~~CONFIDENTIAL~~

European Chemicals Agency

Decision number: CCH-D-0000001699-60-07/F Helsinki, 30 March 2012

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

For Allyl alcohol, CAS 107-18-6 (EC No 203-470-7), 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 dossier for **Allyl alcohol,** CAS No. 107-18-6 (EC No. 203-470-7) submitted by [redacted] (the "Registrant"), latest submission number [redacted], for 1000 tonnes or more per year.

The compliance check was initiated on 21 December 2010.

On 10 June 2011 ECHA notified the Registrant of its draft decision and invited him pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

On 7 July 2011 the Registrant provided to ECHA comments on the draft decision. ECHA considered the information received and did not amend the draft decision.

On 29 July 2011 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 to amend the draft decision within 30 days. Subsequently, Competent Authorities of the Member States submitted proposals for amendments to the draft decision.

On 31 August 2011 ECHA notified the Registrant of proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments within 30 days of the receipt of the notification. Based on the proposed amendments ECHA decided not to modify its draft decision.

On 12 September 2011, the draft decision was referred to the Member State Committee.

On 26 September 2011, the Registrant provided comments on the proposed amendments. The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 2-4 November 2011, the Member State Committee amended the draft decision and a unanimous agreement of the Member State Committee on the amended draft decision was reached on 3 November 2011.

This compliance check decision does not prevent ECHA to initiate further compliance checks on the present dossier at a later stage.

II. Information required

1) Pursuant to Articles 41(1)(a), 41(3), 10(a)(vii) and Art. 12(1)(e) as well as Annexes VII-X of the REACH Regulation the Registrant shall submit the information using the test method as indicated on:
   a) *In vitro* gene mutation study in bacteria with an additional, fifth strain of bacteria (Annex VII, 8.4.1) following an updated recommendations of EU Method B.13/14 (OECD Test Guideline 471)
   b) *In vivo* genotoxicity (somatic cell test) (Annex X, 8.4.; EU Method B.39 (OECD test guideline 486))
   c) Developmental toxicity study on another species than rat by oral route (Annex X, 8.7.2.; EU Method B.31 (OECD test guideline 414))

2) Pursuant to Articles 41(1)(a), 41(3) and 10(a)(vii) and Art 12(1)(e) as well as Annex VIII of the REACH Regulation the Registrant shall update the registration dossier so that all relevant information that is available to him on the substance is included. Thus it is requested that following robust study summaries are included in the dossier for the following end point study records:
   a) *In vitro* cytogenicity study in mammalian cells (Annex VIII, 8.4.2.; EU Method B.10), Report no. SV1223, 2004
   b) *In vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3., EU Method B.17), Report no. VV0306, 2004

3) Pursuant to Articles 41(1)(c), 41(3) and 10(b) as well as Annex I of the REACH Regulation, the Registrant shall submit in the chemical safety report the following information:
   a) Worker exposure assessment, which includes a description how the exposure assessment for workers was carried out.
   b) Risk characterization for physico-chemical properties.

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated IUCLID dossier to ECHA by **2 April 2013**.

III. Statement of reasons

Based on the examination of the technical dossier, ECHA concludes that the information therein, submitted by the Registrant for registration of the above mentioned substance in accordance with **Article 6** of the REACH Regulation, does not comply with the requirements of Articles **10, 12, 13 and 14 and with Annexes I, VII, VIII and X** thereof. Consequently, the Registrant is requested to submit the information mentioned above that is needed to bring the registration into compliance with the relevant information requirements.

1) Missing information related to endpoints

Pursuant to Articles 10(a)(vii) and 12(1)(e) of the REACH Regulation, a registration for a substance produced in quantities of 1000 tonnes or more per year shall contain as a minimum the information specified in Annexes VII - X of the REACH Regulation.

a) *In vitro* gene mutation study in bacteria with an additional, fifth strain of bacteria

ECHA notes that for the endpoint 8.4.1 of Annex VII, the Registrant provided data from an *in vitro* gene mutation study in bacteria performed in *Salmonella typhimurium* according to OECD Test Guideline (TG) 471 in force at that time and in accordance with the OECD good laboratory practice (GLP) principles.
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.

