ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114303243-67-01/F Helsinki, 30 June 2015

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For but-2-ene-1,4-diol, CAS No 110-64-5 (EC No 203-787-0), 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 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration for but-2-ene-1,4-diol, CAS No 110-64-5 (EC No 203-787-0), submitted by [redacted] (Registrant).

The scope of this compliance check is limited to the standard information requirements of Annex IX, Sections 8.7.2. and 8.7.3. of the REACH Regulation. ECHA stresses that it has not checked the information provided by the Registrant for compliance with requirements regarding the identification of the substance (Section 2 of Annex VI).

This decision is based on the registration 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 submitted after 05 March 2015, 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 compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

The compliance check was initiated on 8 November 2013.

On 10 July 2014 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted].

On 29 July 2014 ECHA received comments from the Registrant on the draft decision, concerning the information requirements of Annex IX, Section 8.7.2, and Annex X, section 8.7.3. The compliance check requirement to submit information of a two-generation reproductive toxicity study (EU B.35, OECD TG 416) or an extended one-generation reproductive toxicity study (EU B.56, OECD TG 443) has been removed from this draft decision due to the legislative amendments to the REACH Regulation regarding Annex X, Section 8.7.3. In light of this, ECHA Secretariat did not consider further the Registrant's comments and update concerning the information requirement of Annex X, Section 8.7.3. However, ECHA Secretariat did consider further the Registrant's comments and update

concerning the information requirement of Annex IX, Sections 8.7.2. On the basis of all this information and change of scope, Sections II and III were amended.

On 5 March 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.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Information required

Pursuant to Articles 41(1), 41(3), 10(a)(vi) and/or (vii), 12(1)(e), 13 and Annex IX of the REACH Regulation the Registrant shall submit the following information using the indicated test method and the registered substance subject to the present decision:

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

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated registration to ECHA by **7 July 2016**.

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.

III. Statement of reasons

Pursuant to Article 41(3) of the REACH Regulation, ECHA may require the Registrant to submit any information needed to bring the registration into compliance with the relevant information requirements.

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities of 1000 tonnes or more per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

1. Pre-natal developmental toxicity study (Annex IX, 8.7.2.)

A "pre-natal developmental toxicity study" for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. 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.

The Registrant has sought to adapt this information requirement. The justification of the adaptation given by the Registrant in the updated dossier (submission number [redacted]) is that "*in keeping with Regulation (EC) 1907/2006 Annex X Column 2 and for reasons of animal welfare, the dossier does not need additional results of a pre-natal development study (on a second species) or a 2-generation reproductive study, since there are no serious concerns about the potential for adverse effects on fertility or development based on available data and read across data from analogue substances. Further, the NOAEL for systemic effects is similar to the NOAEL for development.*"

In addition to one combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test (test method: OECD 422) with the registered substance, the Registrant provides in the updated dossier endpoint study records for three additional studies with substances other than the registered one: "Teratology and Multigeneration Reproduction Studies with Maleic Anhydride in Rats," no guideline followed; "Teratology and Multigeneration Reproduction Studies with Maleic Anhydride in Rats", OECD 416; and "Preliminary Study of the prenatal toxicity of 2-Butyne-1,4-diol in rats after oral administration (gavage)", OECD 414.

In their comments the Registrant refers to the adaptation possibility of Annex XI, 1.5. (grouping of substances and read-across approach) and applies a read-across from the source substances but-2-yne-1,4-diol (ByD) and maleic anhydride (MA) to the registered substance subject to the present decision (but-2-ene-1,4-diol) as target substance.

ECHA notes, firstly, that a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD 422) does not provide the information required by Annex IX, Section 8.7.2., because it does not cover key parameters of a pre-natal developmental toxicity study like examinations of foetuses for skeletal and visceral alterations.

Secondly, the read-across approach of the Registrant cannot be accepted for the following reasons:

Hypothesis provided by the Registrant:
According to the Registrant the read-across hypothesis is based on the following: "*Data on the toxicokinetics of 1,4-Butenediol (B2D) is limited and not well characterized. However, it is supported by limited test data and by some similarities to better studied substances of similar structure. It is predicted that B2D is metabolized* to maleic acid. B2D's toxicological profile is very similar to maleic acid's toxicological profile." Furthermore, the Registrant seeks to support the hypothesis with a read-across to the analogue substance, but-2-yne-1,4-diol (B3D) and to maleic anhydride, which is considered by the Registrant to be analogue to 2-Butene-1,4-diol "*as it is also metabolically hydrolyzed to maleic acid*".

Information submitted by the Registrant to support the read-across hypothesis:
The justification for the read-across approach is given in the endpoint summary on toxicokinetics, metabolism and distribution (IUCLID section 7.1) of the updated dossier. In addition, the endpoint summary for Toxicity to reproduction (IUCLID section 7.8) refers to data from a Prenatal Developmental Toxicity Study (OECD Guideline 414) with rats exposed to but-2-yne-1,4-diol (B3D): "The maternal NOAEL was 40 mg/kg bw. Since B2D is considered to be a less active molecule than B3D, this result supports the key value for B2D" and to a 2-generation reproductive toxicity study in rats exposed to maleic anhydride

("Maleic anhydride is considered to be analogue to 2-Butene-1,4-diol as it is also metabolically hydrolyzed to maleic acid.")

