EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114289313-47-01/F Helsinki, 16 December 2014

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

For 1,1-dichloroethylene, CAS No 75-35-4 (EC No 200-864-0), 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 1,1-dichloroethylene, CAS No 75-35-4 (EC No 200-864-0), submitted by [redacted] (Registrant).

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 16 July 2013.

On 5 December 2013 ECHA sent the draft decision to the Registrant and invited him to provide comments within 45 days of the receipt of the draft decision. That draft decision was based on submission number [redacted].

On 20 January 2014 ECHA received comments from the Registrant on the draft decision. On 20 February 2014 the Registrant updated his registration dossier with the submission number [redacted].

The ECHA Secretariat considered the Registrant's comments and update. On the basis of this information, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

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.

Subsequently, proposals for amendment to the draft decision were submitted.

On 18 July 2014 ECHA notified the Registrant of the proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposals for amendment received and amended the draft decision.

The draft decision was split into two draft decision documents: one relating to the request for a two-generation reproductive toxicity study and one relating to the request for transgenic rodent somatic and germ cell gene mutation assay (TGR) or in vivo alkaline single-cell gel electrophoresis assay for DNA strand breaks (comet assay), revised risk characterisation ratios (RCRs) for local releases, a revised risk characterisation for the marine compartment for the relevant exposure scenarios and documentation for the recommended personal protective equipment.

The present decision relates solely to a compliance check requesting information in form of relating to the request for transgenic rodent somatic and germ cell gene mutation assay (TGR) or in vivo alkaline single-cell gel electrophoresis assay for DNA strand breaks (comet assay), revised risk characterisation ratios (RCRs) for local releases, a revised risk characterisation for the marine compartment for the relevant exposure scenarios and documentation for the recommended personal protective equipment. The other compliance check requirement of two-generation reproductive toxicity study is addressed in a separate decision although all information requirements were initially addressed together in the same draft decision.

On 28 July 2014 ECHA referred the draft decision to the Member State Committee.

By 18 August 2014, in accordance to Article 51(5), the Registrant provided comments on the proposals for amendment. In addition, the Registrant provided comments on the draft decision. The Member State Committee took the comments of the Registrant on the proposals for amendment into account. The Member State Committee did not take into account the Registrant's comments on the draft decision as they were not related to the proposals for amendment made and are therefore considered outside the scope of Article 51(5).

After discussion in the Member State Committee meeting on 16-18 September 2014, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 16 September 2014.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

A. Information in the technical dossier derived from the application of Annexes VII to XI

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

1. Transgenic rodent somatic and germ cell gene mutation assay (TGR) in rats, via inhalation route during 28 consecutive days (Annex X, 8.4., column 2; test method: OECD 488).
   The TGR somatic assay shall be conducted in liver, lung and kidney.
   or

In vivo alkaline single-cell gel electrophoresis assay for DNA strand breaks (comet assay), in male rats, via inhalation route on liver, lung, kidney and bone marrow (Annex X, 8.4., column 2; test method: draft OECD 489).

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 requests in this decision, or to fulfil otherwise the information requirements with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

B. Information related to chemical safety assessment and chemical safety report

Pursuant to Articles 41(1)(c), 41(3), 10(b), 14 and Annex I of the REACH Regulation the Registrant shall submit in the chemical safety report:

1. Revised risk characterisation ratios (RCRs) for local releases (Annex I, section 6 of the REACH Regulation). The Registrant shall provide correct calculations for RCRs for local releases, as specified in section III.B.1 below;
2. The risk characterisation for the marine compartment for the relevant exposure scenarios (Annex I, section 6 of the REACH Regulation). The Registrant shall provide the RCRs for the marine compartment for the relevant scenarios or demonstrate that no direct releases occur to the marine compartment, as specified in section III.B.2 below;
3. Documentation for the recommended personal protective equipment (Annex I, 5.1.1. in conjunction with Annex II, 0.1.2. and 8.2.2.2(b)), as specified under section III.B.3 below.

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 **23 December 2015**.

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.

A. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 10(a) (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 IX, and X of the REACH Regulation.

1. Transgenic rodent somatic and germ cell gene mutation assays (Annex X, 8.4., column 2)

"Mutagenicity" is an information requirement as laid down in Annex VIII, Section 8.4. of the

REACH Regulation.

Column 2 of Annex X, 8.4 indicates the following: "If there is a positive result in 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."

Adequate information needs to be present in the technical dossier for the registered substance to meet this information requirement.

The Registrant has provided 15 *in vitro* studies. From these 15 studies, 12 tests showed positive genotoxic activity: three gene mutation studies in bacteria (Ames tests), one gene mutation study in yeast cells, one mammalian cell gene mutation tests, three chromosomal aberration tests, one sister chromatid exchange test, and one unscheduled DNA synthesis test. The three negative tests were: two Ames tests (in one test there was no metabolic activation used) and one gene mutation study in mammalian cells. The Registrant concludes that the registered substance "*appears to show genotoxic activity in in vitro testing systems, especially in the presence of metabolic activation*".