In the present case, the test submitted was carried out according to GLP and to OECD TG 471. However, since the test was conducted, significant changes have been made to OECD 471 and this means that the study does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI.

The version of the EU Test Method B.13/14/OECD TG 471 in force since 1997 introduces the need for performing the test in at least 5 strains of bacteria whereas the OECD TG 471 in force in 1992 only required testing in a minimum of 4 bacterial strains. The required 5th bacterial strain, i.e. *Escherichia coli WP2* strains or *S. typhimurium TA102*, has the potential to detect certain types of mutagens, such as cross-linking agents or oxidising mutagens, which the 4 bacterial strains recommended in the former version of the OECD TG 471 may not detect.

Consequently, the Registrant is required to complete the data set on mutagenicity by performing an *In vitro* gene mutation study in bacteria (Annex VII, 8.4.1) using one missing bacterial strain which may detect mutagens, such as cross-linking agents or oxidising mutagens, i.e. one *E. coli WP2* strain or *S. typhimurium TA102*, following recommendations of EU Method B.13/14 laid down in Commission Regulation (EC) No 440/2008 or OECD Test Guideline 471.

b) *In vivo* genotoxicity

According to Annex X, 8.4 "if there is a positive result of any of the *in vitro* genotoxicity studies in Annexes VII or VIII, a second *in vivo* somatic cell test may be necessary, depending on the quality and relevance of all the available data". There are altogether two positive *in vitro* gene mutation studies in the technical dossiers (including original and updated dossier) submitted by the Registrant for that substance. The dossier already also contains three negative *in vivo* genotoxicity studies. However, all of the *in vivo* studies are only relevant for the endpoint of chromosome aberration. Since there are positive *in vitro* gene mutation studies in the technical dossiers submitted by the Registrant for that substance, an *in vivo* study for the gene mutation endpoint is needed to evaluate the potential of allyl alcohol to cause gene mutations *in vivo*. A suitable test for this purpose is an unscheduled DNA synthesis (UDS) test with mammalian liver cells *in vivo* (OECD 486), since allyl alcohol is shown in the 90-day study to have effects in liver.

Accordingly, the Registrant is requested to carry out an *in vivo* genotoxicity study using OECD 486 or EU Method B.39 (unscheduled DNA synthesis (UDS) test with mammalian liver cells *in vivo).*

c) Developmental toxicity study

A developmental toxicity study on a first species is required under Annex IX, 8.7.2 to the REACH Regulation, and a developmental toxicity on a second species is required according to Annex X, 8.7.2, subject to all appropriate column 2 or Annex XI data adaptations.

ECHA observes that in the technical dossier, the Registrant has provided data on developmental toxicity in rats in allyl alcohol, and no adverse effects on prenatal development were observed in a study on the first species. To fulfil the information requirement for a developmental toxicity on a second species, the Registrant has provided data for the prenatal developmental toxicity in rabbits dosed with acrolein.

However, if the Registrant provides a study carried out on a substance other than the registered substance, the grounds of the read-across should be described. More specifically, Annex XI, section 1.5 provides that substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances. Application of the read-across approach requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) by interpolation to other substances in the read-across approach.

ECHA notes that read-across from acrolein to allyl alcohol is not acceptable for several reasons.. Firstly, allyl alcohol and acrolein do not have similar toxicological properties: acrolein is acutely much more toxic than allyl alcohol, whereas allyl alcohol has effects in a different spectrum of organs than acrolein after subchronic exposure (90-day study). Secondly, as shown in the study of Patel et al. (1980) in the dossier, allyl alcohol is metabozed to acrolein in the liver tissue, but not in lung tissue. Therefore, this study shows that local and systemic effects may not be reliably predicted from studies on acrolein by inhalation route. Thirdly, acrolein has adverse effects mainly at

the site of contact, whereas allyl alcohol may exhibit local effects at low doses whereas at high doses systemic effects are also seen.

Thus, ECHA considers that the toxicological properties of the registered substance may not be predicted from the properties of the read-across substance, as required under Annex XI, section 1.5. For these reasons, the requirements of Annex XI, section 1.5 in conjunction with Article 13(1) and third introductory paragraph of Annex X of the REACH Regulation are not met.