Analysis of the read-across hypothesis in light of the requirements of Annex XI, 1.5. of the REACH Regulation:
Based on the information provided, ECHA understands that the read-across hypothesis is based on

(i) the degradation and/or metabolism of the registered substance;
(ii) similarity of the registered substance to an analogue substance.

ECHA notes that

(i) As regards maleic anhydride (MA), it is indeed likely that both, MA and the target are metabolized to maleic acid, although no direct toxicokinetic evidence is provided.

The Registrant further assumes that the effects in the pre-natal developmental toxicity study are solely determined by maleic acid. ECHA indeed finds it highly likely that this is the case for MA. However, the same conclusion cannot be drawn for the target substance based on the information provided, even if it is assumed that this substance is also metabolized to maleic acid.

As is clearly shown by the Registrant, the putative metabolism of the target to maleic acid requires several steps, each of them characterized by its own intermediate. Read-across would only be acceptable if the systemic exposure after external exposure to the target is limited to maleic acid. Any significant systemic exposure to the target substance itself (parent compound) and the intermediate products should be absent, to prevent any direct contribution of these substances to the considered toxicological endpoint. It is nowhere demonstrated by the Registrant that there is no systemic exposure to the registered substance, or to its metabolites (not including maleic acid). Thus, ECHA considers that the Registrant's scientific justification for read-across from maleic acid does not in principle address the properties of the Registered substance, nor intermediate metabolites (before maleic acid). Accordingly, ECHA considers that the proposed read-across from maleic acid does not meet the requirement of Annex XI, 1.5, that the human health effects of the Registered substance may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

(ii) For but-2-yne-1,4-diol (ByD) the Registrant states that this substance is "*the more active analogue*", but does not further elaborate the meaning of this statement. The Registrant does not explain in which respect the presumed analogue is more active, whether this greater activity pertains to the same effects than the ones that might be caused by the target substance, why ByD is anyhow expected to cause the same effects as the target substance or whether a worst-case approach can be followed.

The Registrant does thus not provide a scientifically credible explanation as to why the source substances cause the same effects as the target substance when tested in the pre-natal developmental test. ECHA notes that the structural difference between source and target (a triple bond versus a double bond) is nowhere related to the toxicokinetic properties and the toxicodynamic properties of the two substances, let alone that it is convincingly argued that this difference will not affect the possibility to read across. Accordingly, ECHA considers that the proposed approach of read-across from but-2-yne-1,4-diol does not allow that the human health effects of the

Registered substance may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

Conclusion
ECHA notes that the Registrant has not provided reliable data to support the metabolism of the target and source substances. In addition, the rate and extent of metabolism and thus the impact of the parent compounds and the impact of different metabolites on toxicity profiles has not been addressed by the Registrant. These are further reasons why the read-across hypothesis based on a specific metabolic path of the registered substance is not a sufficient basis whereby the human health effects of the registered substance may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

According to Annex XI, 1.5. (2), the similarities of a group may be based on the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which results in structurally similar chemicals. The Registrant claims that B2D is metabolized to maleic acid and that the toxicological profile is very similar to maleic acid's toxicological profile. However, as explained above, the Registrant has not demonstrated that common and non-common products metabolites are formed nor provided any quantitation thereof. Thus the extent to which there are common breakdown products is entirely unclear, and ECHA cannot verify that this criterion is satisfied. Moreover, for the reasons set out above, ECHA considers that the Registrant's proposed adaptation does not satisfy the requirement of Annex XI, 1.5, that the human health effects of the Registered substance may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

Pursuant to Article 41(1) of the REACH Regulation, the adaptation of the standard information requirements in the technical dossier, based on the read-across and grouping of substances, does not comply with the general rules of adaptation as set out in Annex XI, 1.5.

Consequently there is an information gap and it is necessary to provide information for this endpoint.

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.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD 414) in rats or rabbits by the oral route.

Notes for consideration by the Registrant

In addition, a pre-natal developmental toxicity study on a second species is part of the standard information requirements as laid down in Annex X, Section 8.7.2. for substances registered for 1000 tonnes or more per year (see sentence 2 of introductory paragraph 2 of Annex X).

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; 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 scientific justification that the study in a second species is not needed. 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. If the Registrant comes to the conclusion that no study on a second species is required, he should update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex X, 8.7.2.

2. Deadline for submitting the required information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 36 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also contained a two-generation reproductive toxicity study (EU B.35, OECD TG 416) or an extended one-generation reproductive toxicity study (EU B.56, OECD TG 443) (Annex X, Section 8.7.3.). As these studies are not addressed in the present decision, ECHA Secretariat considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 12 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

IV. Adequate identification of the composition of the tested material

ECHA stresses that the information submitted for identifying the substance has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation. The Registrant is reminded of his responsibility to ensure that his registration covers one substance only and that the substance is correctly identified in accordance with Annex VI, Section 2 of the REACH Regulation.

In carrying out the studies]required by the present decision it is important to ensure that the particular sample of substance tested 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 studies must be suitable to assess these.

In relation to the information required by the present decision, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given 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.

Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the studies 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 an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on 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.

[redacted]
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