The Registrant has also provided 9 *in vivo* studies: four micronucleus assays (addressing chromosomal aberration), two dominant lethal assays by inhalation route (addressing chromosome aberration), one sex-linked recessive lethal test in Drosophila (addressing lethal mutations in germ cells) and two mechanistic studies. All of these studies were negative and the Registrant considers them as sufficient weight of evidence to conclude that the substance does not produce *in vivo* genotoxicity.

ECHA notes that according to OECD test guideline 478 "*dominant lethals are generally accepted to be the result of chromosomal aberrations (structural and numerical anomalies), but gene mutations and toxic effects cannot be excluded*". Therefore, all the conducted *in vivo* studies address only chromosomal aberrations and thus, there is still a concern for potential somatic cell/germ cell genotoxicity.

As explained above, the information available 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.

In light of the physical and chemical properties of the substance (liquid with high vapour pressure) and the information provided on the uses and human exposure (intermediate in closed systems, exposure during maintenance operations), ECHA considers that testing by the inhalation route is most appropriate.

The Registrant is requested to perform the TGR assay in liver, lung, germ cells and kidney. The reason for tissue selection is outlined in the test guideline (OECD 488 paragraphs 37 and 38). The liver was chosen to evaluate mutations in the organ that is primarily responsible for metabolism of xenobiotics. The lung was chosen due to inhalation administration to evaluate mutations at the site of contact with the body. The kidney was chosen because carcinogenicity was observed in this organ indicating a concern for possible genotoxic action. In addition, germ cells from testes shall be sampled three days after cessation of exposure, in line with the provisions of OECD test guideline 488. These germ cells only need to be analysed for mutation frequency, if positive test results are obtained for any of the somatic cells. This requirement is proportionate because it avoids unnecessary additional animal testing in the case of positive findings in somatic cells.

The Registrant has proposed, in his comment as well as in his dossier update an alternative testing strategy to the one requested in the original draft decision. The Registrant "*proposes to conduct an in vivo genotoxicity study in which the alkaline Comet assay and the Pig-a*

assay would be used to generate the required information". The Registrant also states that "*the alkaline Comet assay is able to detect DNA damage such as single or double DNA strand breaks (SSB or DSB), alkali-labile sites, DNA-DNA / DNA-protein cross-linking and SSB associated with incomplete excision repair sites. Such DNA damage can results in various outcomes including gene mutations. A draft OECD guideline already exists and a final version is pending. As stated in the draft OECD guideline, the Comet assay has been reviewed and recommendations have been published by various international groups. The Comet assay has recently undergone an international validation which was led by Japan. The experimental phases started in 2006 and the validation reports were peer reviewed in January and February 2013. The validation and the peer review reports were endorsed April 2013 and are available on the OECD website. The use of the alkaline Comet assay has already been endorsed by several European and international regulatory organisations. The Comet assay has been recently included in the ICH S2(R1) guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use and the European Food Safety Authority has confirmed that the in vivo alkaline Comet assay can be used to assess the genotoxicity of a great variety of chemical compounds which include food additives, flavourings, food contact materials, foodborne by-products, feed additives, pesticides, contaminants, etc. In ECHA guidance R7a, the comet assay is listed among the possible in vivo genotoxicity assays together with the transgenic rodent mutation assay.*"

The details on the proposed test protocol for Comet Assay were included in the comments and in Annex I to this decision with the reference documents being the proposed draft OECD guideline and EFSA guidance document. Although there is no internationally agreed guideline for the Comet assay, ECHA considers that the proposed *in vivo* Comet Assay is adequate to further investigating the potential gene mutation effects of the registered substance and is therefore an appropriate in vivo study according to Annex VIII, 8.4., column 2 of the REACH Regulation.

