirement of Annex VIII, Section 8.4.3.

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.

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.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation, you s assert there is no scientific justification for performing this study, as the only two assays, which are widely considered to be pivotal in genetic toxicology are Ames test and an *in vivo* mammalian erythrocyte micronucleus test ([redacted] 2013). Both these assays were performed with the registered substance, giving negative results up to the highest recommended concentration, with no premises for any concern about genotoxic potential. You also highlight that the *in vivo* test is not a standard information requirement for Annex VIII and gives much higher level of information on the possible mechanisms of action than any *in vitro* test.

ECHA Secretariat remains of the opinion that an *in vitro* gene mutation study in mammalian cells should be performed as it is a standard requirement for Annex VIII. This test cannot be replaced with an *in vivo* micronucleus assay, because that assay is not designed for detection of gene mutations. Instead, it is tailored towards detecting cytogenetic damage which results in the formation of micronuclei containing either lagging chromosome fragments or whole chromosomes and to detect damage to the mitotic apparatus of erythroblasts.

Hence, the test is appropriate to detect both clastogenic and aneugenic substances, but not appropriate to identify substances which primarily induce gene mutations.

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).

Deadline to submit the requested information in this decision

In the draft decision communicated to you, the time indicated to provide the requested studies and submit the study results to ECHA in a dossier update was 30 months from the date of adoption of the decision. As two requests, Pre-natal developmental toxicity study in a second species (rat), oral route and Extended one-generation reproductive toxicity study in rats, oral route with the registered substance were removed following a tonnage band change , ECHA has amended the deadline to 12 months.

Appendix 2: Procedural history

You were notified that the draft 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. However, following your comments on the draft decision and the inter-related new and substantial information provided in the updated dossier, ECHA has taken into account all the updated information, relevant, to the draft decision. Based on the average production and/or import volumes for the three preceding calendar years, ECHA has changed the tonnage band from > 1000 tonnes per year (submission number: [redacted]) to 10 – 100 tonnes per year (Latest submission number: [redacted]).

The compliance check was initiated on 12 May 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 all the updated information of submission [redacted]. As a result, the requests for information on Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rat), oral route with the registered substance and Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:

- Ten weeks remating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animal

to produce the F2 generation were removed. In addition, for the request for information on 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, only Appendix 1 was modified.

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.