Consequently, since read-across from acrolein to allyl alcohol has failed to satisfy the requirements of Annex XI 1.5, the study provided by the Registrant cannot be taken into consideration as relevant data for the purpose of evaluation of allyl alcohol. Therefore, there is an information gap and information on prenatal developmental toxicity on second species has to be provided.

Accordingly, the Registrant is requested to carry out a developmental toxicity study on another species than rat by the oral route using the registered substance, allyl alcohol. EU Method B.31 (or OECD test guideline 414) shall be used.

2) Missing information in the updated dossier (robust study summaries) related to *in vitro* genotoxicity

According to Article 12 of the REACH Regulation, the technical dossier shall include all toxicological information that is relevant and available to the registrant.

The original dossier submitted on 11 May 2010 contained relevant robust study summaries: *in vitro* chromosome aberration test in human lymphocytes and an *in vitro* cell gene mutation test in allyl alcohol. In the updated dossier (submission date 16 July 2010) these study summaries were no longer included. Instead, Registrant provided information originating from another substance (*acrolein)* than the registered substance for the endpoint *in vitro* cytogenicity (Annex VIII, 8.4.2.) and a gene mutation study (Annex VIII, 8.4.3.) in allyl alcohol.

All relevant and available information for the substance should be presented in one dossier. Thus, it is essential that robust study summaries of all these studies are transferred back to the technical dossier.

Accordingly, the Registrant is requested to update the technical dossier so that all relevant *in vitro* genotoxicity studies are included.

3) Missing information related to Chemical Safety Report

Annex I sets out the general provisions for assessing substances and preparing chemical safety reports (CSR).

a) Exposure assessment for workers

Annex I, point 5.2.4. requires that an estimation of exposure levels shall be performed for all human populations, including workers. In the CSR the Registrant indicates that ECETOC TRA has been applied for worker exposure estimation. Appendix 1 of the CSR mentions that worker exposure assessment is "in Appendix 1a Attached in the

end of this document". However, no Appendix 1a was found anywhere in the CSR or in the IUCLID dossier. Consequently, it is not possible to assess the validity of the exposure estimation performed by the Registrant, as the basic assumptions and defaults used for exposure estimation are missing.

Accordingly, the Registrant is requested to update the Chemical Safety Report so that the method, basic assumptions and defaults used in the worker exposure assessment are described in detail.

b) Risk characterization for physicochemical properties

According to Article 14(4) of the REACH Regulation, an exposure assessment and risk characterisation shall be included in the chemical safety assessment if the substance fulfils the criteria for certain hazard classes or categories set out in Annex I to Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (the CLP Regulation), or is assessed to be a PBT or vPvB.
Annex I, point 6.3 requires that an assessment of the likelihood and severity of an event occurring due to the physicochemical properties of the substance is carried out.

The substance is classified by the Registrant as highly flammable. However, the Chemical Safety Report submitted by the Registrant does not contain risk characterisation for physico-chemical properties.

Accordingly, the Registrant is required to carry out this assessment and to update the CSR.

4) Deadline for submitting the required information

In the draft decisions communicated to the Registrant the time indicated to provide the requested information was 24 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a 2-generation reproductive toxicity study in order to comply with the information requirement set out in Annex X, 8.7.3.. As it was ultimately decided not to address in this decision any potential deficiencies with respect to the compliance of the dossier with the standard information requirement set out in Annex X, 8.7.3., ECHA considers that a reasonable time period for providing the remaining 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. General requirements for the generation of information and Good Laboratory Practice

ECHA always reminds registrants of the requirements of Article 13(4) of the REACH Regulation that reads:

> "*Ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or the Agency and with the provisions of Directive 86/609/EEC, if applicable.*"

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2008 as adapted to the technical progress or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

National authorities monitoring good laboratory practice (GLP) maintain lists of test facilities indicating the relevant areas of expertise of each facility.

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. The procedure is described in the Board of Appeal's "Preliminary instructions to Appellants" that can be found at the ECHA website. 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.

Done at Helsinki,

Jukka Malm
Director of Regulatory Affairs