Decision number: CCH-D-2114292054-52-01/F Helsinki, 27 February 2015

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

For 1-bromopropane, CAS No 106-94-5 (EC No 203-445-0), 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-bromopropane, CAS No 106-94-5 (EC No 203-445-0), 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 tonnes per year. This decision does not take into account any updates submitted after 4 September 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 12 August 2013.

On 18 November 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 16 December 2013 ECHA received comments from the Registrant on the draft decision.

On 14 May 2014 the Registrant updated his registration dossier with the submission number [redacted]

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

On 4 September 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 10 October 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.

On 20 October 2014 ECHA referred the draft decision to the Member State Committee.

By 10 November 2014 the Registrant did not provide any comments on the proposals for amendment.

A unanimous agreement of the Member State Committee on the draft decision was reached on 24 November 2014 in a written procedure launched on 13 November 2014.

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

II. Information required

A. Tests required pursuant to Article 40(3)

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

Pursuant to Articles 41(1), 41(3), 10(a)(vii), 12(1)(e), 13 and Annex X 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:

- Transgenic rodent somatic and germ cell gene mutation assays (Annex X, 8.4., column 2; test method: OECD 488). The test shall be conducted in female mice treated for 28 days via inhalation route, and the lung and liver tissues shall be harvested three days after the cessation of treatment. Mutation frequency shall be assessed in lungs and liver.

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

B. Deadline for submitting the required information

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 **5 September 2016**.

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 Annex X of the REACH Regulation.

Mutagenicity, *in vivo* (Annex X, 8.4.)

According to Annex X, section 8.4. of the REACH Regulation, in case any *in vitro* test required at Annex VII or VIII revealed positive results, a second *in vivo* somatic cell test may be necessary, depending on the quality and relevance of all the available data.

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 Agency as being appropriate.

According to ECHA Guidance on information requirements and Chemical Safety Assessment, Endpoint specific guidance (Chapter R.7a, version 2.2, August 2013, page 348)"*If the first in vivo test is negative, the need for a further in vivo somatic cell test should be considered. The second in vivo test should only then be proposed if it is required to make a conclusion on the genotoxic potential of the substance under investigation; i.e. if the in vitro data show the substance to have potential to induce both gene and chromosome mutations and the first in vivo test has not addressed this comprehensively. In this regard, on a case-by-case basis, attention should be paid to the quality and relevance of all the available toxicological data, including the adequacy of target tissue exposure.*"

In the present case, ECHA notes that information on an *in vitro* gene mutation fulfilling the information requirements of Annexes VII and VIII has been submitted. These test results were positive. The results from such *in vitro* mutagenicity studies indicate that the registered substance induce gene mutation. No information from an appropriate follow-up *in vivo* assay for gene mutations has been submitted, while the information requirement for somatic cell genotoxicity of Annex IX, section 8.4 has been addressed with an *in vivo* assay for structural and numerical chromosome damage (OECD 474) and dominant lethal (no test guideline followed). The reliability (Klimisch) scores of all these tests were 2. The results of the tests were negative. ECHA points out that the submitted *in vivo* assay is a relevant *in vivo* test for the endpoint chromosome aberration, but not for the endpoint gene mutation. There is no other data or adaptation addressing the endpoint gene mutation available in the dossier.

On the basis of the above *in vitro* studies and other data available, ECHA considers that the substance has an alert for gene mutation within the meaning of Annex X, section 8.4. of the REACH Regulation and there is no *in vivo* study addressing this endpoint in the registration dossier.

Regarding the test method, ECHA considers that the Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays (TGR assay) (OECD Test Guideline 488) is the most appropriate and suitable test to follow-up *in vivo* gene mutation. The test can measure gene mutations in any tissue of an animal. In the OECD Test Guideline 488 it is said: "The test substance is usually administrated by gavage using a stomach tube or a suitable intubation cannula. In general, the anticipated route of human exposure should be considered when designing an assay. Therefore, other routes of exposure (such as, drinking water, subcutaneous, intravenous, topical, inhalation, intratracheal, dietary, or implantation) may be acceptable where they can be justified. "

ECHA considers the inhalation route as the most appropriate in the present case, since the substance has a high vapour pressure (14.772 kPa at 20 °C). Therefore, the inhalation route is the anticipated route of human exposure.

The Registrant is requested to carry out the test in female mice, since female mice had the highest incidence of tumours (at 28% in lung) in the NTP carcinogenicity study. In female rats only adenomas in the intestine (10% incidence) were observed in this study. In male rats skin tumours were also observed up to 20% incidence. However, skin (specifically, dermis, or the hair follicle for keratoacanthomas) is potentially a difficult tissue to sample. Therefore, the test should be carried out in female mice.

The Registrant is requested to perform the TGR assay in lungs and liver. The reasons for tissue selection, as outlined in the test guideline (OECD 488 paragraphs 37 and 38), are that lungs should be chosen due to administration by inhalation route and to evaluate mutation at the initial site of contact with the body. The second reason for choosing lungs is that in female mice high incidence of lung tumours was observed. Liver is chosen to study an effect on a tissue that is also exposed to systematically available substances and as it is a main site of metabolism.

The Registrant, in his comments submitted according to Article 50(1) of the REACH Regulation, notes that the dossier already contains three *in vivo* genotoxicity studies (two micronucleus, one dominant lethal). He also notes that in the ECHA endpoint specific guidance it is said that "Substances for which there is a formal agreement to classify them in category 1, 2 or 3 for mutagenicity and/or category 1 or 2 for carcinogenicity will usually not require additional testing in order to meet the requirements of Annexes VII-X." He proposes to "amend the carcinogenicity classification assigning 1-bromopropane to carcinogenicity Category 2." and expressed the intention to provide a revised dossier shortly, with restrictions of uses to completely enclosed and sealed systems (PROC 1 and PROC 8b).

ECHA notes that the dossier has been updated on 15 May 2014 (submission number: [redacted]). The substance has now a classification and labelling ("proposed classification") for carcinogenicity: Carc. 2. However, since this is a self-classification, there is no formal agreement on the classification for carcinogenicity. Furthermore, it should be noted that in the version of the Guidance referred to by the Registrant "category 1 and 2" refer to classification and labelling according to Directive 67/548/EEC (classification, packaging and labelling of dangerous substances) which would correspond to category 1A or 1B under the CLP Regulation, while the Registrant uses category 2 according to CLP Regulation. Therefore, the current carcinogenicity classification is not a valid adaptation argument for *in vivo* genotoxicity. Furthermore, in the updated dossier the reported uses are not restricted to "completely enclosed and sealed systems (PROC 1 and PROC 8b)", since processes (PROC) 4 ("Use in batch and other process (synthesis) where opportunity for exposure arises") for manufacture and formulation and 5 ("Mixing and blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)") for formulation include uses of the substance. Therefore, there may be significant worker exposure. The section II of the decision requiring transgenic rodent somatic and germ cell gene mutation assays was 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: Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays (test method: OECD 488) using the registered substance. In line with the OECD 488 Test Guideline, the test shall be conducted in female mice treated for 28 days via inhalation route, and the tissues concerned (lungs and liver) shall be harvested three days after the cessation of treatment. Mutation frequency shall be assessed in the collected lungs and liver.

Notes for consideration by the Registrant

The Registrant is reminded that according to the column 2 of section 8.4 of Annex X of the REACH Regulation, if positive results from an *in vivo* somatic cell study are available, "the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered".

IV. Adequate identification of the composition of the tested material

In carrying out the study 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 study must be suitable to assess these.

Furthermore, 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.

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 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.

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/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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