Thus, the Registrant is given an alternative option to meet the information requirements for this endpoint: Comet Assay to be conducted in liver, lung, kidney and bone marrow. The liver was chosen to evaluate mutations in the organ that is primarily responsible for metabolism of xenobiotics and it is a known target issue for the registered substance. The lung was chosen due to inhalation administration to evaluate mutations at the site of contact with the body. The kidney was chosen because it is a known target tissue for the registered substance. Bone marrow was chosen because it is a rapidly dividing tissue.
In order to optimize the use of animals, gonadal cells may be sampled at the same time as the somatic tissues and analysed in the Comet assay. Such analysis may provide a proof that the tested substance and/or its metabolites have reached the gonad and cause genotoxic effects. The registrant should however be aware that: i) the standard alkaline Comet assay as described in the draft OECD guideline 489 is not considered appropriate to measure DNA strand breaks in mature germ cells. Indeed, protocol modifications together with improved standardization and validation studies are deemed necessary before the comet assay on mature germ cells (e.g. sperm) can be included in the test guideline. Moreover, the recommended exposure regimen described in this guideline is not optimal for a meaningful analysis of DNA strand breaks in mature sperm, and ii) gonads contain a mixture of somatic and germ cells. Therefore, positive results in whole gonad are not necessarily reflective of germ cell damage but they indicate that tested substance(s) and/or its metabolites have reached the gonad and cause genotoxic effects.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit either of the following studies derived with the registered substance subject to the present decision: Transgenic rodent somatic and germ cell gene mutation assay (test method: OECD 488) in rats treated via inhalation route in liver, lung, and kidney, or an *in vivo* alkaline comet assay (draft OECD 489) in rats treated via inhalation route on first site of contact tissue (lung), liver, kidney and bone marrow.

Notes for the consideration by the Registrant

The Registrant proposed to perform a Pig-a assay in addition to the Comet assay (details on the proposed test protocol were included in the comments and in Annex I to this decision). ECHA notes, that it is at the Registrant's discretion to perform the intended test and use the results to ensure the safe use of the substance. However, ECHA also notes that this test should not jeopardize the results from the Comet assay and it should not require the use of more animals. In addition, the Registrant is reminded that the reliability and validity of the Pig-a assay has not yet been demonstrated and that animal testing should only be used as a last resort.

B. Information related to the chemical safety assessment and chemical safety report

Pursuant to Articles 10(b) and 14(1) of the REACH Regulation the registration shall contain a chemical safety report (CSR) which shall document the chemical safety assessment conducted in accordance with Article 14(2) to (7) and with Annex I of the REACH Regulation.

1. Revised risk characterisation ratios (RCRs) for local releases (Annex I, section 6 of the REACH Regulation)

Annex I, section 6 of the REACH Regulation requires the Registrant to characterise the risk for each exposure scenario. The risk characterisation shall consider the human population (exposed as workers, consumer or indirectly via the environment and if relevant a combination thereof) and the environmental spheres for which exposure to the substance is known or reasonable foreseeable, under the assumption that the risk management measures described under exposure scenario in Section 5 have been implemented. In addition, the overall environmental risk caused by the substance shall be reviewed by integrating the results for the overall releases, emissions and losses from all sources to all environmental compartments.

In the CSR provided by the Registrant the risk characterisation ratios (RCRs) for local releases (reported in section 10 and the appendix 2c of the CSR) cannot be reproduced. For instance for freshwater and exposure scenario 4 "1,1-dichloroethene used as monomer in amount [redacted]", the PNEC is 9.12e-3 mg/L and the local PEC [redacted]. Thus, the RCR should be [redacted] instead of the value reported in the CSR, i.e. [redacted]. This raises concerns about the figures reported in the registration dossier.

In his comments, following the procedure set out in Article 50(1) of the REACH Regulation, the Registrant indicated his intention to provide this information in the CSR in the updated dossier. ECHA notes, however, that this information is not present in the dossier update (Submission No. [redacted]).

Therefore, pursuant to Articles 10(b) and 14(1) of the REACH Regulation, the Registrant is requested to recalculate the risk characterisation ratios for local releases, or to provide a justification for the calculation of the RCRs reported in the current registration dossier.

2. The risk characterisation for the marine compartment for the relevant exposure scenarios (Annex I, section 6 of the REACH Regulation)

Annex I, section 6 of the REACH Regulation requires the Registrant to characterise the risk for each exposure scenario. The risk characterisation shall consider the human population (exposed as workers, consumer or indirectly via the environment and if relevant a

combination thereof) and the environmental spheres for which exposure to the substance is known or reasonable foreseeable, under the assumption that the risk management measures described under exposure scenario in Section 5 have been implemented. In addition, the overall environmental risk caused by the substance shall be reviewed by integrating the results for the overall releases, emissions and losses from all sources to all environmental compartments.

In the CSR provided by the Registrant the risk characterisation ratios (RCRs) for local releases in the marine environment are missing. In particular, for exposure scenario 4 "1,1-dichloroethene used as monomer in amount [redacted]", there is no information in the dossier that demonstrates that direct releases into the sea do not occur. For this exposure scenario, RCRs higher than 1 are obtained by comparing the local PEC for the marine compartment as reported in Appendix 2b and section 9.4 of the CSR with the PNECs reported in Section 7 of the CSR for the marine compartment. Therefore, there might be a risk for marine water and sediment if local releases occur in the marine environment.

In his comments, following the procedure set out in Article 50(1) of the REACH Regulation, the Registrant indicated his intention to provide this information in the CSR in the updated dossier. ECHA notes, however, that this information is not present in the dossier update (Submission No. [redacted]).

