ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-0000005483-73-04/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 *tert*-butyl acetate, CAS No 540-88-5 (EC No 208-760-7), 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 for *tert*-butyl acetate, CAS No 540-88-5 (EC No 208-760-7), 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 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 100-1000 tonnes per year. This decision does not take into account any updates submitted after 24 July 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 4 April 2013.

On 13 August 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 12 September 2013 ECHA received comments from the Registrant on the draft decision. On 12 september 2013 the Registrant updated his registration dossier with the submission number [redacted].

On 12 May 2014 the Registrant updated his registration dossier with the submission number [redacted].

The ECHA Secretariat considered the Registrant's comments and updates.

The information is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

On 24 July 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 proposals for amendment were 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)(d), 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)(d) 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 the *in vitro* or *in vivo* mammalian cell gene mutation information requirements. Cytogenicity studies and gene mutation studies correspond to 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.

Read across hypothesis and documentation:

In his comments, the Registrant proposed that read across from *tert*-butyl alcohol, a metabolite of *tert*-butyl acetate could be used. More specfically the Registrant referred to two publications in which a L5178Y TK+/− mutagenesis assay was conducted ([redacted], (1981)) and McGregor, *et al* (1989). The Registrant argues that the read across from the alcohol to the acetate ester is possible because the latter substance is rapidly metabolised to the alcohol and acetic acid and because *tert*-butyl acetate and *tert*-butyl alcohol are chemically similar, both are short chain oxygenated hydrocarbons with a *tert*-butyl side chain and either an acetate or alcohol group. The Registrant refers to two toxicokinetic studies that are summarized in the IUCLID dossier ([redacted] (2000a) and Groth and Freundt (1994)) to support its statement that, following inhalation exposure, tertiary butyl acetate that is absorbed undergoes rapid metabolism primarily to tertiary butyl alcohol with further oxidation to 2-hydroxyisbutyric acid and excretion in the urine.

ECHA assessment of the read across:

It is noted that the L5178Y TK+/− mutagenesis studies [redacted], (1981) and McGregor, *et al* (1989) were not included in the dossier as end point study summaries nor were they described in more detail in the comments or the CSR. Therefore, ECHA was unable to assess these studies.

The study of [redacted] (2000a) clearly shows that the ester is metabolised after inhalation via two main routes: 1) hydrolysis of the ester and 2) hydroxylation of a methyl group of the tertiary butyl moiety, whereby the ester bond remains intact. After inhalation a substantial part of *tert*-butyl acetate is thus not metabolized via the *tert*-butyl alcohol, but via another pathway. This means that the results of an *in vitro* genotoxicity test with the alcohol provide no information on the relevant metabolites that have the ester bond intact.

The other toxicokinetic study (Groth and Freundt, 1994) shows that during exposure via inhalation of rats to *tert*-butyl acetate (440 ppm and 900 ppm) this compound is present in the blood in higher concentrations than *tert*-butyl alcohol. After the termination of exposure, the blood concentration of the ester is reduced by 50% in 45 min. This study thus shows that under the exposure conditions a significant systemic exposure to the ester occurs, and does not therefore support the justification of the read across. Moreover, no other metabolites were measured in this study.

Furthermore, ECHA notes that data on the metabolism of *tert*-butyl acetate are only available for exposure of animals via inhalation (i.e. in absence of a liver homogenate used in an *in vitro* genotoxicity test for metabolic activation). It cannot be ruled out that the relative importance of the two major metabolic pathways is different in an *in vitro* genotoxicity test in the presence of a liver homogenate for metabolic activation or that other metabolites are formed under these conditions. Moreover, the metabolic rates may differ under *in vitro* conditions, leading to differences in exposure to the ester. The absence of information on the *in vitro* metabolism of the ester precludes conclusions as to how the possibilities to read across would be influenced by differences with the *in vivo* situation.

The read across proposed by the Registrant is rejected.

Conclusion:

Therefore, pursuant to Article 41(1) and 41(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 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 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.

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.

[redacted]
Leena Ylä-Mononen
Director of Evaluation