Decision number: CCH-D-0000004339-69-03/F Helsinki, 27 November 2014

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

For 2-butene, CAS No 107-01-7 (EC No 203-452-9), 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 2-butene, CAS No 107-01-7 (EC No 203-452-9), submitted by [redacted] (Registrant). The scope of this compliance check is limited to the standard information requirement of Annex VIII, Section 8.4.3. of the REACH Regulation. ECHA stresses that it has not checked the information provided by the Registrant and other joint registrants 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 12 June 2014, 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 15 May 2013.

On 12 June 2013 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 11 July 2013 ECHA received comments from the Registrant on the draft decision.

The ECHA Secretariat considered the Registrant's comments. The information is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

On 12 June 2014 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)(vii), 12(1)(e), 13 and Annex VIII 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:

- *In vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3.; test method: EU B.17/OECD 476).

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 **4 December 2015**.

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. The scope of the present decision is the *in vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3. of the REACH Regulation).

- *Mutagenicity,* in vitro *gene mutation study in mammalian cells.*

In accordance with Articles 10(a)(vii), 12(1)(e) and with Annex VIII, section 8.4.3. of the REACH Regulation, the *in vitro* gene mutation study in mammalian cells is required if there is a negative result in the *in vitro* studies specified under Annex VII, section 8.4.1. and Annex VIII, section 8.4.2. The registration dossier reports negative results for both *in vitro* studies. Therefore the REACH Regulation requires that information on *in vitro* gene mutation in mammalian cells (Annex VIII, 8.4.3.) is provided in the dossier. ECHA notes furthermore that a cytogenicity study (be it *in vitro* or *in vivo*) cannot be used for *in vitro* or *in vivo* mammalian cell gene mutation information requirements. Cytogenicity studies and gene mutation studies correspond to two different endpoints and two distinct mechanisms of genotoxicity: cytogenicity studies detect structural and numerical chromosome aberrations whereas gene mutation studies detect gene or point mutations. ECHA concludes that the Registrant has neither provided this standard information nor adapted the requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The Registrant has in his comments to the draft decision referred to an *in vivo* mutagenicity study with mouse lymphoma cells using 2-methylpropene (EC: 204-066-3) as the test substance. The reference for this study is mentioned in the Chemical Safety Report (CSR) but the IUCLID dossier contains no end point study summary of the results.

ECHA notes that the mutagenicity studies in the dossier were reported to be negative. The dossier contains two *in vivo* micronucleus assays with 2-methylpropene. The *in vitro* studies reported in the CSR contain two bacterial reverse mutation assays with 2-butene (the registered substance), one with 1-butene and four with 2-methylpropene. In addition there is an *in vitro* mammalian chromosome aberration test and the in vitro mammalian cell transformation assay referred to by the registrant (gene mutation, mouse lymphoma L5178Y cells) with 2-methylopropane. The Registrant also lists an *in vitro* mammalian cell gene mutation assay (gene mutation) in human lymphocytes, which was negative (not mentioned in the comments).

The Registrant refers to a defined category "Lower Olefins and Aromatics" which consists of the following category members: 1-Butene, 2-Butene (cis/trans), 2-methylpropene, and butenes, mixed isomers. The Registrant has given the following category rationale:

"The Butenes category consists of substances that are C4 olefins or contain a mixture of the C4 olefins. The CAS number 107-01-7 describes two isomers (cis and trans) and the CAS number 25167-67-3 describes a mixture of C4 olefins.
The substances considered in the category share similar physical chemical properties and environmental fate and effect properties. The Butenes are gases at standard temperature and pressure and the majority of the substances will partition to the atmosphere, reducing the likelihood of the substances being bioaccumulative or toxic. QSAR estimates show that the Butenes are predicted to degrade rapidly, with an estimated half-life of 2.8 days and to have a low toxicity to aquatic organisms. The Butenes are not predicted to meet the screening criteria for persistence, bioaccumulation or and toxicity.
For mammalian endpoints members of the Butenes category behave in a similar manner where test data is available. None of the substances are classified for Human Health effects. Due to their similarities in structure, phys-chem properties, predicted environmental fate/effects and human health profile, it is justified to evaluate the substances as a category and read-across between members is acceptable.
For full details and further see the attached file on the butene this category and the attached categorymatrix report."

ECHA assessment of the read across

The read across that the Registrant is presenting is based on structural similarity and perceived equal effects in so far as test data are available.

The Registrant's read across justification document gives no reference to the metabolism of butenes, in particular the formation of epoxides and their further detoxification. Any genotoxic and related effects would ultimately be caused by the epoxides formed during e metabolism. The balance between formation and breakdown and reactivity to biological macromolecules determines whether genotoxicity may be expected or not. Formation, disappearance and reactivity may very well differ from one butene to another.

Several toxicokinetic studies underpin the importance of the epoxidation mechanism, e.g., demonstrating the formation of DNA adducts and haemoglobin adducts by 1-butene. Because of this mechanism the butenes deserve special attention when it comes to evaluating their genotoxicity. Therefore it is not possible to read across from a genotoxicity study from one butene to another without taking these metabolism aspects into account. Modelling, for example, could help this assessment but there is none present in the justification.

The available genotoxicity data of all three butenes shows that isobutene is apparently non-genotoxic in all three *in vitro* tests and in the *in vivo* micronucleus test. There is one negative Ames test with 1-butene; no other tests are available for this substance. 2-Butene is also negative in the Ames test and there is one *in vitro* chromosomal aberrations test with rat lymphocytes that does not show effects. However, in ECHA's opinion this does not constitute sufficient evidence. The negative effects of 2-butene in the two studies can be the result of the sensitivity of the specific genotoxicity endpoints to the epoxide, i.e., the epoxide might only cause gene mutations and no chromosomal damage. An additional contributing factors are the actual presence of the epoxide (concentration X time) and the metabolic activation system applied and whether the DNA in bacteria is reached by the epoxide formed outside the bacteria. That is to say, the negative results in these studies do not exclude the possibility of a positive effect in the gene mutation study, because the epoxide can cause gene mutations and the DNA can be reached. Therefore, absence of an effect in the *in vitro* gene mutation test with the read across substance isobutene cannot be accepted because differences in the presence (concentration X time) between the epoxides and/or their propensity to cause the required initial DNA damage are not considered.

In the absence of comparative information on the formation and the disappearance, as well as the reactivity to DNA, on the butenes that are members of the category the read across is rejected. Section 2 of the draft decision is therefore not amended.

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: *In vitro* mammalian cell gene mutation test (test method: EU B.17./OECD 476).

IV. Adequate identification of the composition of the tested material

ECHA stresses that the information submitted by the Registrant and other joint registrants 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 and that of joint Registrants to ensure that the joint registration covers one substance only and that the substance is correctly identified in accordance with Annex VI, Section 2 of the REACH Regulation.

In relation to the information required by the present decision, the sample of substance used for the new study 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.

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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new study must be suitable to assess these grades.

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

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Leena Ylä-Mononen
Director of Evaluation