Therefore, pursuant to Articles 10(b) and 14(1) of the REACH Regulation, the Registrant is requested to provide the RCRs for the marine compartment for the relevant scenarios or demonstrate that no direct releases occur to the marine compartment.

3. Documentation for the recommended personal protective equipment (Annex I, 5.1.1. in conjunction with Annex II, 0.1.2. and 8.2.2.2(b))

Article 14(6) as well as Annex I, 0.1., 5.1.1., 5.2.4. and 6.2. of the REACH Regulation require registrants to identify and apply appropriate measures to adequately control the risks identified in a CSR. The exposure shall be estimated and risks shall be characterised in the CSR under the assumption that relevant risk management measures have been implemented.

Pursuant to Annex VI, section 5 and Annex II, section 0.1.2. of the REACH Regulation the information provided in the registration dossier shall be consistent with that in the Safety Data Sheet (SDS). The requirements of Safety Data Sheets are specified in Annex II of the REACH Regulation (amended by Commission Regulation (EU) No 453/2010).

According to Annex I, 0.3., 0.5. and 5.1.1. the applied Risk Management Measures (RMM) have to be indicated in the CSR. Annex II, section 8.2.2.2. (b)(i), requires the Registrant to describe the relevant RMM in detail (e.g. the type of gloves to be worn shall be clearly specified based on the hazard of the substance or mixture and potential for contact and with regard to the amount and duration of dermal exposure) in order to minimise the exposure for workers handling the registered substance. In particular, the following requirements for hand protection in order to avoid dermal exposure need to be provided consistently in the SDS and CSR:

- The type of material and its thickness,
- The typical or minimum breakthrough times of the glove material.

In the CSR, the Registrant indicated the following for hand protection: "*Wear chemically resistant gloves (tested to EN374) in combination with specific activity training [PPE17]*".

In section 11 of the technical registration dossier in the part for Exposure controls/personal protection, the following is stated: "*hand protection: - wear suitable gloves; - suitable material: PVA, Fluoroelastomer*".

ECHA notes that the substance is classified as Carc. 2.

To ensure the safe use of a substance it is essential to have detailed guidance on risk management measures, e.g. personal protective equipment. Although the gloves are reported in the CSR and IUCLID section 11 as required personal protective equipment to prevent dermal exposure to the substance, only the material type of gloves to be worn is specified, but thickness and typical or minimum breakthrough time when handling the substance are not.

Therefore, pursuant to Article 41(1)(c) and 41(3) of the REACH Regulation the Registrant is requested to provide documentation for the thickness and the typical or minimum breakthrough time for the glove type recommended with regard to the amount and duration of dermal exposure.

Notes for consideration by the Registrant:

Regarding how to report the gloves specifications, the information should be included both in section 11 of the technical IUCLID dossier (Guidance on Safe Use) which is the disseminated part of the dossier and in the CSR where the appropriate measures to adequately control the risk are to be reported.

It is the responsibility of the Registrant to ensure consistency of the information within the CSR, and between the CSR, IUCLID section 11 and the safety data sheet.

C. 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 addressed another study (two-generation reproductive toxicity study, Annex X, Section 8.7.3). As this study is not addressed in the present decision, ECHA 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 by 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.

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.

In addition, it is important to ensure that the particular sample of substance tested in the new studies 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 studies 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 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/web/guest/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

[redacted]
Leena Yla-Mononen
Director of Evaluation

Annex I

Study details for Comet Assay
Species: rat
Sex: males
Group size: ≥ 5
Treatment groups - negative. control - 1,1-dichloroethylene, 3 doses - positive. control.
Treatment protocol: repeated dosing, ≥ 3
Route of administration: lung
Tissues investigated: Comet assay: lung, liver, kidney, bone marrow Pig-a assay: reticulocytes and erythrocytes Histopathology: the tissues used for the genotoxicity parameters
Analyses: General parameters specified in the draft OECD guideline to assess the status of the animals Comet assay: cytotoxicity, tail parameters (primarily: percentage of DNA in tail) for at least 150 cells per animal, presence of ghost/hedgehog cells Pig-a assay: Frequency of reticulocytes, an index of bone marrow toxicity, expressed as percent of total erythrocytes, frequency of mutantphenotype erythrocytes, expressed as number per 1,000,000 total erythrocytes, Frequency of mutant-phenotype reticulocytes, expressed as number per 1,000,000 total reticulocytes

Reference documents cited by the Registrant:

- OECD, "Rodent alkaline single cell gel electrophoresis (Comet) assay," 2012. Available: http://www.oecd.org/env/ehs/testing/OECD_draft_Comet[1].pdf
- European Food Safety Authority, "Minimum Criteria for the acceptance of in vivo alkaline Comet Assay Reports," EFSA J., vol. 10, no. 11, p. 2977, 2012.